SOLVOLYSIS KINETICS OF ETHYL 3-ETHOXY-3-IMINOPROPANOATE

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Kinetics have been studied of hydrolysis and methanolysis of ethyl 3-ethoxy-3-iminopropanoate. The methanolysis rate constant is lower than the hydrolysis rate constant by about 3 orders of magnitude. The rate-limiting step of the hydrolysis consists in the nucleophilic attack of the protonated substrate by a water molecule, whereas that of the methanolysis consists in the decomposition of tetrahedral intermediate which is several orders of magnitude slower than the decomposition of the intermediate formed in the hydrolysis.

The 1-aryl-5-pyrazolone derivatives substituted with various arylamino groups at 3 position serve as important dyestuff intermediates and also are used for syntheses of colour couplers in colour photography[1]. Syntheses of these derivatives start from imidoesters — derivatives of alkyl 3-alkoxy-3-iminopropanoate[2]. The key step consists in preparation of $Ar-N=C(OCH_3)CH_2CO_2C_2H_5$ by reaction of ethyl 3-ethoxy-3-iminopropanoate hydrochloride (*II*) with anilines carrying electron--acceptor substituents in anhydrous methanolic medium[3].

As imidoesters and their salts react with methanol to give esters, orthoesters, or amides[4], we submitted this reaction to a detailed study in the case of the imido ester *II*. Also studied was the hydrolysis of ethyl 3-methoxy-3-iminopropanoate (*I*) in order to better understand reactivity of the primary tetrahedral intermediate formed.

EXPERIMENTAL

Reagents

The hydrochlorides of ethyl 3-methoxy-3-iminopropanoate (*I*) and ethyl 3-ethoxy-3-iminopropanoate (*II*) were prepared by addition of methanol and ethanol, respectively, to ethyl cyanoethanoate by a known procedure[5]. According to the same ref.[5] we also prepared the free base of compound *II*, *i.e.* ethyl 3-ethoxy-3-iminopropanoate (*III*). Ethyl methyl malonate (*IV*) was obtained by stepwise addition of 20 g (0·11 mol) compound *I* to 100 ml 0·1 mol l^{-1} hydrochloric acid with stirring. After 15 min the reaction mixture was extracted with 2 × 50 ml benzene. The benzenic extracts were dried with sodium sulphate and distilled. The required ester *IV* was isolated as a fraction boiling at 59—62°C/780 Pa in the yield of 11 g (69%), and its structure was confirmed by ^1H NMR spectra.

Measurement of Dissociation Constants

The dissociation constant of compound *II* in methanol was measured spectrophotometrically (Specord UV-VIS) in the following way: 50—500 µl fresh solution of compound *II* in methanol (concentration $2\cdot2 \cdot 10^{-2}$ mol l^{-1}) was injected into 10—9·5 ml methanol at 25°C, and the absorbance was measured immediately in a 1 cm quartz cell. The absorbance of the base of *II* (0·1 to 1 cm cell) was determined after addition of 1 drop of 0·5 mol l^{-1} sodium acetate, and that of the hydrochloride *II* itself was determined by measuring the same amount of compound *II* in methanolic hydrochloric acid ([HCl] = $5 \cdot 10^{-3}$ mol l^{-1}). The dissociation constant was calculated from Eqs (*1—3*), and the results are given in Table I.

$$K_A = [H^+][III]/[II] = [III]^2/[II] \tag{1}$$

$$[III] = ((A - A_{II})/(A_{III} - A))[II]_{anal} \tag{2}$$

$$[II] = [II]_{anal} - [III] \tag{3}$$

The dissociation constant of compound *II* in water was measured also spectrophotometrically in acetate and phosphate buffers at $\lambda = 261$ nm at the ionic strength $I = 1$ (KCl). The value of the dissociation constant was calculated from Eq. (*4*).

$$pK_A = pH - \log((A - A_{II})/(A_{III} - A)), \tag{4}$$

where A_{II}, A_{III}, and A mean the absorbances of the substrate, its conjugated base, and the solution measured, respectively. As the compound *II* is rapidly hydrolyzed in aqueous solutions, the values used for the calculation were absorbances from the kinetic measurements extrapolated to zero time. The pK_A value of compound *II* determined from the values extrapolated in this way is $5\cdot19 \pm 0\cdot02$.

