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84. **Tokuji Suzuki and Yuichi Tanimura :** General Base Catalysis of Hydrolysis of Alkylaminoethyl Esters of Carboxylic Acids.

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General base-catalyzed hydrolysis for several choline salt esters of carboxylic acids as well as succinylcholine chloride was investigated. Acetylcholine chloride, a part of succinylcholine chloride molecule, also was subject to general base-catalyzed hydrolysis. The ratio, k_{AC^-} to k_{OH^-}, of acetylcholine chloride was almost equal in magnitude to that of succinylcholine chloride. Degree of the influence of catalytic effect of general bases on the overall rate constant of ester hydrolysis was discussed. Imidazole was a less effective catalyst than phosphate dianion for the hydrolysis of the choline salt esters of carboxylic acids. The general base-catalyzed hydrolysis for these esters appears to represent classical general base catalysis rather than nucleophilic catalysis, as shown in the catalytic hydrolysis for the esters activated in acyl portion, ethyl haloacetates.[5] An attempt was made to compare the effect of acetate ions on the hydrolytic rate constants of the choline salt esters with that of the corresponding tertiary aminoesters. The catalytic contribution of acetate ions for the latter esters became less pronounced. The logarithms of rate constants of alkaline hydrolysis and acetate ion catalysis were not linearly related.

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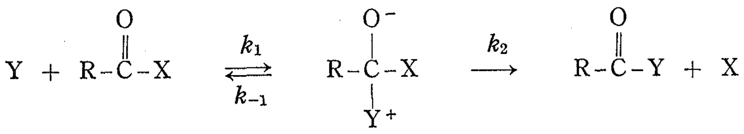
It has been shown that hydrogen ions and hydroxyl ions are not the only effective catalysts on hydrolytic degradation of carboxylic acid esters,[1~5] though evidences for reality of general acid-base (Brönsted acid-base) catalysis in the ester hydrolysis were doubtful.[6] Bender and Turnquest[1] and Bruice and Schmir[2] showed that bases such as acetate ions and tertiary amines catalyzed the hydrolysis of *p*-nitrophenyl acetate in the same mathematical fashion as general base catalysis. It was suggested in Bender's later report[7] that nucleophilic catalysis should be adopted as the proper term for the catalytic reaction, since the Brönsted bases act as nucleophilic reagents toward the carbonyl carbon of the ester in the reactions with *p*-nitrophenyl acetate, while classical mechanism of general base catalysis involves nucleophilic attack of bases toward hydrogen and rate-determining proton transfer.[6] The function of the base (nucleophile) toward carbonyl carbon is to form an unstable intermediate, acylated base, which is rapidly hydrolyzed to acetic acid and the regenerated base. The rate constant of formation of the unstable intermediate may depend upon k_1 and k_2/k_{-1} represented by the following equation.[8] The rate constant (k_1) for the initial addition



$$Y + R-\overset{\overset{O}{\|}}{C}-X \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} R-\underset{\underset{Y^+}{|}}{\overset{\overset{O^-}{|}}{C}}-X \xrightarrow{k_2} R-\overset{\overset{O}{\|}}{C}-Y + X$$

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1) M.L. Bender, B.W. Turnquest : J. Am. Chem. Soc., **79**, 1652, 1656 (1957).

2) T.C. Bruice, G.L. Schmir : *Ibid.*, **79**, 1663 (1957).

3) E.R. Garrett : *Ibid.*, **79**, 5206 (1957).

4) *Idem* : *Ibid.*, **80**, 4049 (1958).

5) W.P. Jencks, J. Carriuolo : *Ibid.*, **83**, 1743 (1961).

6) R.P. Bell : "Acid-Base Catalysis," (1941), Oxford University Press, London.

7) M.I. Bender, Y.L. Chow, F. Chloupek : J. Am. Chem. Soc., **80**, 5380 (1958).

