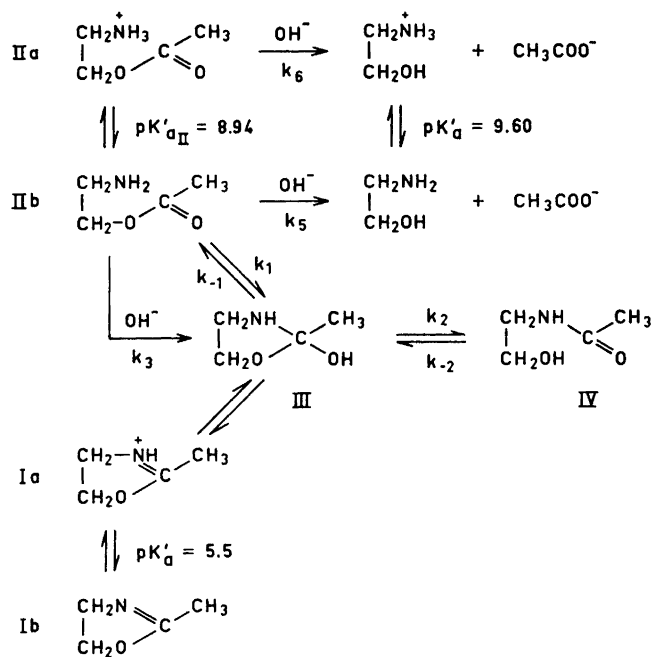# Kinetics of the Reactions of O-Acetylethanolamine

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The reaction rates of O-acetylethanolamine (II), $pK_a' = 8.94$, in 0.07 M $KClO_4$ at 25° have been studied at pH 7.0−9.7. The formation of N-acetylethanolamine (IV) from the amine form of II (II b) is the main reaction, and a hydroxyl ion catalyzed hydrolysis of the ammonium form of II ($k = 3-5$ M^{-1} sec^{-1}) is the side reaction. 2-Methyl-Δ^2-oxazoline could not be detected as a reaction product. The formation of IV is suggested to go *via* 2-methyl-2-hydroxy-oxazolidine (III), II b $\rightleftharpoons$ III → IV. II b → III and III → II b are first order reactions. The rate of III → IV is proportional to [III] and [OH⁻]. At high pH-values II b → III ($k = 0.01-0.03$ sec^{-1}) is rate determining because III → II b and III → IV are faster reactions. At low pH-values III → IV is slower than II b → III and the former is then rate determining.

2-Methyl-Δ^2-oxazoline (I a + I b), O-acetylethanolamine (II a + II b) and N-acetylethanolamine (IV) form a group of compounds which theoretically and/or practically can be transformed into each other. 2-Methyl-2-hydroxy-oxazolidine (III) has been suggested as a common intermediate in these transformation reactions. Rearrangements of this type have been known for many years [1,2], but the first kinetic studies on them appeared only recently. Porter *et al.*[3] suggested that N-acetylethanolamine is formed from the amine form of O-acetylethanolamine (II b) under hydroxyl ion catalysis. They also determined the rate constant for the formation of O-acetylethanolamine from the ammonium form of 2-methyl-Δ^2-oxazoline (I a). Martin and Parcell [4] confirmed this rate constant and also calculated a number of the other rate constants of the transformations in Scheme 1. The kinetic investigation of the reaction I a → II has later been repeated by Greenhalgh [5]. In some respects, opposing ideas are introduced in the mentioned papers, and therefore it is pertinent to report the results of a study of the reactions of O-acetylethanolamine in alkaline solution.

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IIa $\overset{+}{CH_2NH_3}$ ... CH_3 $\xrightarrow[k_6]{OH^-}$ $\overset{+}{CH_2NH_3}$ $+$ CH_3COO^-
$CH_2O-C\underset{O}{\overset{CH_3}{<}}$ CH_2OH

$\updownarrow$ $pK'_{a_{II}} = 8.94$ $\updownarrow$ $pK'_a = 9.60$

IIb CH_2NH_2 ... CH_3 $\xrightarrow[k_5]{OH^-}$ CH_2NH_2 $+$ CH_3COO^-
$CH_2-O-C\underset{O}{\overset{CH_3}{<}}$ CH_2OH

$\underset{k_{-1}}{\overset{k_1}{\rightleftarrows}}$

$\xrightarrow[k_3]{OH^-}$ CH_2NH ... CH_3 $\underset{k_{-2}}{\overset{k_2}{\rightleftarrows}}$ CH_2NH ... CH_3
$CH_2O-C\overset{CH_3}{\underset{OH}{<}}$ CH_2OH $C\overset{CH_3}{\underset{O}{<}}$

III   IV

Ia $CH_2-\overset{+}{NH}$ ... CH_3
$CH_2O-C<$

$\updownarrow$ $pK'_a = 5.5$

Ib CH_2N ... CH_3
$CH_2O-C<$

Scheme 1.

