Kinetics and Mechanism of the Acetate Catalysed Hydrolysis of 4-Methoxyphenyl Chloroformate and 4-Methoxyphenyl Fluoroformate in Aqueous Dioxan. Evidence for Rate-determining Attack of Acetate Ions on an Intermediate Mixed Anhydride

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Esters of fluoroformic acid hydrolyse more rapidly than the corresponding chloroformate esters, suggesting that carbon–halogen bond breaking is not greatly advanced in the rate-determining step. The rate of reaction of 4-methoxyphenyl fluoroformate with aqueous dioxan is markedly decreased in the presence of acetate ions whereas the rate of reaction of 4-methoxyphenyl chloroformate is increased. The rate curves for the latter reaction are sigmoid in shape. The results are interpreted in terms of the formation of an intermediate mixed anhydride for both reactions, which then undergoes nucleophilic attack by acetate ions to yield acetic anhydride and the phenol. This step is rate determining in the case of the fluoroformate.

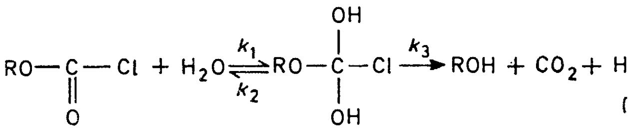
THERE is considerable evidence [1-3] indicating that esters of chloroformic acid hydrolyse bimolecularly and that the mechanism involves the rate-determining formation of tetrahedral intermediates, at least in some cases [mechanism (1)]. This conclusion is now supported by our observation that fluoroformate esters hydrolyse more rapidly than the corresponding chlorides, so that carbon–halogen bond breaking cannot be far advanced in the rate-determining process. Table 1 lists data for some reactions in 70% aqueous acetone, a solvent we have used in much of our previous work.[4,5]

TABLE 1

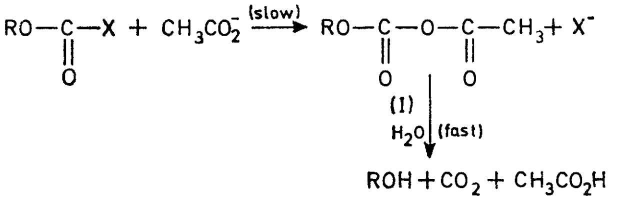
First-order rate constants for the hydrolysis of chloroformate and fluoroformate esters (ROCOX) in 70% aqueous acetone and 60% aqueous dioxan

T/°C	Solvent	R	10^4k_{Cl}/s^{-1}	10^4k_F/s^{-1}	k_F/k_{Cl}
1.8	60% Aqueous dioxan	$MeOC_6H_4$	3.22 ±0.03	104 ±1	32.2
30.1	70% Aqueous acetone	Me	0.711 ±0.004	5.09 ±0.03	7.16
		Et	0.303 ±0.001	1.65 ±0.02	5.46
		Pr^n	0.287 ±0.001	1.42 ±0.01	4.95
		Pr^i	0.381 ±0.002	0.414 ±0.003	1.09

Little work has been carried out on the effects of bases on the hydrolysis of halogenoformate esters, but a recent study [6] of the acetate catalysed hydrolysis of phenyl chloroformate has been interpreted in terms of a two-step mechanism in which slow formation of the mixed anhydride (I: R = Ph) is followed by rapid hydrolysis of this intermediate [mechanism (2)].



$$\mathrm{RO{-}}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}Cl} + \mathrm{H_2O} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RO{-}}\underset{\mathrm{OH}}{\overset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}Cl} \xrightarrow{k_3} \mathrm{ROH} + \mathrm{CO_2} + \mathrm{HCl} \qquad (1)$$



$$\mathrm{RO{-}}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}X} + \mathrm{CH_3CO_2^-} \xrightarrow{\text{(slow)}} \underbrace{\mathrm{RO{-}}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}O{-}}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}CH_3}}_{\text{(I)}} + \mathrm{X^-} \qquad (2)$$
$$\text{(I)} \xrightarrow[\mathrm{H_2O}]{\text{(fast)}} \mathrm{ROH} + \mathrm{CO_2} + \mathrm{CH_3CO_2H}$$

In this work, the substituent effects on the rate of solvolysis of aryl chloroformates were found to correlate with σ and not σ^-, so that nucleophilic displacement of phenoxide rather than chloride ion was discounted. The mechanism of nucleophilic attack on phenyl chloroformate was described as S_N2, a classification that implies direct displacement of the leaving group, whereas the fluoride : chloride ratio, $k_F > k_{Cl}$, supports a scheme similar to mechanism (1). Also, the proposed mechanism for the acetate catalysed reaction [mechanism (2)] requires that phenyl chloroformate should be much less reactive than the mixed anhydride (I; R = Ph) and we consider this assumption to be open to question.

