The Hydrolysis of Amides, Esters, and Related Compounds in Acid Solution. Part IV.[1] Phenyl Chloroformate and the 1-(Methoxycarbonyl)-imidazolium and -pyridinium Ions

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The kinetics of hydrolysis of these three substrates in moderately concentrated solutions of H_2SO_4, $HClO_4$, and HCl has been studied. None of these reactions is acid catalysed. Medium effects are compared with those found in similar but acid-catalysed reactions. The reactivity of the cations, which serve as models for *N*-protonated carbamates, are compared with those of similar models for *N*-protonated amides, and in the light of the comparison the mechanism of hydrolysis of protonated carbamates is discussed.

In previous papers, the $A2$ reaction of amides and carbamates in strongly acidic media have been investigated.[2,3] Independent investigations of the extent of protonation of the substrate [4] made possible the investigation of medium effects upon the rate constant, k_p, for the rate-determining step, the attack of water on the protonated substrate. This study of medium effects was however necessarily restricted to the range over which the fractions protonated could be measured with reasonable precision, and could not be extended to the dilute acid region. It was found that plots of log k_p against the logarithm of the activity of water were curved, and that the curves relating to hydrolysis in sulphuric acid and perchloric acid were not coincident, so that the assumption that $\gamma_{SH^+}/\gamma^{\ddagger}$, the activity coefficient ratio of protonated substrate and transition state, is invariant with medium is invalid, and the deduction of the number of water molecules, p, needed to take the protonated substrate into the transition state is not possible.

$$SH^+ + (H_2O)_p \xrightarrow{k_p} \ddagger$$
$$k_p = k_p{}^0 a_w{}^p \gamma_{SH^+}/\gamma^{\ddagger} \qquad (1)$$

Bunton, O'Connor, and their co-workers [5] have attempted to explain the curvature of plots similar to those referred to above by postulating the competition of two mechanisms, involving protonation on oxygen and on nitrogen respectively. In this paper the substrates were chosen because, as will be shown below, their hydrolysis does not involve complications arising from protonation. The rate constants for hydrolysis of phenyl chloroformate, 1-(methoxycarbonyl)pyridinium, and (1-methoxycarbonyl)imidazolium (the latter has a pK_a of *ca.* 3·6 and is therefore completely protonated in the media discussed here); all fall rapidly with increasing acidity. Medium effects upon the rate constants may therefore be studied over an extended range, and cannot arise from alternative sites for protonation. The cations are good models for *N*-protonated carbamates, and a further objective of the present work was to compare their reactivity with that of similar models for *N*-protonated amides.[6,7] The study of the neutral substrate phenyl chloroformate the hydrolysis of which, in water only, has previously been studied by Queen [8] helps to show how much if any of the observed medium effect is connected with the charge type of the substrate.

EXPERIMENTAL

Materials.—Acid solutions were prepared by dilution of the AnalaR concentrated acid, and concentrations were estimated either using a density balance or by titration. Acetonitrile was distilled from phosphorus pentoxide and stored over molecular sieves. Cyclohexane was Spectrograde, used directly. Phenyl chloroformate was the commercial material, and was used directly. The (1-methoxycarbonyl)pyridinium ion was generated *in situ* for the kinetic studies, as described below. (1-Methoxycarbonyl)imidazole was prepared as follows.

To a solution of imidazole (0·2 mol) in benzene (180 cm^3) at 7 °C was added dropwise with stirring a solution of methylchloroformate (0·1 mol) in benzene (50 cm^3). The mixture was stirred for a further 3 h and then solid imidazolium chloride was filtered off; the filtrate was evaporated to give white crystals (3·92 g, 31%). After recrystallisation from ether–light petroleum it had m.p. 41—42 °C (Found: C, 46·4; H, 4·75; N, 22·1. $C_5H_6N_2O_2$ requires C, 47·6; H, 4·80; N, 22·2%). The product had limited stability at room temperature and was stored at 0 °C and recrystallised before use.

Kinetic Procedures.—In all cases runs were followed by measurement of the change in u.v. absorption spectrum using a Unicam SP 500 spectrophotometer with the cell block thermostatted to ±0·1° of the required temperature. Runs were usually followed for 2—3 half-lives and infinity readings taken after 8—10 half-lives. First-order rate constants were determined graphically from plots of log (|absorbance − absorbance at ∞|) *vs.* time. Good straight lines were obtained.