EXPERIMENTAL

N-Acetylethanolamine

Synthesis. The compound was prepared according to Wenker's method [6] and twice distilled. B.p. $100-120°/0.1$ depending on the rate of distillation; n_D^{25} 1.4715.

Behaviour in aqueous solution. A 0.01 M solution in 0.07 M $KClO_4$ was titrated at 25° from pH 9.5 to pH 3.7. No buffering effects of the compound were observed.

The pH of the above solution is stable at pH 9.5 for at least several minutes. A drop in pH should result if the compound were hydrolyzed.

The pH of a 0.02 M solution was brought to 5.10 by addition of HCl. The pH-value remained constant for 20 h at 25°. Hydrolysis to ethanolamine and acetic acid or rearrangement of the amide to I or II would have raised the pH.

O-Acetylethanolamine hydrochloride

Synthesis. 2-Aminoethanol hydrochloride and an excess of acetyl chloride were refluxed together for one hour. The excess acetyl chloride was evaporated under vacuum. The solid residue was twice recrystallized from ethanol-acetone. M.p. 132°. Kirkwood and Wright [7] observed $130.0-130.9°$. (Found: C 34.3; H 7.4. Calc. for $C_4H_{10}ClNO_2$ (139.6): C 34.4; H 7.2).

pK_a'. $0.25-0.50$ ml of 0.1 M NaOH were rapidly added to $0.1-0.2$ mmole of O-acetylethanolamine hydrochloride in 30 ml 0.07 M $KClO_4$ (25°C, nitrogen atmosphere). The decrease of pH was followed for a few minutes. By extrapolation a pH value was obtained for the time immediately after the addition of NaOH. This value was used for calculation of pK_a'. Experiments were made using two different batches of the ester and both a Beckman G pH-meter and a Radiometer Titrator. Four runs all gave $-\log(a_{H^+} \times [\text{II b}]/[\text{II a}]) = pK_a' = 8.94$ or $-\log(a_{H^+} \times a_{IIb}/a_{IIa}) = pK_a = 8.84$.

Reaction products. A 0.006 M solution of the ester hydrochloride in 0.07 M $KClO_4$ was titrated with NaOH at pH 8.8 until the pH became stable. Exactly one equivalent was required. If the ester had been hydrolyzed to 2-aminoethanol ($pK_a' = 9.60$[8]) more than one equivalent would have been needed. On back-titration to pH 3.8 with HCl not more than 0.02 equivalents of acetic acid and no 2-methyl-Δ^2-oxazoline ($pK_a' = 5.5$[4]) could be detected on the titration curve.

0.003—0.03 M solutions of the ester were allowed to partially react at pH 7.8 and 7.2, and were then titrated with HCl. No 2-methyl-Δ^2-oxazoline was found and less than 10 % of the reacted ester had given acetic acid.

Order of reaction. When 7.9 mg of O-acetylethanolamine hydrochloride in 30 ml solution were titrated with NaOH at pH 8.3, the consumption of titrant during the first 10 min was found to be twice that when 3.9 mg were titrated under the same conditions.

Kinetics. Hydrogen ions are liberated when O-acetylethanolamine hydrochloride reacts in alkaline solution. The rate of hydrogen ion formation at 25° in 0.07 M $KClO_4$ solution was measured with a recording pH-stat[9]. In the pH region 7.6—9.7 solutions 0.3—1 mM in II a + II b were used, and the reactions were followed until more than 50 % of II a + II b had reacted (for details see Ref.[10]). Using Guggenheim's method[11] first order rate constants, k_{obs}, were calculated.

