

Hydrogen Bonding, Ionization, and Rate of Hydrolysis of Aliphatic Ammonium Esters

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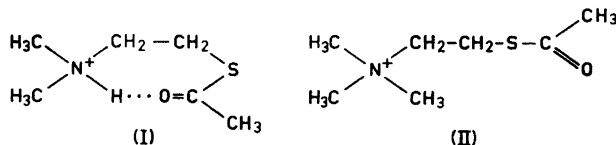
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Comparison of infrared spectra of hydrobromides of tertiary ammonium esters, $[\text{HMe}_2\text{N}^+(\text{CH}_2)_n\text{COOMe}]\text{Br}^-$ and $[\text{HMe}_2\text{N}^+(\text{CH}_2)_n\text{OCOMe}]\text{Br}^-$, where $n = 1, 2,$ and $3,$ with the spectra of the corresponding trimethyl-substituted esters shows that the tertiary esters give no intra- or intermolecular $\text{N}^+-\text{H}\cdots\text{O}=\text{C}$ association in solid phase or in acetonitrile solution. In chloroform solution the $\text{C}=\text{O}$ group seems, however, to be engaged in hydrogen bonding when six- and seven-membered rings can be formed.

The $\text{p}K_a$ -values of the tertiary esters in water reveal normal inductive transmission effect through the hydrocarbon chain.

The rates of acid hydrolysis of the tertiary ammonium esters are almost identical with the rates of acid hydrolysis of the corresponding quaternary esters. Great differences in rate are, however, observed for the alkaline hydrolysis of the same esters. Reasons for the reactivity differences are discussed.

Several hydrobromides of aliphatic tertiary ammonium esters have been shown to hydrolyse much more rapidly in neutral or weakly alkaline water solution than do their quaternary analogs.¹⁻⁶ Thus, Hansen¹ has reported that the thiocholine ester (I) hydrolyses 240 times as fast as (II) at $\text{pH} = 7.$ Assistance from intramolecular hydrogen bonding, making the carbonyl group more susceptible to nucleophilic attack by hydroxyl ions, has been invoked to explain the rate increase:¹⁻⁶



The present paper reports infrared, ionization, and hydrolysis measurements of the tertiary and quaternary ammonium esters, $[\text{HMe}_2\text{N}^+(\text{CH}_2)_n\text{COOMe}]\text{Br}^-$ and $[\text{Me}_3\text{N}^+(\text{CH}_2)_n\text{COOMe}]\text{Br}^-$, as well as $[\text{HMe}_2\text{N}^+$

$(\text{CH}_2)_n\text{OCOCH}_3\text{Br}^-$ and $[\text{Me}_3\text{N}^+(\text{CH}_2)_n\text{OCOCH}_3]\text{Br}^-$, where $n = 1, 2,$ and 3 . It was hoped that such comparative studies might give insight into the reason for the difference in hydrolytic reactivity of tertiary and quaternary esters.

EXPERIMENTAL

The bromides of the tertiary and quaternary ammonium esters were made from the methyl esters of bromoacetic acid, β -bromopropionic acid, and γ -bromobutyric acid, on treatment with dimethylamine or trimethylamine, respectively.⁷

Infrared measurements on the esters were performed in acetonitrile solution using a Unicam S.P. 100, Mk. 2 infrared instrument.

The $\text{p}K_a$ -values of the tertiary amine esters were determined by potentiometric titration of a 2.5×10^{-3} M aqueous solution of the amine with 0.1 M hydrochloric acid.

The acid hydrolysis of the esters were performed by an ordinary back titration method. The zwitterion formed on neutralisation of the hydrolysis product was titrated until $\text{pH} = 5.5$.

The base catalysed hydrolysis in the pH -region 7–9.5 was followed potentiometrically with an automatic titrator. The second order rate constants, k_{OH^-} , recorded in Table 1 refer to the hydrolysis of the ester cations and not to the neutral amine ester. The concentration of the ester cations was calculated from the respective $\text{p}K_a$ -values of the esters.

RESULT AND DISCUSSION

The infrared carbonyl absorption frequencies of the trialkylamino-substituted esters together with those of the corresponding quaternary ammonium esters are listed in Table 1. The spectra were recorded in potassium bromide briquet, and in acetonitrile and chloroform solution. The identical band positions of corresponding tertiary and quaternary ammonium esters in solid phase and also in acetonitrile solution exclude the presence of intramolecular hydrogen bonding in the tertiary ammonium esters in these systems. The results thus confirm previous findings for corresponding phosphoric esters.⁸ The tertiary ammonium esters in solid phase also show strong infrared absorption in the region 2200–2800 cm^{-1} ; this absorption is typical for $\text{N}-\text{H}^+\cdots\text{Br}^-$ association.

