KETIMINE-ENAMINE TAUTOMERISM OF 2-ETHOXYCARBONYLMETHYLENE-4-METHYL-3-OXO-1,2,3,4-TETRAHYDROQUINOXALINE: A KINETIC STUDY*

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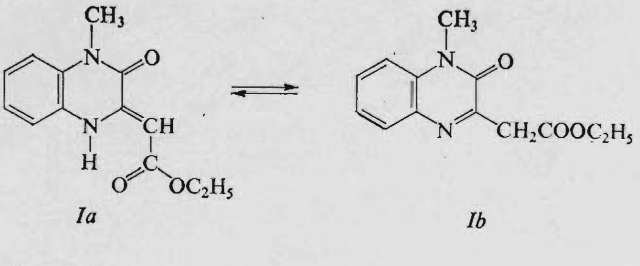
Tautomerism of the title compound in methanol in the presence of buffers is subject to general acid and base catalysis. The rate-limiting step of the acid-catalyzed reaction consists in addition of the proton to the methine carbon atom of the enamine form, whereas that of the base catalyzed reaction consists in protonation of the formed conjugated base of the enamine. Solvent effects on the equilibrium constant of the isomerization have been measured.

In our previous paper[1] we dealt with determination of thermodynamic parameters of ketimine–enamine tautomeric equilibrium of derivatives of 2-methylene-3-oxo-1,2,3,4-tetrahydroquinoxaline by means of ^{1}H-NMR. Value of the equilibrium constant depends on temperature, solvent and substituent at 2-position which activates the ketimine-enamine isomerization. The present paper presents a study of kinetics and mechanism of the isomerization of 2-ethoxycarbonylmethylene-4-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline (*I*) in methanol and solvent effects on the value of the equilibrium constant.



EXPERIMENTAL

The ester *I* was prepared according to ref.[2]. The hydrochlorides of the amines were prepared by mixing the free bases with hydrochloric acid and vacuum evaporation at 100°C. Sodium chloroacetate was obtained by precipitation of concentrated solution of chloroacetic acid with 3 M-CH_3ONa solution and by washing with methanol.

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The buffers were prepared by mixing either carboxylic acids with their salts, or hydrochlorides of the amines with the respective free bases. In the case of carboxylate buffers ionic strength was adjusted at 0·2 by addition of sodium bromide. The $\mathrm{p}K_\mathrm{a}$ values of equilibrium mixture of the isomers were determined spectrophotometrically at 405 nm in solutions of sodium methoxide (concentrations of 1 to 2·5 mol l^{-1}); the values were calculated from the relations[3]:

$$\mathrm{p}K_\mathrm{a} = \log I + \mathrm{H}_\mathrm{M}\,, \quad I = c_\mathrm{SH}/c_{\mathrm{S}^-}\,,$$

where H_M means the acidity function in methanol.

At higher methoxide concentrations the substrate is increasingly decomposed and the measured absorbance values had to be extrapolated to zero time (the time of mixing of the solutions). The dependence of I on H_M was linear, but its slope had a value of 1·25. The value $\mathrm{p}K_\mathrm{a} = 18{\cdot}17 \pm \pm 0{\cdot}05$ was determined graphically, and it corresponds to the H_M value at $\log I = 0$ (the methoxide concentration 1·86 mol l^{-1}).

The kinetic measurements were carried out spectrophotometrically at 405 nm using a Specord UV VIS and VSU 2 apparatus (Zeiss, Jena) at 25°C in methanol. Fresh methanolic solutions of the samples were injected to the buffers. The observed rate constants were calculated for pseudomonomolecular reaction[4]. The equilibrium constants were determined directly from the absorbance decrease at 405 nm after addition of catalyst to the solution, because the ketimine does not absorb at the given wavelength.

RESULTS AND DISCUSSION

The studied compound exists as the enamine tautomer *Ia* in solid state, whereas in solution an equilibrium between the enamine and the ketimine tautomers is established[1,5]. The equilibrium constant is greatly influenced by the solvent used (Table I). In cyclohexane solution the tautomer *Ia* is favoured, which indicates a higher stability of enamine in accordance with the HMO calculation[6]. Effect of medium is similar to that observed with keto-enol tautomerism, the reasons being obviously similar, too, *viz.* solvation of the more polar form[7].