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[1] E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 1962, 1076.

[2] A. Kivinen, *Acta Chem. Scand.*, 1965, **19**, 845.

[3] A. Queen, *Canad. J. Chem.*, 1967, **45**, 1619.

[4] D. M. McKinnin and A. Queen, *Canad. J. Chem.*, 1972, **50**, 1401.

[5] A. Queen and T. C. Matts, *Tetrahedron Letters*, 1975, 1503.

[6] A. R. Butler, I. H. Robertson, and R. Bacaloglu, *J.C.S. Perkin II*, 1974, 1733.

In this respect, it is noteworthy that the use of borate buffers led to the precipitation of boric esters,[6] which implies that these compounds did not react more rapidly than the chloroformates.

For these reasons, it seemed likely that a comparison of the effects of acetate ions on the rates of hydrolysis of chloroformate and fluoroformate esters might provide useful information about the reaction mechanisms. Since the traditional S_N2 mechanism envisages concerted nucleophilic attack by acetate and carbon–halogen bond cleavage, this mechanism would be expected to exhibit a marked leaving group effect, $k_F \ll k_{Cl}$. Bimolecular reaction through a tetrahedral intermediate would, however, be characterized by $k_F > k_{Cl}$.[7] Moreover, if the rate-determining step were not acetate attack on the halogenoformate but attack on an intermediate mixed anhydride, k_F and k_{Cl} would be the same. Various combinations of these limiting situations would also be possible, including cases where the rate is greater than first order in acetate. Unfortunately, phenyl fluoroformate is too reactive for the proposed studies and we have, therefore, used the 4-methoxyphenyl halogenoformates instead. Since spectrophotometry was the most convenient method of following the reactions, by monitoring the appearance of 4-methoxyphenol at 293 nm, aqueous acetone could not be used as the solvent. Rather inconsistent results were obtained in water, possibly due to incomplete dissolution, and 60% aqueous dioxan was finally chosen as the solvent.

RESULTS

Leaving group effects for the solvolyses of halogenoformate esters are shown in Table 1 and in each case the ratio $k_F/k_{Cl} > 1$.

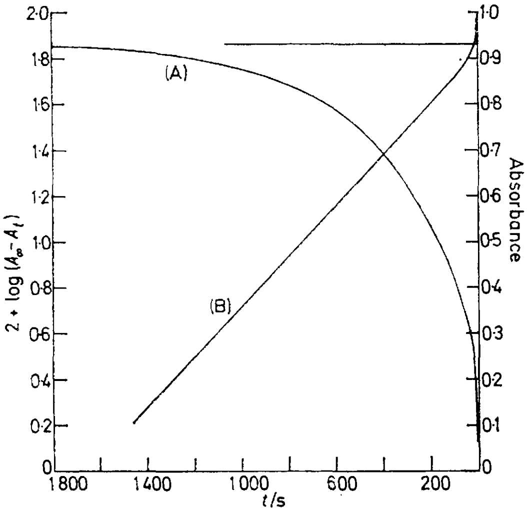

FIGURE 1 Reaction of 4-methoxyphenyl fluoroformate with 0.101 9M-sodium acetate in 60% aqueous dioxan at 1.8 °C: variation of (A) absorbance and (B) $\log(A_\infty - A_t)$ with time

The absorbance–time profiles for the reaction of 4-methoxyphenyl fluoroformate with buffered solutions of sodium acetate in 60% aqueous dioxan showed, in each case, two distinct portions. An initial steep part covering 40—60% of the total reaction, depending on the acetate concentration, followed by a slower exponential curve up to complete reaction. Figure 1 shows a typical reaction curve as well as a superimposed plot of log $(A_t - A_\infty)$. Although we have not yet measured the initial fast rates, they appear to be more rapid than the rate of neutral hydrolysis of the fluoroformate. The integrated first-order rate constants for the final slow reactions are given in Table 2.

