

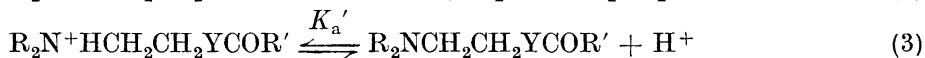
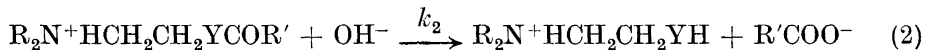
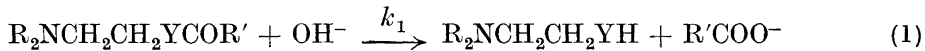
## Kinetics of the Alkaline Hydrolysis of Aminoalkyl Esters of Carboxylic Acids

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The rates of the alkaline hydrolysis of the acetate esters of 3-dimethylamino-1-propanol (IV), 2-dimethylamino- (I), 2-diethylamino- (II), and 2-diisopropylaminoethanol (III) have been measured in 0.07 M KClO<sub>4</sub> at 25°. The rates of the reactions between hydroxyl ions and the amino forms of the esters are of the same magnitude as for ethyl acetate (for I,  $\log k = -1.0$ , and for IV,  $-0.85$ ;  $k$  in  $\text{l mole}^{-1}\text{sec}^{-1}$ ). Hydroxyl ions react more rapidly with the ammonium forms of the esters than with acetyl choline ( $\log k$  for I, 1.63; II, 1.56; III, 1.47 and IV, 0.77). This can be explained in terms of catalysis by an intramolecular hydrogen bond. The  $\text{p}K_a'$ -values are for I, 8.45; II, 9.09; III, 9.40 and IV, 9.27.

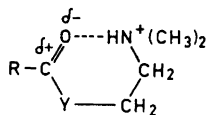
In a previous paper<sup>1</sup> a method for the determination of the dissociation constant,  $K_a'$ , and the two rate constants,  $k_1$  and  $k_2$  as defined below, of the alkaline hydrolysis of compounds containing an ionizable group was described. The method was based on rate measurements at constant pH at a number of pH-values. It was tested with 2-dimethylaminoethyl thiolopropionate for which values of  $K_a'$  and  $k_2$  but not for  $k_1$  could be determined. The value of  $k_2$  was interesting because it was found to be 240 times greater than the second order rate constant of the reaction between the 2-trimethylammoniummethyl thiolopropionate (propionyl thiocholine) and hydroxyl ions<sup>2</sup>.



Y = O or S

In a recent paper<sup>3</sup> Ågren *et al.* reported the same phenomenon for some aromatic esters of 2-diethylaminoethanol. As an explanation of these rate differences several authors<sup>3-6</sup> have proposed that an intramolecular hydrogen

bond of the type shown below is possible in the 2-dimethylammoniumethyl ester but not in the 2-trimethylammoniumethyl ester. Such a hydrogen bond is expected to increase the positive charge of the carbonyl carbon atom which is thus more easily attacked by a hydroxyl ion in an  $S_N2$  reaction. Also the

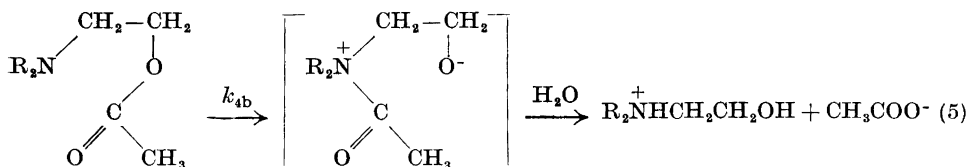
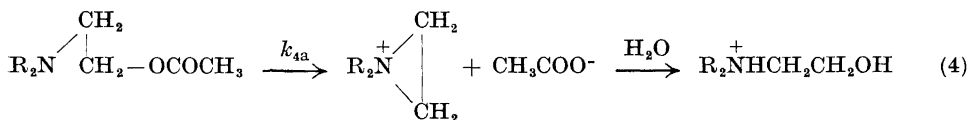


neutral hydrolysis of an ester is catalyzed by a dimethylammonium group in the alcohol part as shown by Shafer and Morawetz<sup>7</sup> for 2-dimethylaminoethyl hydrogen phthalate.

