The Hydrolysis of Amides, Esters, and Related Compounds in Acid Solution. Part II.[1] Carbamates

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The kinetics of the hydrolysis in acid solution of ethyl *N*-methylcarbamate, ethyl *NN*-dimethylcarbamate, ethoxycarbonylglycine, ethyl *NN*-di-isopropylcarbamate, ethyl *NN*-di-n-propylcarbamate, phenyl carbamate, and phenyl *NN*-dimethylcarbamate have been studied. Either the $A_{Ac}1$ or the $A_{Ac}2$ mechanism prevails depending on the acid concentrations. A satisfactory picture of the $A_{Ac}2$ reaction is one in which water displaces the protonated alkoxy- or aryloxy-group. The results permit a number of other possible mechanisms to be discarded.

In this Series the hydrolytic stability and modes of decomposition of ions of the type $(CXYZ)^+$ (where X, Y, and Z are chosen from R, NHR, NR_2, NH_2, OH, or OR) are compared. The set includes protonated amides,[2] esters,[3] and imidates[4] which have been repeatedly studied, as well as protonated carbamates and ureas, which have received less attention. Where necessary, separate studies of the protonation equilibria are made[5] and the kinetic studies are mainly restricted to conditions where the extent of protonation can either be measured or estimated with some certainty. In Part I[1] a comparison was made between the kinetics of hydrolysis of protonated amides, carbamates, and ureas which revealed differences in mechanism. We now present a more detailed study of the decomposition of a series of substituted carbamates in acid solution.

[1] Part I, V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 1099.

[2] R. B. Moodie, P. D. Whale, and T. J. Whaite, *J. Chem. Soc.*, 1963, 4273; (*b*) K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43**, 429; K. Yates and J. C. Riordan, *ibid.*, p. 2328; (*c*) J. A. Leisten, *J. Chem. Soc.*, 1959, 765; (*d*) C. A. Bunton, C. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1968, 1835.

[3] (*a*) C. A. Lane, M. F. Cheung, and G. F. Dorsey, *J. Amer. Chem. Soc.*, 1968, **90**, 6492; (*b*) K. Yates and R. A. McClelland, *ibid.*, 1967, **89**, 2686; (*c*) C. A. Bunton, J. H. Crabtree, and L. Robinson, *ibid.*, 1968, **90**, 1258.

[4] (*a*) R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, 1968, **90**, 4413; (*b*) T. C. Pletcher, S. Koehler, and E. H. Cordes, *ibid.*, p. 7072; (*c*) R. H. De Wolfe and F. B. Augustine, *J. Org. Chem.*, 1965, **30**, 699.

[5] (*a*) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 275; (*b*) V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *Chem. Comm.*, 1968, 1362.

EXPERIMENTAL

Materials.—The preparations of most of these were described.[1,5] Commercial phenyl carbamate was recrystallised from chloroform. Phenyl *NN*-dimethylcarbamate, m.p. 44—45°, (lit.,[6] 44—45°) (Found: C, 65·2; H, 6·5; N, 8·4. Calc. for $C_9H_{11}NO_2$: C, 65·4; H, 6·8; N, 8·9%), ethyl *NN*-di-n-propylcarbamate, b.p. 82—84°/17 mm. (Found: C, 61·9; H, 10·9; N, 8·2. Calc. for $C_9H_{19}NO_2$: C, 62·4; H, 11·0; N, 8·1%), and ethyl *NN*-di-isopropylcarbamate, b.p. 71—73°/17 mm. (lit.,[7] 83—87·5°/20 mm.) (Found: C, 62·2; H, 11·1; N, 8·0. Calc. for $C_9H_{19}NO_2$: C, 62·4; H, 11·0; N, 8·1%) were prepared by a standard method.[8]

