KINETICS OF CYCLIZATION OF S-ETHOXYCARBONYLMETHYLISOTHIOURONIUM CHLORIDE TO 2-IMINO-4-THIAZOLIDONE

Vladimír MACHÁČEK, Said A. EL-BAHAI* and Vojeslav ŠTĚRBA

Organic Chemistry Department,
Institute of Chemical Technology, 532 10 Pardubice

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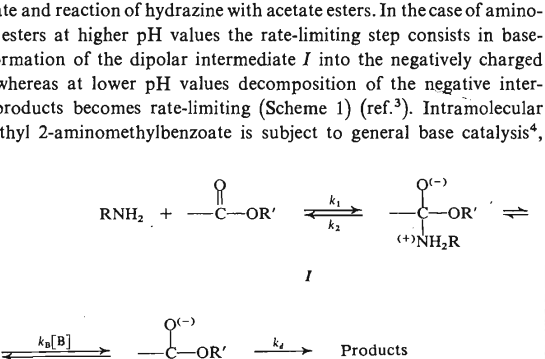
Kinetics of formation of 2-imino-4-thiazolidone from S-ethoxycarbonylmethylisothiouronium chloride has been studied in aqueous buffers and dilute hydrochloric acid. The reaction is subject to general base catalysis, the β value being 0·65. Its rate limiting step consists in acid-catalyzed splitting off of ethoxide ion from dipolar tetrahedral intermediate. At pH < 2 formation of this intermediate becomes rate-limiting; rate constant of its formation is $2 \cdot 10^4$ s^{-1}.

A number of reports[1] deal with mechanism of aminolysis of carboxylate esters. Recently Jencks[2,3] studied kinetics of reaction of aliphatic amines and hydrazine with methyl formate and reaction of hydrazine with acetate esters. In the case of aminolysis of the alkyl esters at higher pH values the rate-limiting step consists in base-catalyzed transformation of the dipolar intermediate *I* into the negatively charged intermediate *II*, whereas at lower pH values decomposition of the negative intermediate *II* into products becomes rate-limiting (Scheme 1) (ref.[3]). Intramolecular aminolysis of methyl 2-aminomethylbenzoate is subject to general base catalysis[4],



SCHEME 1

* Present address: Organic Chemistry Department, Zagazig University, Egypt.

its Brönsted coefficient being $\beta \approx 1$, which would indicate that only the proton-transfer is rate-limiting as it is the case with intermolecular aminolysis of alkyl esters. However, effect of pH and strong bases on the reaction rate is different for intramolecular aminolyses, which made the authors[4] to suppose that mechanism of this reaction is different in some aspects, too.

The aim of this work is determination of mechanism of intramolecular aminolysis of S-ethoxycarbonylmethylisothiouronium chloride.

EXPERIMENTAL

S-Ethoxycarbonylmethylisothiouronium chloride (*III*) was prepared by reaction of thiourea with ethyl chloroacetate in dimethylformamide[5]. Its melting point was 110—112° (decomp.) after precipitation with ethyl acetate from ethanol (ref.[5] gives m.p. 110°C with decomp.). For kinetic measurements a 10^{-2}M solution of this compound in 10^{-2}M ethanolic HCl was used. 2-Imino-4-thiazolidone was prepared by reaction of thiourea with ethyl chloroacetate in ethanol[6], m.p. 253—257°C with decomposition (ref.[6] gives m.p. 255—258° with decomp.). The buffers solutions were prepared from chemicals of *p.a.* purity grade and redistilled water.

Kinetic measurements. One drop of the stock solution 10^{-2}M substrate *III* was added to 2 ml buffer solution or dilute hydrochloric acid, their ionic strength *I* being adjusted at 0·5 by addition of potassium chloride. The cyclization rate was followed by absorbance increase at 250 nm at 25°C using a VSU-2P spectrophotometer (Zeiss, Jena). After the end of the reaction the spectrum of the reaction mixture was, in all the cases, identical with that of 2-imino-4-thiazolidone solution of the same concentration in the same medium.

