Influence of Substituent Groups on Nuclear Reactivity in the Formation of Substituted Biphenyls by Reaction of Aromatic Diazo and Related Compounds with Aromatic Liquids. VI. p-Chlorophenylation

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In a previous paper[1] the determination has been reported of the partial rate factors of nitrobenzene in *p*-methoxyphenylation by the *p*-methoxyphenyl radical derived from *N*-nitroso-*p*-acetanisidide. In order further to examine the effect of the substituent in the attacking radical in the homolytic arylation, competitive *p*-chlorophenylations of nitrobenzene, chlorobenzene, anisole, and toluene using benzene as a reference substrate have been carried out, with *N*-nitroso-*p*-chloro(^{36}Cl)acetanilide as a source of the *p*-chlorophenyl radical, and the products have been analyzed by isotope dilution analysis. We now report the results of this study.

Table I lists the values for the partial rate factor and the relative rate calculated from the relative amounts in which 4-chlorobiphenyl and the three isomeric substituted 4-chlorobiphenyls were formed in the competitive *p*-chlorophenylation. Because of difficulty in isolating radiochemically pure 3,4'-dichlorobiphenyl from the reaction mixture with chlorobenzene, we could not determine the partial rate factor for the meta position of chlorobenzene by means of isotope dilution analysis. The value of 0.87 given in Table I for this partial rate factor was estimated from the value of the partial rate factor for the ortho position obtained by this method and the molar ratio, as determined by means of infrared-spectrophotometry, in which 2,4'- and 3,4'-dichlorobiphenyl were formed by the reaction of non-labelled *N*-nitroso-*p*-chloroacetanilide with chlorobenzene.

Inspection of the table shows that the ortho and para positions are more reactive than the meta position for all aromatic compounds,

1) O. Simamura and T. Migita, This Bulletin, 27, 228 (1954).

TABLE I. PARTIAL RATE FACTORS AND RELATIVE RATES IN *p*-CHLOROPHENYLATION OF MONOSUBSTITUTED BENZENES AT 20.0°C

Compound	Exp. No.	Partial rate factors			Relative rate
		k_o/k	k_m/k	k_p/k	k_x/k_H
$C_6H_5NO_2$	1*	4.53	0.62	5.76	2.68
	2*	4.18	0.60	6.60	2.69
	Mean	4.35	0.61	6.18	2.69
C_6H_5Cl	5	2.69	—	1.30	—
	6	2.70	—	1.35	—
	Mean	2.70	0.87**	1.33	1.41
$C_6H_5OCH_3$	1*	3.81	0.97	1.42	1.83
	2*	4.05	0.90	1.65	1.93
	Mean	3.93	0.94	1.54	1.88
$C_6H_5CH_3$	3	2.97	1.01	1.35	1.55
	4	2.97	1.13	1.29	1.58
	Mean	2.97	1.07	1.32	1.56

* Reaction temperature was 18°C. ** See text.

k, k_o, k_m, and k_p denote the rate constants on one nuclear position of benzene and the ortho, meta, and para position of the substituted benzene, respectively.

$k_x=2k_o+2k_m+k_p$ and $k_H=6k$

and that all substituents, regardless of their polar nature, activate the aromatic ring, especially at the ortho and the para position. This substitution pattern is in keeping with what is already known to be typical of the homolytic aromatic phenylation[2] and is quite different from that found in the electrophilic substitution. Qualitative consideration of the substitution pattern would therefore suggest that the polar influence due to the chlorine atom in the attacking radical is of minor, if any, importance in the chlorophenylation.

It has been reported in Part III[1] that no polar influence has been detected in the *p*-methoxyphenylation of nitrobenzene. The effect of the polarized aryl radical, however, was soon after recognized by Dannley and Sternfeld[3], who examined the isomer distribution of the products from the reactions of *p*-chlorobenzoyl and of *p*-nitrobenzoyl peroxide with benzotrichloride, and by Cadogan, Hey, and Williams[4], who measured the relative rates of the *p*-chlorophenylation of chlorobenzene and of nitrobenzene by means of *p*-chlorobenzoyl peroxide, and subsequently by Chang, Hey and Williams[5], who determined the partial rate factors in the same reaction. In the present study of chlorophenylation, although no simple correlation is apparent between the partial rate factor for the ortho or the para position and the electronic nature of the substituents on the substrates, the partial rate factor of the meta position was found to diminish in the order: toluene>benzene, anisole>chlorobenzene>nitrobenzene, and this order appears to represent the electronic effect of the substituent. Indeed, a plot of the logarithm of the partial rate factor against Hammett's substituent constant for the meta position falls on a straight line with a slope of −0.27, as shown in Fig. 1. This fact, more convincingly than anything else, demonstrates that the *p*-chlorophenyl radical has a measure of electrophilic character due to the polar nature of the chlorine atom.

