

Kinetics of Hydrolysis and Aminolysis of Methyl Chloroformate in Aqueous Solution

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The behaviour in the title reaction of ten primary amines, with a basic pK_a range of 11 units, has been studied. Uncatalysed nucleophilic attack of free base amine and competing uncatalysed hydrolysis are the only reactions found except in the case of hydrazine, where an additional term is attributed to nucleophilic attack of the hydrazinium cation. The Brönsted plot shows that the sensitivity of methyl chloroformate to the basicity of the nucleophile decreases with increase in the latter, and the significance of this is discussed.

THE changing pattern of nucleophilic reactivities with leaving group change in acetyl transfer reactions has been well documented and discussed.¹⁻³ Of particular interest is the sudden loss of sensitivity to the basicity of increasingly basic nucleophiles in the case of substrates with good leaving groups. It is important to know whether this effect is mainly connected with the efficacy of the leaving group or with the overall reactivity of the substrate. Methyl chloroformate was chosen as the substrate for this study because it is of similar reactivity to the 1-acetoxy-4-methoxypyridinium ion;¹ chloride ion is a better leaving group but this factor is offset by acyl deactivation (methoxy in place of methyl). It is known⁴ that the hydrolysis of methyl chloroformate in water [equation (1)] is a bimolecular

$$\text{MeO}_2\text{CCl} + \text{H}_2\text{O} \rightleftharpoons \text{MeOH} + \text{CO}_2 + \text{H}^+ + \text{Cl}^- \quad (1)$$

process. Previous work on reactions of chloroformates with nucleophiles has been excellently reviewed,⁵ but apart from the work of Hall⁶ little has been recorded about aminolysis [equation (2)] reactions in aqueous solution.



RESULTS

The first-order rate constant, k_w , for the background hydrolysis reaction, determined by the pH-stat method at several pH values in 0.2M-sodium perchlorate, was $5.6 (\pm 0.1) \times 10^{-4} \text{ s}^{-1}$ (mean of 7 determinations; error is standard error⁷). This is in satisfactory agreement

¹ W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

² A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5432, 5442.

³ O. G. Oakenfull and W. P. Jencks, *J. Amer. Chem. Soc.*, 1971, **93**, 178; T. C. Bruice, A. F. Hegarty, S. M. Felton, A. Douzel, and N. G. Kundu, *ibid.*, 1970, **92**, 1370.

⁴ A. Queen, *Canad. J. Chem.*, 1967, **45**, 1619.

with the value of $5.64 \times 10^{-4} \text{ s}^{-1}$ reported⁴ for hydrolysis in water initially at zero ionic strength and determined by a more accurate but less versatile method.

For the aminolysis reactions, first-order conditions (excess of total amine over methyl chloroformate) were used throughout. Conditions were chosen as far as possible to avoid the possibility of autocatalysis from hydrogen carbonate ion arising from the competing hydrolysis reaction. Such catalysis would have been evident from departures from first-order kinetics, and was not found. Reaction of methyl chloroformate with the chloroacetate ion (pK_a of conjugate acid 2.75) under these conditions has⁸ $k_B = 3.35 \times 10^{-3} \text{ l mol}^{-1} \text{ s}^{-1}$, which makes it unlikely that hydrogen carbonate ion (pK_a of conjugate acid 3.6, but concentration governed⁹ by the 'effective' pK_a of 6.35) would have $k_B > 3 \times 10^{-2} \text{ l mol}^{-1} \text{ s}^{-1}$ and confirms the impression that such a reaction is negligible under the conditions used.

With the exceptions of the reactions with aniline, and some of the studies with trifluoroethylamine and hydrazine, the pH-stat method was used, in which the amount of alkali added to maintain constant pH is used to monitor the progress of the reaction. Values of pH (which must be greater than 3 and far removed from the pK_a of the conjugate acid of the amine if sufficient sensitivity is to be achieved) are shown in the Table. The results were well fitted by equation (3) in which

$$k_{\text{obs}} = k_w + k_B[\text{B}] \quad (3)$$

[B] is the concentration of free base. No evidence for acidic or basic catalysis terms³ was found.

⁵ D. N. Kevill, 'The Chemistry of Acyl Halides,' ed. S. Patai, Interscience, London, 1972, p. 381.

⁶ H. K. Hall, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 5439.

⁷ J. Topping, 'Errors of Observation and their Treatment,' Chapman and Hall, London, 1955.

⁸ E. A. Castro and R. B. Moodie, unpublished work.

⁹ D. M. Kern, *J. Chem. Ed.*, 1960, **37**, 14.

