298. *Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part II. The Determination of Some Reaction Velocities involving Acetic Chloroacetic Anhydride.*

By A. R. Emery and V. Gold.

The velocity of the hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 w/w) and the influence of added substances upon it have been studied. The chief effect of added acetate or chloroacetate ions seems to be a fairly rapid reaction with the mixed anhydride to give a symmetrical anhydride, the different rate of hydrolysis of which disturbs the first-order nature of the reaction. The results are complex but, on the whole, do not indicate the existence of specific and common-ion intervention by these anions, such as would be expected on the basis of an ionisation reaction mechanism.

The velocities of overall acylation, acetylation, and chloroacetylation of 2 : 4-dichloroaniline have been determined by combining the hydrolysis results with those of competitive acylation–hydrolysis. The effects of added acetate and chloroacetate ions accord with the interpretation of their effect on the hydrolysis velocity.

Although the kinetics of the hydrolysis of symmetrical carboxylic anhydrides, in particular of acetic anhydride, have engaged the attention of a large number of workers, reaction velocities involving mixed anhydrides have been the subject of only two reasonably detailed recorded investigations, both dealing with the hydrolysis of mixed fatty acid anhydrides, mainly acetic propionic anhydride (Verkade, *Rec. Trav. chim.*, 1915, **35**, 299; Kilpatrick and Kilpatrick, *J. Amer. Chem. Soc.*, 1930, **52**, 1418). The main points of interest emerging were : (i) that the reaction is of the first order, thus showing that the substance investigated was homogeneous and not a mixture of the two symmetrical anhydrides; in the latter case the first-order rate coefficients would have decreased with time owing to the different rates of hydrolysis of the two symmetrical anhydrides; and (ii) that the reaction velocity is intermediate between the values for the symmetrical anhydrides.

In the preceding paper two alternative interpretations were given of the drastic effect of the solvent on the proportions of the products formed from acetic chloroacetic anhydride and an aromatic amine. According to one of these, this observation was ascribed to a change of reaction mechanism, the reaction in the more polar solvents being interpreted as proceeding *via* ionisation to $CH_3{\cdot}CO^+$ and $CH_2Cl{\cdot}CO_2^-$.

In the present paper more information about the reaction mechanism in polar solvents is derived from the determination of absolute reaction velocities for hydrolysis, overall acylation of 2 : 4-dichloroaniline, and acetylation and chloroacetylation of that amine, and from the study of the effects of certain anions on these velocities, all measurements relating to 80 : 20 (w/w) acetone–water as solvent. In particular, the kinetic consequences of the ionisation mechanism were tested. The method employed was to determine only the hydrolysis velocity directly and to obtain the other velocities from product analyses of competitive experiments in which hydrolysis and acylation were proceeding at comparable rates.

[•] These considerations would have to be somewhat modified if the introduction of an acid-strengthening group should nevertheless stabilise the derived acylium cation because of a large polarisability which permits a greater delocalisation of the positive charge. It is, however, improbable that such a state of affairs need be gone into more fully in the present case, as is shown by the base-weakening effect of chlorine substitution in aliphatic and aromatic amines.

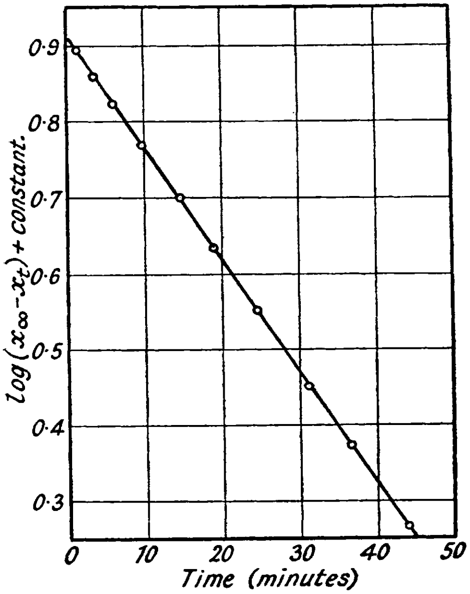
EXPERIMENTAL.

Materials.—Acetic chloroacetic anhydride : see Part I. Acetone–water (80% of acetone by weight) was generally made up from distilled water and AnalaR acetone without further purification, after it had been found that treatment of acetone by the method of Conant and Kirner (*J. Amer. Chem. Soc.*, 1924, **46**, 245) and use of conductivity water did not materially alter the results.

