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THE HYDROLYSIS AND AMINOLYSIS OF ETHYL THIOACETATE

IV. ADDITIONAL EXPERIMENTS AND REACTION SCHEMES

BY

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1. *Introduction*

In some preceding papers we presented the results of measurements at 25° C and 37° C of the alkaline hydrolysis and the aminolysis by glycine of ethyl thioacetate (E.T.A.) [1–5].

Meanwhile, we have carried out some additional experiments, the results of which are presented in this paper. Furthermore, reaction schemes for both processes are proposed.

2. *The alkaline hydrolysis*

The alkaline hydrolysis of E.T.A. proved to occur according to two different mechanisms. One of these involves a reaction which is of first order in OH^- ion concentration over the whole pH range investigated and prevails at high pH (pH > 10). The second mechanism, prevailing at rather low pH (pH < 9), involves a stepwise mechanism with a monomolecular activation reaction or a bimolecular complex formation followed by a reaction of first order in OH^- ion concentration. On the analogy of the ester-water complex formation of oxygen esters, it was assumed [1, 2] that an intermediary E.T.A.-water complex is formed. Consequently, the following reaction scheme was proposed [2] for the alkaline hydrolysis of E.T.A.:

$$\text{E.T.A.} + H_2O \underset{K_1}{\overset{K_2}{\rightleftarrows}} C_1 \qquad \text{and:} \quad \text{E.T.A.} + OH^- \xrightarrow[K_4]{} \text{hydrol. products}$$

$$C_1 + OH^- \xrightarrow[K_3]{} \text{hydrol. products.}$$

A kinetic analysis of this scheme yields the following equation [2] for the disappearance of E.T.A. with the time of incubation:

$$(1) \qquad v_H = -\frac{d\,[\text{E.T.A.}]}{dt} = K_1'\,[\text{E.T.A.}]\,[OH]\,\frac{1}{1 + K_3/K_2\,[OH]}$$

with $K_1' = K_1\,[H_2O]$.

In the first place, the alkaline hydrolysis experiments at high pH and at 37° C were repeated with E.T.A. solutions in 50 vol % water – 50 vol % dioxane mixtures: as K_1 may also refer to a monomolecular activation

reaction, it was hoped that a possible change in K_1' would yield a direct proof of the assumed E.T.A. $-H_2O$ complex formation.

The dioxane proved to disturb the determination of E.T.A. by acetyl hydroxamate formation in the usual way [1, 2]. Therefore we determined the concentrations of the thioester in samples of the reactionmixture according to the method described by HAWKINS and TARBELL [6].

The extinction at 233 mμ due to the thioester was determined in 0.01 N HCl solutions by means of a Unicam ultra-violet spectrophotometer SP 500. Rate constants were calculated from the extinction data in the usual way [2].

The results are listed in table I.

TABLE I

Alkaline hydrolysis of E.T.A. in 50 vol % water — 50 vol % dioxane, at 37° C and at high pH. [OH] was calculated from the composition of the reaction mixtures *). The first order rate constant K_{obs} is defined as:

$$K_{obs} = \frac{-\,d\,[E.T.A.]/dt}{[E.T.A.]}$$

In exp. A8, A9 and A10 [E.T.A.] was equal to [OH]; second order rate constants were calculated directly from the extinction data in these experiments.

Exp. No.	$[OH] \times 10^6$ (mol ml^{-1})	$K_{obs} \times 10^6$ (sec^{-1})	$K_{obs}/[OH]$ (ml mol^{-1} sec^{-1})
A1	135	11500	108
A2	50	6000	120
A3	25	3070	123
A4	12.5	1470	118
A6	7.0	730	104
A7	5.0	640	128
A8	2.5	—	170
A9	1.25	—	230
A10	1.8	—	200

*) We have measured the specific conductivity at 25° C of various concentrations between 0.06 and 0.0006 N NaOH in 50 vol % water — 50 vol % dioxane in order to check whether the NaOH was completely dissociated. The equivalent conductivity was about 111 Ω^{-1} cm^2 gr eq^{-1} independent of the concentration within the rather low accuracy of the experiment.