The reaction of aniline with methyl chloroformate was studied by spectrophotometric observation of the formed methyl *N*-phenylcarbamate at pH values sufficiently low for it to be unnecessary to use a buffer for pH control. The reaction of hydrazine was found to be complicated by further reaction of the methyl hydrazinoformate formed, but preparation and separate study of the latter by the pH-stat method made it possible to choose conditions for the study of hydrazine

as arising from four concurrent reactions, described respectively by equation (1) and three versions of equation (2) in which RNH₂ represents aniline, hydrazine, and the hydrazinium monocation (itself a weak base¹⁰). In accord with this the final absorbance was found to be proportional to $k_{An}[An]/k_{obs}$.

The necessity for including the last term in equation (5) is demonstrated in Figure 1, which includes results obtained both by the pH-stat method and by the

Concentrations used and rate constants obtained for the aminolysis of methyl chloroformate in aqueous solution at 25 °C with the ionic strength maintained at 0.2 mol l⁻¹ with sodium perchlorate

Amine	pH	Total amine concentration/ (mol l ⁻¹)	Number of runs	Rate constant ^a $k_B/1 \text{ mol}^{-1} \text{ s}^{-1}$	pK_a
1 Ethylamine	5.5	0.05—0.02	7	390 (±10)	10.85
	6.0	0.05—0.2	7		
	6.5	0.05—0.2	7		
2 Glycine ^b	4.9—6.2	0.016—0.2	14	430 (±40)	9.68
	5.0	0.08—0.2	6		
3 2-Methoxyethylamine	3.0—5.0	0.2	7	204 (±10) ^c	9.45
	3.0—5.0	0.2	7	199 (±10)	
4 Ethyl glycinate	3.0—4.0	0.2	6	88 (±2)	7.83
	3.8	0.03—0.2	7		
	4.2	0.03—0.14	6		
5 Hydrazine	2.61—2.63 2.92—2.96	0.04—0.07	4	1900 (±100) ^d	8.15
		0.04—0.06	3		
		0.01—0.10	10		
6 Hydrazinium	3.1	0.01—0.07	7	0.025 (±0.0005) ^e	-0.53
7 Trifluoroethylamine	3.5	0.01—0.07	7		
	2.39	0.02—0.12	6	5.9 ^e	5.60
	2.69	0.02—0.12	6		
	2.89	0.01—0.06	6		
	3.0	0.02—0.12	7		
	3.6	0.005—0.06	7		
	3.8	0.005—0.06	7		
8 Aniline	2.38	0.0025—0.0125	5	22.7 (±0.5)	4.83
	2.64	0.0025—0.010	4		
	2.89	0.001—0.006	6		
9 Methyl hydrazinoformate	5.5	0.0005—0.0015	5	4.2 (±0.1)	3.55
	6.0	0.0005—0.0015	5		
10 <i>m</i> -Nitroaniline ^f	5.0	0.006	2	1.66 (±0.02)	2.61
	5.5	0.006	1		
	6.0	0.006	2		
11 <i>p</i> -Nitroaniline ^f	5.0	0.005	2	0.088 (±0.005)	1.14
	6.0	0.005	2		

^a Specific rate constant for reaction of the free base amine with methyl chloroformate. ^b It was found difficult to get good reproducibility with this compound, as is evident from the large standard error. The reason for this is unknown. ^c Amine neutralised with perchloric acid, not hydrochloric acid as was the case elsewhere. ^d Obtainable by least squares as the slope and intercept of Figure 1 (see text). ^e Mean of the values obtained by the aniline kinetic indicator method [5.6 (±0.2)] at the three lowest values of pH and that obtained by the pH stat method [6.2 (±0.2)] at the two highest values of pH. ^f Low solubility precluded study of these compounds over a range of concentration.

under which this further reaction was not a complication. It was only possible to use the pH-stat technique for hydrazine over a restricted range of acidity, and because the results indicated, unlike those for all the other bases studied, some dependence of k_B upon pH, a method of studying the reaction at lower pH was sought. Accordingly aniline was used as a 'kinetic indicator' in the following way. Solutions were made up containing aniline, hydrazine, and acid to give the required pH. The appearance of methyl *N*-phenylcarbamate was followed spectrophotometrically, and found to follow a first-order course as described by equations (4) and (5).

