Kinetics and Mechanism of the Base-catalysed Hydrolysis of Some Substituted Phenyl Chloroformates

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A study of kinetic isotope effects and activation parameters indicates that, in the hydrolysis of phenyl chloroformate, acetate ion and pyridine act as nucleophilic catalysts. Both the spontaneous and pyridine catalysed hydrolyses of substituted phenyl chloroformates fit a Hammett plot. The effect of solvent polarity and added salt indicates that there is little charge separation in the transition state for hydrolysis. The mechanism of reaction is discussed.

THERE have been numerous investigations[1] of base-catalysed ester hydrolysis but the reactions of chloroformates, which have a carbonyl group more susceptible to attack than that of normal esters, have not been studied in such detail. The present paper reports a kinetic investigation of this reaction.

RESULTS AND DISCUSSION

Alkyl chloroformates undergo spontaneous hydrolysis in water[2] and there is a change of mechanism from S_N2 to S_N1 along the series methyl, ethyl, propyl, and isopropyl.[3] The evidence for this comes from a determination of the values of $\Delta H^‡$, $\Delta S^‡$, and ΔC_p, which show variations associated with a change of mechanism. For the hydrolysis of phenyl chloroformate all the evidence favours an S_N2 mechanism[4] but the rate-determining step may be formation of the tetrahedral intermediate[5] or loss of chloride ion. There is evidence[6] for such a change in the reaction of substituted anilines with ethyl chloroformate from a plot of $\Delta H^‡$ against $\Delta S^‡$ (which gives two, distinct, parallel lines) and from a Hammett plot using σ^- constants. Electron-withdrawing substituents give a line of slope 1·57 and electron-donating groups one with slope 5·56. In a previous study[7] of the hydrolysis of substituted phenyl chloroformates in aqueous acetone, electron-donating substituents were found not to fall on a linear Hammett plot using σ or σ^- constants, and this could be interpreted in terms of a change of mechanism. However, all the other evidence (entropy–enthalpy correlations, kinetic isotope effects, and solvents effects) is against a change of mechanism.

To study this matter further we determined the rate of spontaneous hydrolysis of substituted phenyl chloroformates in aqueous dioxan by monitoring the appearance of the substituted phenol spectroscopically.[8] The results obtained give a single, linear relationship between log k_{obs} and the Hammett σ constants, with substituents ranging from *p*-methoxy to *p*-nitro (Figure 1). The correlation coefficient *r* for this line is 0·991, and so there is no evidence for a change of mechanism. The fact that there is correlation with σ rather than σ^- constants indicates that there is little anionic character in the transition state, and the rate-determining step must be attack of water and not loss of phenolate ion. We shall return to this point later.

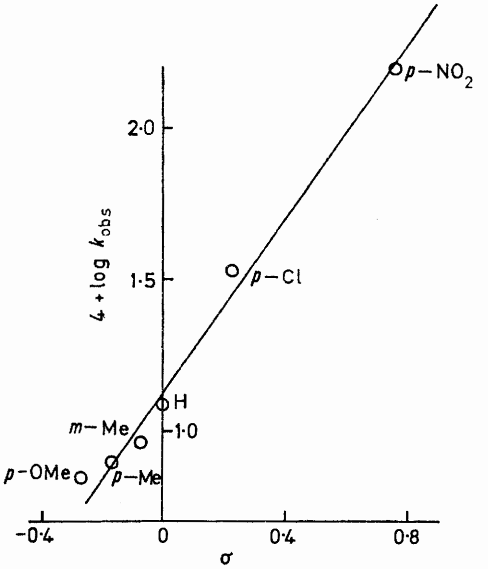

FIGURE 1 Hammett plot for the spontaneous hydrolysis of substituted phenyl chloroformates in water at 25°

For the hydrolysis of phenyl chloroformate a change of solvent from pure water to 10% aqueous dioxan has only a small effect on the rate of reaction (Table 1).

