23. *The Interaction of* N-*Chloroacetanilide with Phenols. The Rate of Formation of Hypochlorous Acid from* N-*Chloroacetanilide by Hydrolysis.*

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Kinetic studies of mixtures of *N*-chloroacetanilide and phenols in aqueous solution indicate that *N*-chloroacetanilide chlorinates partly by preliminary hydrolysis to hypochlorous acid and partly by direct interaction with the phenoxide ion. No direct reaction with the un-ionised phenol was appreciable in a range of phenols. The rate of hydrolysis of *N*-chloroacetanilide is proportional to the hydroxyl ion concentration, the time of half-hydrolysis in neutral solution at 25°, deduced from measurements in alkaline solution, being 256 hours. Combination of the value for the hydrolysis rate with that of the formation of *N*-chloroacetanilide from acetanilide and hypochlorite ion (Mauger and Soper, *J.*, 1946, 71) yields an equilibrium hydrolysis constant for *N*-chloroacetanilide, [NHPhAc][HOCl]/[NPhAcCl], of $3{\cdot}3 \times 10^{-7}$; cf. 7×10^{-7} (Soper, *J.*, 1925, 98) obtained by distillation and solubility measurements.

HALOGENATION by means of a halogenoamine is formulated in a variety of ways. Likhosherstov and Arkhangel'skaya (*J. Gen. Chem. Russia*, 1937, **7**, 1914) regard the interaction of *NN'*-dichlorourea and phenol as involving first the hydrolysis of the chloroamine to hypochlorous acid followed by the conversion of the latter into chlorine by means of hydrochloric acid which then attacks the phenol. Waters (*Nature*, 1944, **154**, 722) suggests that bromination by *N*-bromosuccinimide (Ziegler *et al.*, *Annalen*, 1942, **551**, 80) involves the preliminary formation of a free halogen radical and that such formation may be a common method of halogenoamine reaction. The mechanism may vary with conditions. Orton and King's chlorinations (*J.*, 1911, 1185) involved free chlorine, controlled by the amount of hydrochloric acid present and the equilibrium $:NCl + HCl \rightleftarrows :NH + Cl_2$, whilst in halogenations by a chloroamine and hydrobromic or hydriodic acid (Bradfield, Orton, and Roberts, *J.*, 1928, 782) a mixed halogen is an intermediary. In the interaction of *N* : 2 : 4 : 6-tetrabromoacetanilide and anisole (Israel, Tuck, and Soper, *J.*, 1945, 547), which is dependent on the presence of an acid such as acetic acid, an acyl hypobromite appears to be the brominating agent, the rate of bromination being independent of the concentration of the anisole but dependent on the concentrations of acid and bromoamine. Dewar (*J.*, 1946, 407) suggests that the agent in this case could be a π-complex, $NHPhAcBr^+$, acting as a cationoid reagent and substituting other molecules. This is preferred by Dewar to a mechanism " based on the occurrence of free cations in solution as suggested, for example, by Israel, Tuck, and Soper." Free bromine cations were not suggested, however, by these authors, and substances similar to the halogen acetate (or acyl hypohalogenite) actually suggested as the intermediate in the acid catalysed bromination of anisole by *N* : 2 : 4 : 6-tetrabromoacetanilide appear to operate also in the *N*-chlorination of *N*-methylacetamide (Mauger and Soper, *loc. cit.*) and in the iodination of phenol (Painter and Soper, *J.*, 1947, 342).

In contrast to the many mechanisms involving intermediates which have been formulated in halogenoamine reactions, direct interaction as a mechanism appears to have been avoided. The elucidation of such reactions of chloroamines, particularly in aqueous solution, would be assisted by a knowledge of the rate of hydrolysis of the chloroamine to hypochlorous acid. An estimate of this hydrolysis rate for *N*-chloroacetanilide can be calculated from the equilibrium hydrolysis constant and the specific rate of the reverse reaction, the formation of *N*-chloroacetanilide from acetanilide and hypochlorous acid. The latter rate, determined over a 1000-fold change in the hydrogen-ion concentration, was given by $v = k_{OCl'}[:NH][OCl']$, where at 25° $k_{OCl'} = 336$ mins.$^{-1}$ (Mauger and Soper, *loc. cit.*). The hydrolysis constant K_h of *N*-chloroacetanilide, [NHPhAc][HOCl]/[NPhAcCl], was evaluated (Soper, *J.*, 1925, 98) as 7×10^{-7}. Combining this with the hydrolysis constant of sodium hypochlorite, the equilibrium constant of the reaction

$$:NH + OCl' \underset{k_h}{\overset{k_{OCl'}}{\rightleftarrows}} :NCl + OH' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

is given by

$$\frac{[:NCl][OH']}{[:NH][OCl']} = \frac{[:NCl]}{[:NH][HOCl]} \cdot \frac{[HOCl][OH']}{[OCl']} = \frac{1}{7{\cdot}0 \times 10^{-7}} \cdot \frac{1{\cdot}0 \times 10^{-14}}{4{\cdot}1 \times 10^{-8}} = 0{\cdot}35$$

Hence if the formulation of the formation and hydrolysis of *N*-chloroacetanilide in equation (1) is correct, $k_h = k_{OCl'}/0{\cdot}35 = 960$ mins.$^{-1}$, corresponding to a time of half hydrolysis of 1·2 hours at pH 9.