[Methyl *N*-phenylcarbamate]

$$= (k_{An}[An]/k_{obs})(1 - e^{-k_{obs}t}) \quad (4)$$

$$k_{obs} = k_w + k_{An}[An] + k_{HZ}[HZ] + k_{HZH}[HZH^+] \quad (5)$$

The four terms on the right of equation (5) are identified

method just described, and in which the quantity k_{HZ}' [equation (6)] is plotted against a_{H^+} (taken as 10^{-pH}).

$$k_{HZ}' = (k_{obs} - k_w - k_{An}[An])/[HZ] \quad (6)$$

Clearly, ignoring the last term in equation (5) leads to an apparent specific rate constant for the reaction of hydrazine base with methyl chloroformate, k_{HZ}' , which varies linearly with a_{H^+} . We prefer to attribute this to an additional nucleophilic reaction involving hydrazinium monocation, rather than to acidic catalysis of the nucleophilic attack of the free base hydrazine, because the specific rate constant for the hydrazinium monocation k_{HZH} , so deduced (slope of Figure 1 multiplied by the acidity constant of hydrazine), fits reasonably well on the Brønsted plot (Figure 2), and because hydrazine was the only diacid base studied and the only base

¹⁰ J. J. Christensen, R. M. Izatt, D. P. Wrathall, and L. D. Hansen, *J. Chem. Soc. (A)*, 1969, 1212.

which showed such a term. The reasons why nucleophilic reactivity of the hydrazinium monocation is not normally encountered are first that it is not normally

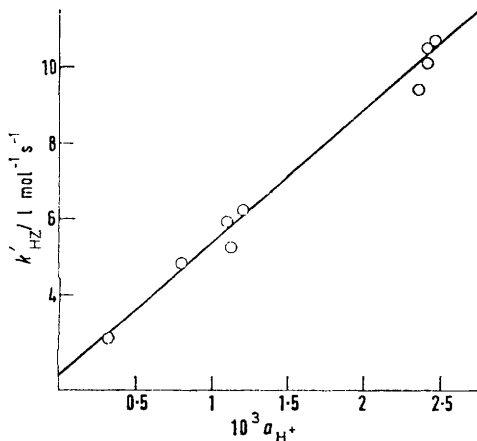


FIGURE 1 Plot of $k'_{\text{HZ}}/l \text{ mol}^{-1} \text{ s}^{-1}$ vs. a_{H^+} for the reaction of hydrazine with methyl chloroformate

necessary to study the reaction of hydrazine at such low values of pH, and secondly that the present reaction is abnormally insensitive to the basicity of the base.

Trifluoroethylamine was also studied by the pH-stat method and by the aniline kinetic indicator method; in this case no dependence of the catalytic constant upon pH was found (Table).

The rate constants and errors reported in the Table are weighted means, and standard errors from the weighted means, of $(k_{\text{obs}} - k_{\text{w}})/[\text{B}]$, with weights assigned as $[\text{B}]^2/(k_{\text{obs}}^2 + k_{\text{w}}^2)$, except in the cases of hydrazine and the hydrazinium cations, for which rate constants and standard errors were obtained as the slope and intercept of Figure 1 by least squares analysis.

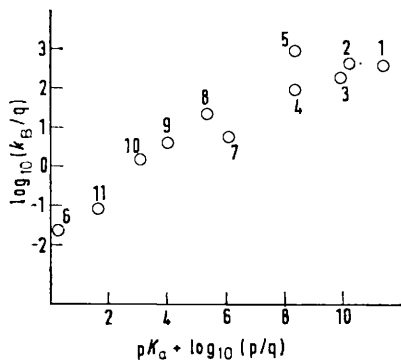


FIGURE 2 Plot of $\log_{10}(k_{\text{B}}/l \text{ mol}^{-1} \text{ s}^{-1}) - \log_{10}q$ vs. $pK_{\text{a}} + \log_{10}(p/q)$ where p and q are the statistical corrections defined in ref. 11; the numbering of the bases is the same as in the Table

DISCUSSION

The statistically corrected¹¹ Brönsted plot (Figure 2) reveals that methyl chloroformate shows decreasing sensitivity to the basicity of the attacking amine with

¹¹ R. P. Bell and P. G. Evans, *Proc. Roy. Soc.*, 1966, **291A**, 297.

¹² W. E. Hall, T. Higuchi, I. H. Pitman, and K. Vekama, *J. Amer. Chem. Soc.*, 1972, **94**, 8153.

increasing pK_{a} , as is found with reactive acetyl compounds^{1,2} and anhydrides.¹² The fact that aniline is more reactive than trifluoroethylamine despite its lower basicity, as is found with the 1-acetoxy-4-methoxypyridinium ion,¹ shows that factors other than basicity determine the difference in reactivity between anilines and aliphatic amines, and for this reason no attempt has been made to draw a single curve through the points. Hydrazine shows enhanced (α -effect) reactivity if comparison is made, as is usually done,^{1,12} with the primary aliphatic amines, but the magnitude of the enhancement is modest, in accord with the noted¹³ relation between the magnitude of the α -effect and the Brönsted slope. Methyl hydrazinoformate (which is similar in structure and basicity to semicarbazide) cannot be compared with aliphatic amines of similarly low basicity, but shows no α -effect if comparison is made with the anilines.