TABLE 2

Hydrolysis of 4-methoxyphenyl fluoroformate in an acetate buffer * in 60% aqueous dioxan at 1.8 °C

$[CH_3CO_2^-]/M$	0.101 9	0.081 52	0.061 14	0.040 76	0.020 38
$10^4k_{obs}/s^{-1}$	25.2 ±0.2	20.0 ±0.2	14.9 ±0.2	9.81 ±0.21	5.32 ±0.06

* $[CH_3CO_2^-]/[CH_3CO_2H] = 0.857$; $[CH_3OC_6H_4OCOF] = 10^{-5}M$; $10^3k_M^{OAc} = 24.5 \pm 0.01$ l mol^{-1} s^{-1}; $10^6k_M = 6.1 \pm 10.5$ s^{-1}.

The plots of absorbance against time for the corresponding reactions of 4-methoxyphenyl chloroformate are distinctly sigmoid. A typical curve is shown in Figure 2.

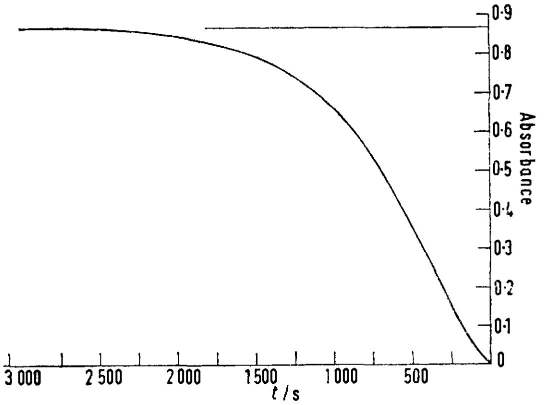

FIGURE 2 Reaction of 4-methoxyphenyl chloroformate with 0.1019M-sodium acetate in 60% aqueous dioxan at 1.8 °C

Table 3 lists values of the integrated first-order rate constants at various times during the courses of some of these reactions. It can be seen that the values of k increase, approaching but never quite reaching the corresponding values given in Table 2.

DISCUSSION

The large leaving group effect, $k_F/k_{Cl} = 32.2$, for the solvolyses of 4-methoxyphenyl halogenoformates in 60% aqueous dioxan (Table 1) favours mechanism (1) and argues against direct S_N2 displacement.

The effect of acetate ions in buffered solution on the rate of hydrolysis of 4-methoxyphenyl fluoroformate provides direct evidence that mechanism (2) cannot apply to our system. The initial steep parts of the reaction curves are interpreted as being due to a combination of hydrolysis of the fluoroformate and its rapid conversion to the mixed anhydride (I; R = $4\text{-}CH_3OC_6H_4$). The final slow reactions have lower rates than the neutral hydrolysis by a factor of 5—20, depending on the acetate concentration. We propose that this is due to attack of acetate ions on the mixed

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[7] R. E. Parker, 'Advances in Fluorine Chemistry,' Butterworths, London, 1963, vol. 3, p. 63.

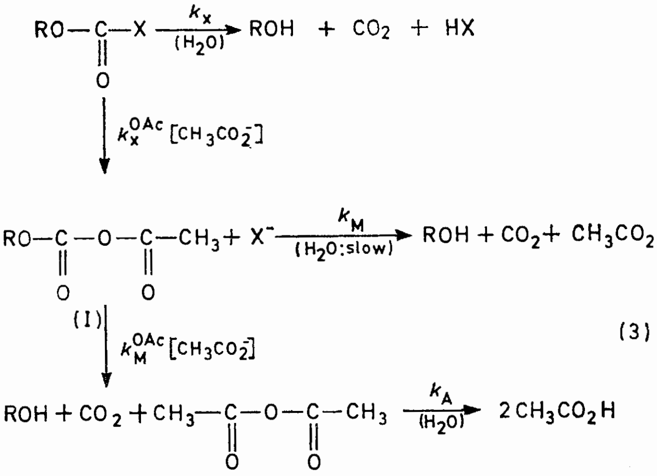
TABLE 3

Changes in the first-order integrated rate constants for the hydrolysis of 4-methoxyphenyl chloroformate in an acetate buffer * in 60% aqueous dioxan at 1.8 °C