Protonation Equilibria.—The absorbances at chosen wavelengths between 240 nm. and 265 nm. of solutions containing various concentrations of sulphuric acid but a constant stoicheiometric concentration of phenyl *NN*-dimethylcarbamate were measured with a Unicam SP500 spectrophotometer. An isosbestic point was not observed, nor could one be generated by simple lateral shifts of the absorption curves in the manner first suggested by Hammett and Deyrup[9] and no attempt to correct for medium effects in this way was made. Plots of A_{240} (the absorbance at 240 nm.), A_{265}, and[10] $A_{240} - A_{265}$ against[11] H_0 gave sigmoidal curves from which ionisation ratios were determined. Phenyl carbamate was found to decompose rapidly in the more strongly acidic solutions which prevented scanning of the spectra. Absorbances at 258·5 nm. and 265 nm. were recorded at one minute intervals and plots of absorbance against time were extrapolated to zero time. Plots of $A_{258·5}$ and A_{265} against H_0 were sigmoidal, whence ionisation ratios were obtained. The parameters c and d in equation (1), were derived as described before[5] and are

$$\log I = cH_A + d \qquad (1)$$

recorded in Table 1. The wide disparity in the values obtained by different method precludes accurate determination of values of I, but the values are sufficient to indicate the basicities of the compounds relative to other carbamates.[5]

TABLE 1

Protonation equilibria in aqueous sulphuric acid at 23° ± 2°

		Parameters in equation (1)				
Compound	λ(nm.) [a]	$-c$	α_c [c]	$-d$	$\alpha \log I$ [d]	$-d/c$
PhO·CO·NH_2	258·5	0·66	0·09	2·14	0·20	−3·22
PhO·CO·NH_2	265	0·67	0·06	2·28	0·12	−3·39
PhO·CO·NMe_2	240	1·32	0·07	5·41	0·09	−4·08
PhO·CO·NMe_2	265	0·83	0·02	3·14	0·04	−3·78
PhO·CO·NMe_2	240, 265 [b]	1·04	0·02	4·15	0·05	−3·96

[a] Wavelength at which measurements were made. [b] Method of Davis and Geissman.[10] [c] Standard error of the slope parameter. [d] Standard error of points from the linear regression line in the log I direction.

Kinetic Procedures.—In most runs method (*a*) was used.[1] Good first-order kinetics were observed in all runs except that for ethyl *NN*-di-isopropylcarbamate in 98% H_2SO_4 (see section on product analysis). In the cases of the hydrolyses of phenyl carbamate and phenyl *NN*-dimethylcarbamate, a spectrophotometric method (*d*) was employed for some of the runs, which utilised the increase in absorption at 269 and 274 nm. in quenched samples due to the production of phenol. Where comparison was possible (Table 2) the agreement between the rate constants obtained by the two methods was satisfactory.

Oxygen-18 Labelling Experiments.—The oxygen exchange of methanol in aqueous perchloric acid[12] has a higher activation energy and a steeper acidity dependence than the hydrolysis of methyl carbamate. In order that the former reaction should be negligible during the progress of the latter, it was necessary to use rather 'slow' conditions for the hydrolysis. A sample (5 ml.) of a solution 0·5M in methyl carbamate and 1M in perchloric acid in which the solvent water contained 1·67 atoms % excess of oxygen-18 was heated at 64° for 6½ days, a time corresponding to one half-life for the hydrolysis. Aqueous sodium hydroxide (initially 5M, then 1M) was added dropwise to *ca.* pH 2, and the solution was then distilled from bulb to bulb under high vacuum. Methanol in the initial distillate (0·5 ml.) was separated from water on an Aerograph Autoprep gas chromatograph (polyethylene glycol on Celite). This gave methanol, sample *A*, which was analysed for isotopic content on an A.E.I. MS. 10 mass spectrometer. Methanol, sample *B*, the purpose of which was to establish that the work-up procedure led to no loss of isotopic label, was recovered and analysed in an identical manner from a solution of methanol in a similar oxygen-18-enriched aqueous acid solution which had been heated for 67 hr. in a sealed tube at 140°, conditions which lead to essentially complete oxygen exchange between methanol and solvent water.[12] Sample *C* was AnalaR methanol.

The methyl carbamate remaining after one half-life for hydrolysis under similar conditions was recovered from the residue from the bulb-to-bulb distillation (mentioned above in the preparation of methanol sample *A*) by evaporation of the remaining water followed by extraction with methylene chloride (2 × 2 ml.) and purified by sublimation, giving methyl carbamate sample *D*. Sample *E* of methyl carbamate was from the bottle. Samples *D* and *E* were analysed for isotopic content with a Hitachi Perkin-Elmer R.M.U. mass spectrometer.

