299. *Quantitative Studies of the Reactivities of Mixed Carboxylic Anhydrides. Part III. The Hydrolysis and Some Acylation Reactions of a Series of Acetic Chloroaliphatic Acid Anhydrides.*

By A. R. Emery and V. Gold.

The mixed anhydrides of acetic acid with dichloroacetic, trichloroacetic, α- and β-chloropropionic, and γ-chlorobutyric acid have been prepared, and their hydrolysis velocities and the velocity of acylation of 2 : 4-dichloroaniline in acetone–water, as well as the product ratios for acylation of aromatic amines in different solvents, have been determined. The structural factors governing the reactions are discussed on the basis of the mechanisms proposed in the preceding papers. For acylation in benzene solution the activating inductive effect of chlorine substitution is opposed by a steric factor.

In the preceding two papers a method of investigation into the nature and reaction mechanisms of mixed acid anhydrides was outlined, acetic chloroacetic anhydride being chosen as first example. The present paper deals with an extension of this work to other mixed anhydrides in which one of the parent acids is acetic acid and the other a carboxylic acid derived by substitution of one or more chlorine atoms in acetic, propionic, or *n*-butyric acid; some of the anhydrides are now reported for the first time. In this way a limited but systematic survey of the consequences of structural changes was carried out. The choice of the particular series of compounds investigated permitted their preparation by the keten method, and the employment of analytical methods which involved only minor modifications of those developed for acetic chloroacetic anhydride.

Experimental.

Most of the procedure and analytical methods for kinetic and product experiments are described in the preceding two papers.

Mixed anhydrides were prepared by the action of keten on the chloro-aliphatic acid in benzene solution and suspension, followed by vacuum-distillation at as low a temperature as practicable. Every specimen

Table I.*

Summary of results.

All data are for 25°. Results for k_1 and k_2 are for acetone–water (80 : 20 w/w) as solvent; for k_2 the amine used was 2 : 4-dichloroaniline.

Anhydride of acetic acid with	Chloroacylation ratio with aniline in			k_1/k_2.	$k_1 \times 10^6$.	$k_2 \times 10^5$ (overall).	$k_2 \times 10^5$ for chloroacylation portion.	$k_2 \times 10^5$ for acetylation portion.	Dissociation constant of chloroacid $\times 10^5$.†
	benzene.	acetone.	acetone–water (80 : 20 w/w).						
Chloroacetic acid	6·1	1·6	0·69	0·78	576	74	21	53	155
Dichloroacetic acid	2·25	0·29	0·20	1·36	30,000	2,200	200	2,000	5,140
Trichloroacetic acid	0·08	0·07	—	—	Too rapid	—	—	—	120,000
α-Chloropropionic acid	0·94	0·45	0·27	0·32	205	65	8	57	147
β-Chloropropionic acid	0·29	0·25	0·20	0·16	13	7·9	0·8	7·1	8·6
γ-Chlorobutyric acid	0·36	0·37	0·41	—	6·2	—	—	—	3
Acetic acid	1	1	1	0·18	5·9	3·3	1·65	1·65	1·8

* Symbols are defined in the preceding paper.
† Since thermodynamic dissociation constants have not been measured in all cases, classical dissociation constants are quoted throughout.

5 A

used was analysed for (i) chlorine content, (ii) the amount of acid produced on complete hydrolysis of a weighed sample, (iii) the amount of acid produced after reaction with excess of dry aniline in the cold (see *J.*, 1950, 1443), and usually all analyses were within 1% of the theoretical values. The purity was also checked by (*a*) constancy of refractive index during distillation (within ± 0.0005), and (*b*) strict first-order character of all hydrolysis velocities. In all reaction-velocity measurements it was verified that the arresting solution employed (aniline in either the solvent used in the hydrolysis or in acetone) was satisfactory. For determination of reaction products it was verified that the chloroacyl derivative was stable under the conditions of the extractions.

Most of the results are summarised in Table I; some additional data are given below under the appropriate headings for each anhydride.

(i) *Acetic dichloroacetic anhydride* (b. p. 34—37°/$\sim$0.01 mm., $n_D^{17.5}$ 1.4498). The sample did not crystallise on cooling to $-80°$. See Tables II and III.

TABLE II.

