333. *Acid Catalysis in Non-aqueous Solvents. Part III. The Rearrangement of* N-*Iodoformanilide in Anisole Solution.*

By R. P. Bell and J. F. Brown.

In Parts I and II (Bell, *Proc. Roy. Soc.*, 1934, *A*, **143**, 377; Bell and Levinge, *ibid.*, 1935, **151**, 211) it has been shown that the rearrangement of *N*-bromo- into *p*-bromo-acetanilide in a number of non-dissociating solvents constitutes a simple case of general acid catalysis, and that the catalytic constants of the acids used are simply related to their dissociation constants (in water). With most catalysts, this reaction proceeds inconveniently slowly at the ordinary temperature, and it is difficult to extend measurements to a greater variety of catalysts and solvents on account of the very reactive nature of *N*-bromoacetanilide in oxidising or brominating other substances. (The latter difficulty made it impossible to use ketones, esters, or ethers as solvents.) It was therefore decided to investigate a *N*-iodoacylanilide, which would be expected to rearrange more rapidly and to be less active as an oxidising and halogenating agent.

The only known compound of this class is *N*-iodoformanilide, prepared by Comstock and Kleeberg (*Amer. Chem. J.*, 1890, **12**, 497) by the action of iodine on silver formanilide, and shown to give *p*-iodoformanilide in presence of acids. These authors supposed it to have the structure $C_6H_5{\cdot}N{:}CH{\cdot}OI$, since silver formanilide gives an *O*-ether on treatment with methyl iodide. However, its physical and chemical properties are very similar to those of the *N*-chloro- and *N*-bromo-acylanilides, and there can be little doubt that the correct formula is $C_6H_5{\cdot}NI{\cdot}CHO$.

In all the solvents used in the work on *N*-bromoacetanilide it is probable that carboxylic acids exist almost entirely as double molecules. The present work was therefore carried out in anisole solution. Although there are no actual molecular-weight determinations for carboxylic acids in this solvent, they are known to exist as single molecules in a number of other ethers (cf. Bell and Arnold, J., 1935, 1432). Anisole was chosen because it is less liable to autoxidation than most other liquid ethers.

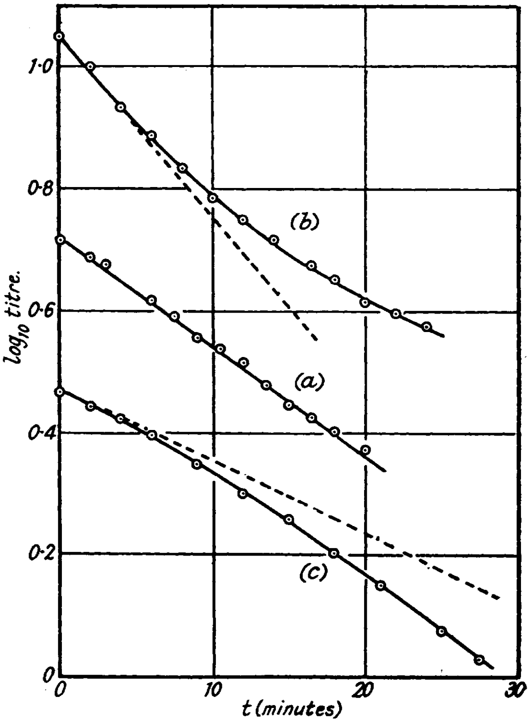
EXPERIMENTAL.

Preparation of Materials.—Silver formanilide. This was prepared by adding sodium hydroxide solution to the theoretical quantities of formanilide and silver nitrate dissolved in 50% alcohol. After being filtered off and pressed, the precipitate was kneaded with a little ligroin :

this caused the water to separate out in large drops which could be removed with filter-paper. It was finally dried to constant weight in a vacuum desiccator in the dark (Found, by ignition : Ag, 47·30, 47·41. Calc. : Ag, 47·35%) ; yield 66%. An alternative method of preparation, in which solid sodium formanilide was first isolated, gave a smaller yield and a less pure product.