In the interval pH 7.0—7.8 values of $(k_{obs})_{uncorr}$ were calculated from the rates of hydrogen ion formation during reaction of the initial 3—4 % of ester in 8 mM solutions. Because of the equilibrium between II a and II b, only $1/(1 + K_a'/a_{H^+})$ moles of hydrogen ions are liberated when one mole of II a + II b gives one mole of IV. Therefore, $(k_{obs})_{uncorr}$ was corrected using the formula $k_{obs} = (1 + K_a'/a_{H^+}) \times (k_{obs})_{uncorr}$. A similar correction should, theoretically, have been made because of the equilibrium between the amine and ammonium forms of the by-product, ethanolamine, but as an estimation showed that this correction is of no practical significance, it was omitted. One to six runs were made at each pH. In Fig. 1 the mean values of log k_{obs} are plotted against pH. The maximum error was 0.03—0.04 units of log k_{obs}.

RESULTS AND DISCUSSION

The pK_a' of O-acetylethanolamine is found to be 8.94 at 25°. Other authors have found $pK_a' = 9.1$ at 25°[4] and $pK_a' = 8.6$ at room temperature[3]. Based on the pK_a-values of tertiary 2-aminoethyl acetates, a calculated value $pK_a' = 9.01$ has been reported[10] which is in good agreement with the found value.

Order of reaction. The initial rate of liberation of hydrogen ions in moles sec^{-1}, at constant pH, is found to be proportional to the amount of ester used. Thus, in the concentration range used, the reactions in which O-acetylethanolamine, II a and II b, participates are first order with respect to the ester.

Reaction products. The main reaction product of O-acetylethanolamine in alkaline solution is N-acetylethanolamine as previously reported[3,4]. Back-titrations of the reaction mixture with HCl also show that some acetic acid, $pK_a' = 4.7$, is formed. This fact has not apparently been mentioned before. At pH 8.8—9.0 the acetic acid constitutes only 1—2 % of the reaction products, but at pH 7.2 it may be as high as 10 %. The titration curve shows that the solution has no buffer zone around pH = 5.5. Consequently, measureable amounts of 2-methyl-Δ^2-oxazoline ($pK_a' = 5.5$) cannot have been formed as this compound has a half-life of more than 15 min[4] and thus would not be completely destroyed during the titration with HCl.

For the kinetic measurements an indirect method was used as there is no simple way in which the concentrations of II a, II b, and IV can be measured. The method used is based on the fact that hydrogen ions are released in the
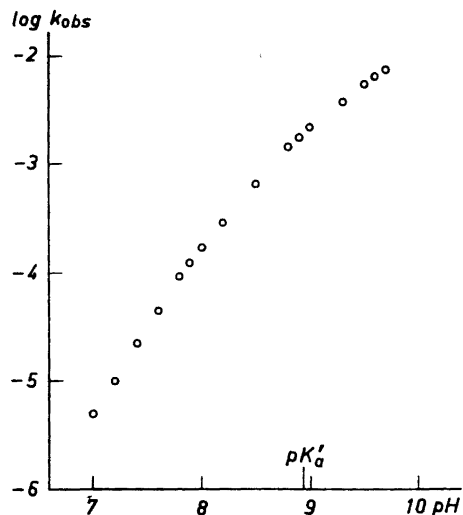
Fig. 1. Plot of log k_{obs} against pH. k_{obs} is the observed first order rate constant in sec^{-1} for the disappearance of O-acetylethanolamine, according to all mechanisms, at 25° in 0.07 M KClO$_4$. pK_a' = 8.94.

overall reaction from II a to IV. The hydrogen ions are not formed in any of the reaction steps II b → III or III → IV in Scheme 1 but as a result of the displacement of the equilibrium between II a and II b accompanying the transacylation. This is to be noted in the following discussion. Similarly, hydrogen ions are formed by the hydrolysis of II. The reaction products, IV, acetic acid and ethanolamine, are stable enough not to interfere with the kinetic observations.
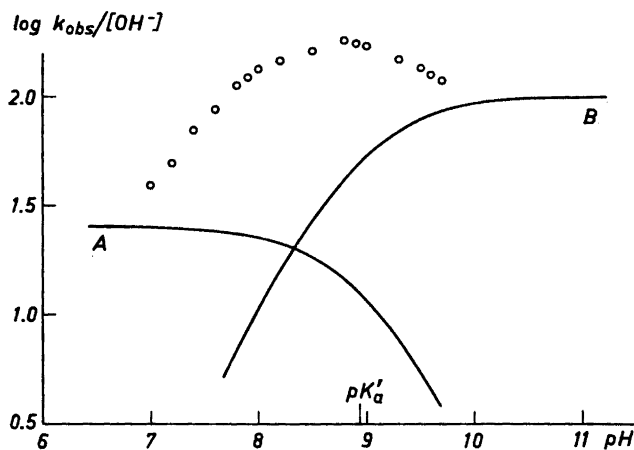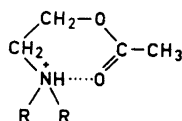