In chloroform solution, however, differences in behaviour of corresponding tertiary and quaternary ammonium esters are observed. This is especially true for the esters where favourable hydrogen-bonded chelate rings (six- and seven-membered rings) can be formed. The lower frequency of the $\text{C}=\text{O}$ group in tertiary esters as compared with the $\text{C}=\text{O}$ group of the corresponding quaternary ester, points to a hydrogen bond interaction between the ammonium hydrogen and the $\text{C}=\text{O}$ group in the tertiary esters. Since chloroform has a very poor acceptor ability for hydrogen bonding as compared with acetonitrile, and since the bromide ion is no longer in a fixed position ready to interact with the N^+-H group as in the solid phase, it is plausible to expect that the $\text{C}=\text{O}$ group of the ester now will play the role as hydrogen bond acceptor for the N^+-H group.

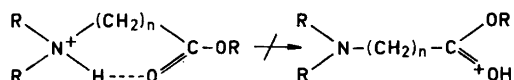
The $\text{p}K_a$ -values of the tertiary ammonium esters are recorded in Table 1. The ionization of the amine hydrobromides is found to depend upon the number of methylene groups between the ester group and the nitrogen atom in the same way as observed for the amino-substituted phosphonic esters.⁸ The

Table I. Infrared, ionization, and hydrolysis data of tertiary and quaternary ammonium esters.

Ammonium ester bromide	C=O vibration, cm^{-1} , in		$\text{p}K_a$ obs.	$\text{p}K_a$ calc.	Rate constants, $\text{M}^{-1} \text{sec}^{-1}$		
	KBr-briquet	CH_3CN CHCl_3			$k_{\text{H}^+} (\mu = 0.1) 25^\circ\text{C}$	$k_{\text{OH}^-} (\mu = 0.1) 25^\circ\text{C}$	
$(\text{CH}_3)_2\text{N}^+\text{HCH}_2\text{COOCH}_3$	1756	1756	1763	7.0	6.5	7.8×10^{-7}	unmeasurably small
$(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{COOCH}_3$	1756	1756	1761	—	—	7.9×10^{-7}	210
$(\text{CH}_3)_2\text{N}^+\text{H}(\text{CH}_2)_2\text{COOCH}_3$	1742	1742	1745	8.5	8.5	6.7×10^{-6}	45.5
$(\text{CH}_3)_3\text{N}^+(\text{CH}_2)_2\text{COOCH}_3$	1742	1742	1753	—	—	7.1×10^{-6}	5.5
$(\text{CH}_3)_2\text{N}^+\text{H}(\text{CH}_2)_3\text{COOCH}_3$	1741	1741	insoluble	9.5	9.5	2.3×10^{-5}	3.8
$(\text{CH}_3)_3\text{N}^+(\text{CH}_2)_3\text{COOCH}_3$	1741	1741	»	—	—	2.0×10^{-5}	1.0
$(\text{CH}_3)_2\text{N}^+\text{H}(\text{CH}_2)_2\text{OCOCH}_3$	1742	1742	1745	8.4	8.5	6.5×10^{-6}	39.1
$(\text{CH}_3)_3\text{N}^+(\text{CH}_2)_2\text{OCOCH}_3$	1742	1742	1756	—	—	2.7×10^{-5}	2.0
$(\text{CH}_3)_2\text{N}^+\text{H}(\text{CH}_2)_3\text{OCOCH}_3$	1748	1748	1748	9.3	9.5	3.1×10^{-5}	5.7
$(\text{CH}_3)_3\text{N}^+(\text{CH}_2)_3\text{OCOCH}_3$	1748	1748	1748	—	—	3.1×10^{-5}	0.56

stronger influence on the ionization of the $N^+—H$ group exerted by the phosphoric ester group than by the carbonic ester group is in agreement with the higher inductive effect of the former. There is no reason to assume participation of internal hydrogen bonding in the ionization process; with an inductive transmission factor of 0.5 as used for the amino-substituted phosphonic esters,⁸ the estimated pK_a -values are in fair agreement with the observed ones (Table 1).

The relative susceptibilities of the tertiary and the quaternary ammonium ester cations towards acid catalysis and towards nucleophilic substitution by hydroxyl ions are illustrated in Table 1. The minor changes in the rates of the acid hydrolysis of corresponding esters make it clear that an internal protonation of the carbonyl oxygen by the $N^+—H$ group is without significance in acid hydrolysis:



Acetylcholine and its tertiary analog is seen to differ in its behaviour from the other ester pairs since the rate constant of acid hydrolysis of the tertiary ester is approximately four times lower than the rate constant of the quaternary ester. But since the effect is opposite to the effect expected from internal protonation, the observation does not change the conclusion that internal protonation is without acceleration effect in acid hydrolysis.