N-*Iodoformanilide*. 3·8 G. of silver formanilide were gradually added with shaking to 3·6 g. of iodine in 350 c.c. of dry, freshly distilled chloroform. The precipitated silver iodide was separated by a sintered-glass filter, and the filtrate evaporated in a current of dry air. The last 40—50 c.c. of chloroform were poured off, and the remaining crystals washed rapidly with dry ether. Light was excluded in all these operations ; yield 40—50%. The purity of the product was tested by dissolving a weighed quantity in a little chloroform, adding potassium iodide solution acidified with acetic acid, and titrating the iodine liberated (Found : I, 50·91. Calc. : I, 51·42%). Analysis at intervals showed that, when kept in the dark, it was stable for at least a fortnight. A sample was warmed with formic acid and the solution diluted with boiling water. On cooling, white needles, m. p. 107·5°, crystallised out (Beilstein gives m. p. 108—109° for *p*-iodoformanilide).

FIG. 1.



Anisole. In order to obtain reproducible results it was found necessary to remove traces of peroxides. A pure material was shaken over-night with acidified ferrous sulphate solution and dried first over anhydrous calcium chloride and then over metallic sodium. It was finally fractionated in the dark in an all-glass apparatus, the fraction, b. p. 151·5—152°, being collected and kept in a desiccator in the dark.

Acids. Benzoic, *o*-nitrobenzoic, *m*-nitrobenzoic, and cinnamic acids were recrystallised from water, monochloroacetic acid from benzene, and 2 : 4 : 6-trichlorophenol from alcohol. All these acids were dried in a vacuum before use. Dichloroacetic acid was fractionally distilled and boiled within 0·2°. Trimethylacetic acid was distilled in a vacuum and then purified by fractional freezing.

Kinetic Measurements.—The reactions were carried out in the vessels previously described (Bell and Levinge, *loc. cit.*), light being excluded by means of tin-foil. About 1 c.c. of solution was withdrawn from time to time, and run into a weighed flask containing 3 c.c. of 10% potassium iodide solution and 2 c.c. of 2*N*-acetic acid. The iodine liberated according to the equation $C_6H_5\cdot NI\cdot CHO + H^{\bullet} + I' \longrightarrow C_6H_5\cdot NH\cdot CHO + I_2$, was titrated with *N*/100—*N*/500-thiosulphate solution from a microburette. By keeping the concentrations of potassium iodide and starch uniform throughout, titrations could be reproduced to ± 0·01 c.c., and any absolute error in the end-point will have little effect on the velocity constants. The reaction was followed until about two-thirds of the *N*-iodoformanilide had disappeared, and 10—15 titrations were carried out in each experiment.

Colorimetric measurements were also made to estimate small amounts of free iodine which appeared during the reaction. The colour of the reaction mixture was compared with that of a standard solution of iodine in anisole, a Hellige Duboscq immersion colorimeter being used. The green mercury line was used, light from a mercury arc being filtered first through an acidified mixed solution of copper sulphate and potassium chromate and then through a thin sheet of didymium glass. *N*-Iodoformanilide has a pale yellow colour in solution, but its light absorption was found to be negligible compared with that of an equivalent quantity of iodine.

Results.—In the following table : c_A = concentration of acid in equivs. per 1000 g. ; c_B = initial concentration of *N*-iodoformanilide in equivs. (of oxidising power) per 1000 g. ; c_{I_2} = final concentration of free iodine in equivs. per 1000 g.; k = unimolecular velocity constant ($\log_{10}$, min.$^{-1}$); $\alpha = k/c_A$ = catalytic constant.

Preliminary experiments on the stability of *N*-iodoformanilide in ordinary dry anisole showed that there was a rapid decrease of concentration during the first few hours, followed by a much slower change. For a given amount of solvent, the absolute amount of *N*-iodoformanilide which disappeared during the initial period was roughly constant and independent of its concentration. Free iodine was also formed in amounts roughly equivalent to the decrease in titre. These facts suggest that the initial instability is due to reaction with a trace of impurity in the solvent. The addition of water had no appreciable effect, but treatment of the solvent with ferrous sulphate (which should remove peroxides) eliminated the rapid initial decrease and reduced the production of free iodine. The following table shows the results obtained with anisole purified as described in the preceding section. It is clear that the percentage decrease in the *N*-iodoformanilide concentration is fairly reproducible and independent of the initial concentration. It was not possible further to increase the stability by more extensive purification of the solvent. Since the slowest catalytic reaction studied had a half time of about 3 hours, the "spontaneous" reaction can be neglected.