8) K.B. Wieberg : *Ibid.*, **77**, 2519 (1955).

depends upon the nucleophilicity of Y, and the ratio $\left(\frac{k_2}{k_{-1}}\right)$ of the rate constants for partitioning of the addition compound to form the reactants or the acylated base, $(R-\overset{\overset{\displaystyle O}{\|}}{C}-Y)$, is related to the relative basicities of X and Y.[1] The nucleophilic catalysis of ester hydrolysis may be expected, when the basicity of X is comparable to that of Y, and the nucleophilicity of Y is large. The basicities of X of ordinary alkyl esters of carboxylic acids are generally too large, as compared with those of attacking bases, Y. Therefore, it appears that the catalysis of ester hydrolysis by the nucleophile is of importance only for carboxylic acid esters, phenyl or thiol ester, containing an alcohol residue which is a reasonably strong acid ($pKa<11$).[9]

Garrett[4] reported that the hydrolysis of both the phenyl ester and the diethylaminoethyl ester of a salicylate diester, diethylaminoethyl acetylsalicylate hydrochloride, were catalyzed by acetate ions. The hydrolysis of the latter ester bond is the case of acetate ion catalysis of an alkyl ester with a weak acid as the alcoholic portion. It was postulated that this special case might be due to facilitation of nucleophilic attack of acetate ions by intramolecular electrophilic catalysis from the β-protonated nitrogen. Jencks and Carriuolo[5] investigated the hydrolysis of alkyl esters, ethyl haloacetates, which were activated by electron-withdrawing substituents in the acyl portion, in buffer solutions, and presented the evidence that the alkyl esters were subject to classical general base catalysis rather than nucleophilic catalysis.

One of the authors reported that the catalytic effect by acetate ions was markedly shown in the hydrolysis of succinylcholine chloride (SCC).[10] It has not been shown, however, that alkyl esters such as atropine,[11] aspirin,[12] and methyl *dl*-α-phenyl-2-piperidylacetate[13] are subject to classical general base catalysis or nucleophilic catalysis. Furthermore, as compared with the catalysis by hydrogen ions and hydroxyl ions, any contribution due to catalytic effect of general acids and bases used in buffers was negligible in the hydrolytic degradation of the alkyl esters containing an alkylaminoethyl group, procaine,[14] 2-diethylaminoethyl-diphenylglycolate methobromide,[15] 2-diethylaminoethylxanthen-9-carboxylate methobromide,[16] and acetyl-β-methylcholine iodide.[17] No observance of general acid-base catalysis for ordinary alkyl esters might be attributed to the relatively large reactivities of hydroxyl and/or hydrogen ions over general acid or base for the esters. It appears, however, that esters activated in the acyl portion are subject to classical general base-catalyzed hydrolysis, while esters activated in the alcohol residue are subject to nucleophilic catalysis.[5]

SCC consists of two molecules of acetylcholine chloride linked together at the α-methylen groups. Neither an alcohol which is a reasonably strong acid nor a strong electron withdrawing substituent in the acyl portion is found in SCC molecule. No catalysis by general bases was mentioned in the hydrolysis of acetylcholine bromide,[1,18] and was also shown in the hydrolysis of propionylcholine iodide and butyrylcholine iodide.[17] However, as will be demonstrated below, it was proved that acetylcholine chloride is subject to acetate ion catalysis to such an extent as found in SCC, when

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[9] M. L. Bender: Chem. Revs., **60**, 53 (1960).

[10] T. Suzuki: This Bulletin, **10**, 912 (1962).

[11] P. Zvirblis, I. Socholitsky, A. Kondritzer: J. Am. Pharm. Assoc. Sci. Ed., **45**, 450 (1956).

[12] L. J. Edwards: Trans. Faraday Soc., **46**, 723 (1950).

[13] S. Siegel, L. Lachman, L. Malspeis: J. Am. Pharm. Assoc. Sci. Ed., **48**, 431 (1959).

[14] T. Higuchi, A. Havinga, L. W. Busse: *Ibid.*, **39**, 405 (1950).

[15] H. Nogami, N. Nakajima: This Bulletin, **6**, 283 (1958).

[16] H. Nogami, M. Horioka, S. Awazu, H. Yamada: *Ibid.*, **6**, 277 (1958).

[17] L. Larsson: Acta Chem. Scand., **8**, 1017 (1954).

[18] J. Butterworth, D. D. Eley, G. S. Stone: Biochem. J., **53**, 30 (1953).

the respective ratios of the catalytic constant of acetate ions to that of hydroxyl ions were compared.