$[CH_3CO_2^-]$/M									
0.101 9	t/s	200	400	600	800	1 000	1 200	1 400	
	10^4k/s^{-1}	19.2	19.4	20.5	21.0	21.3	21.1	21.5	
	% Reaction	80						97	
0.081 52	t/s	200	400	600	800	1 000	1 200	1 400	1 600
	10^4k/s^{-1}	14.5	15.0	15.3	15.6	16.0	16.0	16.2	16.4
	% Reaction	74							92
0.061 14	t/s	200	600	1 000	1 400	1 800	2 200		
	10^4k/s^{-1}	12.9	13.1	13.6	13.7	14.0	14.6		
	% Reaction	76					98		
0.040 76	t/s	200	600	1 000	1 400	1 800	2 200	2 600	
	10^4k/s^{-1}	8.76	8.78	9.06	9.10	9.33	9.29	9.58	
	% Reaction	78						96	

* $[CH_3CO_2^-]/[CH_3CO_2H] = 0.857$; $[CH_3OC_6H_5OCOCl] = 10^{-5}$M

anhydride. Since *ca.* 40—60% of this intermediate is produced in competition with the products of direct hydrolysis of the fluoroformate, nucleophilic attack by water and by acetate ions must proceed at similar rates under our experimental conditions. The products of nucleophilic attack by acetate ions on the mixed anhydride are probably 4-methoxyphenol, carbon dioxide, and acetic anhydride. The subsequent hydrolysis of this latter intermediate would not be observed in our experiments. The proposed reaction scheme for the acetate catalysed



hydrolysis of halogenoformate esters is shown as mechanism (3). In the case of 4-methoxyphenyl fluoroformate, the following conditions apply: $k_x \simeq k_x^{OAc}(CH_3CO_2^-) \gg k_M^{OAc}[CH_3CO_2^-] \gg k_M$. The mixed anhydride is thus formed in a rapid step and then reacts slowly with water and with acetate ions. The individual reactions in mechanism (3) are probably two-step processes through tetrahedral intermediates.[8]

The results indicate that the slow first-order process that takes place during the last part of the reaction can be referred to steps k_M^{OAc} and k_M. As required by this proposal, plots of k_{obs} against acetate concentration are linear and the derived rate constants at 1.8 °C are $k_M^{OAc} = 2.45 \pm 0.001 \times 10^{-2}$ l mol^{-1} s^{-1}, $k_M = 6.1 \pm 10.5 \times 10^{-6}$ s^{-1}. This latter figure is similar to the value of $k = 1.2 \times 10^{-5}$ s^{-1} for the spontaneous hydrolysis of acetic anhydride in 60% aqueous dioxan [9,10] at 0 °C. The ratio $k_M^{OAc}/k_M = 4\,000$, which is large compared to previously reported values for the acetate catalysed hydrolyses of aryl acetates,[11,12] where the values vary between 5 and 90. It is also very much larger than the value of 21 reported for the acetate catalysed hydrolysis of phenyl chloroformate, which is disturbing. However, acid fluorides are known to be much more sensitive to nucleophilic attack than acid chlorides,[13] so that mixed anhydrides may be similarly more sensitive to nucleophilic attack than symmetrical anhydrides. Moreover, we shall show later in this paper that the results for the reactions of chloroformates should probably not be correlated with the steps k_M^{OAc} and k_M (alone), as we have done for the case of 4-methoxyphenyl fluoroformate. Rather, all the steps of mechanism (3) must be taken into account, even though first-order rates and a linear dependence of rate on acetate concentration are observed. Hence, the slope of the plot k_{obs} against [acetate] gives $(k_x^{OAc} + k_M^{OAc})$ and the intercept $(k_x + k_M)$. Moreover, it is emphasized that each of these rate constants are probably composite terms referring to multistep processes similar to mechanism (1). The values of the various rate constants corresponding to k_1—k_3 are likely to have different sensitivities to substituent effects and to different reaction types. If this is so, large differences in the ratio k^{OAc}/k^0 are not surprising and are not, in themselves, necessarily diagnostic of a particular type of catalysis.