Stability of N-*iodoformanilide in anisole.*

$100\,c_B$		3·31	2·15	1·44	1·19	0·945	0·346
After 24 hrs.	Decrease in titre, %	18·8	21·4	27·6	26·8	17·2	24·8
	$100\,c_{I_2}$	0·15	—	0·26	0·11	0·070	0·049

In the catalytic experiments the velocity constants were evaluated by plotting the logarithm of the titre (per g. of solution) against the time. This sometimes gave a straight line, but more often there was a slight acceleration or retardation as the reaction progressed: this is indicated by a + or a — sign respectively in the last column of the following tables. The velocity constant was then determined by taking the initial slope of the plot. Typical examples of each kind of plot are shown in Fig. 1, the corresponding experiments being marked (*a*), (*b*), and (*c*) in the tables. (In the figure, the logarithm scale is displaced for the sake of clearness.) In a few cases (notably with trimethylacetic acid) the departure from linearity is very pronounced, but in the most unfavourable cases the ambiguity in the initial slope is less than 10%.

Results of catalytic experiments.

Dichloroacetic acid : c_B = 0·010 throughout.

	$100\,c_A$.	$100\,c_{I_2}$.	$100\,k$.	α.	
(*c*)	0·926	0·080	1·67	1·78	+
	0·676	<0·005	1·11	1·62	+
	0·490	—	0·822	1·66	+
	0·381	0·040	0·610	1·60	+
	0·239	0·015	0·480	2·01	+
			Mean	1·73	

o-Nitrobenzoic acid : c_B = 0·010 throughout.

$100\,c_A$.	$100\,c_{I_2}$.	$100\,k$.	α.	
1·13	0·043	1·55	1·38	+
0·794	0·041	1·09	1·37	+
0·523	0·031	0·608	1·16	+
0·194	0·045	0·285	1·34	+
		Mean	1·31	

m-Nitrobenzoic acid : c_B = 0·010 throughout.

$100\,c_A$.	$100\,c_{I_2}$.	$100\,k$.	α.	
3·16	0·12	2·95	0·934	—
2·09	0·12	1·55	0·742	—
1·61	0·13	1·05	0·652	—
0·796	0·11	0·390	0·490	—
0·704	0·13	0·290	0·412	—
		Mean	0·646	

Benzoic acid.

	$100\,c_A$.	$100\,c_B$.	$100\,c_{I_2}$.	$100\,k$.	α.	
(*b*)	7·98	1·00	0·005	3·00	0·375	—
	3·95	0·346	0·013	1·41	0·356	—
	3·95	1·00	0·023	1·51	0·376	—
	3·95	3·61	0·025	1·20	0·307	—
	1·85	1·00	0·023	0·620	0·335	—
	0·966	1·00	0·039	0·315	0·327	—
				Mean	0·353	

Monochloroacetic acid.

	$100\,c_A$.	$100\,c_B$.	$100\,c_{I_2}$.	$100\,k$.	α.	
(*a*)	1·65	3·66	0·04	1·80	1·09	
	1·64	0·334	0·018	2·00	1·22	+
	1·58	1·00	0·01	1·80	1·14	+
	1·26	1·00	0·025	1·60	1·27	
	0·874	3·67	0·036	0·870	1·00	—
	0·636	1·00	0·016	0·540	0·85	
	0·397	3·65	0·070	0·430	1·08	—
	0·297	1·00	0·007	0·345	1·16	+
	0·185	3·62	0·050	0·185	1·00	—
	0·185	1·00	—	0·172	0·93	—
				Mean	1·07	

Cinnamic acid : c_B = 0·010 throughout.

$100\,c_A$.	$100\,c_{I_2}$.	$100\,k$.	α.	
6·94	0·051	1·82	0·265	—
4·94	0·054	1·35	0·273	—
3·19	0·068	0·801	0·253	—
1·49	0·072	0·400	0·270	—
		Mean	0·265	

Trimethylacetic acid : c_B = 0·010 throughout.