Sodium acetate, potassium acetate, and sodium chloroacetate used were anhydrous salts, the last prepared by nearly neutralising, with cooling, a concentrated solution of chloroacetic acid in water with concentrated sodium hydroxide solution, precipitating the anhydrous salt by addition of a large volume of acetone, washing the solid with dry acetone and benzene, and drying it in a vacuum-desiccator. The salt gave a neutral reaction and contained the theoretical amount of chlorine.

FIG. 1.

Illustration of first-order course of the hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 *w/w*) *at* 25°.



*Chloroaceto-*2 : 4*-dichloroanilide* was prepared by mixing cold benzene solutions of chloroacetyl chloride and 2 : 4-dichloroaniline and crystallising the precipitated anilide from alcohol. It formed needles, m. p. 101·5° (Found : C, 40·6; H, 2·6; N, 5·9; Cl, 44·6. $C_8H_6ONCl_3$ requires C, 40·4; H, 2·5; N, 5·9; Cl, 44·6%).

Determination of Hydrolysis Velocity.—The progress of the reaction was followed by periodically pipetting samples into an " arresting solution " of aniline in aqueous acetone and titrating the liberated acid with carbonate-free sodium hydroxide solution (cf. Vles, *Rec. Trav. chim.*, 1933, **52**, 809). The anhydride still present in solution reacts practically instantaneously with aniline, liberating one mole of acid per mole of anhydride, the total amount of acid in the sample from this reaction and the hydrolysis being given by

$$x_t = 2(a_0 - a_t) + a_t + f_0$$
$$= 2a_0 - a_t + f_0$$

and

$$x_\infty = 2a_0 + f_0$$

where a_0, a_t, a_∞ are the amounts of anhydride in the sample, x_0, x_t, x_∞ are the amounts of acid after treatment with aniline at times $t = 0$, $t = t$, $t = \infty$, and f_0 is the amount of free acid in the sample due to the free acid content of the anhydride preparation. For a first-order hydrolysis we get for the rate constant of the reaction

$$k_1 = \frac{1}{t}\ln\frac{(x_\infty - f_0)}{2(x_\infty - x_t)} \quad \ldots\ldots\ldots\ldots \quad \text{(i)}$$

The first-order nature of the " spontaneous " hydrolysis is confirmed by (*a*) the linear nature of the graphs of log ($x_\infty - x_t$) against t (Fig. 1), from the slopes of which the first-order rate coefficients were usually evaluated and (*b*) the absence of a significant dependence of the rate-coefficients on initial concentration of anhydride. For comparison, the velocity coefficients of the two symmetrical anhydrides were determined in the same manner.

TABLE I.

Velocity of hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 w/w).
$[\text{MA}]_0 \sim 0{\cdot}05\text{M}$.

Temp.	$k_1 \times 10^4$ (sec.$^{-1}$).*	*E*.	Frequency factor.
0·1°	1·27	9·9 kcals.	10^4
25·0°	5·76		

* In this and the succeeding paper rate constants are expressed in terms of seconds and moles/l. The symbols k_1 and k_2 are reserved for the experimental velocity coefficients of hydrolysis and acetylation, defined by equations (i) and (vi).

Determination of Velocity of Acylation of 2 : 4*-Dichloroaniline by Competition Experiments.*—If hydrolysis and acylation proceed competitively the total concentration of acid at the end of the reaction is a measure of the extent of the competing reactions, since the hydrolysis reaction yields *two* moles of acid and acylation *one* mole of acid per mole of anhydride reacting. If [X], [A], and [B] represent, respectively, the concentration of total acid, mixed anhydride, and amine (base) at the times indicated by the suffixes, we get

$$[\text{X}]_\infty = 2[\text{A}]_0 - ([\text{B}]_0 - [\text{B}]_\infty) \quad \ldots\ldots\ldots\ldots \quad \text{(ii)}$$

and

$$[\text{X}]_\infty = 2k_1\int_{t=0}^{t=\infty}[\text{A}]^k\text{d}t + k_2\int_{t=0}^{t=\infty}[\text{A}]^a[\text{B}]^b\text{d}t \quad \ldots\ldots \quad \text{(iii)}$$

where k_1 and k_2 are the velocity coefficients for hydrolysis and acylation respectively and h, a, and b are undetermined reaction orders. For one set of values of the exponents the expression (iii) becomes equivalent to Wegscheider's test, but it can also be transformed into useful equations for other particular values of h, a, and b. In the present case it seemed reasonable to try an analysis of the experimental data on the assumption that the hydrolysis remains a first-order reaction as before and that the acylation reaction is of the first order with respect to each reaction partner. Then,

$$-\frac{d[A]}{dt} = k_1[A] + k_2[A][B] \qquad \text{(iv)}$$

and

$$-\frac{d[B]}{dt} = k_2[A][B] \qquad \text{(v)}$$

Hence,

$$\int_{[A]_0}^{0} d[A] = \frac{k_1}{k_2}\int_{[B]_0}^{[B]_\infty}\left(\frac{1}{[B]} + 1\right)d[B]$$

