MECHANISM OF BASE-CATALYZED CYCLIZATION OF ETHYL N-(SUBSTITUTED AMINOCARBONYL)GLYCINATES

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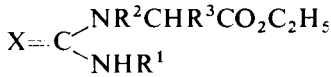
The cyclization rate constants have been measured of substituted ethyl N-(phenylaminocarbonyl)-, N-(alkylaminocarbonyl)-, and N-(phenylaminothiocarbonyl)glycinates $RNHCXNHCH_2CO_2.C_2H_5$ (X = O, S). Logarithms of these constants increase with decreasing basicity of the amines down to the value of $pK_a(RNH_2) = 5{\cdot}5$. The rate-limiting step of the reaction is formation of the tetrahedral intermediate. With ethyl N-(phenylaminocarbonyl)glycinates (whose $pK_a(RNH_2)$ values are higher) this dependence, on the contrary, slightly decreases, and the acid-catalyzed splitting off of ethoxy group from the cyclic intermediate becomes rate-limiting. The cyclization rate of a series of ethyl N-(phenylaminothiocarbonyl)glycinates is practically independent of the $pK_a(RNH_2)$ values, the change in the rate-limiting step would take place at pH about 9.

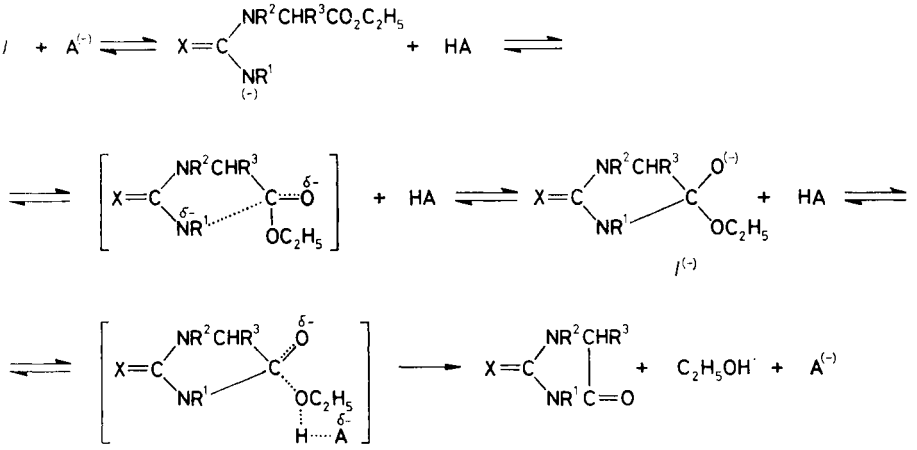
In our previous report[1] kinetics and mechanism was studied of base-catalyzed cyclization of ureido- and thioureidoesters *I* giving 5-substituted-2,4-imidazolidinediones and 5-substituted-2-thioxo-4-imidazolinones, respectively. With the N-phenylureidoesters (R^1 = phenyl) the cyclization rate always was several orders higher than that of the corresponding methyl derivatives. On the other hand, in the case of the thioureidoesters the phenyl derivatives cyclized by about 1 order of magnitude more slowly than the corresponding methyl derivatives.



Ia, X = O
Ib, X = S

When studying the effect of buffers (phosphate and acetate) on the cyclization rate constants we found the buffer concentration (at a constant ionic strength) to have practically no effect on the cyclization rate of the methyl thioureidoesters (R^1 = = methyl), whereas k_{obs} of the phenyl thioureidoesters slightly increased with increasing concentration of phosphate buffer, the increase being steeper (several times) in acetate buffers. With the phenylureidoesters a small increase of k_{obs} was

found in phosphate buffers, which could be due to specific effects of phosphate ions on the reaction medium (the cyclization was not studied in acetate buffers because of very low velocity in this medium). The catalytic effect of buffer on k_{obs} means that the cyclization is subject to general base catalysis. An acceptable mechanism of such reaction is given in Scheme 1. The rate-limiting step consists in the splitting off of ethoxy group in a generally acid-catalyzed reaction, and, the preequilibrium formation of the anion being subject to specific base catalysis, the result is a general base catalysis. In the cases in which the cyclization is not catalyzed by the buffer the reaction is subject to specific catalysis, and the rate-limiting step consists in the formation of the negatively charged intermediate. The polar effects of the substituent R^1 must be considerably different in these two cases.