The present work was undertaken to investigate the hydrolytic rates of several esters with one or two alkylaminoethyl groups as well as those of SCC at constant pH and ionic strength in the presence of increasing buffer concentrations, and to study the correlation between the catalytic constants of general bases and other kinetic constants for the esters.

Experimental

Materials——Succinylcholine chloride and succinylmonocholine chloride were the same as those reported previously.[19] Acetylcholine chloride and benzoylcholine chloride were commercial products. Bis(2-dimethylamino)ethyl succinate was prepared by the method of Christiansen, *et al.*[20] from succinic anhydride, sodium 2-dimethylaminoethylate and 2-dimethylaminoethyl chloride in dry toluene and was redistilled (b.p. 139∼142° at 1 mm. Hg). Mono-2-dimethylaminoethyl succinate was prepared by the method of Phillips[21] from succinic anhydride and 2-dimethylaminoethanol in dry acetone and was recrystallized from dry acetone (m.p. 73∼74°). 2-Dimethylaminoethyl acetate hydrochloride was prepared by the method of Jones, *et al.*[22] from acetyl chloride and 2-dimethylaminoethanol in dry ether. It was recrystallized by dissolving in absolute ethanol and reprecipitating it with ether (m.p. 129∼130°). 2-Dimethylaminoethyl benzilate hydrochloride was prepared by the method of Horenstein, *et al.*[23] from benzilic acid and 2-dimethylaminoethyl chloride in isopropyl alcohol (m.p. 184∼185°). *Anal.* Calcd. for $C_{18}H_{22}O_3NCl$: C, 64.32; H, 6.60; N, 4.17. Found: C, 64.27; H, 6.49; N, 4.05. Benziloylcholine iodide was prepared from refluxing of 2-dimethylaminoethyl benzilate hydrochloride and excess methyl iodide in isopropyl alcohol (m.p. 196°). *Anal.* Calcd. for $C_{19}H_{24}O_3NI$: C, 51.71; H, 5.48; N, 3.17. Found: C, 51.75; H, 5.55; N, 3.57. 2-Dimethylaminoethyl benzoate hydrochloride was prepared by the method of Vanderhaeghe[24] from mixing equimolecular amounts of benzoyl chloride and of 2-dimethylaminoethanol dissolved in dry benzene. It was recrystallized from acetone (m.p. 140∼141°).

Buffer Solution——The buffers used in this work were acetate buffer (AcONa, AcOH), phosphate buffer (Na_2HPO_4, KH_2PO_4), imidazole buffer (imidazole, HCl), pyridine buffer (pyridine, HCl) and formate buffer (HCOONa, HCOOH). Each buffer was diluted in order to determine the effect of buffer concentrations on the rate of hydrolysis for different esters.

Constant ionic strength was generally maintained at 0.5 by addition of sodium chloride. The values of pKa for acetate ion, formate ion, phosphate dianion, imidazole and pyridine at 60.0° were obtained from pH values of the buffer solutions, where equimolecular acidic and basic form of the buffers were involved. The pH of each buffer was determined at 60.0°. The determination of pH values was carried out with a pH Meter, Model HM-5 (Toa Dempa Kogyo Co., Tokyo).

Assay and Kinetic Procedure——The hydrolysis of the choline esters and the corresponding tertiary aminoesters was followed by measurement of disappearance of absorbance obtained with hydroxylamine-$FeCl_3$ assay.[25] The assay procedures were essentially the same as those previously reported.[19] The reaction was started by adding an appropriate buffer solution at the reaction temperature to a quantity of the ester weighed into 100 ml. volumetric flask and by making up to volume. Eighty mg. of succinylcholine chloride, 80 mg. of succinylmonocholine chloride, 55 mg. of acetylcholine chloride, 135 mg. of benziloylcholine iodide, 60 mg. of benzoylcholine chloride, 60 mg. of bis(2-dimethylamino)ethyl succinate, 70 mg. of mono-2-dimethylaminoethyl succinate, 50 mg. of 2-dimethylaminoethyl acetate hydrochloride, 130 mg. of 2-dimethylaminoethyl benzilate hydrochloride or 70 mg. of 2-dimethylaminoethyl benzoate hydrochloride, was used for each kinetic run.