Identification of Products.—Besides carbon dioxide, the expected products from $R^1OCONR^2R^3$ are R^1OH (and R^1OSO_3H if the hydrolysis is conducted in sulphuric acid[13]) and $R^2R^3NH_2^+$. In oleum solutions sulphamic acids can be formed, but Bieber's results[14] suggest that this is unlikely in <100% H_2SO_4. Solutions of ethoxycarbonylglycine and ethyl *NN*-di-isopropylcarbamate in 80% H_2SO_4, and of ethyl *N*-methylcarbamate, ethyl *NN*-dimethylcarbamate, and ethyl *NN*-di-n-propylcarbamate in 98% H_2SO_4 were heated at 64° for a time corresponding to ten half-lives for the hydrolysis. The n.m.r. spectra of these solutions were identical with those of synthetic solutions of the expected reaction products. Ethyl *NN*-di-isopropylcarbamate in 98% H_2SO_4 however, heated for some time at 64°, slowly gave a complex mixture. This

[6] Bayer and Co., *Chem. Zentr.*, 1913, I, 67; Friedlander's Fortschritte der Teerfarbenfabrikation, Berlin.
[7] N. A. Leister and D. S. Tarbell, *J. Org. Chem.*, 1958, **23**, 1152.
[8] H. Brintzinger and K. Pfannstiel, *Chem. Ber.*, 1948, **81**, 378.
[9] L. P. Hammett and A. J. Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721.
[10] C. T. Davis and T. A. Geissman, *J. Amer. Chem. Soc.*, 1954, **76**, 3507.
[11] M. J. Jorgenson and D. R. Harrter, *J. Amer. Chem. Soc.*, 1963, **85**, 878.
[12] K. G. Oldham and C. A. Vernon, unpublished work.
[13] D. J. Clark and G. Williams, *J. Chem. Soc.*, 1957, 4218.
[14] T. I. Bieber, *J. Amer. Chem. Soc.*, 1953, **75**, 1409.

was not unexpected in view of the departure from first-order kinetics mentioned above.

Stability of Possible Intermediates.—We used ammonium carbamate to show that carbamic acid, like isocyanates [15] and alkyl hydrogen carbamates,[16] rapidly evolves carbon dioxide when dissolved in concentrated sulphuric acid at room temperature.

TABLE 2

Rate constants for hydrolysis

Temp.	Acid (%)	$10^5 k_{obs}$ (sec.$^{-1}$)	$\log_{10} k_p$ (sec.$^{-1}$) [b]	$\log_{10} a_{H_2O}$ [c]
Ethyl *N*-methylcarbamate in sulphuric acid [a]				
64·0°	28·9	1·11	—	—
64·0	39·2	2·57	—	—
64·0	52·8	5·54	−3·74	−0·74
64·0	64·7	4·66	−4·24	−1·02
64·1	74·0	2·16	−4·66	−1·66
64·0	85·5	0·764	−5·12	−2·98
64·0	98·1	0·506	−5·30	−5·33
Ethyl *NN*-dimethylcarbamate in sulphuric acid [a]				
64·0	39·2	9·02	—	—
35·2	40·6	0·720	—	—
49·9	40·6	2·82	—	—
49·9	40·6	2·72	—	—
64·0	40·6	10·0	—	—
64·0	40·6	9·40	—	—
35·1	40·7 [d]	1·09	—	—
35·2	40·7 [d]	1·11	—	—
64·1	40·7 [d]	13·6	—	—
64·1	40·7 [d]	13·0	—	—
64·0	52·8	19·9	−2·97	−0·54
64·0	58·6	23·7	−3·20	−0·74
64·0	64·7	19·7	−3·51	−1·02
64·0	64·7	20·6	−3·50	−1·02
64·0	76·1	6·36	−4·18	−1·85
50·0	80·5	0·963	—	—
63·9	80·5	3·38	−4·47	−2·32
71·8	80·5	6·03	—	—
71·8	80·5	6·20	—	—
79·9	80·5	11·8	—	—
80·1	80·5	12·1	—	—
64·0	85·5	1·42	−4·85	−2·98
64·0	98·1	0·252	−5·60	−5·33
Ethyl *NN*-dimethylcarbamate in perchloric acid [a]				
64·0	29·8	2·04	—	—
64·1	39·9	3·88	—	—
64·1	51·1	8·42	−3·43	−0·54
64·0	55·7	9·10	−3·67	−0·75
64·0	59·9	7·53	−3·96	−1·03
64·0	64·0	4·87	−4·26	−1·37
64·0	70·4	2·21	−4·65	−2·12
Ethyl *NN*-di-n-propylcarbamate in sulphuric acid [a]				
64·0	59·4	0·815		
64·0	71·2	0·700		
64·0	81·5	0·538		
64·0	98·1	0·937		
Ethyl *NN*-di-isopropylcarbamate in sulphuric acid [a]				
64·0	63·7	2·61	−4·51	−0·96
64·0	69·5	3·33	−4·46	−1·31
49·9	80·5	0·584	—	—
64·0	80·5	3·65	−4·44	−2·32
71·9	80·5	9·94	—	—
79·9	80·5	26·9	—	—
80·0	80·5	26·6	—	—
64·0	82·9	3·67	−4·44	−2·64
64·0	89·5	3·49	−4·46	−3·56
Ethoxycarbonylglycine in sulphuric acid				
64·1	60·7	0·326	−4·69	−0·82
64·0	69·8	0·342	−5·15	−1·33
64·0	79·3	0·229	−5·58	−2·17