TABLE 1

Variation of k_{obs} with water content for the hydrolysis of phenyl chloroformate in aqueous dioxan at 25°

% Water (v/v)	10	20	30	40	50	60	70	80	90
$10^3k_{obs}/s^{-1}$	0·34	1·0	1·8	3·1	4·9	6·1	7·8	9·1	10·9

This suggests a transition state in which there is little charge separation, and may indicate simultaneous transfer of a proton from water to the carbonyl group as the chloride ion leaves, through a cyclic transition state (I). In the less aqueous solvents there is a linear correlation between log k_{obs} and the values of the solvent parameter

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[5] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.

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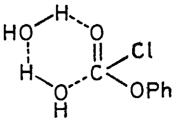
Y for aqueous dioxan[9] with m 0·193. This is substantially different from the values of m noted for a number of S_N1 reactions[10] and this, coupled with the nonlinearity over the complete solvent range, favours an S_N2 mechanism. The relationship between log k_{obs} and the values of E_T for aqueous dioxan[11] is nonlinear over the complete range.



(I)

By analogy with the reactions of other esters, chloroformate hydrolysis should be catalysed by general bases. The rates of hydrolysis of phenyl chloroformate in a number of acetate buffers containing 10% dioxan (added for solubility reasons) at constant ionic strength (0·1M) were determined (Table 2). The results may be understood in terms of a spontaneous reaction (k_0), catalysis by hydroxide ion (k_{OH^-}), and catalysis by acetate ion (k_{OAc^-}). Inspection of the figures in Table 2 show that, at constant acetate ion concentration, the rate is independent of the pH so that catalysis by hydroxide is not detectable in this pH region and may be ignored. The slope of a plot of k_{obs} against [OAc⁻] is k_{OAc^-} and the average value for six buffers is 0·23 l mol⁻¹ s⁻¹. The average value of this intercept (k_0) is $9{\cdot}0 \times 10^{-3}$ s⁻¹. This value does not agree exactly with the extrapolated value from Table 1, but this is due to the effect of a difference in ionic strength.

TABLE 2

Hydrolysis of phenyl chloroformate in various acetate buffers at 25°

$[OAc^-]$/M	0·05	0·06	0·07	0·08	0·09	0·10
pH	$10^2 k_{obs}/s^{-1}$					
4·31	2·10	2·31	2·59	2·85		3·30
4·62	2·28	2·53	2·74	3·04	3·31	3·54
5·03	2·31	2·59	2·72	2·99	3·20	3·45
5·17	2·29	2·56		2·96		3·44
5·31	2·37	2·63	2·81	2·95	3·29	3·43
5·86	2·24			2·86		3·30

$[PhOCOCl]_0 = 10^{-5}$M.

The above determinations were repeated for a single acetate buffer at 10·8 and 35·0° (Table 3) and this gave values for k_{OAc^-} of $5{\cdot}15 \times 10^{-2}$ and $5{\cdot}6 \times 10^{-1}$ l mol⁻¹ s⁻¹ at these two temperatures. An Arrhenius plot of these results is linear and gives $\Delta H^\ddagger$ as 16·1 kcal mol⁻¹ and $\Delta S^\ddagger$ as −4·9 cal mol⁻¹ K⁻¹ for the acetate-catalysed reaction. Values of k_{obs} for an acetate buffer in D_2O containing 10% dioxan are given in Table 4. For reaction in D_2O k_{OAc^-} is 0·20 l mol⁻¹ s⁻¹ and so the solvent isotope effect $k(H_2O)/k(D_2O)$ for acetate catalysis is 1·1. This indicates that the reaction involves nucleophilic rather than general base catalysis, and the proposed mechanism is that shown in Scheme 1. The small negative $\Delta S^\ddagger$ is consistent with this mechanism, as no water molecules are directly involved in formation of the transition state.[12]

TABLE 3

Hydrolysis of phenyl chloroformate in an acetate buffer (pH 5·17) at different temperatures