SCHEME 1

In order to confirm the statement that the introduction of phenyl group instead of methyl group of the thioureides is connected with a change in the rate-limiting step and to find the rate-limiting step of the cyclization of phenylureidoesters, we have studied now the cyclization kinetics of ethyl N-(alkylaminocarbonyl)-, N-(phenylaminocarbonyl)-, and N-(phenylaminothiocarbonyl)glycinates. For the measure of magnitude of the polar effects we took the $pK_a(RNH_2)$ values of the corresponding amines RNH_2.

EXPERIMENTAL

Reagents. Diethyl N,N'-carbonylbisglycinate was prepared by the reaction of ethyl isocyanatoacetate with ethyl glycinate in chloroform. M.p. 146–147°C (ref.[2] gives m.p. 147°C). Ethyl N-(cyanomethylaminocarbonyl)glycinate was prepared in similar way from aminoaceto-

nitrile. Ethyl N-(phenylaminocarbonyl)glycinate, m.p. 110·5–111·0°C, was prepared according to ref.[3], ethyl N-(4-nitrophenylaminocarbonyl)glycinate, m.p. 166–167°C, according to ref.[4], ethyl N-(phenylaminothiocarbonyl)glycinate, m.p. 89–90°C, according to ref.[5], and ethyl N-(methylphenylaminothiocarbonyl)glycinate, m.p. 95–96°C, according to ref.[5]. The other substituted ethyl N-(phenylaminocarbonyl)glycinates and ethyl N-(phenylaminothiocarbonyl)glycinates were prepared by the reaction of ethyl isocyanatoacetate with substituted anilines or by the reaction of substituted phenyl isothiocyanates with ethyl glycinate. The products were recrystallized from a mixture of chloroform and petroleum ether. The melting points and results of elemental analyses are given in Table I.

Kinetic measurements. Solutions of N-substituted ethyl glycinates in methanol were injected into borax buffer (pH 9·06) to make the final concentration of the substrate 10^{-4} mol l^{-1} and the methanol concentration at most 1%. The buffer ionic strength was 0·1. The solutions to be measured were kept at 25°C in cells of a Unicam SP 800B spectrophotometer. The absorbance changes were measured in the region from 215 to 285 nm.

RESULTS AND DISCUSSION

All the kinetic experiments were carried out in the borax buffer at the same conditions. The cyclizations proceeded as pseudo-first-order reactions. The hydrolysis rate of the products formed was several orders of magnitude slower, hence the time dependence of $\log (A_t - A_\infty)$ was linear within the whole range studied (3 half lives at least). The dependence of $\log k_{obs}$ of the cyclization of substituted ethyl N-(alkylaminocarbonyl)-, N-(phenylaminocarbonyl)-, and N-(phenylaminothiocarbonyl)-glycinates (*Ia*, *Ib*) and ethyl 3-(phenylureido)-2-butenoates (ref.[6]) (*II*) on the $pK_a(RNH_2)$ values[7,8] are given in Fig. 1. With diethyl N,N'-carbonylbisglycinate the correction for the statistical factor was made. The pK_a value of N,N-dimethyl-*p*-phenylenediamine (the protonation at the amino group) was calculated from the ϱ constant 2·89 (ref.[7]) and σ constant −0·26 (ref.[9]). The cyclization rate constants and $pK_a(RNH_2)$ values are given in Table II. The cyclization rate is affected by both polar and steric effects of the R^1NH group. The electron-attracting substituents increase the acidity of the ureidoester and, hence, also the concentration of the reactive anion $I^{(-)}$, but, on the other hand, they hinder the attack of carbonyl carbon atom by the nitrogen electron pair and, to a lesser extent, also the splitting off of ethoxy group. If the attack of electron pair on the carbonyl group is rate-limiting, then such substituents accelerate the cyclization by their polar effects, because the ϱ constant of the pre-equilibrium has a greater positive value than that of the attack at the carbonyl group. In this reaction step, the substituent effect makes itself felt only until the moment of formation of the activated complex. If the splitting off of ethoxy group from the negatively charged intermediate represents the rate-limiting step, then the nitrogen atom carries an only small fraction of charge in the activated complex, so that the polar effect of the substituent is either insignificant or causes an only small retardation of the reaction. Steric effects of the substituents are especially significant during formation of the tetrahedral intermediate and retard it strongly. From Fig. 1