The work now presented is an investigation of how the rates of hydrolysis of tertiary aminoalkyl acetates in alkaline water solution are influenced by the N-alkyl groups and by the distance between the amino and the ester groups. Based on these measurements the above and other reaction mechanisms are discussed.

#### THEORY

The hydrolysis of aminoalkyl esters may be the result of several reactions. Reactions with hydroxyl ions, (1) and (2), have been mentioned above, and mechanisms in which the first step is an intramolecular reaction of the amine form of the ester are outlined in formulas (4) and (5). Uncatalyzed direct reactions between water and the ester are also possible, but as such reactions as a rule are much slower than reactions with hydroxyl ions in the pH-range now investigated (8.2–10.9) they will not be considered.

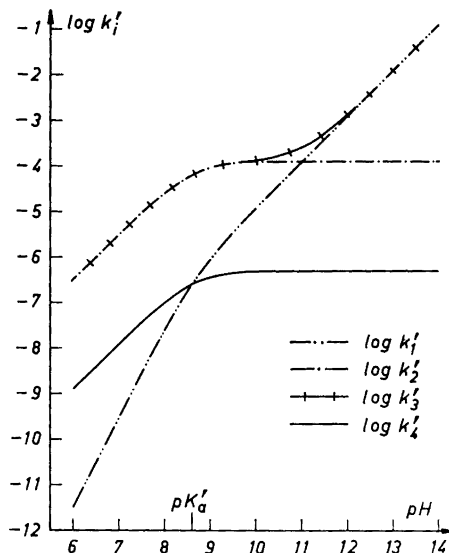


$$k_4 = k_{4a} + k_{4b} \quad (6)$$

Reactions of type (4) are common for 2-aminoethyl halides<sup>8</sup>, and the transacylation step in reaction (5) can be achieved for instance with 2-aminoethyl benzoate<sup>9</sup> and acetate<sup>10</sup>. In all the reactions (1), (2), (4), and (5) the concentrations of the reactants depend on pH. Therefore, to describe the rate of disappearance of the total amount of ester EHE (ammonium form  $EH^+$  and amine form E) the complicated differential eqn. (7) is necessary.

$$\begin{aligned} d[EHE] &= -(k_2[EH^+][OH^-] + k_1[E][OH^-] + k_4[E])dt = \\ &= - \left( k_2[OH^-] \frac{h}{h + K_a'} + k_1[OH^-] \frac{K_a'}{h + K_a'} + k_4 \frac{K_a'}{h + K_a'} \right) [EHE]dt \quad (7) \end{aligned}$$

Fig. 1. The theoretical pH-dependence of the total rate,  $\log k_3'$ , and of the individual rates  $\log k_1'$ ,  $\log k_2'$ , and  $\log k_4'$  of the reactions (1), (2) and (4) + (5). Arbitrarily chosen values,  $pK_a' = 8.60$ ,  $k_1 = 10^{-0.9}$  l mole $^{-1}$  sec $^{-1}$ ,  $k_2 = 10^{1.5}$  l mole $^{-1}$  sec $^{-1}$  and  $k_4 = 10^{-6.3}$  sec $^{-1}$ .



$h$  = hydrogen ion activity,  $[\ ]$  = concentration, and  $K_a' = h[E]/[EH^+]$ . However, if the rate of hydrolysis is measured at constant pH, a much simpler expression (8) is obtained.

$$\frac{d[EHE]}{[EHE]} = -(k_4' + k_2' + k_3') dt = -k_3' dt \quad (8)$$

$$k_1' = k_1[OH^-] \frac{K_a'}{h + K_a'} \quad (9); \quad k_2' = k_2[OH^-] \frac{h}{h + K_a'} \quad (10); \quad k_4' = k_4 \frac{K_a'}{h + K_a'} \quad (11)$$