$100\,c_A$.	$100\,c_{I_2}$.	$100\,k$.	α.	
5·84	—	2·45	0·420	—
4·78	0·055	1·85	0·388	—
2·46	0·029	1·05	0·427	—
1·29	0·025	0·580	0·440	—
		Mean	0·425	

2 : 4 : 6-Trichlorophenol : c_B = 0·010 throughout.

$100\,c_A$.	$100\,c_{I_2}$.	$100\,k$.	α.
8·12	0·22	1·60	0·197
4·06	0·33	1·20	0·287
		Mean	0·242

DISCUSSION.

The rearrangement of *N*-iodoformanilide is clearly analogous to that of *N*-bromoacetanilide, being essentially unimolecular and showing general acid catalysis. With monochloroacetic and benzoic acids as catalysts, the initial concentration of *N*-iodoformanilide has been varied by a factor of 10 without having any appreciable effect on the catalytic constants. [Using trichloroacetic acid as catalyst, Bell and Levinge (*loc. cit.*) found that the catalytic constant varied somewhat with *N*-bromoacetanilide concentration. The absence of this effect in the present instance may be due to the fact that weaker acids were used as catalysts.] No satisfactory explanation can be given for the acceleration and retardation observed during the course of single reactions, but the use of the initial slopes for calculating the velocity constants is justified by the fact that the catalytic constants thus obtained were independent of acid concentration over a ten-fold range.

A complicating factor in the present work has been the invariable production of small amounts of iodine. The behaviour of the reaction in this respect was very erratic, and occasionally large quantities of iodine appeared without apparent cause. The amount formed was much greater in samples of anisole which had not been treated with ferrous sulphate, but no method of purification was found which would eliminate it entirely. Work in this laboratory by Mr. J. Wright has shown that, although solutions of *N*-iodoformanilide in carbon tetrachloride and in benzene are stable, considerable quantities of iodine are formed on adding carboxylic acids to these solutions. It is thus very improbable that its formation in the present case can be attributed to impurities in the anisole. It is not, however, believed that free iodine represents an intermediate step in the normal rearrangement of *N*- to *p*-iodoformanilide. The irregularities in the amount of iodine formed are not reflected in the values of the catalytic constants, and initial addition of free iodine has little effect on the reaction velocity. Moreover, experiments on the rate of reaction between iodine and formanilide in anisole solution show that direct iodination takes place at least 1000 times too slowly to account for the observed rate of formation of *p*-iodoformanilide in the catalytic experiments. It seems therefore certain that the main reaction being studied is the direct migration of an iodine atom without the intermediate formation of free iodine : this conclusion is further supported by the fact that no free bromine is detectable in the allied transformation of *N*-bromoacetanilide under comparable conditions (cf. Bell, this vol., p. 1154).

The nature of the side reaction responsible for the production of free iodine has not been elucidated, but it may well be $2C_6H_5\cdot NI\cdot CHO \longrightarrow C_6H_5\cdot N(CHO)\cdot N(CHO)\cdot C_6H_5 + I_2$. Diformylhydrazobenzene has not been described, but Hodges (J., 1933, 240) isolated the brown diacetyl compound as one of the products of the photochemical decomposition of *N*-chloroacetanilide. In the present work, reaction mixtures in which a large quantity of iodine had been formed were slightly coloured after removal of iodine with thiosulphate, but we could not isolate any crystalline product other than *p*-iodoformanilide.

The measured titres will, of course, include free iodine as well as unchanged *N*-iodoformanilide, and should strictly be corrected to obtain the true rate of disappearance of the latter substance. In a few cases determinations of free iodine were carried out throughout the reaction and the corrected and uncorrected curves compared. Fig. 2 shows such a comparison for the experiment with 0·00926*N*-dichloroacetic acid. The correction does not affect the initial rate by more than a few units %. In most cases the iodine production is still smaller, and the correction would be negligible. In the experiments with trichlorophenol and *m*-nitrobenzoic acid the iodine liberation is abnormally large, and the results for these two acids can only be regarded as approximate.