Integrating between the limits indicated, remembering that [from (ii)] $[B]_\infty = [X]_\infty - 2[A]_0 + [B]_0$, and rearranging, we get

$$\frac{k_1}{k_2} = \frac{[X]_\infty - [A]_0}{\ln\dfrac{[B]_0}{[X]_\infty - 2[A]_0 + [B]_0}} \qquad \text{(vi)}$$

which can be directly applied to experimental data. A simple correction to the equation is necessary if, as is usually the case, the anhydride employed contains a small percentage of free acid which must be determined independently by reaction with aniline followed by acidity titration (see preceding paper). The success of the method depends on the absolute accuracy of the titrations (*i.e.*, careful standardisation of the standard alkali solution is essential) and in the use of product ratios differing not too widely from unity.

Equation (vi) needs considerable modification if an allowance is to be made for the equilibrium which progressively removes some of one of the reactants as the reaction proceeds, *viz.*, the salt formation between the acids generated and the amine. For 2 : 4-dichloroaniline with the acids and solvent employed, the effect appears to be small although, if an appropriate allowance could be made accurately, the value k_1/k_2 would almost certainly be slightly changed. The exact constancy of k_1/k_2 is therefore fortuitous, and k_2 should be regarded as a stoicheiometric rate constant without consideration of the state of the amine (Table II).

TABLE II.

Competitive acylation–hydrolysis experiments with acetic chloroacetic anhydride and 2 : 4-dichloroaniline in acetone–water (80 : 20 w/w).

Temp.	$[A]_0 \times 10^2$.	$[B]_0 \times 10^2$.	Hydrolysis, %.	k_1/k_2.	$k_2 \times 10^4$ (overall).	Chloroacylation ratio.	$k_2 \times 10^4$ for chloroacetylation portion.	$k_2 \times 10^4$ for acetylation portion.
0·1°	8·566	14·80	84·3	0·75	1·69	0·40	0·48	1·21
,,	6·883	67·0	56·2	0·84	1·51	0·45	0·47	1·04
25	5·957	7·41	91·9	0·81	7·1	—	—	—
,,	8·142	14·72	84·3	0·75	7·6	0·38	2·1	5·5
,,	5·860	14·83	83·8	0·75	7·6	0·35	2·0	5·6
,,	6·613	24·57	76·0	0·75	7·6	—	—	—
,,	6·235	37·02	67·1	0·75	7·6	—	—	—
,,	6·189	50·59	61·7	0·79	7·3	—	—	—
,,	6·259	66·83	56·4	0·85	6·8	0·43	2·0	4·8
,,	7·948	67·16	54·7	0·77	7·5	0·40	2·1	5·4

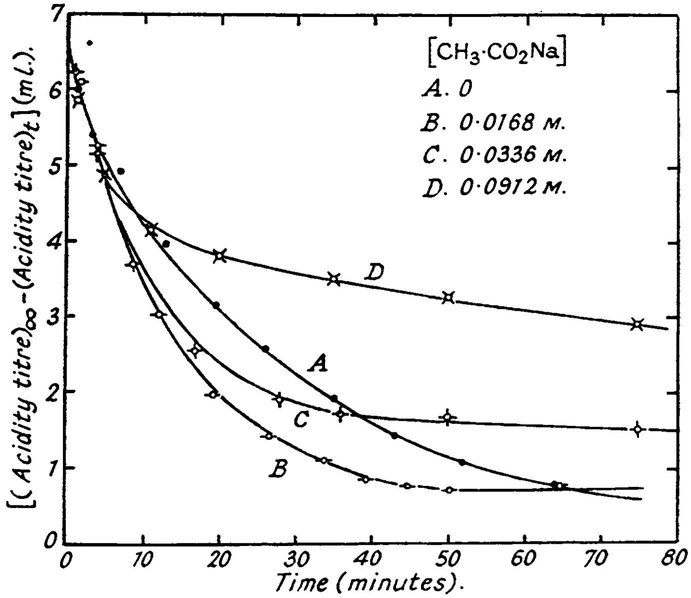
The assumptions (iv) and (v) are not the most general ones which will lead to an expression of the form of (vi). Any reaction scheme