Product composition for the acylation of two primary aromatic amines with acetic dichloroacetic anhydride in different solvents. $[MA]_0 \sim 0.05$M.† $[Amine]_0 \sim 1$M.

| | | | Chloroacylation ratio with | |
Experiment.	Solvent.	Temp.	aniline.	2 : 4-dichloroaniline.
1 (*a*), (*b*)	Benzene	25°	2.25	2.35
2	Benzene–acetone (80 : 20 w/w)	18	1.45	—
3	Benzene–acetone (50 : 50 w/w)	18	0.67	—
4	Acetone	18	0.29	—
5 (*a*), (*b*)	Acetone–water (80 : 20 w/w)	25	0.20	0.12 *
6	Acetone–water (50 : 50 w/w)	18	0.21	—

* In this experiment 73.6% of the total reaction is hydrolysis, giving $k_1/k_2 = 1.36$ moles l.$^{-1}$.
† MA = mixed anhydride.

TABLE III.

Velocity of hydrolysis of acetic dichloroacetic anhydride in acetone–water (80 : 20 w/w).
$[MA]_0 \sim 0.1$M.

Temp.	$k_1 \times 10^3$ (secs.$^{-1}$).	E.
0.3°	6.8	
25.1	30	9.8 kcals.

(ii) *Acetic trichloroacetic anhydride* (b. p. 30—34°/$\sim$0.05 mm., f. p. $-5°$ approx.). Reaction with aniline in acetone–water (80 : 20 w/w) led to 13% hydrolysis and 87% acylation; acylation is 100% in dry solvents. Hydrolysis is too rapid for measurement in 80% acetone–water. Rate of hydrolysis in undried AnalaR acetone (containing 0.5—1% of water) at 25°, $k_1 = 4.2 \times 10^{-4}$ sec.$^{-1}$; after addition of 1.83% of water (w/w), $k_1 = 3.2 \times 10^{-3}$ sec.$^{-1}$

(iii) *Acetic α-chloropropionic anhydride* (b. p. 35—36°/$\sim$0.005 mm., n_D^{17} 1.4295). See Table IV.

TABLE IV.

Competitive acylation–hydrolysis experiments with acetic α-chloropropionic anhydride and 2 : 4-dichloroaniline in acetone–water (80 : 20 w/w). Temp., 25.1°. $[MA]_0 \sim 0.06$M.

$[Amine]_0$.	Hydrolysis, %.	k_1/k_2.	$k_2 \times 10^4$.	Chloroacylation ratio.
0.125	72.5	0.31	6.6	—
0.250	60.1	0.35	5.8	—
0.533	36.1	0.29	7.1	0.15

(iv) *Acetic β-chloropropionic anhydride* (b. p. 41—43°/$\sim$0.01 mm., n_D^{16} 1.4392). The influence of acetate and β-chloropropionate ions on the various reactions is complicated through side reactions. Chloroacylation ratio with 2 : 4-dichloroaniline in acetone–water (80 : 20 w/w) = 0.12.

(v) *Acetic γ-chlorobutyric anhydride* (b. p. 51—54°/$\sim$0.005 mm., $n_D^{15.5}$ 1.4421).
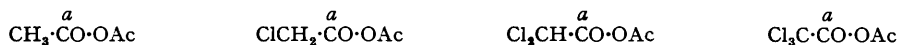
DISCUSSION.

(*a*) *The Chloroacylation Ratios in Benzene.*—In our discussion of the reaction between an aromatic amine and acetic chloroacetic anhydride in benzene solution (*J.*, 1950, 1443) it was argued that the predominant reaction in the attack of molecular anhydride on excess of amine would be the one introducing the acyl group containing the carbonyl-carbon atom which was poorer in electrons, *e.g.*, in the case of acetic chloroacetic anhydride, chloroacetylation would take place to a larger extent than acetylation. Hence, if a series of mixed acetic anhydrides R·CO·O·CO·CH$_3$ were investigated in which the electron attraction of the group R was altered systematically without changing any other structural factors, one should obtain a whole gamut of chloroacylation ratios according to the sequence of electronic-attraction powers.

The results for the mixed anhydrides of acetic acid with the three chloroacetic acids show that a theory which assumes such a naïve model to be applicable to these compounds is too simple, and its failure seems to be due chiefly to the neglect of a steric factor. Alternatively, it would be possible to explain the experimental sequence of chloroacylation ratios by postulating the occurrence of an ionisation mechanism in benzene, but it would be difficult to uphold such a contention on other grounds.