Phenols and *N*-chloroacetanilide in weakly acid media, such as obtain in aqueous unbuffered phenol solutions, show little decomposition, only 0·5% decomposition of the chloroamine occurring in the presence of phenol at 25° in 15 hours. The reactivity increases markedly in slightly alkaline solutions, and at pH 9, in borate buffer, the reaction rates with various phenols, which in the presence of excess of phenol are pseudo-unimolecular, may have times of half-decomposition of a few minutes. Typical results are given in Table I.

TABLE I.

N-Chloroacetanilide = 0·01M; pH = 9·0; temp. = 25·0°.

Phenol concn., M.	$k_1 \times 10^2$.	$t_{\frac{1}{2}}$ (mins.).	$k_1 \times 10^2$.	$t_{\frac{1}{2}}$ (mins.).	$k_1 \times 10^2$.	$t_{\frac{1}{2}}$ (mins.).
	Phenol.		*p*-Cresol.		*o*-Chlorophenol.	
0·02	30·7	2·25	38·7	1·79	13·6	5·95
0·04	61·8	1·12	58·8	1·18	34·5	2·01
0·06	88·9	0·78	101	0·69	48·8	1·42
	o-Nitrophenol		*m*-Nitrophenol		*p*-Nitrophenol	
0·02	0·91	76·3	2·91	23·8	0·53	131
0·03	1·10	63·0	4·13	16·7	—	—
0·04	1·12	61·9	5·30	13·1	0·96	72·2
0·05	1·43	48·4	6·05	11·4	0·98	70·7
0·06	—	—	6·91	10·0	1·06	65·4

For the more reactive phenols, the speed is approximately proportional to the phenol concentration, but where the time of half decomposition exceeds 1 hour, this proportionality does not hold. Although the phenol in its un-ionised state is stable to the chloroamine, at pH 9 appreciable ionisation of the phenol occurs, and the reaction may be due to direct interaction of chloroamine and phenoxide ions, which are known to be much more highly reactive than the un-ionised phenol. Superimposed on this direct reaction there may be production of hypochlorous acid by hydrolysis. Such hypochlorous acid at pH 9 would react very rapidly with phenoxide ions present (Soper and Smith, *J.*, 1926, 1582) and would be immediately removed. If hydrolysis alone were occurring and this were the rate-determining step, increase in phenol concentration would not affect the rate. Thus the reaction rate may be tentatively formulated as

$$= k_1[{:}\mathrm{NCl}] = k_\mathrm{h}[\mathrm{OH}'][{:}\mathrm{NCl}] + k_\mathrm{d}[\mathrm{PhO}'][{:}\mathrm{NCl}]$$

or

$$k_1 = k_\mathrm{h}[\mathrm{OH}'] + k_\mathrm{d}[\mathrm{PhO}']$$

A series of reactions was carried out in order to test the above equation using a constant phenoxide-ion and varying the hydroxyl-ion concentration. *o*- and *p*-Nitrophenols were utilised for this purpose over the pH range 8·7 to 9·3 where since their respective ionisation constants are $9{\cdot}6 \times 10^{-8}$ and $6{\cdot}0 \times 10^{-8}$ (Hantzsch, *Ber.*, 1899, **32**, 3066, 3071) the ionisation of the phenol varies only from 97 to 99·5%, and increasing hydroxyl-ion concentration does not alter appreciably the concentration of phenoxide ions. The graphs (see Fig.) obtained on plotting k_1 against hydroxyl-ion concentration are straight lines and the slopes which, on the above hypothesis, give k_h, are 454, 455, 454, and 452 mols.$^{-1}$ mins.$^{-1}$ respectively for *o*-nitrophenol at concentrations of 0·03 and 0·05M and for *p*-nitrophenol at 0·05 and 0·08M. This is of the same order as the hydrolysis rate, 960 mols.$^{-1}$ mins.$^{-1}$, deduced from the hydrolysis equilibrium constant and the formation rate constant of *N*-chloroacetanilide.