The hydrolysis of phenyl chloroformate was followed by observing the increase in absorbance at 270 nm due to the phenol produced. In some of the early runs the substrate was added as a stock solution in acetonitrile to give a final solution containing *ca.* 2% acetonitrile. In later runs the substrate was used directly. Rate constants obtained by

[1] Part III, D. W. Farlow and R. B. Moodie, *J. Chem. Soc.* (*B*), 1971, 407.
[2] V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 1099.
[3] V. C. Armstrong and R. B. Moodie, *J. Chem. Soc.* (*B*), 1969, 934.
[4] V. C. Armstrong and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 275.
[5] C. A. Bunton, C. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1967, 1835.
[6] S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.*, 1962, **84**, 232.
[7] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5432.
[8] A. Queen, *Canad. J. Chem.*, 1967, **45**, 1619.

the two methods fell on the same smooth curves; the medium effect of the acetonitrile was negligible.

(1-Methoxycarbonyl)imidazole was dissolved in acetonitrile and runs were started by adding 0·05 to 0·1 cm³ of this stock solution to 10 cm³ of the appropriate acid at 25·0 °C. The decrease in absorbance at 250 nm was monitored.

Separate studies [9] have shown that methyl chloroformate in a pyridine buffer reacts very quickly, by a process which is first order in methyl chloroformate and first order in free pyridine and with a rate constant of *ca.* 60 dm³ mol⁻¹ s⁻¹, to give the (1-methoxycarbonyl)pyridinium ion which is then hydrolysed in dilute aqueous solution by a first-order process with a rate constant of $2·7 \times 10^{-2}$ s⁻¹. Accordingly the following method was used to follow the decomposition of this ion in strongly acidic media. Into the larger limb of an unsymmetrical inverted U-tube was introduced 20 cm³ of the appropriate acid solution, and into the smaller limb, 1·0 cm³ of a pyridine buffer, containing 0·02 mol dm⁻³ of pyridine and 0·01 mol dm⁻³ of perchloric acid. The contents of the larger limb of the U-tube were brought to the appropriate temperature (slightly less than the run temperature, see below) and 0·1 cm³ of an acetonitrile solution containing 0·2 mol dm⁻³ of methyl chloroformate was added to the smaller limb; after *ca.* 20 s the contents of the limbs were mixed and a spectrophotometer cell was filled with the resulting solution. The decrease in absorbance at 275 nm was monitored. Blank runs without substrate were used to discover the appropriate starting temperature to achieve the required final temperature after mixing. Allowance was made for the dilution in calculating the final acid concentration. This method assumes that the concurrent hydrolysis of small quantities of methyl chloroformate which have not reacted with pyridine before mixing does not interfere with the measurements, a reasonable assumption since neither reactants nor products of such hydrolysis absorb at 275 nm, and the concentrations are too low to introduce a medium effect. After mixing of the contents of the U-tube, the acidity is too high for further reaction of methyl chloroformate with pyridine, a reaction which requires the latter to be in the free base form.

Distribution of Phenyl Chloroformate between Cyclohexane and Aqueous Acid.—The ratio of the distribution coefficients between aqueous perchloric acid (7·50 mol dm⁻³, log $a_w = -0·600$) and cyclohexane on the one hand and between aqueous sulphuric acid (8·06 mol dm⁻³, log $a_w = -0·600$) and cyclohexane on the other was found to be 3·5 (±0·5). The following method was used. A solution of 0·05 cm³ of phenyl chloroformate in 2 cm³ of cyclohexane was extracted with 3 × 10 cm³ of aqueous acid to remove traces of phenol; the washings were discarded. 1 cm³ of the cyclohexane solution was mixed with 50 cm³ of the cyclohexane solution which had been previously brought to 25 °C. The mixture was shaken for 2 min and then allowed to separate. 0·5 cm³ of the cyclohexane layer was diluted to 25 cm³, and the absorbance of the solution in a cell of 1-cm path length at 257 and 277 nm was recorded. The absorbance of the aqueous acid layer in a cell of 4-cm path length at 240 and 274 nm was also recorded. The whole operation was completed in <15 min during which time the extent of hydrolysis of the phenyl chloroformate was <5% (see rate constants in the Table); the absorbance at 240 nm (aqueous acid) and at 257 nm (cyclohexane) are mainly due to phenyl chloroformate but the contribution due to phenol is not quite negligible. This was corrected for using the measured absorbance at 274 nm (aqueous acid) and 277 nm (cyclohexane) and the extinction coefficient ratios for phenol ($E_{240}^{\text{aq. acid}}/E_{274}^{\text{aq. acid}} = 0·077$ and $E_{257}^{\text{cyclohexane}}/E_{277}^{\text{cyclohexane}} = 0·28$) obtained from independent spectral measurements of phenol solutions. The desired ratio of distribution coefficients was calculated from the relation (1); each term in curly brackets was obtained as the mean of five determinations.