Kinetic Measurements of Solvolyses of Compounds *II* and *I*

For the methanolyses of compounds *II* and *I* fresh solutions of *II* and *I*, resp., were prepared in methanol ($c = 10^{-1}$ to 10^{-4} mol l^{-1}) or in methanolic hydrochloric acid ([HCl] = 10^{-2}

TABLE I

Experimental values of absorbances A ($\lambda = 263$ nm; $d = 1$ cm) and concentrations of compound *II* for calculation of dissociation constant of compound *II* in methanol at 25°C according to Eqs (*1*)—(*3*); $K_A = (2\cdot25 \pm 0\cdot15) \cdot 10^{-5}$.

$10^4\,[II]_{anal}$ mol l^{-1}	$A_{exp} - A_{II}$	$A_{III} - A_{II}$	$10^5\,K_A$
1·1	0·20	0·53	2·5
2·2	0·30	1·09	2·3
4·4	0·44	2·18	1·9
6·6	0·56	3·30	2·3
8·8	0·64	4·41	2·2
11	0·72	5·52	2·2

to 10^{-3} mol 1^{-1}) and temperated at 25°C. At regular time intervals samples were withdrawn and diluted with methanol to make the final analytical concentration $5 . 10^{-5}$ mol 1^{-1}. This solution (2 ml) was placed immediately into a quartz cell, one drop of one-molar sodium acetate in methanol was added thereto, and absorbance of the imidoester was measured at 263 nm. The rate constants were calculated from Eq. (5) and are given in Table II along with the concentration ratios.

$$k_{exp}t = -\log(E_t - E_\infty) + \text{const.} \qquad (5)$$

For identification and determination of the methanolysis products of the imidoesters *I* and *II* we prepared 100 ml solution of *I* ($2 . 10^{-1}$ mol 1^{-1}) and *II* ($1 . 10^{-1}$ mol 1^{-1}), respectively. The methanolysis was followed spectrophotometrically, and when it was finished, methanol was distilled off under reduced pressure, the residue was diluted with 50 ml benzene, shaken with 2×50 ml water, the benzene layer was separated and dried with sodium sulphate, and benzene was distilled off. According to ^{1}H NMR spectra and gas chromatography the distillation residue contained methyl 2-ethoxycarbonylorthoacetate (ethyl 3,3,3-trimethoxypropanoate) and ethyl methyl malonate whose molar ratio was determined.

The hydrolysis of compound *II* was followed in aqueous formiate (pH 3·51—4·18), acetate (pH 4·24—5·55), and phosphate buffers (pH 5·70—6·48) at 25°C at the ionic strength $I = 1$. From a pipette 10 ml temperated buffer was placed into a 25 ml beaker, and 0·4 ml solution of compound *III* in acetonitrile ($c = 0·01$ mol 1^{-1}) was added. The reaction mixture was stirred rapidly, and about 2 ml of the mixture was transferred into a 1 cm quartz cell placed in the temperated cell compartment of the spectrophotometer, and the absorbance decrease was followed at 261 nm. In the formiate buffers (with respect to small absorbance changes) the reaction was followed by the quenching method: 70 ml buffer solution was placed into a 100 ml beaker from a pipette, and 2·1 ml 0·01 mol 1^{-1} solution of compound *III* in acetonitrile was added at 25°C. The reaction mixture was stirred and samples (2 ml) were withdrawn from the beaker within several half-lives of the reaction; the samples were injected into 0·1 mol 1^{-1} borax buffer, whereupon their absorbances were measured at 261 nm.

TABLE II

Experimental rate constants k_{exp} (s^{-1}) of methanolysis of imidoester *II* measured at 263 nm at 25°C at various molar concentrations of compound *II* and hydrogen chloride in methanol

[*II*]	[HCl]	$10^6 k$
$1 . 10^{-4}$	$1 . 10^{-2}$	1·28
$1 . 10^{-4}$	$1 . 10^{-3}$	1·32
$1 . 10^{-4}$	0	0·86
$1 . 10^{-3}$	$1 . 10^{-3}$	1·32
$2·5 . 10^{-2}$	$1 . 10^{-3}$	1·20
$2·5 . 10^{-2}$	0	1·13
$1 . 10^{-1}$	0	1·13
$1 . 10^{-4,a}$	$1 . 10^{-2}$	1·38