A kinetic analysis of the data listed in table I according to eq. (1) (see [2]) leads to the following results and comparisons:

K_1' in 50 vol % H_2O — 50 vol % dioxane: $K_1' = 15 \times 10^{-5}$ sec^{-1}
K_1' in H_2O : $K_1' = 6 \times 10^{-5}$ sec^{-1}
K_4 in 50 vol % H_2O — 50 vol % dioxane: $K_4 = 110$ ml mol^{-1} sec^{-1}
K_4 in H_2O : $K_4 = 150$ ml mol^{-1} sec^{-1}

An increase of K_1' was found instead of the expected decrease at lower $[H_2O]$. Consequently, the assumed E.T.A.-water complex formation is

not necessarily wrong, but its velocity may be dependent on the solvent used. This may also be the case with the hydrolysis reaction catalyzed by OH^- ions (K_4).

It is evident, however, that more data on measurements with other solvents mixtures are needed in order to obtain a clear picture of the reactions involved in the alkaline hydrolysis of E.T.A.

Furthermore, it was desirable to isolate ethyl mercaptane and to determine it semiquantitatively from an alkaline hydrolysis experiment in order to localize the cleavage of the $>C-\underset{\underset{O}{\|}}{C}-S-C<$ group during the alkaline hydrolysis of E.T.A.: ~ 100 % of the theoretical yield of ethyl mercaptane was isolated as the Ag-mercaptide after an alkaline hydrolysis experiment [5].

3. *The aminolysis by glycine*

The aminolysis by glycine of E.T.A. proved to be a rather complicated process: in order to explain our kinetic data we have assumed the following overall reaction scheme:

$$C_1 + RNH_2 \xrightarrow[K_5]{} ??$$

and:

$$\text{E.T.A.} + RNH_2 \xrightarrow[K_6]{} \text{aminol. products}$$

$$\text{E.T.A.} + 2RNH_2 \xrightarrow[K_7]{} \text{,,} \qquad \text{,,}$$

$$\text{E.T.A.} + RNH_2 + OH^- \xrightarrow[K_8]{} \text{,,} \qquad \text{,,}$$

where $RNH_2 = {}^-OOC-CH_2NH_2$.

After some preliminary experiments, we isolated acetyl glycine as the aminolysis product at 37° C and pH ~ 8.5 [1]. Afterwards, it became clear that it was formed during the spontaneous (K_6) and glycinate catalyzed (K_7) aminolysis reactions.

Moreover, from our data it follows that it would be difficult to isolate acetyl-glycine as the product of the reaction between glycinate and complex C_1 (K_5): under the most favourable conditions ([OH] ≈ 0) only a fraction of about 40 % [5] of the total yield would be attributable to this reaction.

4. *A reaction scheme for the alkaline hydrolysis and aminolysis of ethyl thioacetate*

As it has been stated before [5], only a vague suggestion can be made about the first alkaline hydrolysis reaction: both a monomolecular activation reaction and a bimolecular complex formation may be assumed. If this latter assumption would be right, a thioester of the following structure may be involved:

$$CH_3-\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}-S-C_2H_5$$

Intermediate formation of a similar complex between oxygen esters and water has been proved by BENDER [7] and his collaborators. However, at the moment it seems too speculative to propose any structural reaction scheme for the alkaline hydrolysis reaction of E.T.A. involving complex C_1.

A structural reaction scheme for the second alkaline hydrolysis reaction of E.T.A. (K_4) is drawn in fig. 1.

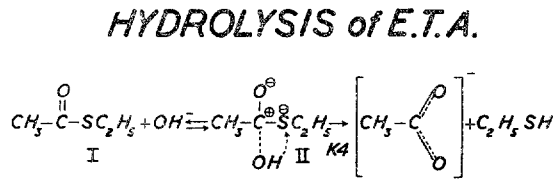

Fig. 1. A reaction scheme for the alkaline hydrolysis of E.T.A. (K_4)

This scheme is quite similar to the commonly accepted reaction scheme for the alkaline hydrolysis of oxygen esters. The E.T.A. molecule (I) is polarized by an approaching OH^-ion and a reactive complex (II) is formed, which decomposes in a rate-determining step into the acetyl ion and an ethyl mercaptane molecule or mercaptide ion. Attention should be drawn to the fact, that water may be involved in the decomposition of complex II.

A structural reaction scheme for the aminolysis of E.T.A. is drawn in fig. 2.