These samples in the flasks were kept in a thermostatically controlled water bath adjusted to 60.0±0.1°. A quantity of the sample solution was taken out periodically at given intervals and cooled immediately in ice water. Five-milliliter aliquots at any time were determined colorimetrically at 530 mμ for the esters except SCC and bis(2-dimethylamino)ethyl succinate. Ten-milliliter aliquots of SCC solution or of bis(2-dimethylamino)ethyl succinate solution were run through a column of a strong cation exchange resin (Amberlite CG-120 Type I) in the Na-form to separate each of the monoesters formed by the hydrolysis, and each of the diesters was determined colorimetrically at 530 mμ with 50 mm. cells in the Hitachi EPU-spectrophotometer as reported in previous report.[10]

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19) H. Nogami, T. Suzuki: This Bulletin, **9**, 646 (1961).
20) J. Christiansen, R.G. Hansen, J. Fakstorp: Acta Chem. Scand., **7**, 128 (1953).
21) A.P. Phillips: J. Am. Chem. Soc., **75**, 4725 (1953).
22) L.W. Jones, R.T. Major: *Ibid.*, **52**, 307 (1930).
23) H. Horenstein, H. Pählicke: Ber., **71**, 1654 (1938).
24) H. Vanderhaeghe: J. Pharm. and Pharmacol., **6**, 55 (1954).
25) S. Hestrin: J. Biol. Chem., **180**, 249 (1949).

The catalytic rate constants of the bases were obtained from the slopes of plots of the observed first-order rate constants against the concentration of basic forms of the buffers.

Results and Discussions

Comparison of General Base Catalysis for Succinylcholine Chloride with That for Other Choline Salt Esters of Carboxylic Acids

The rate of disappearance of succinylcholine chloride (SCC) in aqueous solution may be represented as a consecutive reaction with two first-order steps.[10] The rate of hydrolysis of SCC to succinylmonocholine chloride and of acetylcholine chloride against the concentrations of basic forms of phosphate and imidazole buffer for two different pH values are shown in Fig. 1. The rates increase linearly with the increasing buffer concentrations, and the two second-order rate constants which are calculated from the slopes obtained in the each buffer for each ester are equal within experimental error, indicating that only the basic forms of the buffers are catalytically active. The second-order rate constants (k_b) of the catalytically active species of various buffers and the first-order rate constants (k_0) obtained by extrapolation to zero buffer concentration for various choline salt esters including SCC are summarized in Table I.

General acid or base catalysis are difficult to be observed, when the value of α or β of the Brönsted catalysis law is either extreme of its possiblevalues, near to zero or near to one.[6] Because the catalytic effect of general acid or base can not be satisfactorily compared with the catalytic effect of hydrogen ions, hydroxyl ions or water molecules. Accordingly, general acid or base catalysis will only be detectable in cases in which the rate constant (k_0) obtained by extrapolation to zero buffer concentration (total catalytic effect shown by hydrogen ions, hydroxyl ions and water molecules, $k_0 = k_{H^+}[H^+] + k_{H_2O} + k_{OH^-}[OH^-]$) is reasonably low, as compared with the contribution (k_a [Acid] or k_b [Base]) of general acid or base catalysis. Degree of the contribution of the catalytic effect of the general bases on the rate constants of disappearance of SCC and other choline salt esters at given pH may be expressed as a ratio (k_b/k_0) of the catalytic rate constant of the general base to the value of the intercept. Pronounced contributions were shown in acetate and phosphate buffers, and not shown in formate, pyridine and imidazole buffers (Table I). The value of the intercept will vary with the pH value of the solution, and the ratio depends upon the pH value.

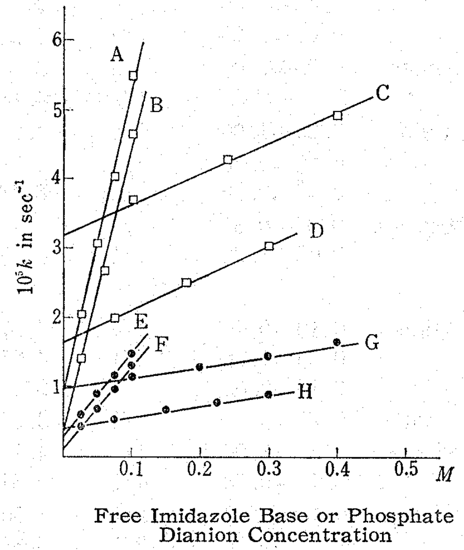

Fig. 1. Effect of Varying Concentrations of Free Imidazole Base or Phosphate Dianion on the First-order Rate Constants of Hydrolysis of Succinylcholine Chloride and Acetylcholine Chloride at Ionic Strength 0.5 and 60.0°

