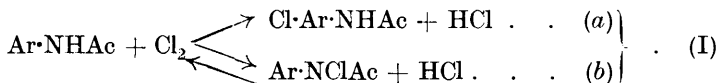


CXXXII.—*The Chlorination of Anilides. Part III.*
N-Chlorination and C-Chlorination as Simultaneous
Side Reactions.

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THE conversion of chloroamines into nuclear-substituted anilides, thought at one time to be a typical intramolecular rearrangement, has been shown (Orton and W. J. Jones, P., 1909, **25**, 196, 233, 305; *Brit. Assoc. Repts.*, 1910, 85) to proceed thus : *



The evidence may be briefly summarised, since it appears to have been largely overlooked or disregarded by some authors, and the older view, that chloroamines are necessary intermediates in the nuclear chlorination of anilides, still finds expression (Francis, *Chem. Rev.*, 1926, **3**, 274; Francis, Hill, and Johnston, *J. Amer. Chem. Soc.*, 1925, **47**, 2230; Francis, *ibid.*, 1926, **48**, 1637; Mathews and Williamson, *ibid.*, 1923, **45**, 2574; Porter and Wilbur, *ibid.*, 1927, **49**, 2145; de Lange, *Rec. trav. chim.*, 1926, **45**, 19; van Alphen, *ibid.*, 1927, **46**, 287, 799). The facts are :

(1) Hydrochloric acid is the agent which brings about the " transformation " (Armstrong, J., 1900, **77**, 1047) and is, further, the only substance which so acts (Orton and Jones, *loc. cit.*).

(2) In solution, an equilibrium is formed, represented by equation (Ib) (Orton and Jones, *loc. cit.*; J., 1909, **95**, 1456).

(3) The same proportions of *o*- and *p*-chloroacetanilides are obtained whether the starting materials are acetanilide and chlorine or *N*-chloroacetanilide and hydrochloric acid (Orton and Bradfield, J., 1927, 986; this vol., p. 351). This holds for all three solvents examined.

(4) In water and in aqueous acetic acid of less than 65% strength, the rate of " transformation " of *N*-chloroacetanilide is less than the rate of nuclear chlorination of acetanilide (Orton and Jones, *loc. cit.*). In water, the rate of " transformation " is equal to the calculated

* Compare Orton, *Brit. Assoc. Repts.*, 1912, 117: " Whether a true intramolecular change is possible under certain conditions has not yet been discovered, but it must not be supposed that the possibility is excluded."

In addition to the references cited, see *Brit. Assoc. Repts.*, 1911, 94; 1912, 116; 1913, 136; 1914, 105; 1915, 82; also Orton and King, J., 1911, **99**, 1185, 1369.

rate of formation of chlorine from *N*-chloroacetanilide and hydrochloric acid (Soper, *J. Physical Chem.*, 1927, **31**, 1192).

Subsequent work has called for no revision of the main conclusion reached in 1909. Further confirmation has now been obtained by actual measurement of the velocities of the two individual reactions, *N*-chlorination and *C*-chlorination, in 40% acetic acid. Moreover, by the use of a new method of analysis, it is shown that, in the reaction between chlorine and anilides, the ratio of the amounts of chloroamine and chloroanilide formed at a given moment is independent of the time. Wegscheider's test (*Z. physikal. Chem.*, 1899, **30**, 593) is thus satisfied, and chloroamine formation and nuclear chlorination are therefore simultaneous.

FIG. 1.

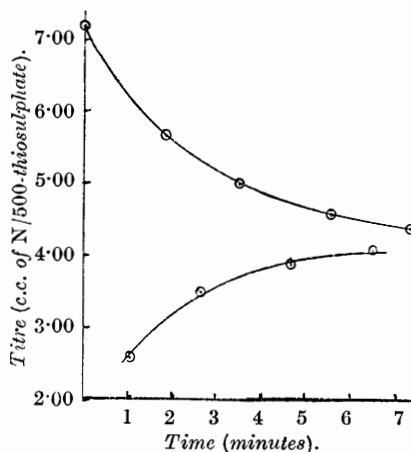
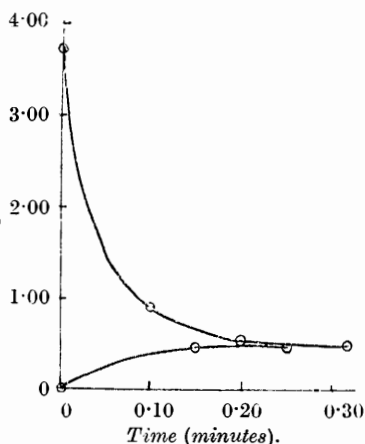
Expt. 27.—*p*-Chloroacetanilide.