^{a} Ethyl 3-methoxy-3-iminoester (*I*)

RESULTS AND DISCUSSION

The hydrochlorides *I* and *II* are dissociated in methanol and in water to give the conjugated bases which exist in two tautomeric forms *V* and *VI*. The enamine form *V*, which absorbs at longer wavelengths $(\lambda_{max} = 260$ nm) due to considerable electron delocalization, predominates in the solution[5] over the tautomer *VI* $(\lambda_{max} = 210$ nm). The equilibrium between the tautomers *V* and *VI* is established so rapidly that it cannot be measured by usual kinetic methods.

$$
\begin{array}{c}
\underset{\textstyle V}{C_2H_5O\overset{\overset{\textstyle O}{\|}}{-}C\overset{\overset{\textstyle NH_2}{|}}{-}CH=C-OR} + H^+ \rightleftarrows C_2H_5O\overset{\overset{\textstyle O}{\|}}{-}C-CH_2\overset{\overset{\textstyle (+)NH_2}{\|}}{-}C-OR \rightleftarrows
\end{array}
$$

$$
\rightleftarrows H^+ + C_2H_5O\overset{\overset{\textstyle O}{\|}}{-}C-CH_2\overset{\overset{\textstyle NH}{\|}}{-}C-OR
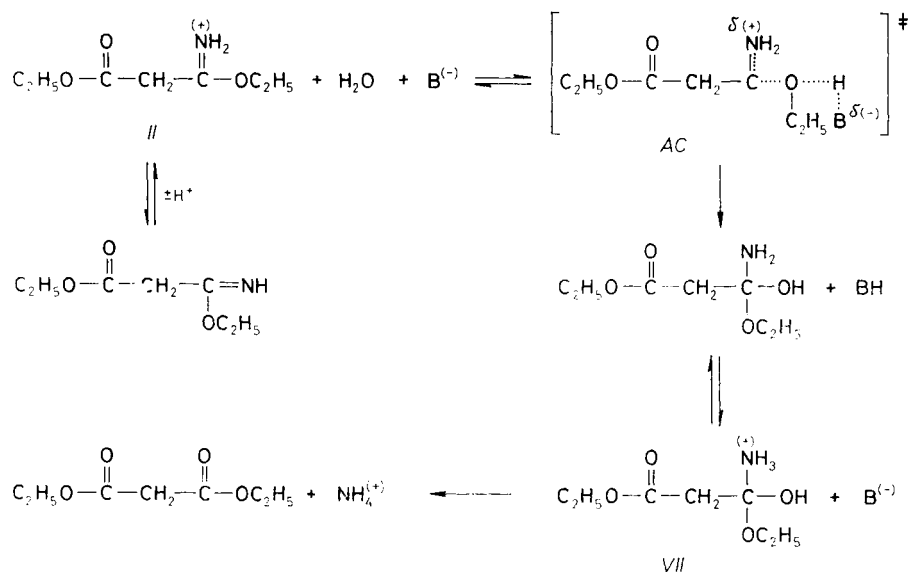$$

$$VI$$
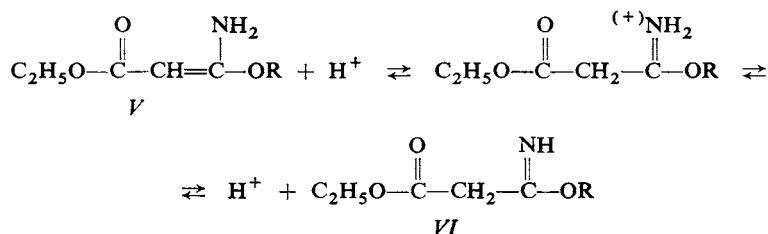
The long-wave absorbance of the enamine form *V* was utilized for measurements of the methanolysis kinetics. The reaction products do not practically absorb in this region, so the absorbance decrease at the λ_{max} (determined after possible addition of sodium acetate) is directly proportional to the concentration decrease of the starting hydrochloride.