RESULTS AND DISCUSSION

The cyclization kinetics of S-ethoxycarbonylmethylisothiouronium chloride was measured in dilute hydrochloric acid solutions, chloroacetate, formate, acetate and phosphate buffers. In all the cases the reaction proceeded as pseudomonomolecular in the whole range measured. Its reaction rate increased linearly with concentration of the basic buffer component, wherefrom it follows that the reaction is subject

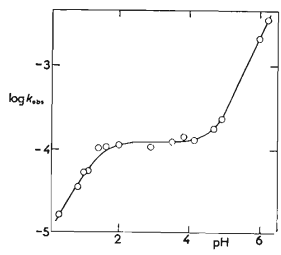


FIG. 1

pH Dependence of Logarithms of the Rate Constants k_{obs} (extrapolated to zero buffer concentration) of Cyclization of the Compound *III* to 2-Imino-4-thiazolidone at 25°C at Ionic Strength 0·5

to general base catalysis. Dependence of logarithms of the rate constants k extrapolated to zero buffer concentration on pH is given in Fig. 1. The section of the curve having the slope zero (*i.e.* within pH 2 to 4) corresponds to catalysis by water, that with the slope unity (*i.e.* at pH above 5) corresponds to catalysis by hydroxyl ion. The reaction rate decrease at pH below 2 is due to change in the rate-limiting step. The observed rate constant for pH > 2 is defined by Eq. (*1*)

$$k_{obs} = k_0 + k_{OH}[OH^-] + k_B[B^-], \qquad (1)$$

where k_0 and k_B are the rate constants of the water-catalyzed and the basic-buffer-component-catalyzed reactions, respectively. The found rate constants are given in Table I. Dependence of log k_B on pK_{BH} is linear, its slope being $\beta = 0{\cdot}65$ (for the correlation the value k_0 was divided by 55).

As far as the rate-limiting step only consists in the proton-transfer between oxygen and nitrogen atoms of the substrates and bases, the value of the Brönsted coefficient β is close to unity and zero for the transfers in thermodynamically favourable and unfavourable directions, respectively[7]. The found value $\beta = 0{\cdot}65$ suggests that the proton-transfer in the rate-limiting step is accompanied by splitting of bonds between "heavier" atoms[8,9]. For this case two rate-limiting steps with the activated complexes *IV* and *VI* can be considered. Existence of the activated complex *IV* is not likely for the following reasons: *a*) The estimated pK_a value of the substrate *III* is 9·4,* but the linear dependence of log k_B *vs* pH is fulfilled for OH^- ion, too, this ion being a stronger base than the substrate *III* by about six orders of magnitude. *b*) Difference between basicity of the used buffers (especially phosphate and acetate) and the substrate *III* is not too large. Therefore, concentration of the neutral form of the substrate (formed in a pre-equilibrium in these buffers) is by only several orders of magnitude lower than that of the far less reactive protonated substrate. In addition to it, the activated complex *IV* is entropically unfavourable, because it contains a bound molecule of base. *c*) According to microscopic reversibility principle, the reverse step $V \rightarrow III$ would have to be subject to general acid catalysis. Rate constant of decomposition of the intermediate *V* into the starting substances has a high value[3] ($k > 10^8\ s^{-1}$), and according to the Hammond principle[9] the activated complex will resemble the intermediate *V* in structure. Basicity of the intermediate *V* is extremely low (the pK_a value of nitrogen-protonated amides (O=C—$\overset{(+)}{\text{—}}$NH$_2$R) is about −8 (ref.[13]), and it is further strongly decreased by substitution

* The pK_a value of S-methylisothiouronium ion is 9·88 (ref.[10]). The Taft substitution constant $\sigma^* = 2{\cdot}00$ for the CO_2CH_3 group[11]. If the value of ϱ^* constant is presumed the same as that for dissociation of carboxylic acids[11] ($\varrho^* = 1{\cdot}72$) and if the lowering of the ϱ^* constant by the factor 2·8 is presumed for the inserted CH_2 group[12] and the same for sulphur atom, then we get the value 9·4 for pK_a of the substance *III*.

of C=O group by $C{=}\overset{(+)}{N}H_2$ group). Therefore, the intermediate will show slight tendency to bind the proton, and it is transformed into the starting substances without any assistance of acid catalyst BH.