—□—□— Succinylcholine chloride:
A, phosphate buffer (pH 6.45);
B, phosphate buffer (pH 6.15);
C, imidazole buffer (pH 6.78);
D, imidazole buffer (pH 6.50).
—●—●— Acetylcholine chloride:
E, phosphate buffer (pH 6.45);
F, phosphate buffer (pH 6.15);
G, imidazole buffer (pH 6.81);
H, imidazole buffer (pH 6.50).

A comparison of the general base catalysis for the different esters would be more directly made by the value of a ratio (k_b/k_{OH^-}) of the catalytic rate constant of general base to catalytic rate constant of hydroxyl ions. The ratios (k_b/k_{OH^-} and k_b/k_0) for SCC and acetylcholine chloride in Table I are in reasonable agreement. Therefore, it is concluded that the prominent catalytic effect[10] of acetate ions for the alkyl ester, SCC, is not characteristic of SCC molecule, but it is also found in its component,

TABLE I. Dependence of First-order Rate Constants for Hydrolysis of Choline Salt Esters of Carboxylic Acids on Varying Buffer Concentrations at 60.0°

Buffer, M		Buffer ratio (A^-/HA)	pH	μ[a]	No. detns	$10^7 k_0$[b] (sec^{-1})	$10^6 k_b$[c] ($L. mol^{-1}. sec^{-1}$)	$10^8 k_b/k_{OH^-}$[d]	k_b/k_0
				Succinylcholine Chloride[e]					
Acetate	0.25~1.00	1/4	3.98	0.2	4	1.39[f]	13.8[f]	30.0	100
	0.10~0.40	1/1	4.67	0.2	4	3.89[f]	13.9[f]		34.8
	0.06~0.25	4/1	5.29	0.2	4	13.0[f]	14.4[f]		11.1
Formate	0.25~1.00	1/1	3.56	0.5	3	2.15	3.55	7.62	16.5
	0.16~0.63	4/1	4.18	0.5	3	2.00	3.68		18.4
Pyridine	0.25~1.00	1/1	4.91	0.5	3	13.0[g]	4.54[g]	9.78	3.5
Imidazole	0.15~0.60	1/1	6.50	0.5	3	171	44.0	94.4	2.6
	0.15~0.60	2/1	6.78	0.5	3	328	41.6		1.3
Phosphate	0.08~0.30	1/2	6.15	0.5	3	45.0	403	865	89.6
	0.05~0.20	1/1	6.45	0.5	4	110	402		36.5
				Acetylcholine Chloride					
Acetate	0.10~0.40	1/1	4.67	0.2	3	1.00	4.08	32.1	40.8
	0.25~1.00	1/1	4.67	0.5	4	1.40	3.20	26.2	22.9
	0.16~0.63	4/1	5.24	0.5	4	2.70	3.18		11.8
Formate	0.25~1.00	1/1	3.56	0.5	3	4.13	1.69	13.3	4.1
Pyridine	0.25~1.00	1/1	4.91	0.5	3	3.80	2.02	15.9	5.3
	0.16~0.63	4/1	5.51	0.5	3	9.20	2.02		2.2
Imidazole	0.15~0.60	1/1	6.50	0.5	4	40.0	17.4	135	4.4
	0.15~0.60	2/1	6.81	0.5	4	96.0	17.0		1.8
Phosphate	0.08~0.30	1/2	6.15	0.5	4	14.1	113	898	80.1
	0.05~0.20	1/1	6.45	0.5	4	32.1	114		35.6
				Succinylmonocholine Chloride					
Acetate	0.06~0.25	1/1	4.67	0.2	4	16.8[g]	5.58[h]		3.3
	0.06~0.25	4/1	5.29	0.2	4	21.9[g]	3.55[h]		1.6
	0.13~0.55	10/1	5.60	0.5	3	21.9	2.50[i]	33.8	1.1
Pyridine	0.25~1.00	1/1	4.91	0.5	3	21.7	2.14[h]		1.0
Imidazole	0.10~0.40	1/1	6.45	0.2	4	41.1	12.2	165	3.0
Phosphate	0.05~0.20	1/1	6.50	0.5	3	34.1	52.9	715	15.4
				Benziloylcholine Iodide					
Acetate	0.25~1.00	1/1	4.63	0.5	3	2.8	1.90	2.10	6.8
	0.16~0.63	4/1	5.24	0.5	3	15.1	1.90		1.3
				Benzoylcholine Chloride					
Acetate	0.16~0.63	4/1	5.24	0.5	3	0.810	0.643	10.9	7.9
	0.14~0.56	8/1	5.56	0.5	3	2.20	0.730		3.3