FIG. 2.

Expt. 93.—Aceto-*p*-toluidide.

The position of the equilibrium (Ib) depends greatly on the composition of the medium; in glacial acetic acid, chloroamine is indetectable, but as the medium is diluted with water, the equilibrium is displaced until, in 50% acetic acid, it lies entirely on the chloroamine side (Orton and Jones, *loc. cit.*). The position of equilibrium in 40% acetic acid thus allows chloroamine formation to be treated as though it were an irreversible reaction. 2:4-Dinitroacetanilide is an exception in that the equilibrium mixture in this medium contains a considerable amount of free chlorine.

The aspiration method for the analysis of mixtures containing both chloroamine and free chlorine (Orton and Jones, *loc. cit.*) has been replaced by one in which the chlorine is removed by a suitable reagent, leaving the chloroamine for titration. Acetanilide, aromatic ethers, and phenols have been used as absorbers of chlorine,

p-cresol being especially suitable, for it reacts instantaneously with chlorine but has no appreciable reaction on the chloroamines under investigation, and, in acid solution, does not react with iodine.

The reaction is followed by transferring known volumes of the (naturally, already acid) reacting mixture *alternately* to (a) aqueous potassium iodide, which gives the chlorine + chloroamine concentrations, and (b) aqueous *p*-cresol, which removes chlorine, whereupon the chloroamine is determined by addition of potassium iodide and titration. The titres (in c.c. of *N*/500-thiosulphate) are plotted against time (in minutes) in Figs. 1 and 2. The lower section of the curve in the diagram corresponds to (b) and represents the course of the *N*-chlorination, whilst the upper branch is formed from the titres of (a), and its fall shows the extent of *C*-chlorination. These curves are used to calculate k_N and k_C from the equations

$$k_N + k_C = \frac{2.303}{t(a-b)} \log \left[\frac{b}{a} \frac{a - (x+y)}{b - (x+y)} \right]; \quad k_N/k_C = y/x,$$

where k_N and k_C are the velocity coefficients of *N*- and *C*-chlorination respectively, and y and x are the concentrations (in the same units) of chloroamine and chloroanilide formed. Owing to the great speed of the reactions, it is not possible to determine experimentally a large number of points on the curves, but we have found that the effect of a slight error in drawing the curves is negligible. The results obtained for seven anilides are given in Table I.

TABLE I.

Temp., 18° (\pm 0.02°). Medium, 40% acetic acid.

	k_N .	k_C .
<i>o</i> -Chloroacetanilide	286	27.5
<i>m</i> -Chloroacetanilide	172	3,140
<i>p</i> -Chloroacetanilide	115	135
<i>p</i> -Bromoacetanilide	123	116
Aceto- <i>o</i> -toluidide	140	1,390
Aceto- <i>p</i> -toluidide	2,540	18,500
Acetanilide	96	11,000

The constancy of k_N/k_C for each anilide throughout the reaction is shown by Table II and by the examples of experimental figures given below.

EXPERIMENTAL.

Materials.—The anilides were specially prepared for these experiments and recrystallised at least twice from alcohol or dilute acetic acid. Acetanilide was sublimed.

The reaction medium (40% acetic acid by weight, *i.e.*, 6.90*M*-acetic acid at room temperature) was made up by mixing glacial acetic acid, stabilised to chlorine by the method of Orton and Brad-

field (J., 1924, 125, 960; 1927, 983), with water purified by distillation successively from chromic acid and from baryta in a modified form of the apparatus of Moseley and Myers (*J. Amer. Chem. Soc.*, 1918, 40, 1409). Velocity measurements made with independently prepared specimens of anilide and different preparations of medium gave results which were indistinguishable.

Chlorine. "Cylinder" chlorine was washed with water and passed into 40% acetic acid. Measurements with chlorine solutions are liable to error through chemical instability of the solvent and/or volatility of the solute. Solutions prepared as above were sufficiently stable for one hour at 18° and were used as the source of chlorine for the reactions.

p-Cresol. B.D.H. or Kahlbaum specimens were redistilled and used in saturated aqueous solution (0.185*M*).