In the series of experiments at pH 9·0 and varying phenol concentration (Table I), if $k_1 = k_\mathrm{h}[\mathrm{OH}'] + k_\mathrm{d}[\mathrm{PhO}']$, extrapolation of k_1 to zero phenol concentration should give $k_\mathrm{h}[\mathrm{OH}']$ and provide a further value of k_h, which should be independent of the nature of the phenol. At pH 9·0, the extrapolated values of k_1 for *o*-, *m*-, and *p*-nitrophenols are approximately 0·5, 0·5, and $0{\cdot}4 \times 10^{-2}$ mins.$^{-1}$, whence $k_\mathrm{h} = 5$, 5 and 4×10^2 mols.$^{-1}$ mins.$^{-1}$, which is in harmony with the previously obtained value. The extrapolation is not of sufficient accuracy to be of use in the case of the more reactive phenols.

The Direct Interaction of N-*Chloroacetanilide and Phenols.*—The comparatively low specific rate of hydrolysis to hypochlorous acid, of approximately $0{\cdot}5 \times 10^{-2}$ mins.$^{-1}$ at pH 9, clearly indicates that all the phenols examined react to a great extent by some other mechanism than that involving the intermediate production of hypochlorous acid. In weakly acidic solution, reaction is found to be very slight, which negatives a direct interaction of chloroamine and un-ionised phenol. Such a reaction should be independent of the hydroxyl-ion concentration, whilst if phenoxide ions react as given by $k_1 = k_\mathrm{h}[\mathrm{OH}'] + k_\mathrm{d}[\mathrm{PhO}']$ then at pH's at which

$k_h[OH']$ is negligible $k_1 = k_dK_a([PhOH] + [PhO'])/(K_a + [H^{\bullet}])$. If the ionisation constant of the phenol, K_a, is small compared with the $[H^{\bullet}]$ of the solution, $k_1 = k_dK_a[\text{phenol}]/[H^{\bullet}]$, and will increase in proportion to the hydroxyl-ion concentration. This is illustrated in Table II for the interaction of *o*-chlorophenol ($K_a = 7{\cdot}7 \times 10^{-11}$) over the pH range 6·4 to 7·2. For *m*-nitrophenol ($K_a = 1{\cdot}0 \times 10^{-8}$) over the pH range 6·8 to 7·6, $k_1/[OH']$ is not constant, but the use of the more exact expression for $k_d = k_1(K_a + [H^{\bullet}])/K_a$ [total phenol], gives values which show satisfactory consistency, as seen from Table III.

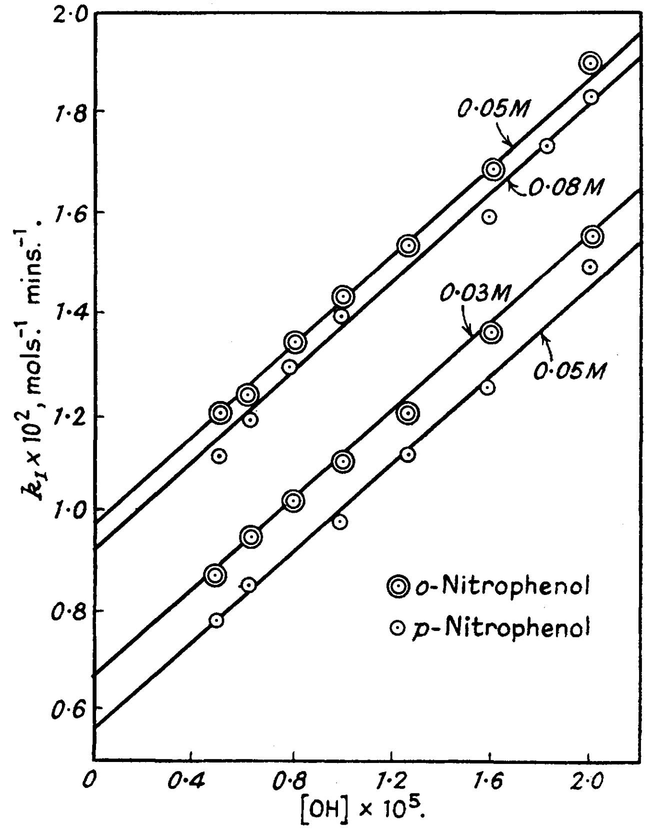

TABLE II.

o-Chlorophenol = 0·04M; :NCl = 0·01M.

pH.	$[OH'] \times 10^8$.	$k_1 \times 10^2$.	Mean $k_1 \times 10^2$.	$k_1/[OH'] \times 10^5$.
6·4	2·51	0·80, 0·79	0·795	3·17
6·8	6·31	1·94, 1·96	1·95	3·09
7·0	10·0	3·00, 3·03	3·02	3·02
7·2	15·9	4·95, 5·02 5·01	4·99	3·15