$$A \rightleftharpoons X \rightleftharpoons \cdots\cdots \rightleftharpoons Z \begin{cases} \xrightarrow[k_1]{+H_2O} 2\text{ Acid} \\ \xrightarrow[k_2]{+RNH_2} 1\text{ Acid} \end{cases}$$

where Z is the form of the anhydride which is divided in the competition between amine and water, will produce a constant ratio k_1/k_2 evaluated according to (vi). However, the rate of product formation may be controlled by the slow occurrence of any one of the preceding steps. Therefore, the constancy of k_1/k_2 for a nine-fold change in the amine concentration (Table II) only demonstrates the validity of the more general scheme of which our assumptions (iv) and (v) form the special case where there are no *rate-controlling* intermediate stages. For this reason, if the k_1 and k_2 of this fraction are to be identified with the experimental velocity coefficients for hydrolysis and acylation, it is essential to show that the assumptions (iv) and (v) are valid. Suppose that in the reactions of acetic chloroacetic anhydride there is an intermediate rate-determining step (*viz.*, ionisation into acetylium and chloroacetate ions); then, although the velocity of disappearance of anhydride would not depend on the concentration and the nature of the amine, the amine would still compete for its share of acetylium ions with a degree of success proportional to its concentration. We have not measured the dependence of the rate of disappearance of anhydride upon amine concentration but have carried out a simpler test and shown that, under conditions when the hydrolysis is measurably slow, the addition of aniline to the reaction solution causes the chemical change, which is now exclusively formation of anilide, to be complete when the first measurement is made after 5 minutes; *i.e.*, the presence of amine must have hastened the reaction rate by a factor of the order of 100 at the least. The reaction with aniline cannot, therefore, involve a slow ionisation stage in which the amine does not participate. Since the chloroacylation ratios for aniline and 2 : 4-dichloroaniline are similar it seems plausible to assign the same mechanism to both acylations and not to look on the reaction with aniline as involving molecular anhydride when that with 2 : 4-dichloroaniline does not. Therefore, the partitioning of the acylating agent between water and amine occurs during a slow step, as expressed in the equations (iv) and (v).

FIG. 2.

The effect of sodium acetate addition on the hydrolysis of acetic chloroacetic anhydride.



Solvent: *acetone–water* (80 : 20 w/w). *Temp.*: 25°. $[MA]_0$ ~0·13M.

By accepting these equations and the validity of (vi), we obtained values for the second-order overall acylation velocity coefficient k_2 by combining the k_1/k_2 values with the result for k_1, from the hydrolysis velocity measurements. The temperature dependence of k_2 leads to a value of approx. 10 kcals. for the activation energy of the overall acylation.

For comparison similar, but less extensive, measurements were carried out for the two symmetrical anhydrides (Table III).

TABLE III.

Comparison of hydrolysis and competition experiments for acetic chloroacetic anhydride and the corresponding symmetrical anhydrides in acetone–water (80 : 20 w/w). Temp. 25°.

Anhydride.	$[A]_0 \times 10^2$.	[2 : 4-Dichloroaniline].	Hydrolysis, %.	k_1/k_2.	$k_1 \times 10^6$.	$k_2 \times 10^6$.
Ac_2O	6·34	0·670	21·5	0·175	5·9	34
$CH_2Cl{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3$	7·95	0·672	54·7	0·77	576	750
$(CH_2Cl{\cdot}CO)_2O$	3·53	0·670	59·3	0·96	6500	6800

Evaluation of Velocity Coefficients for Acetylation and Chloroacetylation of 2 : 4-Dichloroaniline by Acetic Chloroacetic Anhydride.—The second-order acylation velocity coefficients evaluated above are composite, as they are made up of contributions from the acetylation and the chloroacetylation reactions. By determining product ratios as described in Part I, making appropriate allowance for the fact that only part of the anhydride is used up for amine acylation, it is then possible to calculate the velocity coefficients for the constituent reactions, provided that both are of the same kinetic order as the overall reaction, and this seems to be a plausible assumption. The results obtained are given in the last two columns of Table II. The very small temperature dependence of the chloroacylation ratio indicates that acetylation and chloroacetylation by acetic chloroacetic anhydride must have very similar activation energies.

Effect of Added Substances on Velocities.—(a) *Hydrolysis.* Table IV summarises the effect of some substances upon the velocity coefficients whose addition did not disturb the strictly first-order course of the reaction. The effects are small and of the order of magnitude often found as salt or medium effects in heterolytic reactions.

TABLE IV.