The hydrolysis of compound *II* was followed in aqueous solutions of formiate, acetate, and phosphate buffers. The hydrolysis proceeded kinetically as a pseudo--first-order reaction, and the observed rate constants increased linearly with the buffer concentration. The reaction mechanism is given in Scheme 1. The compound *II* is the reactive component which produces the tetrahedral intermediate *VII* in the rate-limiting step. The formation of the intermediate represents a general acid--catalyzed reaction. The hydrolysis rate constant is defined by the kinetic equation (6)

$$
k_{obs} = \left(k_o + k_B[B^{(-)}]\right)\left([H^+]/(K_A + [H^+])\right), \tag{6}
$$

where k_o is rate constant of the non-catalyzed reaction, k_B is rate constant of the base-catalyzed reaction, and the fraction $[H^+]/(K_A + [H^+])$ represents the portion of the protonated (reactive) form of compound *II*. For K_A introduced was the value $10^{-5,19}$ obtained by measurement of the dissociation constant (see Experimental). The rate constants k_B $(1$ mol^{-1} s$^{-1})$ and k_o (s^{-1}) of the hydrolysis catalyzed by formiate, acetate, phosphate anions and water, respectively, were calculated from Eq. (6) and have the following respective values: $(7\cdot4 \pm 0\cdot4)\cdot10^{-3}$, $(8\cdot9 \pm 0\cdot8)\cdot$ $.\,10^{-3}$, $(11\cdot2 \pm 0\cdot7)\cdot10^{-3}$, and $(4\cdot6 \pm 0\cdot6)\cdot10^{-3}$. The little differences between the values of rate constants indicate that the bases play little role in the activated

complex $(AC$, see Scheme 1), because the protonated intermediate is very reactive to water.

$$C_2H_5O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle NH_2^{(+)}}{\|}}{C}-OC_2H_5 \;+\; H_2O \;+\; B^{(-)} \;\rightleftharpoons\; \left[\; C_2H_5O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle \delta(+)\, NH_2}{\|}}{C}\cdots\underset{\underset{\displaystyle C_2H_5\;B^{\,\delta(-)}}{|}}{O}\cdots H \;\right]^{\ddagger}$$

II   *AC*

$\big\Downarrow \pm H^+$

$$C_2H_5O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\underset{\underset{\displaystyle OC_2H_5}{|}}{C}=NH \qquad\qquad\qquad C_2H_5O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle NH_2}{|}}{\underset{\underset{\displaystyle OC_2H_5}{|}}{C}}-OH \;+\; BH$$

$\Big\Updownarrow$

$$C_2H_5O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-OC_2H_5 \;+\; NH_4^{(+)} \quad\longleftarrow\quad C_2H_5O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle NH_3^{(+)}}{|}}{\underset{\underset{\displaystyle OC_2H_5}{|}}{C}}-OH \;+\; B^{(-)}$$

VII

SCHEME 1

The methanolysis rates of compound *II* were measured in the substrate concentration range from $1 \cdot 10^{-1}$ to $1 \cdot 10^{-4}$ mol l^{-1} with possible addition of hydrochloric acid. The results are given in Table II. Logarithm of the absorbance changes shows linear time dependence within the whole range of the measurement in all the cases except the experiment with $[II] = 10^{-4}$ mol l^{-1} without hydrochloric acid. This means that the reaction takes the pseudo-first-order course. In a parallel experiment carried out with compound *I* under the same conditions we found the same rate constant (within experimental error) as that found for the hydrochloride *II*. In the experiment with the concentration $[II] = 1 \cdot 10^{-4}$ mol l^{-1} without added hydrochloric acid, the rate constant found from the initial reaction phase was substantially lower, and slope of the dependence of logarithm of absorbance vs time decreased during the reaction course. This decrease is due to that compound *II* is considerably dissociated at low concentrations (pK_A $4 \cdot 65 \pm 0 \cdot 05$, see Table I), hence concentration of the reacting protonated component is lower than the analytical concentration, and the dissociation degree increases with proceeding methanolysis. In the presence of hydrochloric acid or at higher concentrations of hydrochloride *II* the dissociation is practically suppressed. The hydrolysis rate constant of compound *II* is $4 \cdot 6 \cdot 10^{-3}$ s^{-1}, which means that the hydrolysis is faster than the methanolysis by three orders of magnitude.

