

Alkaline Hydrolysis of Positively Charged Methyl and *p*-Nitrophenyl Esters of Dimethyl- and Trimethylglycine

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The rate constants for the alkaline hydrolysis of the cation forms of methyl and *p*-nitrophenyl esters of dimethylglycine have been measured and compared with the corresponding quaternary esters of trimethylglycine. The two to four times higher rate constants of the latter esters exclude assistance from internal hydrogen bonding during hydrolysis of dimethylglycine ester cations.

In a previous study¹ we reported data for hydrolysis of different ammonium esters. When the ester group was more than one methylene group apart from the ammonium group, the rate of alkaline hydrolysis of tertiary ammonium esters were 4 to 20 times higher than the rate of corresponding quaternary esters. Several authors^{2,3} have attributed the acceleration effect to internal hydrogen bonding during hydrolysis. With the potentiometric titration method used in the previous study, we were not able to measure the rate of hydrolysis of the cation form of dimethylglycine methyl ester, but it was concluded that the rate must be much slower than the rate of the corresponding trimethylglycine methyl ester, *i.e.* opposite in behaviour of the other ammonium esters. Recently Hay *et al.*⁴ and Robson⁵ have estimated the rate of alkaline hydrolysis for the cation forms of methyl and ethyl esters of glycine from measurements of the rate of ester hydrolysis around pH 10. Since this is 2.5 pH units above the *pK*-values of the esters, the concentration of the cation forms are very low, and their contribution to the total rate of hydrolysis is correspondingly small. It seemed to us that a better method for determination of the rate of the cation form of tertiary esters might be to measure the rate of fall of pH during hydrolysis at so low pH that a considerable amount of the ester is still present in the cation form.

The rate of hydrolysis of the cation form of the *p*-nitrophenyl ester of dimethylglycine was very high even in the neighbourhood of the *pK*-value of the ester. In this case measurements of the alkali consumption at constant pH was found to be the best method for evaluation of the rate constant.

EXPERIMENTAL

Materials. The bromides of the methyl esters of dimethyl- and trimethylglycine were made from the methyl ester of bromoacetic acid on treatment with dimethylamine, respectively trimethylamine.¹ The corresponding *p*-nitrophenyl esters could not be made according to this method because the labile *p*-nitrophenyl ester of bromoacetic acid underwent aminolysis in preference to substitution at the α -carbon atom on treatment with amines. These esters were, however, obtained from *p*-nitrophenol and the acid chlorides, $[(\text{CH}_3)_2\overset{+}{\text{N}}\text{HCH}_2\text{COCl}]\text{Cl}^-$ and $[(\text{CH}_3)_3\overset{+}{\text{N}}\text{CH}_2\text{COCl}]\text{Cl}^-$. The crude ammonium esters were recrystallized several times from methanol/ether.

$[(\text{CH}_3)_2\overset{+}{\text{N}}\text{HCH}_2\text{COOC}_6\text{H}_4\text{-}p\text{-NO}_2]\text{Cl}^-$: (Found: Cl 14.0. Calc. for $\text{C}_{10}\text{H}_{13}\text{O}_4\text{N}_2\text{Cl}$: Cl 13.60). $[(\text{CH}_3)_3\overset{+}{\text{N}}\text{CH}_2\text{COOC}_6\text{H}_4\text{-}p\text{-NO}_2]\text{Cl}^-$: (Found: Cl 13.0. Calc. for $\text{C}_{11}\text{H}_{16}\text{O}_4\text{N}_2\text{Cl}$: Cl 12.92).

Kinetic measurements

Method A. Measurement of rate of fall of pH. The reaction mixture contained approximately 5×10^{-3} M ester in 0.1 M sodium chloride. The rate of fall of pH was measured with an accuracy of ± 0.02 pH units. Several runs with different initial pH between 7 and 8.5 were performed. Usually 10–15 readings were taken in each run. Since the rate of hydrolysis of the neutral ester is negligible compared to the protonated ester, and the concentration of hydroxyl ions is low compared to the concentration of ester cation, in the pH-region studied, the equation evaluated by Bell and Collier⁷ reduces to:

$$k_{\text{OH}^-} = 2.303 \cdot \frac{d(\text{pH})}{dt} \cdot \frac{K_a}{K_w}$$

where K_a and K_w are the ionization constants of the ammonium ester, respectively water, and $d(\text{pH})/dt$ is the rate of fall of pH in pH units per sec.