The homolytic aromatic arylation is considered[2] to proceed through the rate-determining step of the addition of an aryl radical to

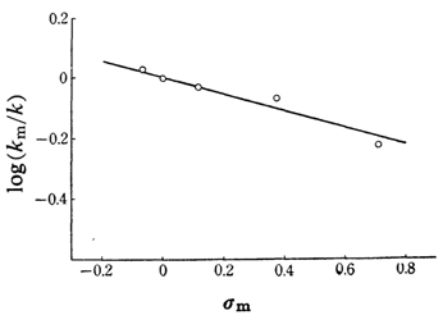

Fig. 1. The Hammett plot for the *p*-chlorophenylation.

2) D. R. Augood and G. H. Williams, *Chem. Revs.*, **57**, 123 (1957); T. Migita, *Yuki Gosei Kagaku Kyokai Shi*, **15**, 74 (1957); G. H. Williams, "Homolytic Aromatic Substitution", Pergamon Press, Oxford (1960).

3) R. L. Dannley and M. Sternfeld, *J. Am. Chem. Soc.*, **76**, 4543 (1954).

4) J. I. G. Cadogan, D. H. Hey and G. H. Williams, *J. Chem. Soc.*, **1955**, 1425.

5) Chang Shih, D. H. Hey and G. H. Williams, ibid., **1958**, 1885.

an aromatic ring, giving an arylcyclohexadienyl radical. The generally observed ortho-para orientation suggests that the major factor controlling the orientation of the entering group is the degree of stabilization of the transition state due to the delocalization of the odd electron. Thus, when the addition occurs at the ortho or the para position to a substituent, the odd electron, in the transition state, can conjugate with the substituent group through the π-electron system of the aromatic nucleus; consequently, the substituent contributes to the stabilization of the transition state. In substitution at the meta position, however, it is obvious that no such conjugation, and hence no such stabilization, is possible, with the result that all substituents direct the homolytic substitution mainly to the ortho and the para position.

In the *p*-chlorophenylation at the ortho and the para position, the subtle influence of the polar character of the radical is masked by the foregoing major factor, that is, the conjugative effect; it is consequently not revealed in the variation of either the partial rate factor or the relative rate. On the other hand, when the addition occurs at the meta position, the odd electron, in the transition state, conjugates only with the π-electrons on the aromatic ring, and the conjugation does not, to the first approximation, extend further into the substituent group. The stabilization due to the conjugative effect therefore will have nearly equal magnitude for every monosubstituted benzene, and the effect of the polar nature of the attacking radical will become significant enough to be reflected in the sequence of the reactivity of the meta position of aromatic compounds, as has actually been observed.

Experimental

Melting points are uncorrected.

Solvents. — Thiophene-free benzene was purified by repeated fractional distillations through a Vigreux column, b. p. 79.5°C. Nitrobenzene was purified by heating commercial material with an aqueous solution of potassium bichromate, distilling it in steam and then under reduced pressure, and finally freezing it fractionally, m. p. 5.9°C. Toluene was purified by shaking it with concentrated sulphuric acid and then fractionating through a Vigreux column, b. p. 109°C. Anisole was prepared from purified phenol and dimethyl sulphate and was purified by distilling it through a Vigreux column, b. p. 153°C. Commercial chlorobenzene was purified by fractionating it through a Vigreux column, b. p. 131°C.

4-Chlorobiphenyls.—A variety of substituted 4-chlorobiphenyls, including several new compounds, which were used as carriers in the isotope dilution analysis were prepared as follows:

4-Chlorobiphenyl was prepared by reaction of *N*-nitroso-*p*-chloroacetanilide with benzene, m. p. 78.5°C (from methanol).