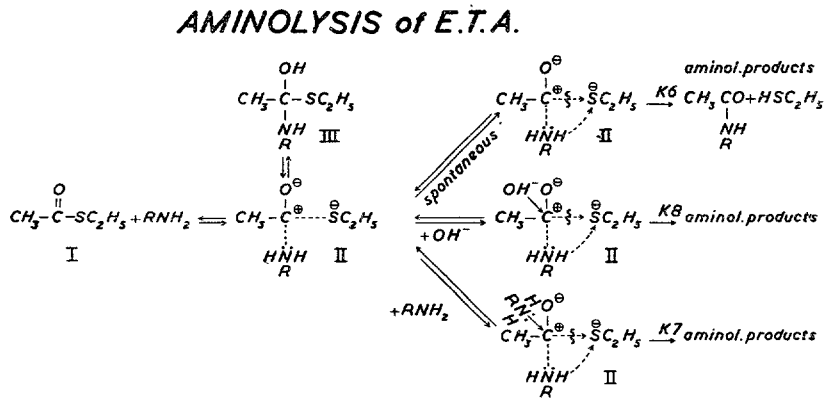

Fig. 2. A reaction scheme for the aminolysis of E.T.A. (K_6, K_7 and K_8)

An E.T.A. molecule (I) is polarized by an approaching glycine (RNH_2) molecule, which causes an inductomeric or I_d effect, specially on the sulfur atom. An activated complex (II) is formed, which is in equilibrium with complex III. Complex II decomposes spontaneously in a rate determining step into the aminolysis products, acetyl glycine and ethyl mercaptane (K_6). This decomposition, however, is catalyzed by the approach of another RNH_2 molecule or an OH^-ion: the sulfur atom is polarized somewhat more than in the complex II and the ethyl mercaptide ion is repelled

electrostatically by the RNH_2 molecule (K_7) or the OH^-ion (K_8). Bond-formation occurs between the carbonyl carbon and the aminogroup nitrogen. Of course, complex III may give similar reactions, but then a proton has to be repelled from the carbonyl oxygen. Generally speaking, the scheme for the uncatalyzed aminolysis reaction has very much in common with KOSHLAND's [8] scheme for the aminolysis of acyl-phosphate derivatives and with SCHWYZER's [9] scheme for the aminolysis of thioester compounds.

The reaction catalyzed by an amino group has not been described before. It may be, however, that physiological analogues of this type of reaction can be found in the transpeptidation processes. Let us assume, for example, that a di- or polypeptide $R_1-CO-NH-R_2$ reacts with a sulfhydryl group of the catalyzing enzyme to form an activated complex of similar structure as complex II in fig. 2. Then the $=C-S$-bond may be disrupted on the approach of another peptide or amino acid R_3-NH_2. Moreover, in the transition state bond formation may occur between the activated carbonyl carbon of the peptide bond and the nitrogen of R_3-NH_2: then a new peptide, $R_1-CO-NH-R_3$ is formed under removal of R_2NH_2 from the complex. An outline of this reaction is given in fig. 3.

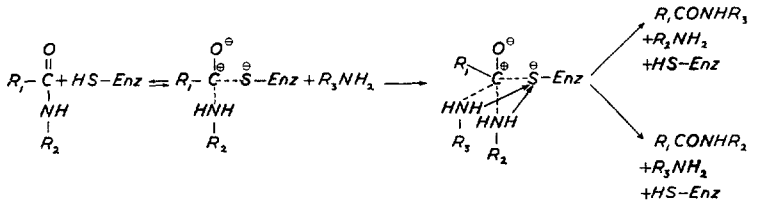

Fig. 3. A hypothetical transpeptidation reaction, outlined as an analogue of the aminogroup catalyzed aminolysis of E.T.A.

The OH^-ion catalyzed aminolysis reaction has been described by HAWKINS and TARBELL [6]. These authors have proposed a reaction scheme differing slightly from that drawn in fig. 2. They assume that the OH^-ion catalysis would be a removal of a proton from the aminogroup nitrogen by an OH^-ion.

Finally, little – if anything – can be said about the reaction between complex C_1 and glycine. If the assumption of a rate-determining ester-hydrate formation would be right, a repelling interaction of the RNH_2 molecule might be involved: in this case hydrolysis products might be formed during the reaction between complex C_1 and a RNH_2 molecule. However, a striking parallelism may be noticed between the OH^-ion – and RNH_2 – catalyzed breakdown of the E.T.A. – RNH_2 complex and the similar reactions of complex C_1. K_6 would then correspond to a spontaneous decomposition of C_1 which should occur but which is probably too slow to be measurable. K_7 corresponds to K_5 (RNH_2-catalysis) and K_8 to K_3 (OH^-ion catalysis).

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5. *Summary*

Additional data are presented, obtained during a study on the alkaline hydrolysis of ethyl thioacetate in 50 vol % water – 50 vol % dioxane mixtures.

Furthermore, reaction schemes are proposed for both the alkaline hydrolysis and aminolysis of ethyl thioacetate.

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