The hydrolysis at constant pH may be treated as a sum of three first order reactions, for as shown by eqns. (9), (10), and (11), each of the values of  $k_1'$ ,  $k_2'$  and  $k_4'$  do not change during the duration of the reactions. But  $k_1'$ ,  $k_2'$  and  $k_4'$  are functions of the hydrogen ion concentration, and their contributions to  $k_3'$  depend on pH. This is illustrated in Fig. 1 with arbitrarily chosen values of  $k_1$ ,  $k_2$  and  $k_4$ . With the values used in Fig. 1  $k_3'$  at low pH-values is dominated by  $k_2'$  and at high pH-values by  $k_4'$  while  $k_1'$  is without influence. Fig. 1 also shows that the  $\log k_2'/pH$ -curve and the  $\log k_4'/pH$ -curve have the same form. That means that there are values of  $k_2$  and  $k_4$  (in this case  $k_2 = 10^{-0.9}$  l mole $^{-1}$  sec $^{-1}$  and  $k_4 = 10^{-3.9}$  sec $^{-1}$ ) such that  $\log k_4'$  and  $\log k_2'$  can change places in Fig. 1. If  $k_1$  is given the same value as before, the resulting  $k_3'$  will also be the same as before but now dominated by  $k_4'$  at low pH-values while  $k_2'$  has no influence.

Inversely, if the experimental determination of the rate of hydrolysis of an aminoalkyl ester gives a  $\log k_3'/pH$ -curve of the type occurring in Fig. 1, the conclusion can be drawn, that at high pH-values the reaction (1) is the most important. At low pH-values the main reaction is either (2) or an intramolecular reaction of the amine form of the ester, *e.g.* (4) and (5), or all three types

at the same time. Accordingly, for a separation of the reactions (2), (4), and (5) other methods must be used, for instance, as in this report, comparisons of some homologous compounds.

In an earlier paper<sup>1</sup> a graphic method for the calculation of  $K_a'$ ,  $k_1$  and  $k_2$  from  $k_3'$  was described. The possibility of intramolecular reactions was then not recognized. But as there is a simple relation (12) between  $k_2$  and  $k_4$ , obtained by putting  $k_2' = k_4'$ , the graphic method may be used also for the calculation of  $k_4$

$$\log k_4 = \log k_2 + pK_a' - \log f_{OH^-} - pK_w \quad (12)$$

where  $f_{OH^-}$  = activity factor and  $K_w = h[OH^-]/f_{OH^-}$ .

### EXPERIMENTAL

*Materials.* One mole of dialkylaminoalcohol and 1.1 mole of acetic anhydride were mixed. When the exothermic reaction had ceased, the reaction mixture was dissolved in 10–15 parts of dry ether, and dry hydrogen chloride was led over the surface of the solution. The precipitated dialkylaminoalkyl acetate hydrochloride was recrystallized from acetone or from an ethanol/acetone mixture. The analyses are given in Table 1.

The quaternary salts were obtained by treating a solution of the ester in ether or acetone with alkyl iodide instead of hydrogen chloride. The compounds were recrystallized from ethanol/ether.

*Kinetic measurements.* The rate of hydrogen ion formation was measured with a recording pH-stat<sup>13</sup>. The compounds were dissolved in 30 ml of 0.07 M potassium perchlorate solution and automatically titrated at  $25.0 \pm 0.05^\circ$  with sodium hydroxide from a 0.5 ml syringe.

The tertiary aminoalkyl ester hydrochlorides were titrated at 5–10 pH-values with 0.02, 0.05 or 0.1 M sodium hydroxide. The reactions were followed until they were 60–80 % complete. The rate constant  $k_3'$  was calculated according to Guggenheim's method.