$$\frac{D_{H_2SO_4}}{D_{HClO_4}} = \left\{\frac{A_{240}^{\text{aq. acid}} - 0·077A_{274}^{\text{aq. acid}}}{A_{257}^{\text{cyclohexane}} - 0·28A_{277}^{\text{cyclohexane}}}\right\}_{\text{aq. } HClO_4} \Bigg/ \left\{\frac{A_{240}^{\text{aq. acid}} - 0·077A_{274}^{\text{aq. acid}}}{A_{257}^{\text{cyclohexane}} - 0·28A_{277}^{\text{cyclohexane}}}\right\}_{\text{aq. } H_2SO_4} \quad (1)$$

It was not possible to extend these studies to lower acidities, because the increased rate of hydrolysis leads to large errors.

Observed first-order rate constants for hydrolysis at 25·0 °C [a]

$[H_2SO_4]$ / mol dm⁻³	10^5k/s⁻¹	$[HClO_4]$ / mol dm⁻³	10^5k/s⁻¹	[HCl] / mol dm⁻³	10^5k/s⁻¹
		Phenyl chloroformate			
2·94	289	0	1300 [b]	3·27	322, 327
3·94	157, 160	1·72	371, 378	6·80	49·1
4·77	86	3·77	73	8·35	21·4
6·07	31·8	4·62	22·1, 23·0	10·19	8·1
6·74	17·2	5·74	10·8	10·41	7·2
7·87	6·8, 6·8	5·86	9·1, 9·9		
8·06	5·4	6·94	3·33, 3·38		
8·23	5·3, 5·2	7·14	2·37, 2·40		
		7·63	1·37, 1·40		
		1-Methoxycarbonylimidazolium ion			
4·77	1·54, 1·67	0·10	17·1, 19·2	4·06	3·55
5·90	0·80	0·20	18·4, 17·8	5·82	1·87, 1·86
7·52	0·301	3·72	1·09, 1·09	7·86	0·60, 0·77
		4·94	0·38, 0·36		
		5·76	0·18, 0·19		
		7·21	0·036, 0·036		
		1-Methoxycarbonylpyridinium ion			
2·94	510, 500	0	2700 [f]	3·86	414, 413
4·63	112, 118	3·84	78, 75	5·55	140, 142
5·65	46·0, 45·9	4·72	27·9, 27·9	7·48	47·3
7·18	12·2, [c] 11·9 [c]	5·50	10·9, 10·9	9·13	16·3, 16·1
7·18	32·1, [c,d] 31·4 [c,d]	7·23	1·38		
7·18	115, [c,e] 116 [c,e]				

[a] Unless otherwise noted. [b] In pure water, mean of 12 determinations. This value is a little lower than that obtained (1380) from Queen's activation parameters.[8] [c] These rate constants give $E_A = 72$ kJ mol⁻¹, log $(A/s^{-1}) = 8·66$. [d] At 35·0 °C. [e] At 50·0 °C. [f] From other studies.[9]

RESULTS

Rate constants are given in the Table, which also records the activation parameters for the hydrolysis of the (1-methoxycarbonyl)pyridinium ion in aq. H_2SO_4 (7·18 mol dm⁻³). The value of log (A/s^{-1}), which corresponds to a value of $\Delta S^{\ddagger} = -87$ J K⁻¹ mol⁻¹, is in accord with the conclusion that the reaction is a bimolecular one, and is similar to that found in similar reactions.[2,8] The hydrolysis of phenyl chloroformate in concentrated solutions of KCl and $NaClO_4$ was also studied; the following rate

[9] E. A. Castro and R. B. Moodie, unpublished work.

constants were obtained: [KCl] = 2·0 mol dm^{-3}, k = 1·1 × 10^{-2} s^{-1}, [KCl] = 4·0 mol dm^{-3}, k = 6·6 × 10^{-3} s^{-1}; [$NaClO_4$] = 7·55 mol dm^{-3}, k = 3·6 × 10^{-4} s^{-1}.