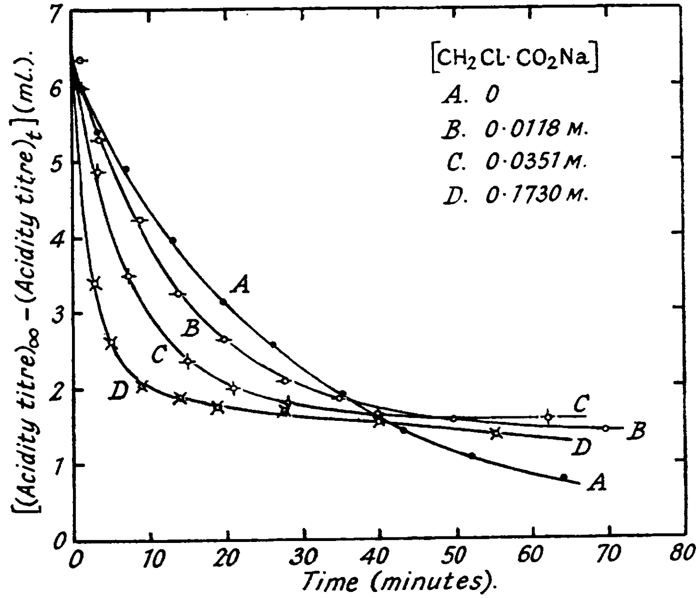
Effect of various substances on the rate of hydrolysis of acetic chloroacetic anhydride in acetone–water (80 : 20 w/w) *at* 25°. $[MA]_0$ ~0·05M.

Substance added.	Concn., M.	$k_1 \times 10^4$.
—	—	5·76
KBr	0·1	6·43
$CH_2Cl{\cdot}CO_2H$	0·1	5·45
H_2SO_4	0·05	6·35

On the other hand, the addition of sodium acetate and sodium chloroacetate had a more pronounced effect on the course of the reaction. This is illustrated by representative curves in Figs. 2 and 3.

FIG. 3.

The effect of sodium chloroacetate addition on the hydrolysis of acetic chloroacetic anhydride.



Solvent : acetone–water (80 : 20 w/w). *Temp. :* 25°. $[MA]_0$ ~0·13M.

Comparative data for the effect of added salts upon the velocity of hydrolysis of acetic anhydride in 50 : 50 (w/w) acetone–water are given in Table V. In these cases there is no corresponding disturbance of the accurate first-order course of the reaction, although sodium acetate and chloroacetate both accelerate the reaction. The change of solvent was dictated by the inconveniently slow hydrolysis of acetic anhydride in 80 : 20 (w/w) acetone–water.

TABLE V.

Effect of added salts on the rate of hydrolysis of acetic anhydride in acetone–water (50 : 50 w/w) *at* 25°. $[Ac_2O]_0$ ~0·07M.

Substance added.	Concn., M.	$k_1 \times 10^5$.
—	—	9·8
KBr	0·1	9·9
CH_3CO_2Na	0·1	25·0
CH_2ClCO_2Na	0·1	20·0

(b) *Competitive experiments.* The results are summarised in Table VI. Owing to the complicated character of the hydrolysis curves it was not possible to analyse the results of the competitive hydrolysis–acylation experiments in the presence of salt by the method described above.

Table VII summarises comparison experiments with acetic anhydride and 2 : 4-dichloroaniline, and Table VIII the effect of added salts upon the chloroacylation ratio for aniline.

It was verified that the α-chloroacetanilides were stable in the presence of acetate ions, therefore, any increase in the experimentally determined content of chloride in the aqueous layer must reflect a genuine change in the proportions of the competing reactions occurring. Before these results are discussed it must also be decided whether the anion effects can be caused by the changed acidity of the medium. The smallness of the effect of addition of sulphuric acid shows that the change is not due to suppression of acid catalysis. On the other hand, hydrolysis reactions of this kind are very strongly catalysed by OH^- ions (*e.g.*, Ac_2O; Skrabal, *Monatsh.*, 1922, **43**, 493), even in extremely low concentration. To account for our results we would have to assume that there is appreciable hydroxyl-ion catalysis of hydrolysis in acid solutions, since even after addition of sodium acetate or chloroacetate the solutions are definitely acidic after a small amount of reaction has taken place. Such an explanation is finally ruled out (i) by the fact that the course of the hydrolysis is not radically changed if an equivalent amount of acetic acid is introduced in addition to sodium acetate, and (ii) by the strictly first-order course of the " spontaneous " hydrolysis.

TABLE VI.

Effect of added substances in the competitive reactions of acetic chloroacetic anhydride with 2 : 4-dichloroaniline and water in acetone–water (80 : 20 w/w).