It is well known that in the bimolecular nucleophilic replacement reactions of the series of alkyl halides

$$CH_3 \cdot CH_2 \cdot X \qquad MeCH_2 \cdot CH_2 \cdot X \qquad Me_2CH \cdot CH_2 \cdot X \qquad Me_3C \cdot CH_2 \cdot X$$
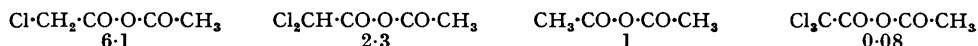
the reaction velocity decreases throughout the series. This decrease has been attributed to the combined operation of an electronic and a steric effect, the latter being of more decisive importance for the later members of the series (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 620; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173; cf. A. G. Evans, *Trans. Faraday Soc.*, 1946, **42**, 719). In the case of our series

$$\overset{a}{CH_3} \cdot CO \cdot OAc \qquad \overset{a}{ClCH_2} \cdot CO \cdot OAc \qquad \overset{a}{Cl_2CH} \cdot CO \cdot OAc \qquad \overset{a}{Cl_3C} \cdot CO \cdot OAc$$

the steric effect of successive chlorine substitutions on a bimolecular nucleophilic replacement reaction at a would be expected to exert a retarding influence analogous to the effect of methyl groups in the above series of β-methylated ethyl halides, the two structures being very similar. On the other hand, the electronic effect will be in the opposite direction. Thus, for the β-methylated ethyl halides steric hindrance and electron repulsion of methyl groups towards the seat of substitution tend to reinforce each other in reducing the reaction rate; however, in the chloroacetyl acetates the electron withdrawal by the chlorine atoms favours substitution, whereas the steric hindrance effect will tend to retard it. By analogy with the results of Dostrovsky, Hughes, and Ingold (*loc. cit.*) we expect the electronic effect to be most important near the beginning of the series and the steric effect most important for the highly substituted members. As a consequence the highest reactivity for nucleophilic substitution at a may be found in a member somewhere along the series and not necessarily at one of its ends. The case of the chloroacetyl acetates is, however, different from that of the β-methylated ethyl halides, in that the latter compounds cannot undergo any alternative substitution reaction at a carbon atom other than that at which the replacement reaction is sterically hindered, whereas the mixed anhydrides have the alternative centre of substitution b:

$$\overset{a}{Cl_3C} \cdot CO \cdot O \cdot \overset{b}{CO} \cdot CH_3$$
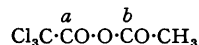
(*i.e.*, replacement of the trichloroacetate group in acetyl trichloroacetate instead of the replacement of the acetate group in trichloroacetyl acetate), and in the competition of the two halves of the molecule for the nucleophilic reagent steric hindrance will favour position b relative to a. The combined operation of the electronic and a steric influence in opposition to each other will therefore explain the observed sequence of chloroacylation ratios:
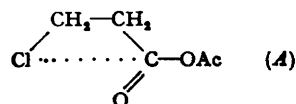
$$\begin{array}{cccc} Cl \cdot CH_2 \cdot CO \cdot O \cdot CO \cdot CH_3 & Cl_2CH \cdot CO \cdot O \cdot CO \cdot CH_3 & CH_3 \cdot CO \cdot O \cdot CO \cdot CH_3 & Cl_3C \cdot CO \cdot O \cdot CO \cdot CH_3 \\ 6 \cdot 1 & 2 \cdot 3 & 1 & 0 \cdot 08 \end{array}$$

In comparing various acetic chloro-aliphatic anhydrides by means of the chloroacylation ratios in benzene it must be appreciated that the " reference half " of the molecule (*i.e.*, the acetyl group) is not really constant throughout the series, since the electronic effect in the other half will be transmitted to it, though somewhat weakened.

The chloroacylation ratio of acetic α-chloropropionic anhydride is readily intelligible on this basis. Steric hindrance by the two groups, methyl and chlorine, may be of the same order of magnitude as that of the two chlorine atoms in acetic dichloroacetic anhydride, but the electronic effect of the methyl group tends to hinder substitution in opposition to the effect of the chlorine atom. The ratio is therefore appreciably lower than for acetic dichloroacetic anhydride.