The  $pK_a'$ -values were determined as follows. Less than one equivalent of sodium hydroxide was added to a solution (< 0.01 M) of the ester hydrochloride. The change of pH was

Table 1. Melting points and analyses

Compound	Mol. wt.	M.p.		Analyses			
				C		H	
		Found	Lit.	Calc.	Found	Calc.	Found
$[(CH_3)_2NHCH_2CH_2OCOCH_3]Cl^-$	167.6	133°	130–131° <sup>11</sup>	43.0	43.0	8.4	8.4
$[(CH_3CH_2)_2NHCH_2CH_2OCOCH_3]Cl^-$	195.7	116°	113–114° <sup>11</sup>	49.2	49.4	9.3	9.4
$[((CH_3)_2CH)_2NHCH_2CH_2OCOCH_3]Cl^-$	223.7	145°		53.8	53.5	9.9	9.9
$[(CH_3)_2NHCH_2CH_2CH_2OCOCH_3]Cl^-$	181.7	120°	118–119° <sup>11</sup>	46.2	46.3	8.8	9.0
				I			
$[(CH_3CH_2)_3NCH_2CH_2OCOCH_3]I^-$	315.2	122°		40.3	40.0		
$[(CH_3)_3NCH_2CH_2CH_2OCOCH_3]I^-$	287.1	95°	80° <sup>12</sup>	44.2	44.0		

followed for a few minutes. A pH-value of the time of mixing was determined and used for the calculation of  $pK_a'$ . The  $pK_a'$ - and  $k_3'$ -values were then used for the determination of  $k_1$  and  $k_2$  (Table 2) by a curve fitting method described in an earlier paper<sup>1</sup>. The rate constants  $k_4$  were calculated from  $k_2$  using eqn. (12).

The rate constants,  $k_2$ , for the quaternary ammonium compounds were calculated from the initial rate of consumption of 0.02 M sodium hydroxide at pH 8.9. The recorded time/sodium hydroxide consumption curves were perfectly straight lines during the hydrolysis of the first two per cent of 0.4 mmole of the ester.

*Infrared spectra* of 0.05–0.1 M solutions of the hydrochlorides of the esters in dry chloroform were recorded at room temperature with a Perkin-Elmer spectrophotometer model 21. Some of the absorption frequencies are given in Table 3.

## RESULTS

The experimental pH/log  $k_3'$  curves showed that the main reaction in the investigated pH-region is either a reaction between hydroxyl ions and the ester in ammonium form (2) or an intramolecular reaction of the amine form (4) and (5). Rate constants  $k_2$  and  $k_4$  for these alternatives are given in Table 2. In some cases the velocity constant,  $k_1$ , of the reaction between the amine form and hydroxyl ions (2) could also be determined.

Hall<sup>17</sup> has demonstrated that the Taft equation  $\log k/k_0 = \sigma^* \rho^*$  can be applied on the relationship between substituents and  $pK_a$  of amines. Using Hall's equation for tertiary amines,  $pK_a = -3.30\Sigma\sigma^* + 9.61$ , and the  $pK_a$ -values for I and II,  $\sigma^* = 0.38$  and  $0.39$  were calculated for  $\text{CH}_3\text{COOCH}_2\text{CH}_2-$ . When  $\sigma^* = 0.39$  was used in the equation<sup>17</sup>  $pK_a = -3.14\Sigma\sigma^* + 13.23$ , a value  $pK_a = 8.91$  was found for 2-aminoethyl acetate. This value is in good agreement with  $pK_a = 8.84$  being the experimentally found value<sup>10</sup>.

Table 2. Rates of hydrolysis of some aminoalkyl esters in 0.07 M  $\text{KClO}_4$  solution at 25°. Unit of  $k_1$  and  $k_2$   $1 \text{ mole}^{-1} \text{ sec}^{-1}$ . Unit of  $k_4$   $\text{sec}^{-1}$ . The values found in the literature have been corrected<sup>14</sup> for the ionic strength and are valid for 0.07 M  $\text{KClO}_4$ ,  $pK_a = pK_a' - 0.10$ .