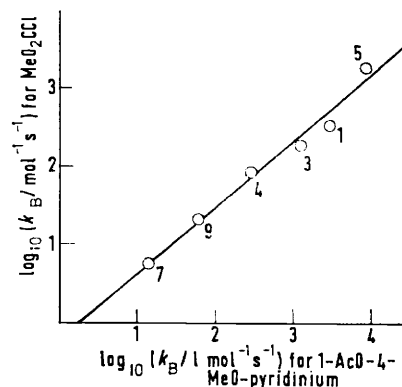


FIGURE 3 Plot of $\log_{10}(k_{\text{B}}/l \text{ mol}^{-1} \text{ s}^{-1})$ for MeO_2CCl vs. $\log_{10}(k_{\text{B}}/l \text{ mol}^{-1} \text{ s}^{-1})$ for 1-AcO-4-MeO-pyridinium; the numbering of the bases is the same as in the Table

The similar pattern of nucleophilic reactivities towards methyl chloroformate and towards the 1-acetoxy-4-methoxypyridinium ion is demonstrated in Figure 3. A reasonable straight line can be drawn through the points with a slope of 0.86 (correlation coefficient 0.985). Clearly methyl chloroformate shows the lower sensitivity to the nature of the nucleophile, despite its slightly lower reactivity. This is not in accord with a 'Hammond postulate' type of effect¹⁴ in a reaction in which tetrahedral intermediate formation is always rate-determining, and highlights the importance of leaving group ability. If there were a change in rate-determining step, for instance from breakdown to formation of a tetrahedral intermediate, with increasing nucleophilic reactivity, and if this change occurred at lower reactivities with methyl chloroformate than with the 1-acetoxy-4-methoxypyridinium ion (because of the difference in leaving group abilities) then Figure 3 might be expected to have near unit slope at the upper end where amine attack is rate-determining for both substrates, and at the lower end where tetrahedral

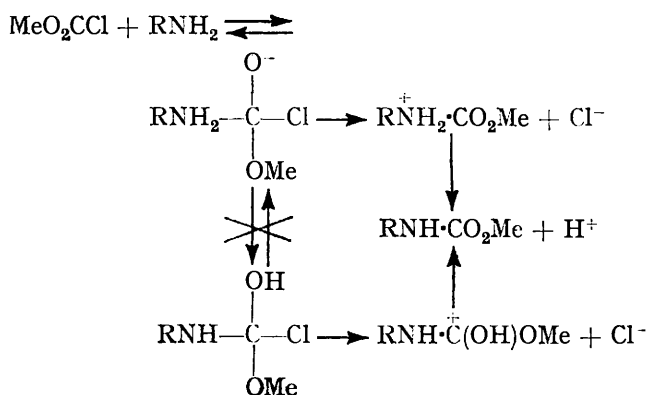
¹³ F. Filippini and R. F. Hudson, *J.C.S. Chem. Comm.*, 1972, 522; J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, 1972, **94**, 2052.

¹⁴ G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

intermediate breakdown is rate-determining for both substrates, but to be flatter in the middle. Such a curve could equally well be drawn through the points and would be no more and no less justified than the line shown.

The curvature of the Brønsted plot (Figure 2) could be attributed to a change of rate-determining step as just described, or to a 'Hammond postulate' type of effect in a one-step mechanism in which nucleophilic attack and leaving group departure are linked. The inadequacy of pK_a as a measure of nucleophilicities of both anilines and primary amines makes a choice based on quantitative consideration of the curvature difficult.

Substituted pyridines offer a homogeneous set of bases covering a sufficiently wide range of pK_a values for quantitative consideration of the curvature of the Brønsted plot.¹⁵ However the generally *higher* reactivity of pyridines compared with primary amines of similar basicity makes it likely that if a tetrahedral intermediate is involved in the primary amine reactions, it does not exist long enough for proton equilibration among its basic sites.¹⁶ Otherwise regression of the intermediate to reactants would be effectively prevented in the primary amines but not in the pyridines, giving the former a decided advantage.