On the other hand, the cases of acetic β-chloropropionic anhydride and acetic γ-chlorobutyric anhydride call for special comment. In both these anhydrides the chlorine substitution might be thought to be sufficiently far removed from the centre of the replacement reaction not to cause any compressional increment in the energy of activation of the reaction, so that the chloroacylation ratios should follow the sequence dictated by the magnitude of the positive charge on the carbonyl-carbon atom of the chloroacyl group; an indication of this sequence

should be given by the acid dissociation constant of the parent chloro-aliphatic acid. However, on this basis the chloroacylation ratios are in the wrong order, the discrepancy being experimentally significant. It is of particular importance that both ratios are less than unity, a fact which is unintelligible if there is no steric hindrance. It is suggested that the lowered reactivity of the chloroacyl group is due to the internal screening of the reaction centre through electrostatic interaction between the chlorine atom and the positive end of the carbonyl group dipole.

$$ \text{Cl} \cdots\cdots\cdots \overset{\displaystyle \overset{CH_2-CH_2}{\diagup \quad \diagdown}}{\underset{\displaystyle \underset{O}{\diagup\diagup}}{C}}-OAc \quad (A) $$

It may well be that the mixed anhydrides for which this effect makes the most significant contribution to the free energy of activation of the reaction are the acetic β-chloro-aliphatic anhydrides, since the " locked " configuration (*A*) will involve a greater loss of entropy in the case of longer chains. It is impossible to specify whether the retardation caused is only due to reduction of the effective positive charge on the carbon atom through induction across space (the old " direct " or " field effect "), or whether it should be regarded as brought about by the blocking of the direction of approach of the nucleophilic reagent by the chlorine atom. Any similar interaction between the chlorine atom and the carbonyl-carbon atom of the more remote acetyl group will presumably be much smaller, but it is not possible to say how important this is. Neither can we assess whether a certain portion of the " steric hindrance " in acetic α-chloro-aliphatic anhydrides should be regarded as a field effect acting in addition to the compression-energy effect discussed by Dostrovsky, Hughes, and Ingold (*loc. cit.*).

(b) *Chloroacylation Ratios in Acetone–Water.*—As was mentioned in Part I, there is a strong dependence of the chloroacylation ratio on the nature of the solvent and we have considered two interpretations of this effect. One of these which assumes a change of reaction mechanism is, however, rendered improbable by the kinetic evidence of Part II. The second explanation, which follows, is based on steric solvent effects which are thought to arise in a similar way to the steric factor which appears in the structural influence on chloroacylation ratios in benzene solution and which was discussed in the preceding section.

We envisage the geometry of the transition states for the two acylation reactions of aniline as follows :

$$ \text{Cl·CH}_2\text{·CO·O} \cdots \overset{\displaystyle \overset{CH_3}{|}}{\underset{\displaystyle \underset{O}{|}}{C}} \cdots \overset{\diagup H}{\underset{\diagdown C_6H_5}{N-H}} \qquad\qquad \text{CH}_3\text{·CO·O} \cdots \overset{\displaystyle \overset{CH_2Cl}{|}}{\underset{\displaystyle \underset{O}{|}}{C}} \cdots \overset{\diagup H}{\underset{\diagdown C_6H_5}{N-H}} $$

The two transition states are very similar and changes in their electrostatic solvation—which will be important to the stability of both structures—are unlikely to bring about a reversal of their relative stabilities. A change in solvent, insofar as its effect on the transition state is that of a solvating dielectric, should therefore make *both* transition states either more or less stable, although probably not to the same extent. Thus it will modify the value of the chloroacylation ratio but it is unlikely to change it from >1 to <1.

The transition state for chloroacetylation involves the possibility of steric repulsion (or interpenetration) between the chlorine atom and atoms in the amine molecule and acetate group. This repulsion would be greater than any analogous effect in the transition state for acetylation where the smaller hydrogen atoms of the methyl group would be involved. Taking account of the relevant distances of the atoms concerned, it seems probable that there will not be much steric strain in either transition state, and it is only when several large atoms are attached to the carbon atoms adjacent to the seat of substitution that the effect will assume any great importance, as discussed above.

However, it is now suggested that steric hindrance may also make itself felt if solute–solvent attraction increases the size of the amine molecule. Such interaction would presumably be unimportant for solutions in benzene. In the presence of water, on the other hand, we may get solvation of the amino-group through hydrogen-bonding. This seems quite plausible when we consider the enhanced solubility, in water, of an organic molecule after the introduction of an amino-group. The amine is also likely to form a hydrogen-bonded complex with acetone, since intramolecular hydrogen-bonding between amino- and carbonyl groups is well established.