TABLE 2 (*Continued*)

Temp.	Acid (%)	$10^5 k_{obs}$ (sec.$^{-1}$)	$\log_{10} k_p$ (sec.$^{-1}$) [b]	$\log_{10} a_{H_2O}$ [c]
Phenyl carbamate in sulphuric acid				
64·0	9·3	0·396 [e]		
64·0	21·2	1·36 [e]		
64·1	28·5	2·49 [e]		
64·0	28·9	2·74 [a]		
50·0	39·4	1·53 [e]		
50·0	39·4	1·52 [e]		
64·0	39·4	6·70 [e]		
71·9	39·4	16·4 [e]		
79·9	39·4	37·7 [e]		
80·0	39·4	41·9 [e]		
64·0	52·8	29·9 [a]		
64·1	57·1	50·7 [e]		
64·1	57·1	51·4 [e]		
Phenyl *NN*-dimethylcarbamate in perchloric acid				
64·0	18·6	1·10		
64·0	29·8	1·96		
64·0	39·5	3·56		
64·1	49·8	7·74		
64·0	59·4	22·5		
64·0	65·4	45·2		
Phenyl carbamate in perchloric acid				
64·0	9·2 [e]	0·294		
64·0	19·2 [e]	0·674		
64·0	30·2 [a]	2·03		
64·0	30·3 [e]	1·78		
64·0	37·1 [f]	3·50		
64·0	37·1 [a]	3·68		
64·0	44·7 [e]	7·78		
64·0	49·6 [e]	14·6		
64·1	51·1 [a]	21·7		
64·0	59·4 [e]	97·4		

[a] Substrate concentration 0·25M, kinetic method (a). [b] See equation (2). [c] Activity of water data are for 25°; see ref. 22 of ref. 1. [d] Deuteriated solvent. [e] Substrate concentration 0·5—1·6 × 10^{-3}M, kinetic method (*d*). [f] Substrate concentration 0·025M, kinetic method (*d*).

RESULTS AND DISCUSSION

Observed first-order rate constants are in Table 2, Arrhenius activation parameters and their probable errors, derived by least-squares analysis, are in Table 3,

TABLE 3

Activation parameters [a] for hydrolysis

Substrate	H_2SO_4(%)	E_A (kcal. mole^{-1})	log [*A* (sec.$^{-1}$)]
EtO·CO·NMe_2	40·6	18·7(±0·3)	8·1(±0·2)
EtO·CO·NMe_2	80·5	18·9(±0·2)	7·8(±0·1)
EtO·CO·$N(Pr^i)_2$	80·5	28·9(±0·2)	14·3(±0·2)
PhO·CO·NH_2	39·4	24·6(±0·5)	11·8(±0·3)
PhO·CO·NMe_2	39·4	19·0(±0·6)	8·3(±0·4)
EtO·CO·NH_2 [b]	40·1	20·6(±0·6)	8·5(±0·4)
EtO·CO·NH_2	79·6	25·8(±0·1)	12·1(±0·1)

[a] Derived from k_{obs} (Table 2). [b] Included from ref. 1 for comparison.

and the results of the oxygen-18 labelling experiments in Table 4.