$[OAc^-]$/M	0·04	0·06	0·08	0·10
Temp./°C	$10^2 k_{obs}/s^{-1}$			
10·8	0·60	0·70	0·81	0·91
35·0	4·75	5·85	7·00	8·10

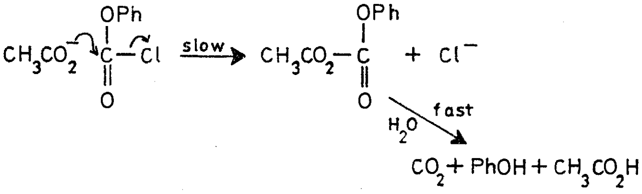
$[PhOCOCl]_0 =$ *ca.* 10^{-5}M.

TABLE 4

Hydrolysis of phenyl chloroformate in an acetate buffer in D_2O (pD 5·17) at 25°

$[OAc^-]$/M	0·05	0·06	0·08	0·10
$10^2 k_{obs}/s^{-1}$	1·47	1·77	2·10	2·50

$[PhOCOCl]_0 =$ *ca.* 10^{-5}M.



SCHEME 1

The ratio k_{OAc^-}/k_0 for this reaction is 21 which is similar to that observed by Gold *et al.*[13] for acetate-catalysed hydrolysis of phenyl acetates, where acetate is also acting as a nucleophilic catalyst, although both reactions are much slower. The value of $\Delta S^\ddagger$ is somewhat less negative than for phenyl acetate hydrolysis and, although there appears to be a large difference in the value of $\Delta S^\ddagger$ for the same species acting as a general base and a nucleophile in the same family of reactions,[14] it seems that the absolute value of $\Delta S^\ddagger$ is not diagnostic.

The work of Gold *et al.*[13,14] indicates that, in hydrolysis reactions, the more reactive the substrate the greater the tendency of acetate to act as a nucleophilic catalyst. This trend continues with the more reactive substrate, phenyl chloroformate. However, acetate is known to catalyse the hydrolysis of the equally reactive substrate, acetic anhydride[15] and must then act, necessarily, as a general base catalyst because nucleophilic attack merely regenerates the starting material. This suggests that general base and nucleophilic catalysis occur con-

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[12] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

[13] V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.* (*B*), 1968, 515.

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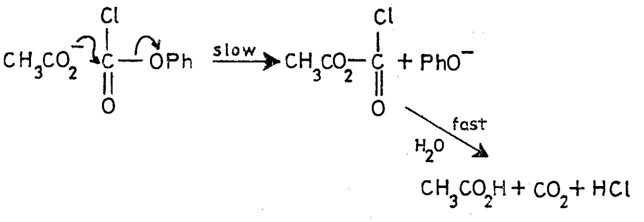
currently and, in our attempts at characterisation, we detect only the predominant pathway. This matter will be discussed in more detail in a later publication. The ratio $k_{\mathrm{OAc^-}}/k_0$ for acetic anhydride hydrolysis[16] is only 1·8, suggesting a different mechanism from that operative with phenyl chloroformate and the phenyl acetates. However, this figure must be interpreted with caution as spontaneous reactions may have different mechanisms: $k_0(\mathrm{H_2O})/k_0(\mathrm{D_2O})$ for acetic anhydride hydrolysis[16] is 2·9 while for ethyl chloroformate[17] the same ratio is only 1·95.

In Scheme 1 it was assumed that the group displaced by nucleophilic attack is the chloride ion, and that the resulting acetyl phenyl carbonate undergoes very rapid hydrolysis. It is possible, however, that phenolate ion is initially displaced to give acetyl chloroformate, which reacts with water in the second step (Scheme 2). However, this is unlikely for the following reasons. (1) As mentioned previously, substituent effects correlate with σ rather than σ⁻ and the latter would be required if phenolate were the leaving group. This seems to be a general effect for a number of related reactions.[18] (2) In the alcoholysis of chloroformates[19] and chlorothioformates[20] the products are carbonates and thiocarbonates, and hydrolysis should follow a similar course. (3) Ethyl hydrogen carbonate decomposes very rapidly in aqueous solution with the production of carbon dioxide and ethanol.[21] Thus Scheme 1, or some slight variation of it, gives a reaction scheme which is consistent with the available evidence.