$[MA]_0$ ~0·07M. $[2:4\text{-Dichloroaniline}]_0$ = 0·672M. Temp. = 25·2°.

		Percentage of total reaction giving			
Added substance.	Concn.	Hydrolysis.	Acetylation.	Chloroacetylation.	Chloroacylation ratio.
—	—	51·5	33·9	14·6	0·43
$CH_2Cl·CO_2H$	0·102	52·3	30·7	17·0	0·55
$CH_3·CO_2H$	0·096	49·0	36·1	14·9	0·41
KBr	0·052	52·8	34·0	13·2	0·39
,, ...	0·076	54·0	32·2	13·8	0·43
,, ...	0·099	60·8	26·5	12·7	0·48
$CH_3·CO_2Na$	0·051	60·6	30·2	9·2	0·30
$CH_3·CO_2K$	0·081	65·8	28·0	6·2	0·22
,, ...	0·092	67·8	26·8	5·4	0·20
$CH_2Cl·CO_2Na$	0·051	66·0	16·7	17·3	1·03
,, ...	0·075	71·2	13·7	15·1	1·10
,, ...	0·102	73·3	12·1	14·6	1·21

TABLE VII.

Effect of added salts on the competitive reactions of acetic anhydride with 2 : 4-dichloroaniline and water in acetone–water (50 : 50 w/w).

$[Ac_2O]_0$ ~0·08M. $[2:4\text{-Dichloroaniline}]_0$ = 0·185M. Temp. = 25°.

Substance added.	Concn., M.	Hydrolysis, %.	Chloroacetylation, %.
—	—	60·4	—
$CH_3·CO_2Na$	0·1	76·4	—
$CH_2Cl·CO_2Na$	0·1	71·7	0

TABLE VIII.

Effect of added salts on the chloroacylation ratio for the reaction between acetic chloroacetic anhydride and aniline in acetone–water (80 : 20 w/w).

$[MA]_0$ ~0·08M. $[\text{Aniline}]_0$ ~0·7M. Temp. = 25°.

Substance added.	Concn., M.	Chloroacylation ratio.
—	—	0·69
$CH_3·CO_2Na$	0·0915	0·75
$CH_2Cl·CO_2Na$	0·0989	0·77

DISCUSSION.

(a) *Characteristic Features of an Ionisation Mechanism for Acetylation. Prediction of Common-ion Effect.*—It was suggested in Part I, as *one* interpretation of the observations on the composition of the acylation product and the change of this composition with solvent variation, that acetylation of an aromatic amine by acetic chloroacetic anhydride in aqueous acetone is largely an ionic reaction in which the anhydride molecule ionises to a small extent, according to the scheme :

$$CH_2Cl·CO·O·CO·CH_3 \rightleftharpoons CH_3·CO^+ + CH_2Cl·CO_2^-$$

and that the amine molecule is then attacked by the acetylium cation. Certain peculiarities may be discovered in the reaction kinetics when such a mechanism operates, including a rate-determining stage independent of the nature of the second reactant (in this case the amine) or of common-ion effects. These tests should be applicable to the reactions of acetic chloroacetic anhydride. In view of the negative outcome of these tests we omit the detailed mathematical analysis of the ionisation mechanism and present only an outline of the arguments.

We have shown that the velocity of acylation depends strongly on the nature of the amine used and, therefore, the existence of a common rate-determining stage is ruled out. Furthermore, the chloroacylation ratio does not depend strongly on the nature and concentration of the amine, as it should if one of the acylation reactions occurred by an ionic mechanism. It would, in fact, be unusual for an organic reaction of this type to have an ionic mechanism in which the subsequent reaction of the ion $R{\cdot}CO^+ + R''{\cdot}NH_2 \longrightarrow R''{\cdot}\overset{+}{N}H_2{\cdot}CO{\cdot}R$ is rate-determining and not the initial bond rupture in the anhydride molecule, though the mechanism cannot be entirely dismissed on this argument alone. It follows, however, that if the first stage *is* a rapid equilibrium, then the reaction should always be strongly retarded by the addition of the common anion (in our case, chloroacetate or, possibly, acetate ions). It has not been possible to study the effect of anions on the velocity of amine acetylation. The common-ion effect on acylation should, however, also be noticeable in the chloroacylation ratios, since it should affect the two types of acylation differently. Added acetate and chloroacetate ions were, indeed, found to have a profound effect on chloroacylation ratios, but it could not be explained on such simple lines.