The results obtained for the acetate catalysed reaction of 4-methoxyphenyl chloroformate also supply evidence supporting mechanism (3). First of all, the changes of absorbance with time are distinctly sigmoid in shape (Figure 2). This corresponds to a situation where an intermediate, presumably (I; R = 4-$CH_3OC_6H_4$), is formed at a rate not greatly different to that at which it subsequently reacts. Moreover, the integrated rate constants increase throughout the reaction and if the

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

[9] C. A. Bunton, N. A. Fuller, S. G. Perry, and V. J. Shiner, *J. Chem. Soc.*, 1963, 2918.

[10] A. R. Butler and V. Gold, *J. Chem. Soc.*, 1961, 2305.

[11] D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Comm.*, 1966, 385.

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

[13] S. L. Johnson and H. M. Giron, *J. Org. Chem.*, 1972, **37**, 1383.

zero time is taken after *ca.* 60—80% of the total reaction has occurred, the values of the rate constants increase towards the corresponding *constant* values obtained for the slow reactions of the fluoroformates, although these figures are never quite reached in the case of the chloroformate reactions. Examples of the changing rate constants are given in Table 3. The results are consistent with mechanism (3) when the following conditions apply: $k_{\rm X}^{\rm OAc}[CH_3CO_2^-] \simeq k_{\rm M}^{\rm OAc}[CH_3CO_2^-] > k_{\rm X} \gg k_{\rm M}$.

Phenyl chloroformate and 4-t-butylphenyl chloroformate also gave sigmoidal rate curves when reacted with acetate ions in 60% aqueous dioxan at 1.8 °C. The 4-methoxyphenyl compound also did so in the highly aqueous dioxan used by Butler *et al.*[6] (90% water v/v) but the same effect could not be observed for phenyl chloroformate in the same medium. However, with this particular solvent and compound at 1.8 °C, the 'infinity' values of the optical densities slowly increased, indicating that solution of the chloroformate was incomplete at this temperature. We were, in fact, unable to dissolve the 4-t-butylphenyl compound sufficiently to obtain a significant optical density change over several hours. For these reasons we have based our analysis of the results we obtained entirely on the data for 60% aqueous dioxan.

A final proof of mechanism (3) and of our proposals required the synthesis of the mixed anhydride and a study of the kinetics of its reaction with acetate ions. A sample of this material has been prepared from 4-methoxyphenyl chloroformate and triethylammonium acetate in ether, following the general procedure given by Tarbell.[14] Unfortunately, our product was not sufficiently stable to be purified by vacuum distillation. When an attempt was made to do this, decomposition occurred to give 4-methoxyphenyl acetate and a solid residue that we were unable to recrystallize. The identification of our material as the mixed anhydride (I; R = $4\text{-}CH_3OC_6H_4$) is based on the i.r. spectrum, which has two carbonyl bands at 1 829 and 1 750 cm^{-1}, similar to those previously reported by Tarbell[15,16] for a wide range of similar mixed anhydrides. Our product decomposed on standing at 0 °C, the process being essentially complete after five days. About 50% of the decomposition products distilled as 4-methoxyphenyl acetate.

A sample of the crude mixed anhydride was reacted at 1.8 °C with acetate ions in 60% aqueous dioxan The pseudo first-order rate constants for reaction in the presence of 0.040 76M- and 0.081 52M-sodium acetate were 9.85×10^{-4} s^{-1} and 19.8×10^{-4} s^{-1}, respectively, in good agreement with the values given in Table 2. The solvolytic rate constant at 1.8 °C was $1.19 \pm 0.02 \times 10^{-4}$ s^{-1}, which does not agree with the smaller value of $k_{\rm M}$ in Table 2. This is probably due to a difference in ionic strength and a similar result has been noted by Butler *et al.*[6] for the reaction of phenyl chloroformate with acetate ions.

EXPERIMENTAL

Materials.—All reagents used were AnalaR grade. The purification of the solvents has been previously described.[3,6] The chloroformates were commercial samples and were distilled before use. Their physical properties were the same as those previously reported.[17-19] 4-Methoxyphenyl fluoroformate was prepared from the chloroformate by reacting it with thallium(I) fluoride[20] and the product purified by fractional distillation as a liquid, b.p. 50 °C at 1 mmHg (lit.,[21] 51 °C at 1 mmHg).