The following table contains the mean values of the catalytic constants for the different acids, together with their dissociation constants in water (K_d), and Fig. 3 shows a plot of

Acid.	K_d.	a.	Acid.	K_d.	a.
Dichloroacetic	$5{\cdot}1 \times 10^{-2}$	1·73	Benzoic	$6{\cdot}7 \times 10^{-5}$	0·353
o-Nitrobenzoic	$6{\cdot}4 \times 10^{-3}$	1·31	Cinnamic	$3{\cdot}7 \times 10^{-5}$	0·265
Monochloroacetic	$1{\cdot}6 \times 10^{-3}$	1·07	Trimethylacetic	$9{\cdot}6 \times 10^{-6}$	0·425
m-Nitrobenzoic	$3{\cdot}5 \times 10^{-4}$	0·646	2 : 4 : 6-Trichlorophenol	$3{\cdot}9 \times 10^{-7}$	0·242

$\log_{10}\alpha$ against $\log_{10}K_d$. A relation of the Brönsted type is obeyed approximately, the straight line in the figure corresponding to $\alpha = 3{\cdot}63K_d^{0{\cdot}21}$. For the transformation of *N*-bromoacetanilide in chlorobenzene at 15° (Bell, *Proc. Roy. Soc.*, 1934, *A*, **143**, 377) the corresponding relation (converted into our present units) is $\alpha = 0{\cdot}0075K_d^{0{\cdot}30}$. It was found for the latter reaction that change of solvent changes the reaction velocity by a factor of 10 at the most, and the work of Fontein (Thesis, " Intramoleculaire Omzettingsnelheden bij Arylacylhalogeenaminen," Leiden, 1927; *Rec. trav. chim.*, 1928, **47**, 635)

FIG. 2.

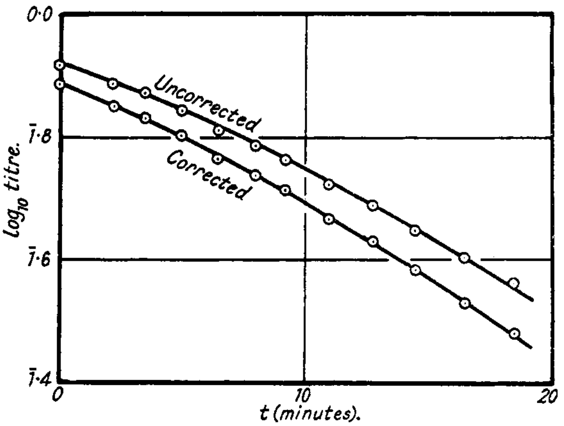
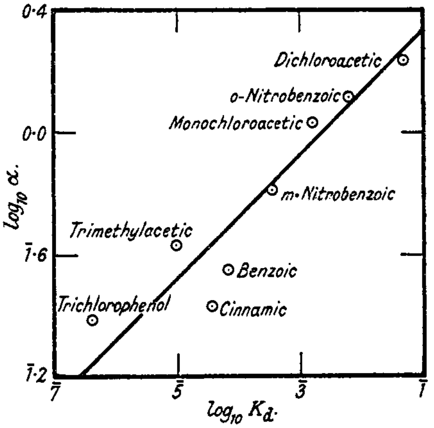


FIG. 3.



shows that the nature of the aliphatic acyl group has little effect on the velocity of rearrangement of *N*-chloroacylanilides : hence the great increase in velocity in going from *N*-bromoacetanilide to *N*-iodoformanilide can be attributed chiefly to the change in the nature of the halogen atom. The corresponding decrease in the exponent of the Brönsted equation from 0·30 to 0·21 is qualitatively in accord with the picture of proton transfer proposed by Polanyi and Horiuti (*Acta Physicochim. U.R.S.S.*, 1935, **2**, 505) and by Bell (*Proc. Roy. Soc.*, 1936, *A*, **154**, 414), since if the substrate has a greater proton affinity, the corresponding potential-energy curve will be steeper and the exponent smaller.

SUMMARY.

1. The kinetics of the transformation of *N*- into *p*-iodoformanilide have been studied at 25° in anisole solutions of mono- and di-chloroacetic, *o*- and *m*-nitrobenzoic, benzoic, cinnamic, and trimethylacetic acids and of trichlorophenol.
2. The initial rate of transformation is directly proportional to the concentration of *N*-iodoformanilide and to the acid concentration.
3. The formation of *p*-iodoformanilide is accompanied by small quantities of free iodine, which however appear to play no part in the main reaction.
4. The catalytic constants of the acids studied bear a simple relationship to their dissociation constants in water.

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