Fig. 2. Plot of log $k_{obs}/[OH^-]$ against pH. $[OH^-] = 10^{pH-13.9}$.
Curve A = log $k_{obs}/[OH^-]$ for a reaction II a + $[OH^-]$ with k_6 = 25 M^{-1}sec^{-1}.
Curve B = log $k_{obs}/[OH^-]$ for a reaction II b + $[OH^-]$ with k_3 = 100 M^{-1}sec^{-1}.

The value of the first order rate constant, k_{obs}, was at pH 7.6 and 7.8, within experimental error, the same when calculated from the initial rate of the reaction as when calculated from runs followed until more than 50 % completion.

First order rate constants, k_{obs}, are plotted against pH in Fig. 1. In Fig. 2 log $k_{obs}/[OH^-]$ has been plotted against pH.

Formation of acetic acid. The observation by Porter et al.[3] that N-acetylethanolamine is not hydrolyzed under mild conditions has been confirmed. Therefore, the acetic acid observed as a reaction product must have been formed from O-acetylethanolamine. It can be assumed that the rate constant, k_5, for the reaction II b + OH$^-$ has a value close to those for the reactions between the basic forms of tertiary aminoethyl acetates and hydroxyl ions,[10] i.e. $k_5 = 0.1-0.15$ M^{-1} sec^{-1}. This means that the rate of II b + OH$^-$ accounts for less than 0.1 % of the total reaction rate. Therefore, the acetic acid must result from the reaction II a + OH$^-$. Curve A in Fig. 2 shows how the rate of this reaction $k_{obs} = k_6/(1 + K_a'/a_{H^+})$ would vary with pH if $k_6 = 25$ M^{-1} sec^{-1}. This value was chosen because it has been found[10] that the second order rate constants for reactions between the ammonium forms of tertiary 2-aminoethyl acetates and hydroxyl ions are $30-43$ M^{-1} sec^{-1}, and a similar value was expected for k_6. If $k_6 = 25$ M^{-1} sec^{-1}, about 50 % of the reaction products at pH 7.2 would be acetic acid, but as less than 10 % of the latter were actually found, the value of k_6 must be $3-5$ M^{-1} sec^{-1}.

It is not easy to explain why k_6 has a much smaller value than expected but the following hypothesis is suggested. Owing to intramolecular hydrogen bond catalysis,[10] tertiary 2-ammoniummethyl acetates are hydrolyzed more rapidly than quaternary esters ($k_6 = 1.5$ M^{-1} sec^{-1} for acetyl choline). The

$$\underset{\underset{R}{\overset{\diagup}{\underset{R}{\diagdown}}}}{\overset{\underset{CH_2}{\overset{CH_2-O}{\diagup}}}{\underset{NH\cdots O}{\overset{\diagup}{\diagdown}}}}C-CH_3$$

steric conditions and the pK_a-values of the tertiary ammoniumalkyl esters and II a are so similar that the catalytic effect of the hydrogen bonding should be at least as significant in II a as in the other compounds. This is obviously not the case. One way to break or reduce the hydrogen bonding effect is to remove a proton from the nitrogen atom. This is a very fast reaction. As there are three alternative protons that can be removed from II a but only one from the other compounds it seems reasonable to expect a shorter half-life for II a in the reaction II a → II b than for the other ammonium ions. Therefore, in the case of II a, the length of time for which the hydrogen bond exists could be so short that the hydrogen bond is broken before a hydroxyl ion having the necessary minimum energy has come close enough to the carboxyl carbon atom to form the transition state.

Formation of N-acetylethanolamine is the main reaction and the rate of this reaction therefore gives the greatest contribution to k_{obs}. To obtain the true rate constants for the reaction II → IV, the rate of formation of acetic acid has to be subtracted from k_{obs}. However, these corrections are so small that

they will not significantly change the appearance of Fig. 1 and Fig. 2 and thus corrected plots have not been made.

Porter *et al.*[3] observed that the rate of the disappearance of O-acetylethanolamine at pH 8.6 to 6.5 is dependent on the concentrations of hydroxyl ions and II b. Martin and Parcell,[4] on the other hand, assumed in their calculations that the rate of formation of III from II b is only proportional to the concentration of II b.