TABLE I

Elemental analyses and melting points of substituted ethyl N-(phenylaminocarbonyl)glycinates and ethyl N-(phenylaminothiocarbonyl)glycinates $YC_6H_4NHCXNHCH_2CO_2C_2H_5$

Y X	M.p., °C	Formula (mol. mass)	Calculated/found		
			% C	% H	% N
4-CH_3	130·5—131·5	$C_{12}H_{16}N_2O_3$	61·00	6·83	11·86
O		(236·3)	60·70	7·02	12·09
4-Br	149—150	$C_{11}H_{13}BrN_2O_3$	43·85	4·32	9·30
O		(301·7)	44·03	4·48	9·22
3-Br	103—104	$C_{11}H_{13}BrN_2O_3$	43·85	4·32	9·30
O		(301·7)	43·76	4·45	9·60
4-$N(CH_3)_2$	142—143	$C_{13}H_{19}N_3O_3$	58·85	7·22	15·84
O		(265·3)	59·03	7·49	15·93
3-NO_2	123—124	$C_{11}H_{13}N_3O_5$	49·43	4·90	15·73
O		(267·5)	49·66	5·50	16·04
3-Br	86—87	$C_{11}H_{13}BrN_2O_2S$	41·64	4·10	8·83
S		(317·4)	41·39	4·34	8·65
4-Br	154·5—155·5	$C_{11}H_{13}BrN_2O_2S$	41·64	4·10	8·83
S		(317·4)	41·57	4·43	8·71
[a]	141—142	$C_7H_{11}N_3O_3$	45·40	5·94	22·70
		(185·9)	45·14	6·66	22·60

[a] Ethyl N-(cyanomethylaminocarbonyl)glycinate.

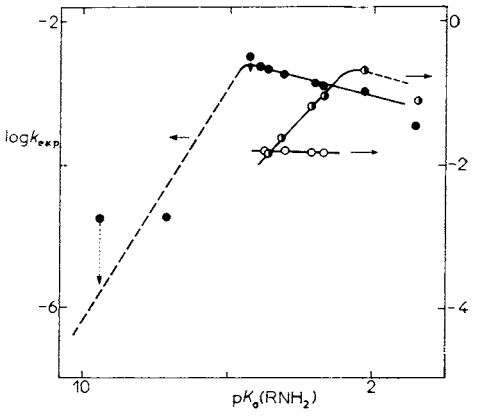


FIG. 1

The dependence of cyclization rates of substituted ethyl N-(alkylaminocarbonyl)glycinates, ethyl N-(phenylaminocarbonyl)-glycinates (●), ethyl N-(phenylaminothiocarbonyl)glycinates (◑), and ethyl 3-(phenylureido)-2-butenoates (○) on the pK_a (RNH_2) values. The correction for steric effects is represented by the dotted line and arrow