4-Chloro-2'- and -4'-nitrobiphenyl were prepared by the nitration[6] of the above 4-chlorobiphenyl and were purified by chromatography on alumina in petroleum ether-benzene and then by recrystallization from methanol or ethanol; they had the melting points of 69°C and 146°C, respectively.

4-Chloro-3'-nitrobiphenyl was prepared by the chlorination of 3-nitrobiphenyl according to the method described by Blakey and Scarborough[7], m. p. 94°C (from methanol).

4-Chloro-2'- and -4'-methoxybiphenyl were prepared by reaction of *N*-nitroso-*p*-chloroacetanilide with anisole. After removal of anisole from the reaction mixture, the residue was distilled with superheated steam, and the distillate was treated with stannous chloride and concentrated hydrochloric acid in methanol to free it from coloured material. Fractional distillation of the mixture, followed by chromatography on alumina in petroleum ether-benzene, gave the 2'-isomer, m. p. 58°C (from methanol) (Found: Cl, 16.17. Calcd. for $C_{13}H_{11}ClO$: Cl, 16.21%), and the 4'-isomer, m. p. 116°C (from ethanol). The structure of the 2'-isomer was established by demethylation by heating it with pyridine hydrochloride[8] into the known 4-chloro-2'-hydroxybiphenyl[9], m. p. 53°C. The 4'-isomer was also prepared by the Ullmann reaction from *p*-iodoanisole and *p*-chloroiodobenzene.

4-Chloro-3'-methoxybiphenyl was prepared by heating a mixture of *m*-iodoanisole and *p*-chloroiodobenzene with copper powder at 230°C for 11 hr. The oily material extracted from the reaction mixture with benzene was fractionally distilled under reduced pressure. The crystals of 4,4'-dichlorobiphenyl which deposited from the cooled distillate (b. p. 197~212°C/27 mmHg) were filtered off, and then the filtrate was heated with pyridine hydrochloride at 210°C for 7 hr. The phenolic fraction was separated and fractionated by chromatography on alumina in benzene, giving 4-chloro-3'-hydroxybiphenyl[10], m. p. 84°C. This was methylated with dimethyl sulphate and aqueous alkali to yield 4-chloro-3'-methoxybiphenyl, m. p. 36~37°C (from methanol) (Found: Cl, 16.02. Calcd. for $C_{13}H_{11}ClO$: Cl, 16.21%).

4-Chloro-2'-, -3'- and -4'-methylbiphenyl were prepared by the *p*-chlorophenylation of toluene with *N*-nitroso-*p*-chloroacetanilide. After removal of the toluene, distillation with superheated steam gave an oily material, which was then fractionally distilled three times under reduced pressure. In each distillation, some 4-chloro-4'-methylbiphenyl (m. p. 124°C) was separated from the after-run in the

6) C. K. Bradsher and L. J. Wissow, *J. Am. Chem. Soc.*, **68**, 404 (1946).
7) W. Blakey and H. A. Scarborough, *J. Chem. Soc.*, **1927**, 3003.
8) V. Prey, *Ber.*, **74**, 1219 (1941); **75**, 350 (1942).
9) J. C. Colbert and R. M. Lacy, *J. Am. Chem. Soc.*, **68**, 270 (1946).
10) V. Prelog, J. Würsch and K. Königsbacher, *Helv. Chim. Acta*, **34**, 258 (1951).

form of crystals, which were collected and recrystallized from methanol. Cooling a methanolic solution of the first fraction (b. p. 101~105°C/2 mmHg) in a dry ice-ethanol bath yielded crystals (m. p. 27°C), which were purified by chromatography on alumina in petroleum ether to afford 4-chloro-2'-methylbiphenyl (Found: Cl, 17.29. Calcd. for $C_{13}H_{11}Cl$: Cl, 17.48%), m. p. 29.5~30.5°C (from methanol). Similarly, the second fraction (b. p. 105~115°C/2 mmHg) gave 4-chloro-3'-methylbiphenyl (Found: Cl, 17.40. Calcd. for $C_{13}H_{11}Cl$: Cl, 17.48%), m. p. 36~37°C (from methanol). The structure of this compound is evident, since it was found to be identical with the unsymmetrically substituted biphenyl obtained from *p*-chloroiodobenzene and *m*-iodotoluene by the Ullmann reaction, and consequently the structure of the 2'-methyl isomer is also established. Incidentally, Otto and Smith[11] prepared this isomer by a similar method and described it as an oil.