$$CH_3CO_2^- + ClC(O)OPh \xrightarrow{\text{slow}} CH_3CO_2C(O)Cl + PhO^- ; \quad CH_3CO_2C(O)Cl \xrightarrow[H_2O]{\text{fast}} CH_3CO_2H + CO_2 + HCl$$

SCHEME 2

Efforts to examine hydrolysis in borate buffers were unsuccessful owing to precipitation of boric esters, an effect which has been noticed previously.[22]

The hydrolysis of esters is catalysed by heterocyclic bases[23] and we decided to examine the same reaction, with phenyl chloroformate as the substrate. In a pyridine buffer the reaction is too fast to follow so we used pyridine at low concentration in an acetate buffer, a technique which proved effective in a study of the pyridine-catalysed hydrolysis of acetic anhydride.[24] The pyridine concentration was changed by dilution of the reaction medium with acetate buffer. There is a linear relationship between k_{obs} and the concentration of free pyridine (Figure 2), and it was assumed that the reaction is not susceptible to general acid-catalysis by the pyridinium ion. From the slope of this curve k for pyridine catalysis is 770 l mol^{-1} s^{-1}. For reaction at 10·0 and 35·0° the values are 390 and 1025 l mol^{-1} s^{-1}. From an Arrhenius plot $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated to be 6·1 kcal mol^{-1} and 24·9 cal mol^{-1} K^{-1}. For reaction in D_2O k for pyridine catalysis is 480 l mol^{-1} s^{-1} giving a $k(\mathrm{H_2O})/k(\mathrm{D_2O})$ ratio of 1·6. It would be expected that pyridine acts as a nucleophilic catalyst as this was found to be the case with acetic anhydride,[24] but the value of $k(\mathrm{H_2O})/k(\mathrm{D_2O})$ is too high to be unambiguously diagnostic. However, most authors[25] consider that any value in the range 1—2 indicates nucleophilic catalysis. The very different values of $\Delta S^\ddagger$ suggest that the mechanism of pyridine catalysis is somewhat different from that of acetate catalysis. The slow step may be hydrolysis of the intermediate (II), formed by displacement of chloride by pyridine. This would be associated with large solvation changes, which is consistent with the observed entropy change and kinetic isotope effect.

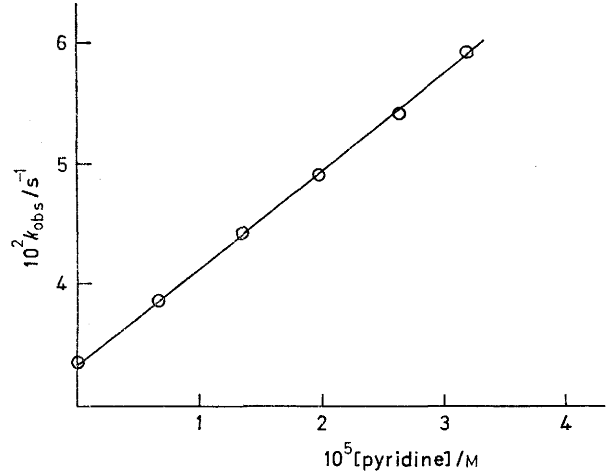
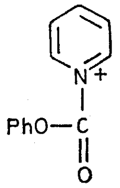


FIGURE 2 Variation of k_{obs} with pyridine concentration for the hydrolysis of phenyl chloroformate in an acetate buffer containing 10% dioxan at 25°



(II)

Pyridine catalysis for the hydrolysis of a number of

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[23] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.
[24] A. R. Butler and V. Gold, *J. Chem. Soc.*, 1961, 4362.
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substituted phenyl chloroformates was examined by the same experimental method. The results fit a Hammett plot (Figure 3), using σ values, to give ρ 0·47. The linear relationship with σ, rather than σ^-, again indicates that the leaving group in the rate-determining process is not the phenolate ion. The very low value of ρ further substantiates this view and indicates that there is little charge separation in the transition state. There is no evidence from the Hammett plot for a change in rate-determining step.