Pre-equilibrium Protonation.—The solvent deuterium isotope effect, $k(H_2O)_{obs}/k(D_2O)_{obs}$, for the hydrolysis of ethyl *NN*-dimethylcarbamate in 40·7% H_2SO_4 is 0·73 at 64° and 0·65 at 35°. These may be compared with

[15] T. I. Bieber, *J. Amer. Chem. Soc.*, 1953, **75**, 1405.
[16] I. Levin, L. A. Pohoryles, S. Sarel, and V. Usieli, *J. Chem. Soc.*, 1963, 3949.

results for amides,[17,2d] methyl acetate,[18] and ethyl carbamate,[1] and although not conclusive evidence for a pre-equilibrium protonation step,[19] we shall as before discuss the reactions in these terms.

TABLE 4

Mass spectrometric results for methanol and methyl carbamate

Methano	$10^3(P_{34}:P_{32})$ [a] Found [b]	Calc. for no enrichment	Calc. for complete enrichment
Sample *A* [c]	1·9	1·9	19
Sample *B*	19	—	19
Sample *C*	2·1	1·9	—

Methyl carbamate	$(P_{77}:P_{76})$ [a] Found	Calc. for no enrichment [e]	Calc. for complete enrichment [d]
Sample *D* [f]	0·20	0·16	0·77
Sample *E* [f]	0·16	0·16	—

[a] Ratios of peak heights for given mass numbers. For methyl carbamate the ratio of the parent peak + 2 to the parent peak + 1 is given, because it was found to be more accurate to compare peaks of similar height on the instrument used. [b] Peak heights were corrected for heavy isotope contributions from other than the molecule ion. Full details are given in V. C. Armstrong, Ph.D. Thesis, Exeter, 1968. [c] J. H. Beynon, 'Mass spectrometry and its Application to Organic Chemistry,' Elsevier, Amsterdam, 1960, p. 291. [d] Of the carbonyl oxygen atom. [e] Mean of two determinations; for sample preparations, see Experimental section. [f] Mean of three determinations.

The Effects of Substituents.—In order to compare the rate constants for hydrolysis without the complication of varying extents of protonation, the observed first-order rate constants have been converted as before [1] into specific first order rate constants for hydrolysis of the protonated substrate, by use of equation (2).

$$k_p = k_{obs}([S] + [SH^+])/[SH^+] \qquad (2)$$

The concentrations of protonated and unprotonated substrate were deduced from published work.[5] Temperature effects on the protonation equilibria of ethyl carbamate have been shown to be small,[1] which justified the use of protonation data for 33·5° in these calculations. To reduce errors, derivation of values of k_p was not attempted if the concentration ratio in equation (2) exceeded 15. Some of the values of k_p so derived are shown in Figure 1. Evidence was previously presented that the mechanism of the hydrolysis of ethyl carbamate changes from one of *A*2 type to one of *A*1 type with increasing acidity. Figure 1 shows that the effect of *N*-methylation is to enhance k_p for the *A*2 reaction. It is clear that the nitrogen protons have no specific role in this mechanism, unlike the reaction of certain carbamates under basic conditions.[20] The same substituents depress the value of k_p for the *A*1 reaction, and the Arrhenius parameters (Table 3) indicate that the *A*2 reaction is still dominant in 80·5% H_2SO_4 for ethyl *NN*-dimethylcarbamate. The *N*-CH_2·CO_2H substituent depresses k_p for the *A*2 reaction, and recent experiments indicate that the *N*-CH_2·CF_3 substituent has an even greater effect in the same direction.[21]

The introduction of two isopropyl groups on the nitrogen atom enhances the rate of the *A*1 reaction and depresses that of the *A*2 reaction so that the latter is