(b) *Kinetic Characteristics of an Ionisation Mechanism for Hydrolysis.*—The hydrolysis of an acid anhydride can be regarded as the acylation of water; it is in many important respects analogous to the acylation of an amine. Thus it is known that structural factors which enhance the reactivity of the anhydride towards one of these reagents will also activate it for reaction with the other, though not to the same extent, the more reactive anhydrides apparently giving a higher value for the ratio k_1/k_2. Water is a very much less active reagent than the two amines (aniline and 2 : 4-dichloroaniline) used by us, and it therefore follows that, if primary ionisation is largely essential to the acylation of an amine, acylation of water molecules probably involves this step, particularly in view of the parallel trends of k_1, k_2 and k_1/k_2. The argument is not quite conclusive but, if accepted, leads to the following formulation of the hydrolysis mechanism :

$$CH_2Cl{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CH_3 \underset{K_{-1}'}{\overset{K_1'}{\rightleftharpoons}} CH_3{\cdot}CO^+ + CH_2Cl{\cdot}CO_2^-$$

$$CH_3{\cdot}CO^+ + H_2O \underset{K_3'}{\longrightarrow} CH_3{\cdot}CO_2H + H^+$$

and hence the rate equation :

$$V_{\text{Hydrolysis}} = \left\{K_H + K_H' + \frac{K_1'K_3'}{K_{-1}'[CH_2Cl{\cdot}CO_2^-] + K_3'}\right\}[MA] \quad . \quad . \quad . \quad . \quad (xii)$$

where K_H and K_H' are the rate coefficients for attack of water on the anhydride molecule in the two possible positions. (Since the reagent water is present in unchanging high concentration in the solvent, the constant K_3' is defined to include the function of the concentration of water on which the velocity depends.) This leads to the result that there should be an experimentally observable effect, according to which the velocity of hydrolysis is a linear function of the reciprocal of the concentration of chloroacetate ions.

(c) *Complicating Effects of Anions on Reactions of Acetic Chloroacetic Anhydride.*—Unfortunately, for several reasons, a straightforward test of this consequence of the ionisation mechanism is impossible : (1) The hydrolysis of symmetrical anhydrides is known to be base-catalysed; hydroxyl ions, anion bases, and tertiary amines have been shown to be effective and we have found pyridine also to be a catalyst for the hydrolysis of acetic chloroacetic anhydride. As a consequence the common-ion retardation by chloroacetate ions may be very largely masked by their opposite catalytic influence.

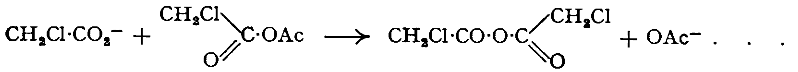
(2) Except at the very start of the reaction, the addition of a certain amount of acetate or chloroacetate ion to the reaction mixture does not produce a solution containing the same concentration of the added ion. Since chloroacetic and acetic acids are being formed throughout the reaction the concentrations of the ions at any moment are those appropriate to the mass law applied to the equilibrium :

$$CH_3{\cdot}CO_2^- + CH_2Cl{\cdot}CO_2H \rightleftharpoons CH_2Cl{\cdot}CO_2^- + CH_3{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad (A)$$

with a secondary effect due to the direct ionisation of the acids.

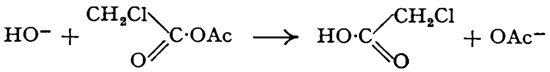
(3) It is possible that the anion effect operates, not only through common-ion intervention in an ionisation mechanism, as discussed so far, but also through a bimolecular attack, and the experimental results of this paper relating to this are probably best explained by assuming this to be indeed an important factor. Since it is known that hydrolysis of an anhydride by hydroxyl ions proceeds at a rate several powers of ten greater than hydrolysis by water under conditions where a bimolecular mechanism is probable (Gold, *Trans. Faraday Soc.*, 1948, **44**,

506), it is not unlikely that the only slightly less nucleophilic acetate or chloroacetate ions can similarly effect a substitution more readily than water molecules. The reaction



$$CH_2Cl\cdot CO_2^- + \overset{CH_2Cl\diagdown}{\underset{O\diagup\!\!\diagup}{}}C\cdot OAc \longrightarrow CH_2Cl\cdot CO\cdot O\cdot C\overset{\diagup CH_2Cl}{\underset{\diagdown\!\!\diagdown O}{}} + OAc^- \quad . \quad . \quad . \quad (B)$$

leads to a symmetrical anhydride with a different tendency to hydrolyse compared with that of the mixed anhydride. It is analogous to :



$$HO^- + \overset{CH_2Cl\diagdown}{\underset{O\diagup\!\!\diagup}{}}C\cdot OAc \longrightarrow HO\cdot C\overset{\diagup CH_2Cl}{\underset{\diagdown\!\!\diagdown O}{}} + OAc^-$$