DISCUSSION

Differences Between the Rate Constants in the Three Strong Acids.—Bunton and his co-workers have drawn attention to the different catalytic effectiveness of $HClO_4$, HCl, and H_2SO_4 in the *A*2 reactions of esters [10] and anhydrides.[11] The present reactions are similar in that they involve nucleophilic attack of water on carbonyl carbon, but differ in that they are clearly not acid catalysed, so that the medium effects can be assigned unambiguously to the rate-determining step. The pattern is closely similar to that observed by Bunton *et al.*; rate constants are considerably lower in every case in perchloric acid than in sulphuric or hydrochloric acid of comparable concentration. For (−log a_w) > 0·3, comparison can be made with the reactions of protonated butyramide and protonated carbamates.[2,3] The ratio of the rate constant in sulphuric acid to that in perchloric acid at the same activity of water is similar in those cases to the three studied here, all falling in the range 3—6. Similar behaviour of the acetylimidazolium ion has been reported.[6] The distribution studies described in the Experimental section show that, in the case of phenyl chloroformate at least, the difference in the rate constants in sulphuric and perchloric acids can largely be attributed to a difference in the activity coefficients of the substrate. Thus the ratio of rate constants in the two acids at log a_w = −0·600 is 3·6 (±0·2) and the ratio of activity coefficients is 3·5 (±0·5). This is similar to the observation of Bunton *et al.*[11] that in the acid-catalysed hydrolyses of certain anhydrides, plots of log (k/γ_s) *vs.* H_0 for the three strong acids fell near the same line. A similar pattern of medium effects on neutral substrates and on rate constants for their acid-catalysed hydrolysis was noted also with esters.[10] It seems likely that in all these cases, discrepancies between rate constants in different acids arise largely from ground-state rather than transition-state differences, though further work is needed to establish this point. Other causes however can now be definitely excluded. General acid catalysis by the hydrogen sulphate ion cannot be involved in the reactions described here, because they are not acid catalysed. Indeed the use of relative rates in sulphuric and perchloric acid to infer the presence or absence of general acid catalysis [12] is probably not reliable. The very large decrease in rate with increasing acidity is unlikely to be due to a change in rate-determining step to base-catalysed breakdown of a tetrahedral intermediate, at least in the case of phenyl chloroformate, because high concentrations of sodium perchlorate produce a similar decrease in rate constant (see Results section). Nucleophilic catalysis by chloride ion in HCl cannot be effective with phenyl chloroformate, because the entering and leaving groups would be identical.

The Curvature of the Plots of log k vs. *log a_w.*—This behaviour is illustrated in Figure 1, and is similar to that found with protonated amides.[2,5,13] There is, therefore, no reason to invoke the idea of competing mechanisms involving different sites for protonation in the latter reaction.[2] The curvature of these plots, like the discrepancies between the lines for different acids, would appear to be common in reactions involving attack of water on carbonyl carbon atom, whether or not the reaction is acid catalysed. The activity coefficient

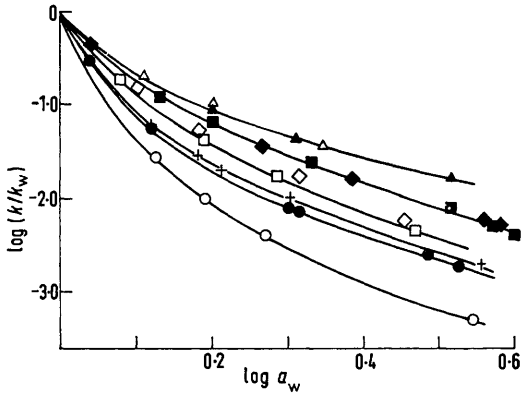


FIGURE 1 Plots of log (k/k_w) *v.s.* −log a_w (k_w is the rate constant in dilute aqueous solution) for the hydrolysis of phenyl chloroformate (full symbols), and 1(-methoxycarbonyl)pyridinium (open symbols) in $HClO_4$ (○), HCl (◇), and H_2SO_4 (□) and of 1(methoxycarbonyl)imidazolium in $HClO_4$ (+), HCl (△), and H_2SO_4 (▲)

ratio in equation (1) clearly varies with the nature and the concentration of the strong acid, so that no estimate of the value of p is possible.