a) Ionic strength, $\frac{1}{2}\Sigma c_i z_i^2$, adjusted by addition of NaCl.
b) Rate extrapolated to zero buffer concentration.
c) Second-order rate constant of basic form of buffer.
d) Expressed as an average value, unless only k_b obtained. Second-order rate constants of hydroxyl ions for succinylcholine chloride and acetylcholine chloride calculated from $k_0/[OH^-]$[*2] in imidazole and phosphate buffers are 46.7[*3] and 12.4[*3] in $L. mol^{-1}. sec^{-1}$, respectively, and those for succinylmonocholine chloride, benziloylcholine iodide and benzoylcholine chloride are 7.4,[26] 90.4 (calculated from $k_0/[OH^{-1}]$[*2] at pH 5.24 in acetate buffer), and 6.3 (calculated from $k_0/[OH^-]$[*2] at pH 5.56 in acetate buffer) in $L. mol^{-1}. sec^{-1}$, respectively.
e) Hydrolytic rate constant of succinylcholine chloride to succinylmonocholine chloride.
f) Previous data[10] obtained by ion exchange chromatographic method.
g) Data[27] calculated by an analog computer.
h) Ionized form and unionized form for carboxyl group of succinylmonocholine chloride ($pK_a=3.85$[27] at 60.0°) coexist at this pH.
i) Second-order rate constant of acetate ions for ionized form of carboxyl group of succinylmonocholine chloride.

[*2] $k_0/[OH^-]=k_0/10^{-(pK_W-pH)}$, $pK_W=12.01$ at 60.0°.

[*3] Used also for calculation of data at $\mu=0.2$.

26) T. Suzuki: This Bulletin, **10**, 1017 (1962).

27) T. Suzuki, Y. Tanimura: *Ibid.*, to be published.

acetylcholine chloride. It is not necessary in acetate ion catalysis for SCC to postulate a specific intramolecular mechanism which is characteristic of SCC molecule.

The k_b/k_0 values for succinylmonocholine chloride in acetate buffers were much less, compared with those of SCC, and the acetate ion-catalyzed reaction is less pronounced. It may be due to enhancement of k_0 by intramoleculer catalysis[28] and hydrogen ion catalysis[27] for ionized form of the carboxyl group of succinylmonocholine chloride. The k_b/k_{OH^-} value of succinylmonocholine chloride is larger than that of SCC because of lower rate constant of hydroxyl ions. However, the contribution of general base catalysis to an overall rate constant at given pH does not depend directly upon the value of k_b/k_{OH^-}, but the value of k_b/k_0. The acetate ion-catalyzed reaction for benziloylcholine iodide was also less pronounced.

The observed catalysis by the general bases for these choline esters appears to be classical general base catalysis rather than nucleophilic catalysis as mentioned for the hydrolysis of ethyl haloacetates.[5] Imidazole was much more reactive than phosphate dianion as a nucleophilic catalyst for the hydrolysis of *p*-nitrophenyl acetate.[29] However, imidazole was less effective than phosphate dianion (Table I), which is of almost equal basicity to imidazole, for the hydrolysis of these choline esters. This implies that the nucleophilicity was not largely concerned with the effectiveness of the catalysis of the choline salt esters. Therefore, it is postulated that the catalysts act as proton accepters, and the rate-determining step is the slow proton transfer from the reactant (probably from the attacking water molecule participating in the hydrolytic reaction).