Compound	$pK_a'$	$\log k_1$	$\log k_2$	$\log k_4$	Measurements in pH-range
I $(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{OCOCH}_3$	$8.45 \pm 0.02^*$	$-1.0 \pm 0.1$	$1.63 \pm 0.02$	$-3.82$	8.2–10.9
II $(\text{CH}_3\text{CH}_2)_2\text{NCH}_2\text{CH}_2\text{OCOCH}_3$	$9.09 \pm 0.02$		$1.56 \pm 0.02$	$-3.25$	8.5–10.9
III $((\text{CH}_3)_2\text{CH})_2\text{NCH}_2\text{CH}_2\text{OCOCH}_3$	$9.40 \pm 0.02$		$1.47 \pm 0.03$	$-3.02$	8.2–10.0
IV $(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{OCOCH}_3$	$9.27 \pm 0.01$	$-0.85 \pm 0.05$	$0.77 \pm 0.03$	$-3.86$	8.8–10.9
V $(\text{CH}_3)_3\text{NCH}_2\text{CH}_2\text{OCOCH}_3$			$0.17^{14}$ $0.17$		
VI $(\text{CH}_3\text{CH}_2)_3\text{NCH}_2\text{CH}_2\text{OCOCH}_3$			$0.12$		
VII $(\text{CH}_3)_3\text{NCH}_2\text{CH}_2\text{CH}_2\text{OCOCH}_3$			$-0.39^{12}$ $-0.34$		
VIII $\text{CH}_3\text{CH}_2\text{OCOCH}_3$		$-0.96^{16}$			

\* Tammelin<sup>15</sup> found  $pK_a = 8.35$ .

However, when,  $pK_a$  for III is calculated, a value,  $pK_a = 9.58$  is obtained which exceeds the actually found one by 0.28. This indicates that in the compound III there is a steric hindrance for the formation of the ammonium ion which does not normally exist for tertiary amines<sup>17</sup>, and consequently  $\Sigma\sigma$  for  $N(\text{CH}(\text{CH}_3)_2)_2$  shall be  $-0.30$  instead of  $2 \times (-0.19)$ .

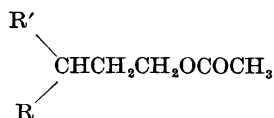
All the esters with ammonium groups have higher infrared  $\text{C}=\text{O}$  absorption frequencies than ethyl acetate (Table 3). The  $\text{C}=\text{O}$  frequency for ethyl acetate is not affected by the presence of 0.05 M triethylamine hydrochloride or trimethylamine hydrobromide. In the region  $2000-2800 \text{ cm}^{-1}$  all the compounds having  $\text{NH}^+$  bonds exhibit one absorption band between  $2400$  and  $2465 \text{ cm}^{-1}$  and another between  $2500$  and  $2580 \text{ cm}^{-1}$ . The dimethylammonium-alkyl and diethylammoniumalkyl esters absorb also at about  $2300 \text{ cm}^{-1}$ . The spectrum of trimethylammonium bromide did not change between  $2000$  and  $2800 \text{ cm}^{-1}$  when 1–10 % (V/V) ethyl acetate was added to the solution.

## DISCUSSION

Of the different proposed reaction mechanisms (1), (2), (4) and (5) for the hydrolysis of dialkylaminoethyl acetate the reaction (1) between hydroxyl ions and the ester in amine form will first be discussed. In this form the ester molecule has no electric charge and no hydrogen atoms at the nitrogen atom which can give a hydrogen bond to the carboxylic group. It may therefore be expected that the molecule will behave like the ester that is obtained if the nitrogen atom is substituted for a CH group, *i.e.* like an acetate of a branched aliphatic alcohol.

Table 3. Infrared absorption frequencies in  $\text{cm}^{-1}$  of chloroform solutions.