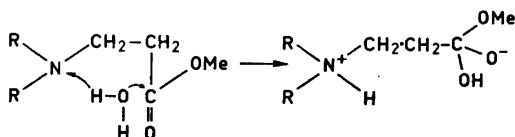
In the alkaline hydrolysis of the tertiary ammonium ester cations (Table 1), specific effects must be operative since the hydrolysis of the 1-substituted tertiary ester is strongly retarded, whereas that of the 2- and 3-substituted esters is considerably accelerated in relation to the hydrolysis of the corresponding quaternary esters. The rate of alkaline hydrolysis of the 1-substituted tertiary ester is in fact so small that we have not been able to measure its rate of hydrolysis by the present method. A similar inertness of $H_3N^+CH_2COOEt$ towards hydroxyl ions has lately been reported by Bell and Collier.⁹

Atomic models show that the ammonium hydrogen atom in the 1-substituted tertiary ester cation should be able to form intramolecular hydrogen bond with the carbonyl oxygen. The present findings of the inertness of the tertiary ammonium ester therefore argue against the assumed acceleration of nucleophilic substitution through internal hydrogen bonding. The same conclusion can also be reached by comparing the rate of hydrolysis of the last ester pair in Table 1. Although no intramolecular hydrogen bonding has been observed for the tertiary ester of this pair in chloroform (Table 1), its base hydrolysis is seen to be 10 times as rapid as the base hydrolysis of the quaternary ester. The rate decrease of the alkaline hydrolysis of the 1-substituted ester cation together with the acceleration observed for the 2- and 3-substituted ester cations (Table 1) suggest that opposing effects contribute to the total result. Apart from hydrogen bonding, the following two counter-acting effects may be of importance:

1. The 1-substituted tertiary ester has a fairly acidic ammonium hydrogen ($pK_a = 7.0$) close to the carbonyl carbon. Most of the collisions between

hydroxyl ions and the positively charged ester will preferentially abstract the proton from the ammonium group, leaving the carbonyl group unaltered. The much higher pK_a -values of the 2- and 3-substituted esters as well as the greater distance between the ammonium hydrogen and the carbonyl group will weaken this effect in the latter esters. A similar explanation is given by Hansen ⁵ for the 10 times lower rate of alkaline hydrolysis of the O-acetyl ethanolanmonium cation relative to the corresponding tri-N-methyl ammonium ester cation.

2. The relatively high basicities of the 2- and 3-substituted amine esters together with the possibility of formation of a ring of favourable size (especially for the 2-substituted esters) may cause the hydrolysis of the neutral ester to proceed by an internal mechanism:



In the pH-region where the present base hydrolysis has been performed (7–9.5), an internal catalysis as above may well be of considerable importance for the more basic esters, in this case the 2- and 3-substituted ones. Presumably, protonation of the tertiary amine group and hydroxylation of the carbonyl carbon need not necessarily proceed synchronously in order to accelerate the substitution process. Any amine group more basic than water will give rise to a higher time average hydroxyl ion concentration in its vicinity than in the bulk of water. This should cause an increased encounter frequency between hydroxyl ions and the carbonyl carbon. The effect would be greatest when the hydroxyl ion concentration is low, *i.e.*, in neutral or weakly alkaline solution since the ratio between the hydroxyl ion concentration around the ester cation and the hydroxyl ion concentration in the bulk of water would then be highest. In this way, the acceleration would not be dependent of the formation of a distinct cyclic transition state which, due to free rotation of the hydrocarbon chain linking the ester group to the ammonium group, might be of very low probability.

REFERENCES

1. Hansen, B. *Acta Chem. Scand.* **12** (1958) 324.
2. Ågren, A., Hedsten, U. and Jonsson, B. *Acta Chem. Scand.* **15** (1961) 1532.
3. Bender, M. L. *Chem. Rev.* **60** (1960) 53.
4. Hansen, B. *Acta Chem. Scand.* **16** (1962) 1927.
5. Hansen, B. *Acta Chem. Scand.* **17** (1963) 1307.
6. Hansen, B. *Acta Chem. Scand.* **17** (1963) 1481.
7. Aksnes, G. and Prue, J. E. *J. Chem. Soc.* **1959** 103.
8. Aksnes, G. and Songstad, J. *Acta Chem. Scand.* **19** (1965) 888.
9. Bell, R. P. and Coller, B. A. W. *Trans. Faraday Soc.* **60** (1964) 1091.

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