Stability of p-Cresol to Chloroamines in Dilute Acetic Acid Medium.—A saturated aqueous solution of *p*-cresol was left in contact with solutions (in 40% acetic acid) of two chloroamines with widely different hydrolysis constants (in 20% acetic acid, Soper and Smith, this vol., p. 138). In neither instance was there any change in the titre obtained after adding potassium iodide solution. 0.01*M*-*N*-Chloroacetanilide (hydrolysis constant, 6.7×10^{-7}) had an initial titre of 19.40 c.c. of 1.0*N*/100-thiosulphate, and after standing for 30 mins. with 10 c.c. of *p*-cresol solution, a similar quantity had a titre of 19.38 \pm 0.02 c.c.: 0.005*M*-*N*-Chloro-*m*-nitroacetanilide (hydrolysis constant, 99×10^{-7}) had an initial titre of 10.57 c.c. of 0.96*N*/100-thiosulphate, and after standing with 20 c.c. of the *p*-cresol solution for 70 mins., the titre was 10.58 c.c.

Velocity Measurements.

The initial concentration of chlorine was usually of the order 0.0005—0.001*M*, and of the anilide 0.001—0.003*M*. The anilide was present in excess in order to avoid complications due to the formation of chloroamines of the primary products of nuclear chlorination (compare Soper, *loc. cit.*), and the reactions were carried out in the presence of hydrochloric acid to suppress the hydrolysis of chlorine (Jakowkin, *Z. physikal. Chem.*, 1899, 29, 613). In 40% acetic acid medium, 0.01*M*-hydrochloric acid was sufficient for this purpose, the rate of reaction being unaffected by alteration of the hydrochloric acid concentration over the range 0.01—0.10*M*. Higher concentrations of acid caused marked changes, not only in the speed of *N*-chlorination (as was to be expected from equation I), but also in the rate of *C*-chlorination; *e.g.*, for *p*-chloroacetanilide:

Conc. of HCl	0.01—0.10	0.50	1.0	3.5
k_0	135 ($k_N = 115$)	108	68.3	30.9

A 5.5*M*-standard solution of hydrogen chloride in 40% acetic acid was used for making up the required concentration of hydrochloric acid in the reaction mixture. In the final experiments, 0.2 c.c. of this solution was added to the anilide solution in a 100 c.c. standard flask. The chlorine solution was prepared as already described. When both solutions had attained the temperature of the thermostat, the reaction was started by running chlorine solution into the anilide from a 5 c.c. pipette, graduated to 0.05 c.c., to fill up to the 100 c.c. mark (about 3 c.c. were needed). For estimation, the first 1 c.c. of the chlorine solution was run directly into aqueous potassium iodide. Control experiments showed that an accurate determination of the initial chlorine concentration was obtained in this way.

The composition of the reaction mixture was then determined by transferring portions at noted times to a series of flasks containing alternately potassium iodide solution and *p*-cresol solution. After addition of potassium iodide to each cresol flask, the iodine was titrated (titration error, ± 0.02 c.c. *N*/500-thiosulphate). Oxidation of hydriodic acid and consequent masking of the end-point was prevented (*a*) by passing a stream of nitrogen through the solutions in the flasks before the experiment for a few minutes and again during titration (Soper, *J.*, 1924, **125**, 1899), or (*b*) by reducing the acidity by the addition of freshly prepared sodium acetate solution. Method (*b*), which was used occasionally, is only applicable in the absence of cresol.

Times were reckoned from the moment of entry of the first extract into the arresting agent and not from the time of mixing the reactants, and were measured by a stop-watch graduated to 0.2 sec.; the timing error was estimated at ± 1 sec. (0.017 min.). With reactions of the speed measured, escape of chlorine into the atmosphere during pipetting is negligible (compare, in particular, the experiments of Soper, *J. Physical Chem.*, 1927, **31**, 1195). The following experiment is given as an example.

Expt. 27. *p*-Chloroacetanilide = 0.002424*M*. Chlorine = 0.000932*M*. HCl = 0.10*M*. Thiosulphate = 1.005*N*/500.