In the activated complex *VI* a very strong base, $C_2H_5O^{(-)}$, is split off. This splitting will be facilitated by any of the conjugated acids BH inclusive of water. The overall mechanism is described in Scheme 2.

It is interesting to compare our results with those found for intramolecular aminolysis of methyl 2-aminomethylbenzoate[4]. Although the both reacting groups of 2-aminomethylbenzoate are fixed by the benzene ring at positions favourable for cyclization, and basicity of amino group is lower by less than an order of magnitude than that of the substrate *III*, the cyclization rate under comparable conditions (pH 6, k_{obs} extrapolated to zero buffer concentration) is lower by almost 4 orders of magnitude. At the same time, slope of the pH dependence of the extrapolated log *K* values is equal to 2, whereas for the substrate *III* the found slope was unity (Fig. 1). The great difference in the rate of the cyclization reactions indicates that the amidine NH_2 group is a far stronger nucleophile than alkylamine of the same basicity, and, in this respect, it obviously resembles nucleophiles with an α effect. The slope 2 found for cyclization of 2-aminomethylbenzoate indicates that deprotonation of NH_2 group of the tetrahedral intermediate *VII* takes place before the rate-limiting step. In the intermediate *V* the positive charge is delocalized on the both nitrogen atoms and, therefore, the tendency to deprotonation is substantially smaller, and splitting off of $C_2H_5O^{(-)}$ from the dipolar intermediate *V* is easier than that from the intermediate *VII*.

At pH < 2 the proton-catalyzed splitting of the intermediate *V* to products becomes faster than the reverse reaction of the intermediate *V* to the starting substances, and formation of the intermediate *V* becomes rate-limiting. The observed rate constant k_{obs} is then defined by Eq. (*2*).

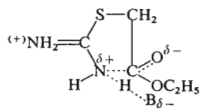
$$k_{obs} = K_A k_1 k_2 / (k_{-1} + k_2[H^+]) \qquad (2)$$

TABLE I

Rate Constants k_B ($l\,mol^{-1}\,s^{-1}$) of Formation of 2-Imino-4-thiazolidone and pK_B Values of the Catalysts BH in Water at 25°C at Ionic Strength 0·5

B	OH^-	H_2O	$ClCH_2CO_2^-$	HCO_2^-	$CH_3CO_2^-$	HPO_4^{2-}
k_B	$2{\cdot}3\,.\,10^5$	$2{\cdot}2\,.\,10^{-6}$	$3{\cdot}5\,.\,10^{-4}$	$1{\cdot}1\,.\,10^{-3}$	$3{\cdot}3\,.\,10^{-3}$	$1{\cdot}6\,.\,10^{-1}$
pK_{BH}	15·7	−1·7	2·70	3·55	4·67	6·65

The calculated value $k_1 = (2{\cdot}0 \pm 0{\cdot}3) \cdot 10^4\ s^{-1}$. This k_1 value is higher than that estimated for the reaction of ethyl acetate with hydrazine[3] by about 5 orders of magnitude.



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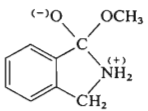
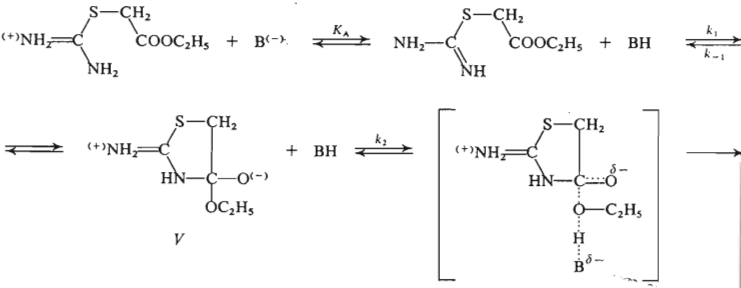


VII



SCHEME 2

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