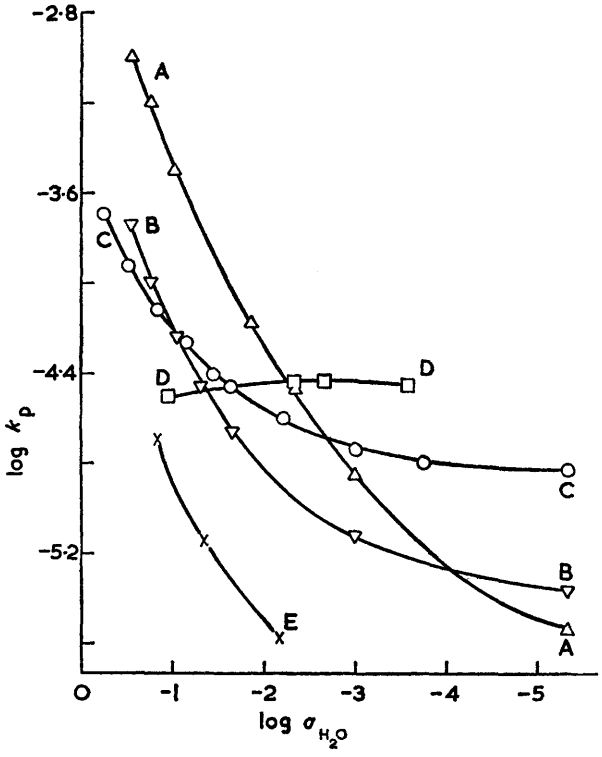


FIGURE 1 Plots of log k_p against log a_{H_2O} for acid-catalysed hydrolysis in aqueous sulphuric acid: A, EtO·CO·NMe_2; B, EtO·CO·NHMe; C, EtO·CO·NH_2; D, EtO·CO·$N(Pr^i)_2$; and E, EtO·CO·NH·CH_2·CO_2H

not observed over the measured range, as is evident from the small change of k_p with acidity (Figure 1) and the value of log *A* in 80% H_2SO_4 (Table 3).

The kinetics of the reactions of phenyl carbamate and phenyl *NN*-dimethylcarbamate were not studied at high enough acidities for the derivation of values of k_p. However the steep dependence of k_{obs} for phenyl carbamate on acidity, and the reversal of the order of catalytic effectiveness of the two acids at the higher acidities with this substrate [1,3c] (Figure 2) suggests that the *A*1 mechanism becomes dominant at relatively low acidities. The Arrhenius pre-exponential factor in 40% H_2SO_4 is greater than that for ethyl carbamate, but the significance

[17] O. Reitz, *Z. Elektrochem.*, 1938, **44**, 693.
[18] J. C. Homel and J. A. V. Butler, *J. Chem. Soc.*, 1936, 1361.
[19] V. Gold, *Trans. Faraday Soc.*, 1960, **56**, 255; C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, 1961, **83**, 3214; C. G. Swain, D. A. Kulm, and R. L. Schowen, *ibid.*, 1965, **87**, 1553.
[20] M. L. Bender and R. B. Homer, *J. Org. Chem.*, 1965, **30**, 3975.
[21] G. S. Dyson, D. W. Farlow, and R. B. Moodie, unpublished work.

of this is blurred by uncertainties about the temperature-dependence of the protonation equilibrium of phenyl carbamate. Phenyl *NN*-dimethyl carbamate is a weaker base than phenyl carbamate (Table 1) and yet is hydrolysed more quickly at the lower acid concentrations, showing that the effect of *N*-methylation is again to enhance the rate of the *A*2 reaction. Finally, a similar comparison of phenyl and ethyl *NN*-dimethylcarbamates shows that k_p in the *A*2 region is greater for the former compound.

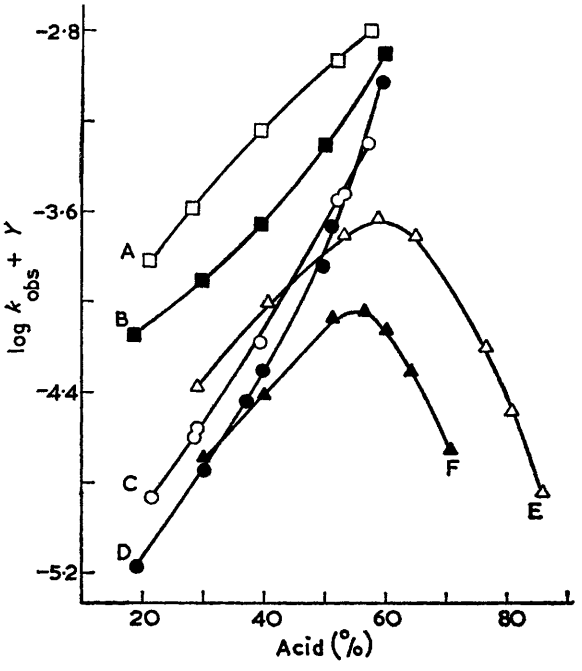


FIGURE 2 Plots of log k_{obs} + Y against % acid; the constant Y is used to adjust the ordinate. A, PhO·CO·NMe_2 in H_2SO_4 (Y = 0·8); B, PhO·CO·NMe_2 in $HClO_4$ (Y = 0·8); C, PhO·CO·NH_2 in H_2SO_4 (Y = 0); D, PhO·CO·NH_2 in $HClO_4$ (Y = 0); E, EtO·CO·NMe_2 in H_2SO_4 (Y = 0); and F, EtO·CO·NMe_2 in $HClO_4$ (Y = 0)