The following discussion is based on the finding that the reaction II → IV is irreversible, and on the assumption that IV is formed from II b as it is difficult to find a mechanism utilizing II a for the transacylation. Two types of reactions will be considered (*a*) a direct reaction II b → IV and (*b*) a reaction involving two steps, II b → III and III → IV.

(*a*) If the disappearance of O-acetylethanolamine is due to a first order reaction of II b with the rate constant k_1, the plot of log $k_{obs}/[OH^-]$ in Fig. 2 would have the same shape as curve A, log $k_{obs}/[OH^-] = $ log $\{k_1/\{[OH^-] \times (1 + a_{H^+}/K_a')\}\}$. This is not the case. Nor has the experimental curve the same shape as curve B, log $k_{obs}/[OH^-] = $ log $\{k_3/(1 + a_{H^+}/K_a')\}$, which represents a second order reaction between II b and hydroxyl ions with the rate constant k_3, even if there is a resemblance below pH 8.5. A third possibility is that the rate should be the sum of the rates of a first order and a second order reaction of II b, giving log $k_{obs}/[OH^-] = $ log $\{(k_3 + k_1/[OH^-])/(1 + a_{H^+}/K_a')\}$. It can be shown that curves log $k_{obs}/[OH^-] = f(pH)$ obtained by using this equation do not have a maximum for any combination of k_1, k_3 and K_a'. However, the experimental curve in Fig. 2 exhibits a maximum, and consequently the reaction II → IV cannot proceed in one step.

(*b*) We shall now assume the existence of an intermediate, III, in the transacylation. As the reaction II → IV is not reversible, one of the steps II → III and III → IV must, over the pH-range studied, be a one-way reaction and the other step must be a reversible reaction. If both steps go to equilibrium, the overall reaction must also go to an equilibrium which is in contradiction to what has been found. If both II → III and III → IV are irreversible reactions, we would obtain for the step II → III, which is that followed kinetically, the same relationship between k_{obs} and pH as has been discussed under (*a*) and found impossible for an irreversible one step reaction II → IV. It may therefore be concluded that II → III is the reversible step and that III → IV the irreversible step, *i.e.* $k_{-2} = 0$.

It was mentioned on p. 4 that it is unimportant if k_{obs} is calculated from the initial or a greater part of the reaction. This implies that a steady state equilibrium II b ⇌ III is rapidly established and in practice may be considered to have a definite value $K_1 = [III]/[II\ b]$ for every pH-value. Based on steady state considerations the following equations may be derived

$$K_1 = \frac{k_1}{k_{-1} + k_2} \ ; \ k_{obs} = \frac{k_1}{1 + k_{-1}/k_2} \times \frac{1}{1 + a_{H^+}/K'_{a\ II}}$$

$$\frac{[II\ b]}{[II\ a] + [II\ b]} = \frac{1}{1 + a_{H^+}/K'_{a\ II}} \ , \ \text{and} \ K'_{a\ II} = \frac{a_{H^+} \times [II\ b]}{[II\ a]}$$
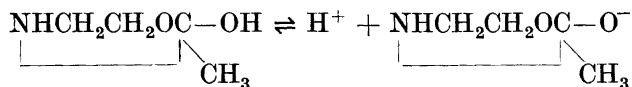
where k_1, k_{-1}, and k_2 may be true constants or functions of pH.

If $k_1/(1 + k_{-1}/k_2)$ is independent of pH, k_{obs} would have the pH dependence valid for a first order reaction of II b. However, as noted under (a), below pH 8.5 k_{obs} increases more rapidly with increasing pH than expected for such a reaction. Thus, $k_1/(1 + k_{-1}/k_2) = k_2 \times K_1$ must increase with increasing pH. A great number of calculations which are too complex to be reported here have been made, showing that, for certain combinations of k_1, k_{-1}, and k_2, it is possible to find curves that conform well with the experimental curves in Figs. 1 and 2. It was observed that a good agreement between the experimental and the calculated curves required either (ba) that k_{-1} and k_2 are constants and k_1 is proportional to $[OH^-]$ or (bb) that k_1 and k_{-1} are constants and k_2 is proportional to $[OH^-]$.