2,4'-Dichlorobiphenyl was prepared by the Sandmeyer reaction from 2-amino-4'-chlorobiphenyl[6]. To a stirred solution of 2-nitro-4'-chlorobiphenyl (5 g.) in benzene (200 ml.), dry iron powder (50 g.) activated by treatment with concentrated hydrochloric acid (10 ml.) was added[12]. After refluxing the mixture for 1 hr., 10 ml. of water was added over a period of 5 hr. under refluxing. The benzene layer was separated from the cooled reaction mixture, and passage of dry hydrogen chloride to the dried benzene solution yielded 4.8 g. of 2-amino-4'-chlorobiphenyl hydrochloride, which was then hydrolysed to 2-amino-4'-chlorobiphenyl (m. p. 43~43.5°C). The amine hydrochloride (14.5 g.) was diazotized by 42 g. of sodium nitrite in aqueous hydrochloric acid. The diazotized solution was filtered quickly and added to a wet precipitate of cuprous chloride prepared from cupric sulphate (19.5 g.) and sodium chloride (6 g.) by reduction with an alkaline solution of sodium bisulphite (4.2 g.). The reaction mixture was left to stand overnight and then distilled with steam. The 2,4'-dichlorobiphenyl thus isolated was purified by chromatography on alumina in petroleum ether, m. p. 44.5°C (from methanol) (Found: Cl, 31.66. Calcd. for $C_{12}H_8Cl_2$: Cl, 31.78%).

3,4'-Dichlorobiphenyl was prepared by a similar method from 4-chloro-3'-nitrobiphenyl. The product was purified by chromatography on alumina in petroleum ether and distillation under reduced pressure, b. p. 125°C/1 mmHg (Found: Cl, 31.55. Calcd. for $C_{12}H_8Cl_2$: Cl, 31.78%).

4,4'-Dichlorobiphenyl was prepared by the Ullmann reaction from *p*-chloroiodobenzene and was purified by chromatography on alumina in benzene, m. p. 147~148°C (from ethanol).

p-Chloro(^{36}Cl)acetanilide.—This was prepared by chlorination of acetanilide with chlorine-36, which had been obtained by oxidation of silver chloride-(^{36}Cl) precipitated from hydrochloric-(^{36}Cl) acid (4.06 mc./mol.). The detailed procedure is described elsewhere[13].

N-Nitroso-p-chloro(^{36}Cl)acetanilide.—To an ice-cooled, stirred mixture of *p*-chloro(^{36}Cl)acetanilide (0.371 g.), fused potassium acetate (0.9 g.), acetic acid (3.2 ml.), acetic anhydride (0.8 ml.), and a trace of phosphorus pentoxide, 4 ml. of an 11.8% solution of nitrosyl chloride in acetic anhydride was added over a period of 18 min. The mixture was kept in ice-water for a further 30 min. and then poured into ice-water to precipitate the *N*-nitroso compound, which was collected, washed with water, and dried in a vacuum desiccator (m. p. 75°C; yield, 0.358 g.).

Decomposition of N-Nitroso-p-chloro(^{36}Cl)acetanilide. — *N*-Nitroso-*p*-chloro(^{36}Cl)acetanilide was allowed to decompose in an equimolar binary or ternary mixture of aromatic solvents, each containing benzene as one component (see Table II). The reaction vessel was immersed in a thermostat kept at 20.0°C and let stand for two days. In experiments 1 and 2, which were carried out at 18°C, at the end of two days the volume of nitrogen evolved reached final values of 77% and 80% of theory, respectively.

General Procedure for Isotope Dilution Analysis.—The reaction mixture was diluted with benzene to a volume of 50 or 100 ml., and the resulting solution was weighed and divided into several weighed portions. To each portion an accurately known amount of each of the biaryls to be assayed was added as a carrier; the solvent was then driven off at atmospheric pressure through a Vigreux column 15 cm. in length and, if necessary, further under reduced pressure. From the residue the labelled biaryl diluted with the carrier was recovered by chromatography on activated alumina in benzene-petroleum ether. The crystalline material thus recovered was purified by repeated crystallization from methanol or ethanol. The purification was considered to be complete when the specific activity of a specimen remained constant on further crystallization.