it is obvious that in the series of *meta* and *para* substituted 3-(N-phenylureido)-2-butenoate esters (except for the 4-nitro derivative) and substituted ethyl N-(alkylaminocarbonyl)glycinates, the cyclization rate increases with increasing $pK_a(RNH_2)$ value, *i.e.* with the tendency of the substituents to attract electrons. With the substituted alkylureidoesters the substitution also changes the steric effect[1]. A predominance of steric effects is observed in the cyclization of 3-(N-alkylureido)-2-butenoates[6] (*II*) whose alkyl is methyl, ethyl, isopropyl, or isobutyl[10]. The differences in polar effects are small and can be neglected, the relative cyclization rates of these compounds being 1 : 0·13 : 0·04 : 0·0225. If it is taken into account that CH_2CN group has a greater steric effect than methyl group, and phenyl or ethoxycarbonyl groups have still greater steric effects, then the slopes of the dependences $\log k_{obs}$ *vs* $pK_a(RNH_2)$ are comparable in the series of substituted ethyl N-(alkylaminocarbonyl)glycinates and 3-(N-phenylureido)-2-butenoates (after the correction for steric effects) (see Fig. 1). On the other hand, the slope is practically zero with the substituted thioureidoesters, being even slightly negative with the oxygen analogues, which indicates a change in the rate-limiting step in the two cases. A similar change is obviously observed with *meta* and *para* nitrosubstituted ethyl 3-(N-phenylureido)-2-butenoates (*II*).

One more question is to be answered: why ethyl N-(phenylaminothiocarbonyl)-glycinates react by one order more slowly than the N-methyl derivative, whereas in the case of the oxygen-esters of this type the N-phenyl derivative reacts faster by two orders of magnitude. Another problem is connected therewith: when does the

TABLE II

The cyclization rate constants ($k \cdot 10^3$, s^{-1}) of ethyl N-(substituted aminocarbonyl)glycinates (*Ia*) and thioglycinates (*Ib*) $RNHCXNHCH_2CO_2C_2H_5$ and ethyl 3-(substituted ureido)-2-butenoates $RNHCONHC(CH_3)=CHCO_2C_2H_5$ (*II*) at 25°C and pH 9·06

R	*Ia*	*Ib*	*IIb*[a]	$pK_a(RNH_2)$[b]
$4\text{-}(CH_3)_2NC_6H_4$	2·80	—	—	5·40[c]
$4\text{-}CH_3C_6H_4$	2·64	20·3	21·7	5·08
C_6H_5	2·20	20·7	31·2	4·60
$4\text{-}BrC_6H_4$	1·85	21	91[d]	3·86
$3\text{-}BrC_6H_4$	1·50	19·7	117[d]	3·58
$3\text{-}NO_2C_6H_4$	1·44	—	307	2·46
$4\text{-}NO_2C_6H_4$	—	—	123	1·00
$CH_2CO_2CaH_5$	0·140	—	—	7·75
CH_2CN	4·26	—	—	5·55
CH_3	0·02	—	—	10·6

[a] The values from ref.[6] recalculated for pH 9·06; [b] refs[7,8]; [c] see the text; [d] the chloro derivatives

change of the rate-limiting step take place. From Fig. 1 it can be assessed that with the ureidoesters this change takes place at $pK_a(RNH_2)$ about 5·5. This means that with the unsubstituted ethyl N-(phenylaminocarbonyl)glycinate the reverse reaction of N—C bond in $I^{(-)}$ is several times faster than the splitting off of ethoxy group. The pK_a value of ethanol is 15·0 (ref.[11]). From the dissociation constants of phenylureas[12] and from the Hammett equation we obtain for the phenylureidoacetate the pK_a value of about 16 (ref.[12]). From our results it follows that the N—C bond splitting becomes faster than the C—O bond splitting, if the pK_a values of the two conjugated acids (ureidoester and ethanol) are the same. The dissociation constants of phenylthioureas are higher by 3 orders than those of the oxygen analogues[12], hence it can be presumed that the change in the rate-limiting step is at $pK_a(RNH_2)$ about 9, *i.e.* on introduction of a substituent more electron-attracting than methyl group. The polar effect of phenyl group can thus cause an only small acceleration which is completely outweighted by the steric effect acting in the opposite direction, so that the net result is a retardation of the cyclization reaction.

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