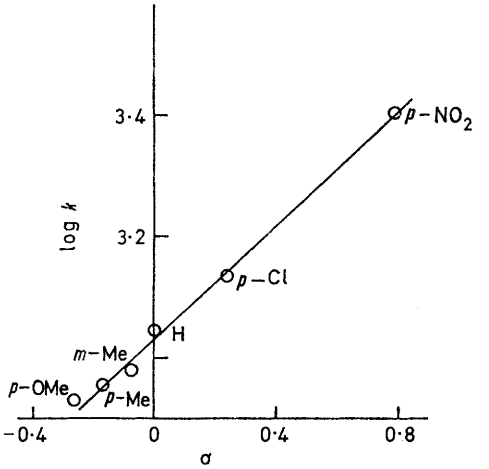

FIGURE 3 Hammett plot for the pyridine-catalysed hydrolysis of phenyl chloroformates in 90% aqueous dioxan at 25°

The small charge separation is also reflected in the small effect [26] of added sodium perchlorate on the rate of hydrolysis of phenyl chloroformate (Table 5). On the other hand, sodium azide has the effect of reducing the rate of reaction markedly. In 0·70M-sodium azide the rate of reaction is one tenth that in the absence of azide.

TABLE 5

Effect of sodium perchlorate on the hydrolysis of phenyl chloroformate in 90% aqueous dioxan at 25°

$[NaClO_4]$/M	0	0·03	0·13	0·25	0·50	0·70	1·00
$10^3k_{obs}/s^{-1}$	11·3	11·1	10·8	10·2	8·83	7·76	6·21

The most probable explanation is that azide ion, which is a good nucleophile, reacts to form an azidoformate, a fairly unreactive species,[27] and so the rate of release of phenolate ion is reduced. An authentic sample of phenyl azidoformate was found to hydrolyse very slowly.

EXPERIMENTAL

Materials.—All reagents used in the kinetic studies were AnalaR grade. Dioxan was refluxed over sodium wire under nitrogen until the metal surface was bright and then distilled. The substituted phenyl chloroformates were prepared by a literature method [28] and are all known compounds.[29]

Sodium azide (0·65 g) dissolved in the minimum quantity of 10% aqueous dioxan was added slowly to a stirred solution of freshly distilled phenyl chloroformate (1·36 g) in dioxan (25 ml). The mixture was stirred for 4 h and the solvents removed under vacuum. The residue was dissolved in ether, washed twice with cold water, and dried ($MgSO_4$). The ether was removed to leave a liquid, which was assumed to be phenyl azidoformate, $\nu_{max.}$ 2150 cm^{-1} (N_3). Further purification and identification was not attempted because of the danger of explosion.

Kinetic Method.—One drop of a solution of the chloroformate was added to the buffer contained in a cuvette in the thermostatted cell holder of a Unicam SP 500 spectrophotometer. The change of absorbance with time was recorded and the first-order plots obtained were linear over three half-lives. Rate constants were calculated by the method of Swinbourne.[30] The wavelength used were as follows: *p*-MeO (293), *m*-Me (275), *p*-Me (282), H (274), *p*-Cl (274), *p*-NO_2 (318), and *m*-NO_2 (318 nm). The ionic strength was kept constant by the addition of KCl. Spectra were recorded on a Unicam SP 800 spectrophotometer. A Beckman ' Research ' pH meter with calomel electrode and general purpose glass electrode was used for the measurement of pH.

One of us (I. H. R.) thanks the S.R.C. for a studentship.

[4/802 *Received, 22nd April,* 1974]

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