Since the dilution was made with a large excess of carriers, the molecular ratio in which two labelled biaryls (A and B) were formed in this reaction is given by the ratio $(f_B M_A C_A / f_A M_B C_B)$, where f_A and f_B denote the ratios to the total reaction mixture of the portions used for the determination of A and B, respectively; C_A and C_B, the specific activities in counts per minute of recovered A and B, and M_A and M_B, the amounts of non-labelled A and B added as carriers. All the numerical results are listed in Table II.

Measurement of Radioactivity.—The radioactivity of ^{36}Cl-labelled compounds was determined by a method described elsewhere[14], which comprises decomposition of the labelled compounds with sodium in boiling isopropyl alcohol, precipitation of the liberated chloride ions as mercurous chloride, and counting the radioactivity of the chloride on an "infinitely thick" layer with an end-window Geiger-Müller counter.

Determination of the Partial Rate Factor for the Meta Position of Chlorobenzene.—*N*-Nitroso-*p*-chloroacetanilide (9.86 g.) was dissolved in 509 g.

11) D. G. Otto and G. G. Smith, *J. Am. Chem. Soc.*, **77**, 2325 (1955).
12) S. E. Hazlet and C. A. Dornfeld, ibid., **66**, 1781 (1944).
13) N. Morikawa, T. Migita and O. Simamura, *Radioisotopes* (*Tokyo*), **10**, 236 (1961).
14) T. Migita, N. Morikawa and O. Simamura, ibid., **5**, 28 (1956).

TABLE II. DECOMPOSITION OF *N*-NITROSO-*p*-CHLORO(^{36}Cl)ACETANILIDE AND RESULTS OF ISOTOPE DILUTION ANALYSES OF THE PRODUCTS

Exp. No.	Ratio of the portion taken to the total reaction mixture $f\times10^2$	Carrier added 4-ClC$_6$H$_4$C$_6$H$_4$X: X	*M*, mmol.	Radioactivity of recovered biaryl as counts of HgCl c. p. m.*	Molar yield relative to biphenyl
1	The nitroso compound, 358 mg.; the substrate, an equimolar mixture (16.9 g.) of nitrobenzene, anisole and benzene				
	5.0	H	10.09	131.9±1.8	1.000
	5.0	2'-NO_2	10.07	199.8±2.6	1.51
	30.0	3'-NO_2	10.03	162.2±2.3	0.205
	5.0	4'-NO_2	10.06	128.0±1.9	0.96
	5.0	2'-CH_3O	10.06	167.8±2.3	1.27
	30.0	3'-CH_3O	10.03	255.9±3.0	0.322
	15.0	4'-CH_3O	7.36	128.3±2.1	0.237
2	The nitroso compound, 460 mg.; the substrate, an equimolar mixture (22.4 g.) of nitrobenzene, anisole, and benzene				
	5.00	H	15.02	65.1±1.9	1.000
	4.99	2'-NO_2	15.05	90.5±1.9	1.39
	30.05	3'-NO_2	15.03	77.9±1.2	0.199
	4.99	4'-NO_2	15.03	71.4±1.2	1.10
	5.00	2'-CH_3O	14.97	88.4±1.5	1.35
	19.98	3'-CH_3O	12.83	90.4±4.1	0.30
	24.99	4'-CH_3O	14.94	89.9±1.4	0.275
3	The nitroso compound, 101 mg.; the substrate, an equimolar mixture (3.81 g.) of toluene and benzene				
	9.99	H	19.96	282.3±2.5	1.000
	4.01	2'-CH_3	20.00	111.9±1.9	0.99
	20.03	3'-CH_3	20.00	190.7±2.4	0.338
	20.03	4'-CH_3	10.13	250.9±3.1	0.225
4	The nitroso compound, 97.5 mg.; the substrate, an equimolar mixture (3.71 g.) of toluene and benzene				
	3.97	H	19.98	109.6±1.5	1.000
	3.96	2'-CH_3	19.98	108.4±1.8	0.99
	11.94	3'-CH_3	19.99	123.9±2.0	0.376
	19.89	4'-CH_3	10.02	187.4±2.6	0.214
5	The nitroso compound, 48.0 mg.; the substrate, an equimolar mixture (2.25 g.) of chlorobenzene and benzene				
	10.01	H	20.62	307.8±1.7	1.000
	10.01	2'-Cl	10.00	284.9±3.0	0.90
	39.96	4'-Cl	10.13	271.3±3.0	0.216
6	The nitroso compound, 47.0 mg.; the substrate, an equimolar mixture (2.13 g.) of chlorobenzene and benzene				
	9.90	H	19.98	317.1±2.1	1.000
	9.90	2'-Cl	10.00	287.6±2.6	1.000
	40.01	4'-Cl	10.00	287.6±2.6	0.225