With a fair excess of acetone most of the amine may, in fact, be associated with acetone. If solvent molecules become attached to the amine in this manner, we may now find that the transition state is sterically strained, *i.e.*, that there is interpenetration of the solvated-amine part and the substituents on the α-carbon atom of the anhydride portion :

$$CH_3.CO.O \cdots C \cdots N \quad (CH_2Cl \ H \ H \ Solvent \ C_6H_5 \ O)$$
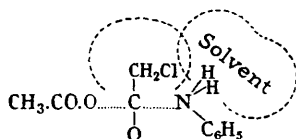
The solvent attachment would, therefore, favour reaction at the less heavily substituted half of the anhydride. This effect may be accentuated by the higher degree of solvent orientation around the more polar, substituted half of the anhydride molecule. The discrimination may become even more marked if solvation of the amine causes a higher electron density at the nitrogen atom, as would be expected if the solvation is due to hydrogen-bonding from one of the hydrogen atoms of the amino-group. In that case the acylation of the solvated amine will be more rapid than that of the unsolvated molecule, provided that steric hindrance does not nullify this increased reactivity.

It follows from such an explanation that the operation of this solvent effect, which favours acetylation at the expense of chloroacylation, would depend on the power of the solvent to attach itself and on the geometry of the complex formed, and no direct significance would attach to the apparent functional dependence of the chloroacylation ratio on the dielectric constants of the particular solvent mixtures employed. In the absence of any tangible evidence of the structure of these complexes we shall not attempt to elaborate this hypothesis by further speculation. If this, or a similar, interpretation is correct, it would mean that the reversal of the chloroacylation ratio is merely due to a minor specific medium effect which assumes a decisive rôle in the case of its differentiating operation towards two reactions which are very nearly equally important.

Experimental results similar to those found for acetic chloroacetic anhydride have been observed for other acetic halogeno-aliphatic acid anhydrides. Again the chloroacylation ratio appears to decrease with increasing polarity of the solvent, but the effect is absent or not marked for those anhydrides which give a low chloroacylation ratio even in benzene. However, this conclusion must be accepted with some reserve since small chloroacylation ratios are liable to larger percentage errors.

(c) *Velocities of Acylation and Hydrolysis.*—It was pointed out in the preceding two papers that both these velocities are complicated, since they express the sum of different reactions. They do not, therefore, correspond to comparable processes in all cases. However, one would still expect an orderly sequence in these velocities, following the electronic effect of the varying group, provided that the substances are sufficiently closely related structurally. Indeed, we find a parallelism between the rates of hydrolysis and the acid dissociation constants of the parent chloro-aliphatic acids.

We have interpreted the fall of the chloroacylation ratio along the series of acetic α-chloro-acetic anhydrides in benzene as due to the intervention of a steric factor. Nevertheless, our data show that the velocity of chloroacylation in acetone–water—which, on either of our interpretations of the solvent effect, has also been attributed to the same bimolecular mechanism—still rises throughout the series, which may appear to contradict the idea of steric hindrance. This apparent contradiction does not arise if the steric explanation of the low chloroacylation ratios in heavily substituted anhydrides is put, more correctly, in a somewhat modified form. When α-chlorine atoms are introduced into one half of the anhydride molecule there is electronic activation of both carbonyl positions. However, since the nearer potential reaction centre is sterically hindered by this same substitution, the activation is *more* noticeable at the more remote carbonyl position, in spite of the fact that the electronic effect is actually weaker there. This is illustrated by a comparison of the eighth and the ninth column of Table I. Both halves of the molecule are seen to be more reactive than in the unhindered anhydride but the increase in reactivity is greater in the unsubstituted half.

(d) *Values of the Ratio* k_1/k_2.—It may be noted that this ratio appears to increase fairly systematically with the reactivity of the anhydride (*i.e.*, its rate of hydrolysis or acylation), both for mixed and symmetrical anhydrides (Table I, and Part II, Table III). This observation

probably constitutes the strongest single item of evidence against a mechanism of acylation by acetic chloro-aliphatic anhydrides through intermediate acylium ions. In an ionic mechanism, the reactions of the mixed anhydrides studied by us would in every instance be the result of attack by the same species, *viz.*, $CH_3 \cdot CO^+$. The ratio of the reactivities of this species for amine and for water should then be independent of the nature of the other half of the molecule which, as anion, would take no direct part in the reactions. For ionic mechanisms of the reactions of these mixed anhydrides, k_1/k_2 should, therefore, be constant.

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