No catalysis of the hydrolysis for ethyl acetate and methylbenzoate by general bases could be detected.[1,5,28] The catalysis by imidazole for acetylcholine bromide was shown to be quite small.[1] In this report the catalytic hydrolysis by charged ions, acetate ions and phosphate dianions, for acetylcholine chloride was found to be pronounced in such a degree as shown for SCC from the comparison of k_b/k_{OH^-} and k_b/k_0. It appears that positively charged amines enhance attack of bases, at least of anions, and that general base catalysis for the charged ammonium compounds is expected in cases in which contributions of other catalysts are of less importance.

The Brönsted plot of the catalytic rate constants of the general bases for the hydrolysis of SCC and acetylcholine chloride has a slope of 0.69 (Fig. 2). The experimental values were plotted without statistical correction. The marked deviation of the uncharged bases may reflect low efficiency of the uncharged bases.

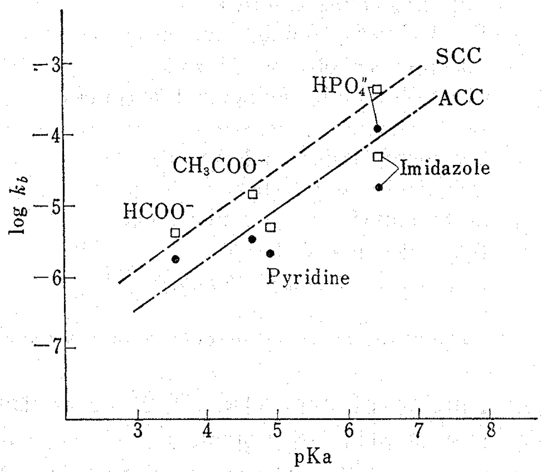

Fig. 2. Brönsted Plot of the Catalytic Constants of General Base-Catalyzed Hydrolysis for Succinylcholine Chloride and Acetylcholine Chloride

—□—□— SCC : Succinylcholine Chloride
—●—●— ACC : Acetylcholine Chloride

Comparison of the Effect of Acetate Ions on the Hydrolytic Rate Constants for the Choline Salts Esters with That of the Corresponding Tertiary Aminoesters

Acetylcholine chloride and 2-diethylaminoethyl acetate are readily hydrolyzed in alkaline solution and these are attributed to general acid catalysis (intramolecular electrophilic catalysis) either by the positively charged nitrogen or by the protonated

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[28] M. L. Bender, F. Chloupek, M. C. Neven : J. Am. Chem. Soc., **80**, 5384 (1958).
[29] T. C. Bruice, R. Lapinski : *Ibid.*, **80**, 2265 (1958).

nitrogen.[30] This intramolecular general acid catalysis results in enhancement of electrophilic reactivity of the carbonyl carbons of the esters, and facilitates to a much extent nucleophilic attack of hydroxyl ions. In general, the more pronounced effect of a protonated nitrogen atom on hydrolysis, compared with a quaternary nitrogen, may be attributed to more efficient stabilization of the transition state by the labile proton.[30,31] The protonated nitrogen of 2-diethylaminoethyl acetate is twenty times more effective as a general acid catalyst[31] than the quaternary nitrogen atom of acetylcholine chloride.

For the purpose of examining the difference of the catalytic effect of acetate ions for the choline salt esters and the corresponding tertiary aminoesters, bis(2-dimethylamino)ethyl succinate, mono-2-dimethylaminoethyl succinate, 2-dimethylaminoethyl acetate hydrochloride, and 2-dimethylbenzilate hydrochloride were hydrolyzed in a series of acetate buffers of constant buffer ratio (A^-/HA:4/1) at 5.24 and 60.0°.[*4] The catalytic rate constants of acetate ions for these tertiary aminoesters together with the data for the corresponding choline salt esters (Table I) are shown for comparison in Table II. The observed rate constants (k_{AC^-}) of acetate ions for the tertiary aminoesters were larger than those for the corresponding choline salt esters. However, the contribution of catalytic effect of acetate ions for the tertiary aminoesters at pH 5.24 becomes mostly less pronounced, compared with that for the corresponding quarternary ammonium salts, because of the far more increase of the rate constants (k_0) obtained by extrapolation to zero buffer concentration. Therefore, the increase of the electrophilicity of the carbonyl carbons of the esters did not result in an increase of contribution of acetate ion-catalyzed hydrolysis to the overall rate constant.