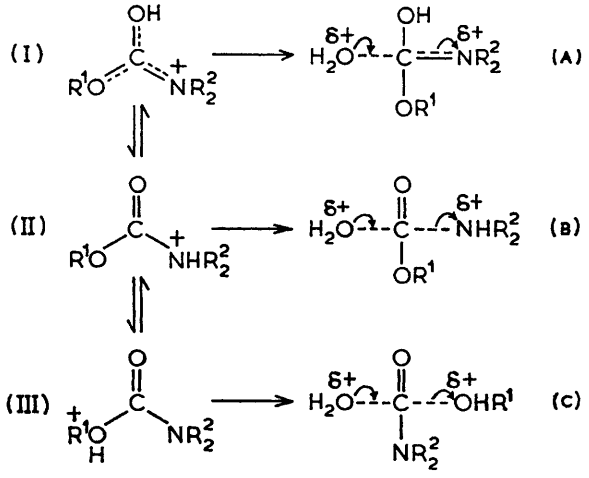
To summarise, the order of reactivity of the protonated substrates towards the *A*2 reaction is PhO·CO·NMe_2 > EtO·CO·NMe_2 > EtO·CO·NHMe > MeO·CO·NH_2 > EtO·CO·NH_2 > EtO·CO·NH·CH_2·CO_2H, EtO·CO·NH·CH_2CF_3, EtO·CO·$N(Pr^i)_2$ and towards the *A*1 reaction is PhO·CO·NH_2 > EtO·CO·$N(Pr^i)_2$ > MeO·CO·NH_2 > EtO·CO·NH_2 > EtO·CO·NHMe > EtO·CO·NMe_2.

Alkyl–Oxygen as Opposed to Acyl–Oxygen Bond Fission.—The *A*2 hydrolyses of primary alkyl esters of carboxylic [22] and carbonic [23] esters occur with acyl–oxygen bond fission, but the deactivation of the carbonyl carbon atom in the present compounds could lead to a change in the preferred electrophilic centre. However the lack of oxygen-18 enrichment of methanol extracted after the hydrolysis of methyl carbamate in 1M-perchloric acid containing excess of $H_2{}^{18}O$ (Table 4 and Experimental section) shows that alkyl–oxygen fission is not involved in this case, and the similarity of the rate profiles (Figure 2) for ethyl *NN*-dimethylcarbamate and phenyl *NN*-dimethylcarbamate again suggests (since aryl–oxygen bond fission in the latter compound cannot be seriously considered) that these also react by the $A_{Ac}2$ mechanism.

Comparison of the rate profiles for ethyl and methyl carbamates was previously used [1] to show that alkyl–oxygen fission is not involved in the *A*1 reaction of these substrates. It is probable however that a carbamate capable of generating a more stable carbonium ion would decompose by such a mechanism; [22] indeed an $A_{Ac}1$ mechanism has been inferred in the hydrolysis of benzyloxycarbonylglycine.[23]

The Transition State for the $A_{Ac}2$ Reaction.—We consider three models for the transition state, each involving nucleophilic attack of water on a different tautomeric form of the protonated substrate.

Attack on the normally dominant [24] tautomer (I) would lead to a tetrahedral intermediate. The observation (Table 4) that methyl carbamate does not pick up a significant amount of oxygen-18 from the solvent water during the course of hydrolysis precludes the postulation of the *pre-equilibrium* formation of such an intermediate. (The small amount of exchange observed is not outside experimental error.) The formation



of a tetrahedral intermediate in a rate-determining step is not ruled out by the results of the oxygen-exchange experiment, and would be analogous to suggested mechanisms for the hydrolysis of protonated esters,[3b] amides,[2] and imidates [4a,b] but the observed accelerative effects of *N*-methyl groups and the rate depression caused by the electron-withdrawing *N*-CH_2·CO_2H and *N*-CH_2·CF_3 groups are not in accord with such a mechanism for carbamates. These effects of *N*-substituents also contrast with those found for amides and imidates. Mono-*N*-methylation of benzamide inhibits the *A*2 reaction (although a second *N*-methyl

[22] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' G. Bell and Sons, London, 1953, p. 768.