(ba) In this case II b → III is the only reaction for which the rate constant is a function of $[OH^-]$, i.e. it is a second order reaction. This means that $K_1 = [\text{III}]/[\text{II b}]$ also increases with increasing pH. Thus for agreement between the experimental and calculated curves it was found necessary that $[\text{II b}] = [\text{III}]$ for a value in the range pH 8—9 and that $[\text{III}]$ should be of the order of 1 % of $[\text{II a}] + [\text{II b}]$ at pH 7.8. However, when the amount of NaOH necessary to maintain the pH at 7.8 was recorded as a function of time, straight lines were obtained from the beginning of the reaction until 3—4 % of II a + II b had reacted. Only if the second order rate constant, k_3, for II b → III has a value of the order 10^4 M^{-1} sec.$^{-1}$, would the recorded curve be uneffected. As this rate constant is very high,* it seems unlikely and (ba) has to be dropped.

(bb) This alternative, implying that the rates of II b → III and III → II b are independent of $[OH^-]$ while the rate of III → IV depends thereon, could explain the experimental values in Fig. 2 in the following way. At low pH-values the reaction III → IV is the rate determining step owing to the low concentration of hydroxyl ions. When the pH is raised, both $[OH^-]$ and $[\text{II b}]$ increase, and $[\text{II b}]$ approaches a maximum as it cannot exceed the total concentration of the ester. This means that the reaction rate of III → IV increases while that of the reaction II b → III reaches a maximum. Finally, the latter reaction becomes the rate determining step. Log k_{obs} in Fig. 1 seems to approach a maximum value of -0.5 to -1.0, corresponding to log k_1, i.e. $k_1 = 0.01 - 0.03$ sec^{-1}. The values of k_{-1} and k_2 cannot be determined independently of each other. However, as mentioned under (ba) the steady state equilibrium II ⇌ III is established very rapidly. This is possible only if $k_{-1} \gg k_1$ which implies that $K_1 \ll 1$ and thus that $[\text{III}]$ is very low.

The pH dependent rate of formation of IV from an intermediate may be explained in two ways which cannot be distinguished by kinetic methods. The first alternative is a reaction III + OH^-. The second alternative is the existence of a fast protolytic equilibrium

$$\text{NHCH}_2\text{CH}_2\text{OC—OH} \rightleftharpoons \text{H}^+ + \text{NHCH}_2\text{CH}_2\text{OC—O}^-$$
$$\overline{}\backslash\text{CH}_3 \qquad \overline{}\backslash\text{CH}_3$$

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* For instance, the rate constants of the alkaline hydrolysis of acetic anhydride [13] and ethyl acetate are about 1000 and 0.1 M^{-1} sec^{-1}, respectively.

in which the amount of anion is small compared to that of the neutral molecule but high enough to be responsible for the formation of IV without hydroxyl ion catalysis,

$$NHCH_2CH_2OC-O^- \rightarrow CH_3CNHCH_2CH_2O^-$$
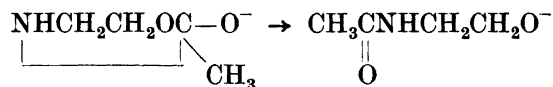
It is not possible to find the correct alternative without further investigations.

The transacylation can also be called an intramolecular aminolysis of an ester. It therefore seems likely that the two-step mechanism suggested under (bb) also, in at least some cases, can be applied to intermolecular ester aminolysis. In fact Bender [12] in his review mentions that such reactions often are hydroxyl ion and general base catalyzed. In addition to the mechanism now suggested, he proposes two other reaction paths for the intermolecular case. However, these cannot be used to explain the actual experimental results when applied to the transacylation in O-acetylethanolamine.

Attempts have been made to calculate all the rate constants in Scheme 1, but it was not possible to obtain any reliable values without further kinetic investigations. Calculations of these constants have also been made by Martin and Parcell [4]. They utilized the observations first made by Porter et al.[3] that the pH of a solution containing I a and I b first rises and then slowly decreases to stable values of 5.3—6.4. They assumed this stabilization to be due to the establishment of an equilibrium between I, II, III and IV. Using their values the equilibrium mixture should contain 3—4 % of I at pH 5.3 to 6.4. They did not prove the presence of any I in the equilibrium mixture. Neither now or earlier [3] has it been possible to find that any I is formed from II or IV under conditions such that a detectable amount would have resulted if Martin's and Parcell's rate constants are correct. The stabilization of the pH of a solution of I may be due to the buffering effect of acetate ions formed in the hydrolysis of II b. Martin's and Parcell's calculation must therefore, in some respects, be treated with reserve.

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