If account is taken of the fact that one water molecule is necessarily involved in the formation of the transition state, and if the empirical Setschenov relation [14] is used for the activity coefficients of neutral species in concentrated electrolyte solutions, the following equation can be derived, applicable to the hydrolysis of phenyl chloroformate where both substrate and transition state are neutral. Plots of log (k/a_w) *vs.* [acid] are reasonably

$$\log (k/a_w) = (k_s - k_t)[\text{Acid}] + \text{Constant} \quad (2)$$

straight (Figure 2) even for sulphuric acid in which medium there is plenty of evidence that the Setschenov relation is not generally applicable over such an extended range.[15] It remains to be seen whether studies of solubilities of stable, neutral compounds chosen as models for substrate and transition state will give

[10] C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 1258.
[11] C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 1966, **31**, 3764.
[12] A. J. Kresge, L. A. Hakko, S. Mylonakis, and V. Sato, *Discuss. Faraday Soc.*, 1965, **39**, 75.
[13] R. B. Moodie, P. D. Wale, and T. J. Whaite, *J. Chem. Soc.*, 1963, 4273; K. Yates and J. C. Riordan, *Canad. J. Chem.*, 1965, **43**, 2328.
[14] J. Setschenov, *J. Physik. Chem.*, 1889, **4**, 117.
[15] R. H. Boyd in 'Solute–Solvent Interactions,' eds. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, Paris, 1969.

comparable constancy for the *difference* in Setschenov parameters.

The Mechanism of Hydrolysis of Protonated Carbamates.—Previously the differences between *N*-substituent effects in the hydrolysis of protonated carbamates and

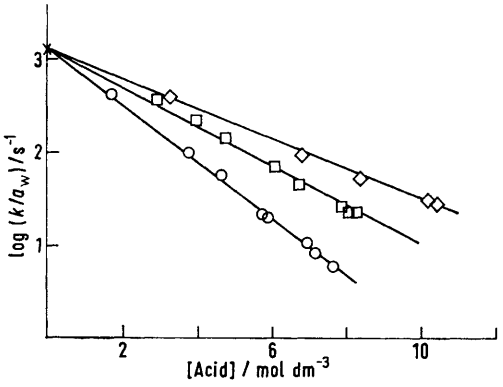
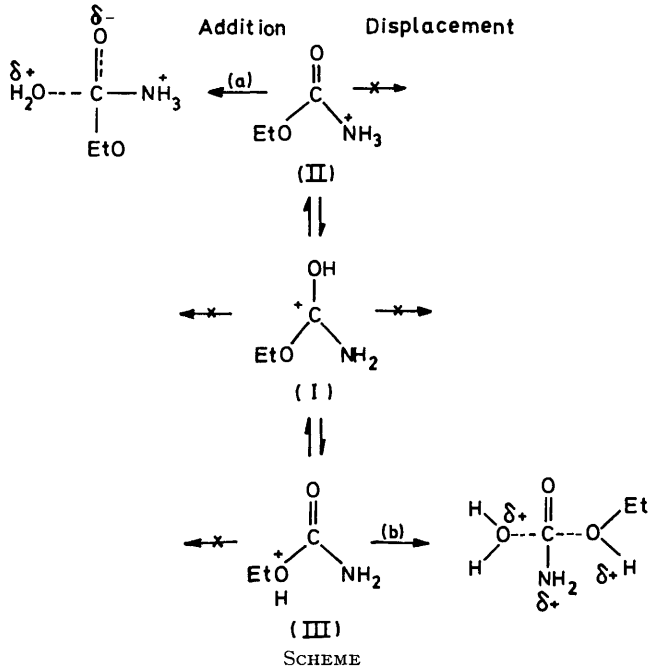


FIGURE 2 Plots of log (k/a_w) *vs.* [Acid] for the hydrolysis of phenyl chloroformate in $HClO_4$ (○), HCl (◇), and H_2SO_4 (□)

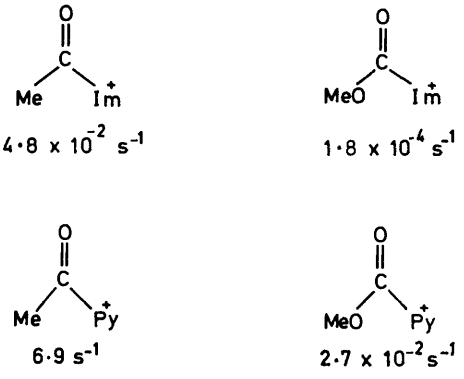
protonated amides has been noted.[3] In the case of carbamates they are such as to suggest an increase in positive charge on nitrogen going from ground state [the predominant [16] carbonyl *O*-protonated carbamate (I)], to transition state. The present work cast some new light on the relative merits of possible mechanisms, and leads to a revision of earlier conclusions.[2] The evidence that the reaction involves rate-determining attack of water on carbonyl carbon, probably without



SCHEME

concurrent proton transfer, has already been presented.[2] We are left with the six possible mechanisms shown in the Scheme, which considers rate-determining addition to (left-hand side) or displacement from (right-hand side) each of three protonic tautomers. The addition steps lead to the formation of a tetrahedral intermediate, whereas in displacement the tetrahedral intermediate is by-passed.