[23] S. Sarel, L. A. Pohoryles, and T. Levin, *J. Chem. Soc.*, 1960, 3079.

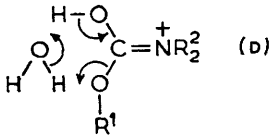
[24] G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, 1968, **90**, 401.

group inexplicably reverses the trend [2d]), 3,5-dinitroacetanilide is hydrolysed more quickly than 4-nitroacetanilide under conditions where the $A2$ reaction prevails,[25] and the rate constant for acidic hydrolysis of ethyl *N*-methylacetimidate [4a] is less than that of ethyl *N*-phenylacetimidate [4b] by a factor which is too great to be accounted for by the 5° difference in the temperatures at which the runs were conducted. It is clear that the $A_{Ac}2$ reaction of carbamates, unlike those of imidates and amides, does not proceed *via* a tetrahedral intermediate. We now consider displacement mechanisms arising from tautomers (II) and (III), noting that these have been considered most likely in the cases of carbonates and carbamates owing to the possibility of back-bonding of the lone-pair electrons on the oxygen or nitrogen atoms into the π^* orbital of the carbonyl group.[26]

Tautomer (II) would be expected to be the second most abundant; it is in fact the dominant form of protonated ethyl *NN*-di-isopropylcarbamate [5b] and displacement of the amine by water [transition state (B)] must now be considered. The effects of *N*-substituents are now opposite on the tautomeric equilibrium and on the rate-determining step, so no prediction is possible. However contrary to the observations, the ethyl carbamates should be hydrolysed more quickly than the phenyl carbamates since the phenyl group would destabilise the partial positive charge on the oxygen in the transition state arising from the back-bonding mentioned above. The predominant *N*-protonation of ethyl *NN*-di-isopropylcarbamate should favour this mechanism, and models suggest that steric hindrance would not be too severe for this mode of attack, yet an $A2$ reaction for this substrate could not be detected.

All the observations can be accommodated in terms of the transition state model (C) arising from tautomer (III). The steric effects of two *N*-isopropyl groups may now be considerable, and the effects of *N*-methyl and *N*-CH_2CO_2H substituents are in accord with their influence on the back-bonding previously mentioned. Another satisfactory feature of this mechanism is that it involves a path which is not available for protonated amides or imidates.

Whilst this appears to be the simplest mechanism consistent with the observations, a host of mechanisms involving cyclic transition states [3a] and one or two water molecules can also be considered, of which the most satisfactory is (D). However a feature of such mechanisms is that they lead to no prediction about substituent effects. They involve proton transfers in the rate-determining step which would suggest (though inconclusively [19]) a normal solvent isotope effect, contrary to observations (Table 2).



(D)

The Catalytic Effectiveness of Sulphuric and Perchloric Acids for the A2 *Reactions.*—The value of k_p is significantly greater in sulphuric acid than in perchloric acid when comparison is made in the region of the $A2$ reactions and at the same value of the activity of water. Bunton *et al.*[3c] have made similar observations regarding esters, although there it was not clear how much of the effect was on the pre-equilibrium protonation. Possible explanations include nucleophilic catalysis by sulphate ion (of which there may [27] or may not [28] be appreciable quantities in the moderately concentrated aqueous acid), the hydrogen sulphate ion acting as a proton-transfer agent [for instance in a transition state like (D)], or as a general acid catalyst,[29] and non-specific medium effects, as suggested by Bunton *et al.* In view of similar observations for amides,[1] where a different mechanism clearly obtains, the last-mentioned explanation seems the most tenable. Whatever the cause, attribution of changes in k_p with medium solely to changes in the activity of water, and consequent deduction of the number of water molecules in the transition state,[2a,b,3a,b] must be unsound.

*The Transition State for the A*1 *Reaction.*—Possibilities include loss of amine from (II) and loss of alcohol from (III), but the substituent effects are not fully in accord with either of these mechanisms, which may well be in competition.

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