TABLE I

Effect of solvents on value of the tautomeric equilibrium constant of the ester *I*

Solvent	Catalyst	K [ketimine/enamine]
Methanol	CH_3COOH	2·95
	$(C_2H_5)_3N$	3·05
Chloroform	CH_3COOH	1·3
Toluene	CH_3COOH	0·4
Cyclohexane	$(C_2H_5)_3N$	0·24

The isomerization of the enamine is catalyzed by the proton, methoxide, as well as by acidic and basic buffer components. Dependences of the observed rate constant on the proton concentration and on methoxide ion concentration are linear in the whole range measured, and the value extrapolated for the zero concentration of the catalysts is zero within experimental error. This finding indicates that no catalysis by solvent takes place in accordance with the fact that a prepared solution of the substrate shows practically the same absorbance for several days.

The observed rate constant is generally described by the relation

$$k_{obs} = k_H[H^+] + k_{HA}[HA] + k_A[A^-] + k_{CH_3O}[CH_3O^-]$$

The calculated rate constants k_H and k_{CH_3O} are similar (Table II), the constant k_{obs} is given as a sum of the rate constants of formation of ketimine and the reverse reaction

$$k_{obs} = \overrightarrow{k} + \overleftarrow{k}\,.$$

As the resulting product is a 1 : 3 mixture of the two isomers, the ratio of these rate constants is 3·0 ± 0·1.

TABLE II

Ionisation constants of the catalysts used and rate constants of isomerization of ester *I*

Acid	pK_a (methanol)	Ref.	k_{HA}	k_A
$ClCH_2COOH$	7·96	9	$(2{\cdot}5 \pm 0{\cdot}5)\,.\,10^{-2}$	$5\,.\,10^{-4}$
$HCOOH$	8·96	10	$(5 \pm 2)\,.\,10^{-3}$	$(1{\cdot}3 \pm 0{\cdot}5)\,.\,10^{-3}$
CH_3COOH	9·52	9	$(1{\cdot}0 \pm 0{\cdot}5)\,.\,10^{-3}$	$(5 \pm 1)\,.\,10^{-3}$
$p\text{-}BrC_6H_4\overset{(+)}{N}H_3$	5·00	11	$(2{\cdot}2 \pm 0{\cdot}3)\,.\,10^{-1}$	—
$p\text{-}CH_3C_6H_4\overset{(+)}{N}H_3$	6·50	—	$(0{\cdot}16 \pm 0{\cdot}2)\,.\,10^{-1}$	—
$CH_3CH_2CH_2CH_2\overset{(+)}{N}H_3$	11·70	12	—	$1 \pm 0{\cdot}2$
$(C_2H_5)_3\overset{(+)}{N}H$	10·88	12	—	$2 \pm 0{\cdot}2$
$(C_2H_5)_2\overset{(+)}{N}H_2$	11·20	—	—	$2{\cdot}55 \pm 0{\cdot}3$
$HOCH_2CH_2\overset{(+)}{N}H_3$	10·75	13	—	$(2{\cdot}55 \pm 0{\cdot}3)\,.\,10^{-1}$
Morpholinium	8·69	12	—	$(4{\cdot}6 \pm 0{\cdot}3)\,.\,10^{-1}$
HCl	—	—	66 ± 4[a]	—
CH_3OH	16·92	14	—	48 ± 4

[a] k_H.

In carboxylate buffers both the acidic and basic buffer components show catalytic action, acetate anion and chloroacetic acid being mainly important in acetate and chloroacetate buffers, respectively, which agrees with the respective acidities. The rate constant extrapolated to zero buffer concentration practically is equal to zero, because concentrations of both the proton and methoxide anion are so low that catalysis by these ions is negligible, and the observed rate constant is given by the relation