* Indicated deviations are probable errors.

of chlorobenzene and allowed to decompose at 20.0°C. After removal of most of chlorobenzene through a Vigreux column (60 cm.), 2 ml. of nitrobenzene was added to the residue. By fractionating the mixture through a concentric column, all the chlorobenzene retained in the mixture and 0.3 ml. of nitrobenzene were driven off. The residue was dissolved in benzene, and the solution was passed through a column of alumina and then treated with 50 g. of iron activated by treatment with hydrochloric acid[12] and 10 ml. of water for reduction of the nitrobenzene contained in the solution. The benzene layer was washed with diluted hydrochloric acid and then with water and dried over calcium chloride. The reddish-brown material obtained by removal of the benzene was fractionated by chromatography on an alumina column using a mixture of ether and petroleum ether (1 : 1) as an eluant into the following fractions: the first fraction (a light yellow oil and a small amount of a crystalline

material): a mixture of 2,4'- and 3,4'-dichlorobiphenyl; the second fraction (a yellowish crystalline material): 4,4'-dichlorobiphenyl; the third fraction: traces of reddish crystals; and the succeeding fractions: traces of crystals and reddish impurities. The first and the second fraction were combined, and the mixture was analyzed for three isomeric dichlorobiphenyls by infrared spectrophotometry in carbon disulphide with a Perkin Elmer-21 spectrophotometer, using absorptions at 883 cm^{-1}, 730 cm^{-1}, and 810 cm^{-1} for 2,4'-, 3,4'- and 4,4'-dichlorobiphenyl, respectively. It was found that the foregoing mixture consisted of 65, 21 and 12% of the respective isomers, giving 3.1 as the molar ratio of the 2,4'- and the 3,4'-isomer formed. This value, in conjunction with the value of the partial rate factor for the ortho position determined by the isotope dilution analysis, leads to the partial rate factor of 0.87 for the meta position, while the value is 1.16 when the molar ratio of the 4,4'-isomer to the 3,4'-isomer is used. The former value is considered to be more reliable for the following reason. From the spectrophotometric result, the ratio of the reactivity of the *o*-position to that of the *p*-position of chlorobenzene towards *p*-chlorophenylation is calculated to be 2.7, which is rather too large when compared with the corresponding value, 2.0, calculated from the results of the isotope dilution analysis. This discrepancy is most probably due to the method of preparing the sample subjected to the spectrophotometric analysis, in which the third fraction containing a little of the least elutable 4,4'-dichlorobiphenyl was discarded to avoid contamination of the sample by any coloured impurities.

Summary

N-Nitroso-*p*-chloro(^{36}Cl)acetanilide has been decomposed in mixtures of benzene and monosubstituted benzene C_6H_5X (X=NO_2, Cl, OCH_3, and CH_3), and the reaction products have been analyzed for 4-chlorobiphenyl and isomeric 4-$ClC_6H_4C_6H_4X$ by the isotope dilution method. On the basis of these results, the partial rate factors for the *p*-chlorophenylation have been calculated to be, for nitrobenzene: *o*, 4.35; *m*, 0.61; *p*, 6.18; for chlorobenzene: *o*, 2.70; *m*, 0.87; *p*, 1.33; for anisole: *o*, 3.93; *m*, 0.94; *p*, 1.54 and for toluene: *o*, 2.97; *m*, 1.07; *p*, 1.32.

The values of the partial rate factor for the meta position give a satisfactory Hammett plot with a slope of −0.27. This fact demonstrates that the *p*-chlorophenyl radical shows a measure of electrophilic character in the homolytic aromatic substitution.

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