Acetic 4-methoxyphenoxyformic anhydride was prepared by slowly adding a solution of anhydrous acetic acid (0.91 g) and freshly distilled triethylamine (1.53 g) in dry ether (50 ml) to a stirred solution of 4-methoxyphenyl chloroformate (2.80 g) in ether at 0 °C. After 45 min, triethylammonium chloride (2.01 g, 97.5%) was filtered off and the filtrate successively washed with cold saturated sodium hydrogen carbonate solution and water. After drying ($MgSO_4$), the ether was removed under vacuum at room temperature to give a pale yellow oil [3.00 g, 95.2% based on the structure (I; R = $CH_3OC_6H_4$)]. The i.r. spectrum showed two carbonyl bands at 1 820 and 1 750 cm^{-1}. The n.m.r. spectrum had $\tau(CCl_4)$ 3.06 (q, C_6H_4), 6.30 (s, CH_3O), and 7.82 (s CH_3); smaller peaks at τ 3.37 and 6.35 were consistent with the presence of *ca.* 10% 4-methoxyphenol. A sample of the crude anhydride decomposed when an attempt was made to distill it under reduced pressure. The products were 4-methoxyphenyl acetate, b.p. 94 °C at 0.05 mmHg (lit.,[22] 135 °C at 18 mmHg), and a brown solid. 4-Methoxyphenyl acetate was identified by means of its mass spectrum which gave a single parent peak at *m/e* 166 when run at 9 eV and by the identity of the i.r. spectra of the compound and an authentic sample of the ester.

Sodium acetate was dried at 100 °C and 0.3 mm Hg over phosphorus pentaoxide. Stock acetate solution (250 ml) was prepared by dissolving sodium acetate (4.178 7 g) and anhydrous acetic acid (3.566 0 g) in 60% aqueous dioxan and the reaction solutions were made up by diluting portions of the stock solution with solvent. 60% Aqueous dioxan was prepared by mixing 60 volumes of dioxan and 40 volumes of water. 70% Aqueous acetone was similarly prepared.

Kinetic Methods.—The reactions in aqueous acetone were followed by titrating the acid released. In the case of the chloroformates, the reactions were quenched with cold dry acetone and lacmoid was used as indicator. The fluoride reactions were measured by quenching the reactions in cold light petroleum, extracting the acid with water and titrating it with sodium hydroxide using Methyl Red–Methylene Blue as indicator.[23]

The reactions in aqueous dioxan were followed at 293 nm using a Beckman DK2A spectrophotometer, fitted with

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[14] D. S. Tarbell and N. A. Leinster, *J. Org. Chem.*, 1958, **23**, 1149.

[15] D. S. Tarbell and E. J. Longosz, *J. Org. Chem.*, 1959, **24**, 774.

[16] J. Michejola and D. S. Tarbell, *J. Org. Chem.*, 1964, **29**, 1168.

[17] M. J. Zabik and R. D. Schuetz, *J. Org. Chem.*, 1967, **32**, 300.

[18] Y. Iwakura and A. Nabeya, *J. Org. Chem.*, 1960, **25**, 118.

[19] J. Urbanski, *Roczniki Chem.*, 1962, **36**, 1441.

[20] S. Nakanishi, T. C. Myers, and E. V. Jenzen, *J. Amer. Chem. Soc.*, 1955, **77**, 3099.

[21] K. O. Christie and A. T. Pavlath, *J. Org. Chem.*, 1965, **30**, 4104.

[22] H. Klemenc, *Monatsh.*, 1914, **35**, 85.

[23] E. Banks, A. Cuthbertson, and W. K. R. Musgrave, *Analyt. Chim. Acta*, 1955, **13**, 442.

a thermostatted cell holder. Temperatures were stable to ±0.05 °C at 1.8 °C. The reactions were initiated by adding small amounts of the compounds on the end of a thin glass rod to the solution in the cuvette. The changes of absorbance with time were recorded. ' Infinity ' values were taken after at least 12 half-lives and integrated first-order rate constants calculated at various times over at least three half-lives. Three separate runs were carried out for each experiment.

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