Time (min.) ...	0	1.00	1.75	2.53	3.40	4.50	5.40	6.30	7.10
Titre (c.c.) ...	7.21	2.58	5.67	3.51	5.00	3.89	4.59	4.10	4.39

From the curves constructed with these figures (Fig. 1), we have :

Time.	KI titre.	:NCl titre.	Diff.	% Change.	$k_N + k_C$.	k_N/k_C .
0	6.45	2.44	4.01	67		0.861
1.25	5.53	3.26	2.27	76	253	0.869
2.25	5.12	3.61	1.51	84	248	0.868
4.00	4.69	3.95	0.74	92	251	0.861
5.25	4.51	4.07	0.44	95	255	0.854
				Mean	252	0.863

The reproducibility is shown by the following figures for *p*-chloroacetanilide.

Expt.	16.	19.	20.	27.	18.	Mean.
$k_N + k_C$	245	247	255	252		$250 \pm 1.5\%$
k_N/k_C	0.821	0.859	0.866	0.863	0.840	$0.850 \pm 1.7\%$

Table II gives the values for the ratio (chloroamine formed)/(chloroanilide formed)—*i.e.*, k_N/k_C —for four other anilides. Over the range accessible to analysis, the ratio is satisfactorily constant. Although the reactions are so fast that it is difficult to examine their early stages, it may be inferred that k_N/k_C is constant throughout, since values calculated from the *initial* concentration of chlorine agree with those obtained by taking a point in the analysed portion of the reaction as starting point. Moreover, special experiments with *p*-chloroacetanilide over the range 10–30% change have given a value of k_N/k_C in agreement with the above.

TABLE II.

<i>o</i> -Chloroacetanilide.			<i>m</i> -Chloroacetanilide.		
Time.	% Change.	k_N/k_C .	Time.	% Change.	k_N/k_C .
0	49	(6.16)	0	64	0.0543
2.00	85	10.35	0.100	71	0.0547
3.10	90	10.52	0.183	76	0.0552
4.00	93	10.50	0.333	84	0.0553
5.00	96	10.45	0.500	89	0.0555
6.50	98	10.50	0.700	92	0.0574
		Mean 10.46	0.900	94	0.0597
		Mean of 3 expts. 10.40		Mean 0.0560	
				Mean of 5 expts. 0.0548	
<i>p</i> -Bromoacetanilide.			<i>Aceto-o</i> -toluidide.		
0	20	1.10	0	52	0.102
0.90	40	1.01	0.250	69	0.109
2.00	58	1.02	0.350	74	0.112
2.95	68	1.07	0.550	81	0.115
5.00	84	1.10	0.850	87	0.115
7.20	91	1.08			
		Mean 1.06		Mean 0.111	
		Mean of 3 expts. 1.06		Mean of 2 expts. 0.102	

Measurement of the Speed of the Faster Reactions.—When the reaction speeds were very fast (acetanilide, aceto-*o*- and -*p*-toluidides, *m*-chloroacetanilide), the experimental procedure was modified as follows. The reactants were mixed very quickly by pouring rapidly a large volume (*e.g.*, 196 c.c.) of anilide solution into a small volume (*e.g.*, 4 c.c.) of chlorine solution in a beaker flask, both solutions being at 18°. The reaction mixture was at once poured alternately into the potassium iodide and cresol flasks which had previously been weighed with corks. Finally, 5 c.c. of potassium iodide solution were run into each of the flasks containing the cresol. The flasks were corked and re-weighed and the iodine was titrated.

Knowing the density of the reaction medium (determined as 1.050 at 18°) and the weight of 5 c.c. of potassium iodide solution added to each cresol flask, the concentrations of chlorine and chloroamine could be calculated. The volume of the reaction mixture was usually 200 c.c., and about 40 g. were poured into each flask. The times at which the reaction mixture was tipped out were memorised.

Control experiments proved that (a) reaction between chloroamine and hydrochloric acid in the cresol flasks pending the addition of potassium iodide and (b) oxidation of hydriodic acid during the second weighing could both be neglected, and further, (c) that volatility of the chlorine is not a disturbing factor.

Although there seems, at first sight, a possibility of considerable timing errors, this method gives satisfactory results for reactions whose time of half-completion is as little as 10 seconds. As illustration, the results obtained for aceto-*p*-toluidide are given. In this case, owing to the great speed of the reaction, the time of mixing had to be taken as zero.