	+ NH					C = O	O—C(=O)	C—O(—C=O)
	Band 1	Band 2	Band 3	$\epsilon_1 : \epsilon_2$	$\epsilon_1 : \epsilon_3$			
$(\text{CH}_3)_2\text{NH}^+\text{CH}_2\text{CH}_2\text{OCOCH}_3\text{Cl}^-$	2400	2560	2300	1.25	1.00	1751	1235	1050
$(\text{CH}_3\text{CH}_2)_2\text{NH}^+\text{CH}_2\text{CH}_2\text{OCOCH}_3\text{Cl}^-$	2400	2550	2310	1.21	1.04	1745	1233	1048
$(\text{CH}_3)_2\text{CH}^+\text{NHCH}_2\text{CH}_2\text{OCOCH}_3\text{Cl}^-$	2420	2520	—	1.19		1744	1233	1049
$(\text{CH}_3)_2\text{NH}^+\text{CH}_2\text{CH}_2\text{CH}_2\text{OCOCH}_3\text{Cl}^-$	2400	2550	2300	1.23	1.01	1740	1239	1051
$(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CH}_2\text{OCOCH}_3\text{Cl}^-$	—	—	—			1748	1230	1053
$\text{H}_3\text{CCH}_2\text{OCOCH}_3$	—	—	—			1732	1250	1049
$(\text{CH}_3)_3\text{NH}^+\text{Br}^-$	2440	2575	—	1.07				
$(\text{CH}_3\text{CH}_2)_3\text{NH}^+\text{Cl}^-$	2425	2560	—	1.22				
$(\text{CH}_3)_2\text{NH}^+\text{CH}_2\text{CH}_2\text{OHCl}^-$	2465	2580	—	1.03				
$(\text{CH}_3)_2\text{NH}^+\text{CH}_2\text{CH}_2\text{BrBr}^-$	2425	2500	—	1.05				



In those two cases when it was possible to determine values of  $k_1$  (Table 2) these values were found to deviate less than 30 % from the value of the rate constant of the reaction between ethyl acetate and hydroxyl ions. This result strongly supports the above assumption that the amine form of a tertiary aminoalkyl acetate is very like an unsubstituted alkyl acetate. The primary 2-aminoethyl acetate does, however, not follow this rule as the acetyl group migrates to the nitrogen atom<sup>9,10</sup>.

As mentioned in the theory it is not possible to distinguish between the reactions (1), (4), and (5) only by looking at the pH-dependence of the measured rate of hydrolysis,  $k_3'$ . For that reason values of both  $\log k_2$  and  $\log k_4$  are given in Table 2. In the following discussion it is assumed that only one of the reactions (1), (4), and (5) occurs. If we first look at the reaction (5) we will see that it gives a ring intermediate containing 5 atoms, *i.e.* a ring with normal bond angles. The reaction is an intramolecular nucleophilic substitution by an amino group, and it seems reasonable to assume a mechanism of  $S_N2$  type. All  $S_N2$  substitutions by amines giving strainless products are known to be slowed down if the N-alkyl group or groups are branched near the nitrogen atom<sup>18</sup>. This is true also for the aminolysis of an ester<sup>19</sup>. But the values of  $k_4$  increase for the compounds, I, II, and III with increasing size of the N-alkyl groups. For that reason reaction (5) may be excluded.

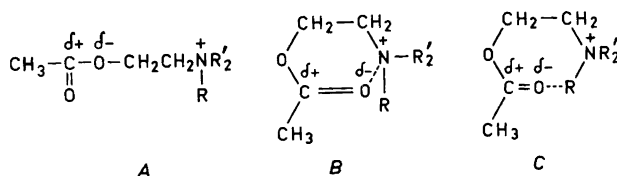
In reaction (4) ethylenimmonium ions are formed. These ions contain strained rings, and the influence of the N-alkyl groups on the rate of their formation is not easy to predict. However, such compounds are easily obtained from 2-dialkylaminoethyl bromides. The rates of their cyclization were measured, and in another paper<sup>8</sup> it is reported that  $\log k$  at 25° for the cyclization of 2-dimethylaminoethyl bromide is  $-2.0$ , for the 2-diethylamino compound  $-0.4$ , and for the 2-diisopropyl compound  $+1.4$ . It may be assumed that the difference between the  $\log k$  values for the formation of two homologous ethylenimmonium ions is of the same order irrespective of whether the leaving group is a bromide or an acetate ion. The differences between the  $\log k_4$ -values for the aminoethyl bromides above have the same sign but are much greater than the differences between the  $\log k_4$  values for the corresponding aminoalkyl acetates I, II, and III. Accordingly, also reaction (4) can be excluded for the hydrolysis of 2-aminoethyl acetates.