The methanolysis mechanism of hydrochloride *II* is given in Scheme 2. In the hydrolysis of compound *II* the rate-limiting reaction step consists in the attack of the protonated imidoester by water; the protonated intermediate *VII* formed (Scheme 1) is rapidly decomposed into ammonium salt and ester. The lower methanolysis rate (3 orders of magnitude) can be due to two factors. Either attack by methanol also represents the rate-limiting step, and it is slower than that by water by 3 orders (which is very unlikely), or splitting off of ammonia from the intermediate *VIII* is by several orders slower than decomposition of the intermediate *VII*.
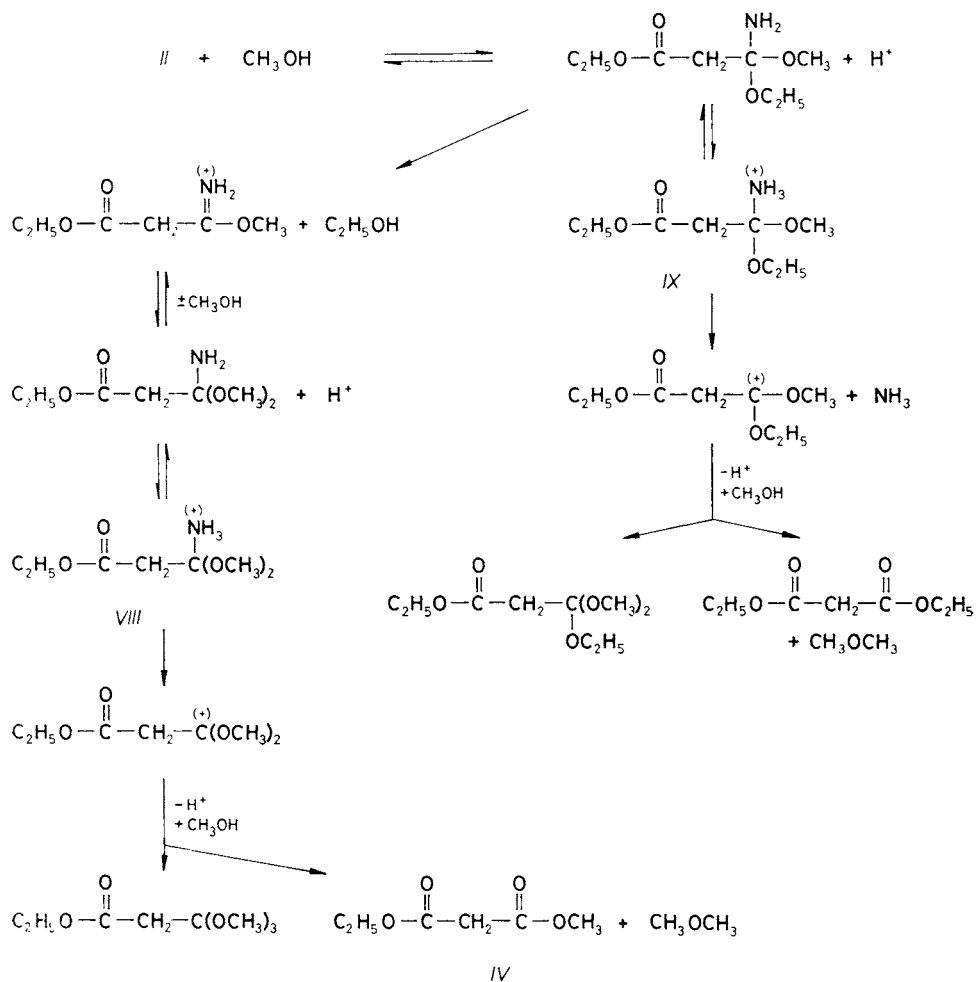
SCHEME 2

Its formation represents a reversible reaction, and its decomposition becomes rate limiting. In the first case methanolysis of compound *II* would produce a mixed orthoester and diethyl malonate, in the second case trimethyl orthoester and methyl ethyl malonate would be formed (Scheme 2). Product of the reaction carried out on preparative scale was analyzed by ^{1}H NMR and gas chromatography, and trimethyl orthoester (75%) and methyl ethyl malonate (25%) were only found. This means that the rate-limiting step of the methanolysis consists in splitting off of ammonia from the intermediate *VIII*. The other reaction pathway (splitting of the intermediate *IX* into the mixed orthoester and diethyl malonate) is practically insignificant, because concentration of *IX* is negligible as compared to that of *VIII*.

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