A rapid reaction according to equation (B) is quite probable; Ruben, Allen, and Nahinsky (*J. Amer. Chem. Soc.*, **1942**, **64**, 3050) have observed that the radioactive exchange reaction :

$$CH_3\cdot \overset{*}{C}O\cdot ONa \text{ (solid)} + (CH_3\cdot CO)_2O \longrightarrow CH_3\cdot \overset{*}{C}O\cdot O\cdot CO\cdot CH_3 + CH_3\cdot CO\cdot ONa$$

without added solvent is half-complete after only twenty minutes at room temperature, although sodium acetate is only slightly soluble in acetic anhydride.

(d) *Interpretation of Anion Effects.*—When these complications are taken into account, our experiments on acetate and chloroacetate ion addition may be interpreted as follows :

(1) Effect of acetate ions upon velocity of hydrolysis : During the early stages of the reaction, hydrolysis competes with the reaction :

$$CH_3\cdot CO_2^- + CH_2Cl\cdot CO\cdot O\cdot CO\cdot CH_3 \longrightarrow (CH_3\cdot CO)_2O + CH_2Cl\cdot CO_2^- \quad . \quad . \quad . \quad (C)$$

and [because of equilibrium (A)] to a smaller extent with the reaction (B). The first portion of the hydrolysis is therefore the rapid hydrolysis of a little chloroacetic anhydride and of mixed anhydride, catalysed by acetate and chloroacetate ions, followed by a slow portion, the length of which increases with the amount of acetate added, which corresponds mainly to hydrolysis of acetic anhydride (Fig. 2). The equilibrium position of reaction (C) is probably entirely on the right-hand side, since addition of chloroacetate ions to acetic anhydride did not produce a similar deviation from the first-order hydrolysis.

(2) Effect of acetate ions upon chloroacylation ratio : As the length of the slow portion of the hydrolysis increases, the proportion of chloroaceto-2 : 4-dichloroanilide in the acylation product decreases, for reactions in which acylation of 2 : 4-dichloroaniline and hydrolysis proceed at comparable speeds (Table VI). This is explained by the supposition that an increasingly larger portion of the acylation reaction is really acetylation by acetic anhydride. On the other hand, for the acylation of aniline, which proceeds at a much faster rate than either hydrolysis or the acetate substitution reaction, the chloroacylation ratio remains unchanged.

(3) Effect of chloroacetate ions upon velocity of hydrolysis : There is now considerable acceleration over most of the course of the reaction (Fig. 3) attributable to the formation and rapid hydrolysis of chloroacetic anhydride. The retardation at the end may be due to the slow hydrolysis of a small amount of acetic anhydride formed by the attack of acetate ions present, through attainment of the equilibrium (A).

(4) Effect of chloroacetate ions upon chloroacylation ratio: In agreement with the interpretation of (3) there is an increase in the chloroacylation ratio for 2 : 4-dichloroaniline with addition of chloroacetate ions, since the chloroacetic anhydride formed will naturally acylate to give exclusively the α-chloroacetanilide. As with acetate ions the chloroacylation ratio with aniline remains unchanged (Table VIII). It is only this last observation which seems to disprove without complication the existence of a common-ion effect in the reactions of acetic chloroacetic anhydride.

(5) Effect of acetate and chloroacetate ions upon the ratio hydrolysis/acylation : With acetic anhydride added basic catalysts hasten the hydrolysis relative to the acylation reaction. The effects observed with the mixed anhydrides (Table VI) do not, therefore, seem to call for a specific explanation, although the results do not, of course, relate to the hydrolysis of mixed anhydride alone, but to the mixed anhydride and an appreciable proportion of one or both of the symmetrical anhydrides.

On the whole, the effects of chloroacetate and acetate ions would seem to be too complex to permit the certain detection of common-ion and specific-ion intervention, and the interpretations of the effects given here are really independent of any assumed detailed mechanism.

Nevertheless, the failure to detect any phenomenon which can be attributed to a common-ion effect, and particularly its absence in the experiments on the chloroacylation ratio with aniline, suggest fairly strongly that an interpretation of the kinetics of the reactions by an ionic mechanism is not a probable one. To account for the absence of such effects in every instance it would be necessary to postulate details of mechanism both involved and at variance with those commonly accepted for ionisation mechanisms of organic reactions.

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