The remaining alternative, besides of reaction (1), is a reaction (2) between hydroxyl ions and the ammonium form of the aminoalkyl ester. This reaction is for the aminoethyl esters 25–30 times faster than for the corresponding quaternary ammonium compounds and about 400 times faster than for ethyl acetate. This increase of  $k_2$  by 400 times may be the result of several effects.

(A) Inductive effect through the carbon atom chain by the positively charged nitrogen atom.

(B) Electrostatic effect outside the chain by the positive charge.

(C) Hydrogen bonding.



(A) From experiments by Holland *et al.*<sup>20</sup> the inductive effect through the chain can be estimated to increase  $k_2$  by 4–5 times when the positive charge and the ester group are separated by two carbon atoms. The correctness of this value is supported by the fact that for several types of quaternary ammonium alkyl ester having two and three  $\text{CH}_2$ -groups between the nitrogen atom and the ester group the relative values of  $k_2$  are  $3.0 \pm 0.2$  and 1.0, respectively (V and VII in Table 2, the corresponding thiolesters<sup>2</sup> and  $\text{CH}_3\text{P}(\text{O})(\text{F})(\text{O}(\text{CH}_2)_n\text{N}^+(\text{CH}_3)_3)^4$ ). The main part of this difference can be explained as a difference in the inductive effect, because the steric conditions for the structure B are not changed very much.

(B) Esters of choline are hydrolyzed about 15 times faster than the corresponding ethyl esters (V and VIII in Table 2, and  $\text{CH}_3\text{P}(\text{O})(\text{F})(\text{OR})^4$ ). As the increase under (A) is 4–5 times, the electrostatic effect outside the chain gives an increase of  $k_2$  by about 3 times. If the N-methyl groups of a choline ester are substituted for ethyl groups the rate of hydrolysis goes down by 10%. This is probably due to an increase of the distance between the nitrogen atom and the carbonyl oxygen atom, as the positive charge and the effect (A) may be regarded unchanged.

(C) In the ammonium form of the tertiary amino ester I the distance between the nitrogen atom and the oxygen atom is a little shorter than in the choline ester, V. This increases the electrostatic effect but not enough to explain more than a small part of the observed 25–30 fold increase of  $k_2$ . The rest of the increase may be explained as the result of a catalytic effect by an intramolecular hydrogen bonding. In monoesters of 1,2- and 1,3-diols it has been observed that the alkaline hydrolysis is 10–15 times faster when the steric conditions are such that an intramolecular hydrogen bonding is possible than when it is impossible<sup>21</sup>. If such a hydrogen-bonded hydroxy group is substituted by a methoxy group the rate goes down to a seventh<sup>22</sup>. The infra-red spectra of I, II, and IV also support the hydrogen bond theory.

As shown in Table 3 these compounds absorb in the N–H stretching region at  $2300\text{ cm}^{-1}$  where no other tertiary ammonium compounds were found to have any absorption peak. The absorption cannot be caused by the solvent, chloroform, because ethyl acetate in chloroform has no absorption in this region. The spectra do not tell anything about which of the oxygen atoms that is hydrogen bonded, but the structure given above is favoured because a hydrogen bond to the ether oxygen atom results in a five-membered ring which can be regarded as less likely than a seven-membered hydrogen-bonded ring<sup>23</sup>. Also IV which has three  $\text{CH}_2$ -groups between the nitrogen and the oxygen



atoms, is rapidly hydrolyzed. The  $k_2$ -value is about 12 times that of the quarternary compound, VII, and the infra-red spectrum indicates a hydrogen bonded NH<sup>+</sup>. In this case the ether oxygen atom is possible as acceptor of the hydrogen bond.

From the discussion it can be concluded that the mechanism of the hydrolysis of tertiary aminoalkyl esters in alkaline solution is better explained in terms of an intramolecular hydrogen bonding than by any other mechanism. In order to confirm this result it would be interesting to study some compounds in which the hydrogen bond for steric reasons is very unlikely.

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