EXPERIMENTAL

Materials.—Methyl chloroformate, aniline, 2-methoxyethylamine, and acetonitrile were purified by distillation. The following compounds were recrystallised from the solvents given in parentheses: *p*-nitroaniline (benzene) *m*-nitroaniline (benzene–light petroleum), trifluoroethylamine hydrochloride (benzene–ethanol), and glycine ethyl ester hydrochloride (chloroform–ethanol). M.p.s were in agreement with literature values. Hydrazinium hydrogen sulphate (B.D.H. AnalaR) and glycine (B.D.H. Chromatographically homogeneous) were used as supplied.

Product Studies.—Methyl hydrazinofornate¹⁷ (ether; m.p. 72°) methyl *N*-phenylcarbamate¹⁸ (light petroleum; m.p. 46–47°), methyl *N*-ethylcarbamate¹⁹ (b.p. 66° at 13 mmHg), and *N*-methoxycarbonylglycine ethyl ester²⁰

(molecular distillation) were prepared by standard methods and purified as indicated. These four compounds were then compared by t.l.c. with the products obtained under conditions as close as possible to those used in the kinetic studies of the reactions of hydrazine, aniline, ethylamine, and ethyl glycinate, respectively with methyl chloroformate, and shown to be identical. These four were chosen as representative and no product studies were made with the other amines.

Kinetic Studies.—A Radiometer 26A pH meter, together with titrator TTT11, syringe burette SBU/1a, and Titrigraph SBR2, was used for the pH stat studies. The glass electrode was Radiometer type G202B, for which sodium ion corrections are negligible under the conditions used. Amine or amine salt solutions (25 ml) were brought to the correct pH and ionic strength generally with hydrochloric acid and sodium perchlorate. [Two similar studies of the reaction of methoxyethylamine using hydrochloric and perchloric and respectively for neutralisation gave rate constants which agreed within experimental error (see Table), which shows that the reaction is insensitive to the nature of the anion.] After thermal equilibration, methyl chloroformate, either pure or as a solution in acetonitrile (10–20 μ l), was added to start the reaction, such that the initial concentration of methyl chloroformate was 10^{-4} – 5×10^{-3} mol l⁻¹.

Where the pH used is lower than the pK_a of the amine, the aminolysis reaction [equation (2)] yields 2 mol of H⁺ for each mol of MeO₂CCl. The ratio of the final amount of sodium hydroxide needed to maintain constant pH to the amount of methyl chloroformate used must therefore be given by $(k_w + 2k_B[B]) / (k_w + k_B[B])$. The results were in accord with this conclusion.

For spectrophotometric kinetic studies a Unicam SP 1800 spectrophotometer was used. Two 1 cm cells each containing 3 ml of a solution of amine after pH adjustment were thermally equilibrated at 25 °C and a solution of methyl chloroformate in acetonitrile (3–4 μ l) was added by syringe to one of them to start the reaction. The initial concentration of methyl chloroformate was 1.3 – 1.7×10^{-4} mol l⁻¹. The production of methyl *N*-phenylcarbamate was monitored at 226 or 234 nm. First-order rate constants were computed either by the 'infinity' method or by a least-squares version of the Swinbourne method.²¹ In all cases reactions were accurately first-order over 2–3 half-lives.

Determinations of pK_a .—The pH meter and electrodes mentioned above were used, and a mean value of pK_a was computed from pH measurements at several concentrations around the half-neutralisation point. The ionic strength was maintained at 0.2 mol l⁻¹ in these experiments. The results are given in the Table and are in satisfactory agreement with published thermodynamic values²² when the appropriate activity coefficient correction is made. The pK_a values of the nitroanilines and the hydrazinium cation were not measured; the values listed in the Table were obtained by adding 0.14 to the listed thermodynamic values.^{10,22}

[3/2256 Received, 2nd November, 1973]

¹⁵ E. A. Castro and R. B. Moodie, *J.C.S. Chem. Comm.*, 1973, 828.

¹⁶ J. P. Fox, M. I. Page, A. Satherthwaite, and W. P. Jencks, *J. Amer. Chem. Soc.*, 1972, **94**, 4729.

¹⁷ O. Diels, *Ber.*, 1914, **47**, 2186.

¹⁸ W. Hentschel, *Ber.*, 1885, **18**, 978.

¹⁹ A. P. N. Franchimont and E. A. Klobbie, *Rec. Trav. chim.*, 1888, **7**, 355.

²⁰ H. Leuchs, *Ber.*, 1906, **39**, 859.

²¹ E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.

²² D. D. Perrin, 'Association Constants of Organic Bases in Aqueous Solutions,' Butterworth, London, 1965.