Table II. Comparison of k_{AC^-} of Dimethylaminoethyl Carboxylate with That of Trimethylammoniumethyl Carboxylate determined in Acetate Buffer ($A^-/HA=4/1$) at pH 5.24 and 60.0°

Substance	μ	No. detns	$10^7 k_0$ (sec^{-1})	$10^6 k_{AC^-}$ (L. mol^{-1}. sec^{-1})	k_{AC^-}/k_0
Succinylcholine Chloride	0.2	4	13.0	14.4	11.1
Bis(2-dimethylamino)ethyl Succinate	0.5	3	244.0	28.6	1.2
Succinylmonocholine Chloride	0.2	4	21.9	3.55[a]	1.6
Mono-2-dimethylaminoethyl Succinate	0.5	3	64.3	3.68[a]	0.6
Acetylcholine Chloride	0.5	4	2.70	3.18	11.8
2-Dimethylaminoethyl Acetate	0.5	3	46.3	4.96	1.1
Benziloylcholine Iodide	0.5	3	15.1	1.90	1.3
2-Dimethylaminoethyl Benzilate	0.5	3	102	18.4	1.8
Benzoylcholine Chloride	0.5	3	0.810	0.643	7.9
2-Dimetylaminoethyl Benzoate	0.5	3	18.7	1.14	0.6

a) Ionized form and unionized form for carboxyl group coexist at this pH.

Correlation of Acetate Ion-catalyzed Hydrolysis with Hydroxyl Ion-catalyzed Hydrolysis for the Choline Salt Esters

Jencks[5] stated that the rate constants of general base-catalyzed hydrolysis of acyl-activated esters showed a close correlation with the rate constants of hydroxyl

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[*4] The ratios, k_{AC^-}, to k_0, for deacetyl hydrolytic reaction and dediethylaminoethyl hydrolytic reaction of diethylaminoethyl acetylsalicylate hydrochloride[4] were 17.3 and 10.0 at pH 4.62 and 30.3°, respectively, and 17.9 and 2.45 at pH 5.21 and 30.3°, respectively. The ratios, k_{AC^-} to k_0, for ethyl dichloroacetate[5] were 11.1 at pH 4.26 and 25.0°, and 10.0 at pH 4.95 and 25.0°.

30) H. J. Smith, H. Williams: J. Pharm. and Pharmacol., **17**, 529 (1965).

31) J. A. Zaslowsky, E. Fisher: J. Phys. Chem., **67**, 959 (1963).

ion catalyzed hydrolysis, based on the linear free energy relationship obtained by Taft.[32] Bender[1] also reported that a linear relationship existed between the logarithms of rate constants of the alkaline hydrolysis and those of imidazole catalysis for a series of phenyl acetates with different alcohol residues. An attempt was made to correlate the catalytic constants of acetate ion-catalyzed hydrolysis for the esters containing the trimethylammoniumethyl group as an alcohol residue with the rate constants of hydroxyl ion-catalysis. The data in Table I were used for the plot illustrated in Fig. 3. An increase in the rate constant of hydroxyl ion-catalyzed hydrolysis does not always cause a parallel increase in the rate constant of acetate ion-catalyzed hydrolysis. This probably reflects different steric requirement between the acetate ion catalysis and the hydroxyl ion catalysis for the hydrolytic reactions of the series of the esters.

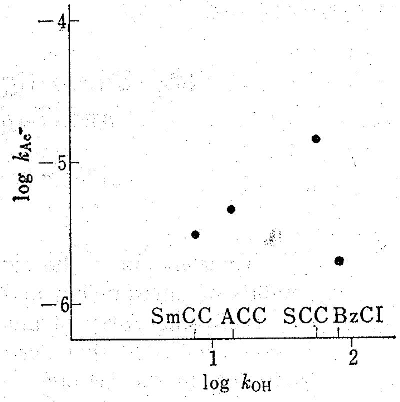

Fig. 3. Relation between Logarithms of k_{AC^-} and k_{OH^-} of Choline Salt Esters of Carboxylic Acids

SSC: Succinylcholine Chloride
SmCC: Succinylmonocholine Chloride
ACC: Acetylcholine Chloride
BzCI: Benziloylcholine Iodide

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[32] R.W. Taft, Jr.: J. Am. Chem. Soc., **74**, 2729 (1952).