TABLE III.

m-Nitrophenol = 0·04M; :NCl = 0·01M.

pH.	$[H^{\bullet}] \times 10^7$.	k_1 (mean) $\times 10^2$.	$k_1/[OH'] \times 10^{-4}$.	k_d.
6·8	1·59	0·235	3·72	0·99
7·0	1·0	0·335	3·35	0·92
7·2	0·631	0·52	3·31	0·95
7·4	0·398	0·805	3·21	1·00
7·5	0·316	0·89	2·83	0·93
7·6	0·257	1·00	2·51	0·89

These experiments, carried out at pH's at which the hydrolysis rate is negligibly small, are in harmony with the hypothesis that the direct interaction is one between phenoxide ions and the chloroamine. Other formulations of the direct reaction for which there is no evidence in the range of solutions so far examined are (*a*) interaction of $NHPhAcCl^+$ and PhOH, and (*b*) interaction of $NHPhAcCl^+$ and PhO′. Reaction (*a*) would require that k_d increase in proportion to the hydrogen-ion concentration of the solution, whilst (*b*) would lead to k_d being independent of the hydrogen-ion concentration. Over the range of pH examined the rate of the direct reaction is proportional to the product of the concentration of *N*-chloroacetanilide and phenoxide ions. Evidently the chlorine in *N*-chloroacetanilide is sufficiently electrophilic to substitute directly in the phenoxide ion. Parallel studies have recently been carried out with Mr. L. O. Brown using diethylchloroamine and phenols where the direct interaction apparently involves the phenoxide ion and the diethylchloroammonium ion. The chlorine of the more basic diethylchloroamine is insufficiently electrophilic in comparison with that in the diethylchloroammonium ion, $NHEt_2Cl^+$, to result in the substitution of the phenoxide ion. This is in sharp distinction to the behaviour of *N*-chloroacetanilide.

A comparison reveals *N*-chloroacetanilide as a much weaker chlorinating agent than hypochlorous acid. The specific rate of chlorination of *m*-nitrophenoxide ions by hypochlorous acid (Soper and Smith, *loc. cit.*) is $5·9 \times 10^3$ mins.$^{-1}$ as compared with 1·0 mins.$^{-1}$ by *N*-chloroacetanilide. The corresponding specific rates for the chlorination of *o*-nitrophenoxide and *p*-nitrophenoxide ions are: by hypochlorous acid $1·01 \times 10^3$ and $0·68 \times 10^3$ and by *N*-chloroacetanilide 0·20 and 0·11. Hypochlorous acid reacts 5000—6000 times more rapidly than *N*-chloroacetanilide with nitrophenoxide ions.

EXPERIMENTAL.

In the preparation of the reaction mixtures, a solution of the phenol and buffer mixture was first made up at double the concentration at which it was to be used. In the series of experiments using 0·08M-*p*-nitrophenol, the results of which are plotted in the Figure, 200 c.c. of stock solution were made up containing 4·450 g. of the phenol (0·032 equiv.) dissolved in water containing 80 c.c. of a 0·25M-borate buffer of pH 9·3, and 0·0319 equiv. of sodium hydroxide added to maintain the pH at 9·3. This was checked using a pH meter. 50 C.c. of this solution were mixed with 50 c.c. of 0·02M-*N*-chloroacetanilide solution to give a reaction mixture at 25·00° ± 0·01° and pH 9·3, containing 0·01M-*N*-chloroacetanilide, 0·08M-*p*-nitrophenol, and 0·05M-borate buffer.

A typical set of results using 0·08M-*p*-nitrophenol is given in Table IV. Each k_1 recorded is a mean value for a particular experiment.

TABLE IV.

pH.	[OH′] × 10^5.	$k_1 \times 10^2$.	Mean k_1.
8·7	0·51	1·09, 1·10, 1·13	1·11
8·8	0·63	1·18, 1·17	1·17
8·9	0·79	1·31, 1·28, 1·29	1·29
9·0	1·00	1·41, 1·36, 1·39	1·39
9·1	1·26	1·50, 1·52	1·51
9·2	1·58	1·58, 1·59, 1·60	1·59
9·26	1·82	1·73, 1·74	1·73
9·3	1·99	1·83	1·83

By extrapolation of the graphs in the Figure to zero hydroxyl-ion concentration, values for k_d relating to the interaction of *o*- and *p*-nitrophenoxide ions and *N*-chloroacetanilide are obtainable. These are 0·20 and 0·11 mols.$^{-1}$ mins.$^{-1}$ and are more precise than the values obtainable by using results given in Table I.

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