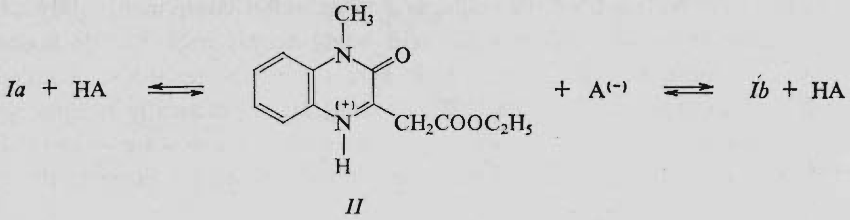
$$k_{\text{obs}} = k_{\text{HA}}[\text{HA}] + k_{\text{A}}[\text{A}^-] \,.$$

Evaluation of the rate constants (Table II) is made difficult by the fact that rate of the base-catalyzed reaction decreases with increasing concentration of acid. This is particularly marked in the case of chloroacetate buffer where the isomerization rate at a given acid concentration decreases even with increasing anion concentration, which prevented determination of the rate constant value in the base-catalyzed reaction in the case of chloroacetic acid.

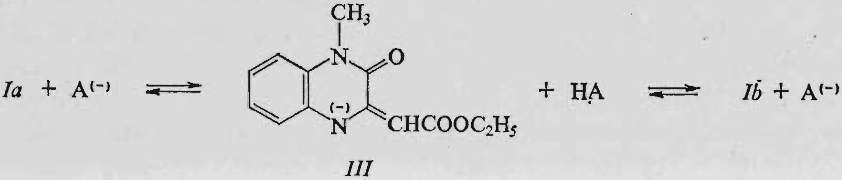
In the case of substituted anilinium ions, which are by several orders of magnitude stronger acids than carboxylic acids (Table II), practically only the acid buffer component made itself felt, being accompanied by catalysis by the proton (especially so in the case of 4-bromoanilinium ion). An opposite situation was encountered with aliphatic amines where only the basic buffer component is catalytically active, in spite of the fact that their pK_a values (Table II) are comparable with those of carboxylic acids. This result is due to the base catalysis being far more marked in this case (up to two orders of magnitude higher than that of carboxylate anions), so that acid catalysis is practically insignificant kinetically. Secondary amines are stronger catalysts than primary amines of similar basicity (determined by measurement in methanol), which could be due to the fact that secondary amines have a much higher intrinsic basicity (determined by measurement in gas phase[8]). In methanolic solution the primary ammonium ions are more solvated than the secondary ammonium ions, whereby their basicities are equalized. In the activated complex the solvation stabilization is less important than in the ammonium ions themselves, and thus the intrinsic basicity is relatively more significant. Tertiary amines should be even stronger catalysts, but sterical effects of three alkyl groups decrease their catalytic activity. Also secondary amines show a certain extent of sterical effect which can be seen in comparison of diethylamine and morpholine: their basicity and catalytic activity ratios are $> 10^2$ and 0·2, respectively.

From the kinetic measurements it is possible to suggest mechanisms of the acid- and base-catalyzed isomerizations (Schemes 1 and 2, respectively).

The rate-limiting step of the acid-catalyzed isomerization consists in addition of the proton to the methine carbon atom of the neutral substrate. As the isomerization rate constants in the both directions stand in the ratio 3 : 1, the rate constant of this step equals to $3/4k_{\text{HA}}$ for the given acid, hence in the proton-catalyzed reaction



SCHEME 1



SCHEME 2

it is 49·5. The base-catalyzed isomerization involves a rapid acid–base pre-equilibrium followed by the rate-limiting protonation of the anion formed at the methylene carbon atom (by the corresponding conjugated acid, *i.e.* *e.g.* by methanol in the case of the methoxide-catalyzed isomerization).

Rate of formation of the ketimine in this case is given by the relation

$$v = k_2[III],$$

where k_2 is the rate constant of protonation with methanol. On the basis of the determined pK_a value the above relation can be transformed to

$$v = 0{\cdot}75k_{obs}[I] = k_2K_A/K_B[CH_3O^-][I],$$

$$k_2 = 0{\cdot}75k_{CH_3O} \cdot 10^{1.25} = 640.$$

As there are 33 mol CH_3OH in 1 000 ml methanol, the rate with one mol is 33 times smaller, *i.e.* about 19, which means that the rate constant of protonation of methine group in neutral enamine is practically identical with that of protonation of the ketimine anion with neutral methanol.

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