The most straightforward explanation of the substituent effects is that addition of water to the *N*-protonated tautomer (II) takes place [route (a) in the Scheme], this clearly involves an increase in positive charge on nitrogen going from the ground state to the transition state. It is not clear, however, why such a path should be preferred by carbamates and not by amides, yet *N*-substituent effects in the two classes of compound are quite different. There are two steps involved, the pre-equilibrium between the dominant *O*-protonated tautomer (I) and the minor *N*-protonated form (II), and the rate-determining nucleophilic attack of water on (II). The latter step might be expected to be easier for amides than it is for carbamates, a view which is strengthened by a comparison below of the following amide-like and carbamate-like models for (II) where proton transfer is precluded, *viz.* *N*-acetyl- and *N*-methoxycarbonyl-imidazolium and -pyridinium cations. The figures are rate constants for hydrolysis in water at 25 °C (Table and refs. 6 and 8).

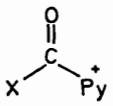


In both cases the acetyl compound reacts faster than the methoxycarbonyl compound by a factor of *ca.* 300. If comparison of rate constants in highly acidic media is made, as is possible in the imidazolium cases (ref. 6 and Table) the factor is somewhat larger (*ca.* 4000 in 7M-$HClO_4$). Clearly if carbamates and not amides prefer route (a), carbamates must have a much higher equilibrium concentration of *N*-protonated substrate. Some indication that this might, in fact, be the case comes from our recent demonstration that carbamates can be induced to undergo predominant *N*-protonation more easily than can amides. Ethyl *NN*-di-isopropylcarbamate (in which steric effects presumably decrease the stability conferred by resonance on the *O*-protonated form) undergoes predominant *N*-protonation, whereas *NN*-di-isopropylacetamide and *NN*-di-isopropylbenzamide do not.[17] The pK_a values of *N*- and *O*-protonated

[16] G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, 1968, **90**, 401.
[17] V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *Chem. Comm.*, 1968, 1362.

amides have been estimated to differ by as much as 7 units.[18] The difference may be much smaller with carbamates, and it is clear that route (a) in the Scheme could be preferred by carbamates and not by amides, in spite of the opposite preference in the rate-determining step.

The alternative hypothesis, that carbamate hydrolysis proceeds by route (b) in the Scheme, was originally put forward.[3] However, predictions made on the basis of this hypothesis have not been fulfilled. Thus, for instance, if as suggested [3] the amino-group because of its π-donor properties can stabilise the transition state in which the protonated alkoxy-group is displaced, then one might expect the hydrolysis of the *NN*-dimethylcarbamoylpyridinium ion to be particularly simple. In fact the data of Johnson and Rumon [19] for the hydrolysis of this compound, when compared with the data for the *N*-acetyl- and *N*-methoxycarbonyl-pyridinium ion given above, show that the rate constants for the hydrolysis of the compounds lead to a linear $\sigma\rho$ plot ($\rho = 5{\cdot}0$) when σ^+ constants are used for X. There is no evidence for enhanced reactivity of the dimethyl-carbamoyl compound.



(X = Me,MeO,Me_2N)

Route (b) then cannot be ruled out, but now appears less likely. Route (a) in the Scheme, *viz.* nucleophilic attack of water on the *N*-protonated tautomer, seems the most plausible mechanism for carbamate hydrolysis. With amides, on the other hand, the rate-determining step is probably the attack of water on the predominant * *O*-protonated form to give a tetrahedral intermediate, particularly since Yates and Smith have shown that protonated imidates, which are models for *O*-protonated amides with proton transfer precluded, hydrolyse slightly faster than amides.[21]

We thank Professor Yates for a view of his work prior to publication.

[1/1696 *Received, September 16th*, 1971]

* A referee has pointed out that predominant *O*-protonation in amides has not been unequivocally established. See for instance ref. 20.

[18] A. R. Fersht, *J. Amer. Chem. Soc.*, 1971, **93**, 3504.
[19] S. L. Johnson and K. A. Rumon, *J. Amer. Chem. Soc.*, 1965, **87**, 4782.
[20] M. Liler, *J. Chem. Soc.* (*B*), 1971, 334, and references quoted therein.
[21] K. Yates and C. Smith, unpublished work.