Method B. Measurement of alkali consumption at constant pH. The measurements were performed on a recording pH-stat, Radiometer T.T.T.I., in the presence of 0.1 M NaCl. The hydrolysis was studied as a pseudo 1. order reaction, and the method of Guggenheim⁸ was used for evaluation of the rate constants. From the observed pH-values the hydroxyl ion concentrations were calculated using the equation of Davis.⁹

DISCUSSION

The rate constant for the alkaline hydrolysis of the cation forms of methyl and *p*-nitrophenyl esters of dimethyl- and trimethylglycine are summarized in Tables 1, 2, and 3. The rate constant of trimethylglycine methyl ester, $k_{\text{OH}^-} = 79.4 \text{ l mole}^{-1} \text{ sec}^{-1}$, is nearly three times less than the value reported by us in a previous paper.¹ We do not know the reason for the error of the former value, but we suspect that there must have been some fault in the glass electrode. The reliability of the present value can be seen from the approximate constancy of the calculated rate constant over an interval of 2.5 pH units. The earlier reported value was estimated within a narrow pH-interval around pH 7.

The present data confirm the earlier suggestion that the cation form of dimethylglycine esters hydrolyse considerably slower than the corresponding trimethylglycine esters. Whether the ammonium group in the ester is tertiary or primary, *i.e.* contains one or three hydrogen atoms linked to nitrogen, seems

Table 1. Rate of alkaline hydrolysis of $[(\text{CH}_3)_2\text{NHCH}_2\text{COOCH}_3]\text{Br}^-$ at 25°C in 0.1 M NaCl (Method A).

Initial pH	7.21	7.41	7.42	7.49	7.52	7.79	8.00	8.83	
$d(\text{pH})/dt \text{ sec}^{-1} \times 10^6$	2.71	3.15	2.78	2.65	2.34	2.97	3.12	3.02	Mean value
$k_{\text{OH}^-} \text{ l mole}^{-1} \text{ sec}^{-1}$	19.7	22.9	20.2	19.3	17.0	21.6	22.7	21.9	20.6

Table 2. Rate of alkaline hydrolysis of $[(\text{CH}_3)_3\text{NCH}_2\text{COOCH}_3] \text{Br}^-$ at 25°C in 0.1 M NaCl (Method B).

pH	7.00	7.20	7.30	7.50	8.50	8.70	8.80	8.90	9.00	9.10	9.50	
$k_{\text{obs}} \text{ sec}^{-1} \times 10^5$	1.04	1.78	2.08	3.35	31.9	53.6	61.4	81.0	100	121	331	Mean value
$k_{\text{OH}^-} \text{ l mole}^{-1} \text{ sec}^{-1}$	80.0	86.2	80.0	81.6	78.5	82.4	74.8	78.5	77.0	73.9	80.5	79.4

Table 3. Rate of alkaline hydrolysis of $[(\text{CH}_3)_2\text{NHCH}_2\text{COOC}_6\text{H}_4\text{NO}_2]\text{Cl}^-$ and $[(\text{CH}_3)_3\text{NCH}_2\text{COOC}_6\text{H}_4\text{NO}_2]\text{Cl}^-$ at 25°C in 0.1 M NaCl (Method B).

	$(\text{CH}_3)_2\text{NHCH}_2\text{COOC}_6\text{H}_4\text{NO}_2$			$(\text{CH}_3)_3\text{NCH}_2\text{COOC}_6\text{H}_4\text{NO}_2$							
pH	6.42	6.51		6.60	6.70	6.99	7.00	7.21	7.30	7.51	
$k_{\text{obs}} \text{ sec}^{-1} \times 10^4$	1.46	1.79	Mean value	5.0	6.3	12.0	12.2	20.2	26.0	38.0	Mean value
$k_{\text{OH}^-} \text{ l mole}^{-1} \text{ sec}^{-1} \times 10^{-3}$	4.3	4.3	4.3	9.7	9.7	9.5	9.4	9.6	10.0	9.1	9.6

to play a minor role, since the rate of hydrolysis of the glycine methyl ester cation estimated by Hay *et al.*,⁴ $58 \text{ l mole}^{-1} \text{ sec}^{-1}$, is only 26 % lower than the value for trimethylglycine methyl ester reported in this study.

The present findings argue against participation of internal hydrogen bonding during hydrolysis of the cation forms of primary, secondary and tertiary glycine esters.¹ It may be that the strongly bent intramolecular hydrogen bond which have to be formed in these esters (5-membered ring) is energetically unfavourable for proton transfer to the carboxyl group, and that intermolecular protonation from the solvent is therefore preferred.

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