Expt. 93. Aceto-*p*-toluidide = 0.001120*M*. Chlorine = 0.000259*M*. HCl = 0.01*M*. Thiosulphate = 1.39*N*/500. Vol. of reaction mixture = 200 c.c.

Time (min.)	0	0.100	0.150	0.200	0.250	0.317
Wt. (g.)		30.96	48.88	31.40	37.31	53.09
Titre (c.c.)		1.32	1.09	0.79	0.87	1.26
Calc. titre for 20 c.c....	3.73	0.90	0.47	0.53	0.49	0.50

From the curves constructed with these titres (Fig. 2), we find :

Time.	KI titre.	:NCl titre.	Diff.	% Change.	$k_N + k_C$.	k_N/k_C .
0	3.73	0	3.73			
0.080	1.11	0.34	0.77	79	20,000	0.130
0.100	0.90	0.39	0.51	86	20,500	0.138
0.160	0.64	0.47	0.17	95	21,900	0.152
				Mean	20,800	0.140

Expt. 94. Aceto-*p*-toluidide = 0.000956*M*. Chlorine = 0.000264*M*. HCl = 0.01*M*. Thiosulphate = 0.991*N*/500. Vol. of reaction mixture = 250 c.c.

Time (min.) ...	0	0.083	0.133	0.167	0.217	0.250	0.325
Wt. (g.)		32.52	58.04	51.88	28.95	39.21	31.10
Titre (c.c.)		2.41	1.56	2.40	0.55	1.52	1.03
Calc. titre for							
40 c.c.	10.66	3.12	1.13	1.95	0.80	1.63	1.39

From the curves :

Time.	KI titre.	:NCl titre.	Diff.	% Change.	$k_N + k_C$.	k_N/k_C .
0	10.66	0	10.66			
0.083	3.12	0.87	2.25	79	22,500	0.116
0.133	2.19	1.13	1.06	89	22,000	0.133
0.167	1.95	1.22	0.73	93	20,600	0.140
0.210	1.73	1.31	0.42	96	20,100	0.147
				Mean	21,300	0.134

The other results obtained by this method were :

Acetanilide (3 expts.), $k_C = 11,000 \pm 1.8\%$; *m*-chloroacetanilide (3 expts.), $k_N + k_C = 3310 \pm 3.5\%$; aceto-*o*-toluidide (2 expts.), $k_N + k_C = 1530, 1530$.

Determination of k_N/k_C for Acetanilide.—With this substance, the rate of *N*-chlorination ($k_N = 96$) is small in comparison with the rate of *C*-chlorination ($k_C = 11,000$) and cannot be followed in a velocity experiment. The ratio k_N/k_C is determined by using higher concentrations of acetanilide and chlorine and measuring the residual titre when reaction is complete. A large excess of acetanilide must be used and precautions are necessary in order to minimise the formation of the chloroamines of *o*- and *p*-chloroacetanilides which would give too high a value for k_N/k_C (Soper, *loc. cit.*). No concordant results could be obtained until the following procedure had been developed.

0.2 C.c. of a 5.5*M*-solution of hydrogen chloride in 40% acetic acid was added to 50 c.c. of the acetanilide solution. After being adjusted to 18°, a standard solution of hypochlorous acid * in 40% acetic acid was run in, drop by drop, from a burette graduated to 0.05 c.c., to the solution, which was stirred mechanically. After the addition, potassium iodide was added and the iodine was titrated in an atmosphere of nitrogen.

Experiments were made with two different specimens of hypochlorous acid, (A) prepared by the action of chlorine on mercuric oxide, and (B) by the action of carbon dioxide on bleaching powder solution; seven experiments gave for the ratio k_N/k_C (*i.e.*, residual titre/fall of titre) the value $0.00873 \pm 1.6\%$. The chlorine concentration was of the order 0.002—0.008*M*, and the proportion of acetanilide to chlorine was varied from 16/1 up to 52/1.

One of us (G. W.) wishes to express his thanks to the Advisory Council of the Department of Scientific and Industrial Research for a maintenance grant. We desire also to thank the Royal Society for a grant which has partially defrayed the cost of this investigation.

* The interaction between hypochlorous acid and acetanilide to form the *N*-chloro-derivative has been measured in these laboratories and found to be slow (unpublished research).

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