KINETICS AND MECHANISM OF REVERSIBLE, BASE-CATALYZED RING CLOSURE OF 3-(METHOXYCARBONYL)PROPIONANILIDE AND O-(METHOXYCARBONYLMETHYL)-N-PHENYLCARBAMATE

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The rate constants of reversible, base-catalyzed ring closure of 3-(methoxycarbonyl)propionanilide (*I*) and O-(methoxycarbonylmethyl)-N-phenylcarbamate (*II*) to 1-phenyl-2,5-pyrrolidinedione (*III*) and 3-phenyl-2,4-oxazolidinedione (*IV*), respectively, and the rates of solvolyses of the cyclization products *III* and *IV* in water and methanol have been measured. In both cases, an equilibrium is established between the starting ester and the cyclization product in methoxide solutions which is strongly shifted in favour of the starting ester. In the case of ester *II* in methoxide solutions, the cyclization is followed by a much slower splitting of the cyclization product to give glycolic acid anilide. The effects of the group X = NH, CH_2, O, S in the esters $RNHCOXCH_2.COOCH_3$ on the rates of the cyclization and solvolysis of the cyclization products is discussed.

Our previous papers[1,2] dealt with the kinetics of base-catalyzed ring closure of the esters $RNHCOXCH_2COOCH_3$ ($X = S$, $R = CH_3$; $X = NH$, $R = C_6H_5$) and with that of the solvolyses of 3-phenylhydantoin in methanol and water. This present paper is focused on the kinetics of cyclization and solvolysis of the cyclization products with the esters having $X = CH_2$ or O and $R = C_6H_5$, and the effect of the group X on both the reactions is discussed.

EXPERIMENTAL

The ^1H NMR spectra of the compounds prepared were measured with the use of c. 5% solutions in C^2HCl_3 (for compound *II*), CCl_4 (for compounds *IV*, *V*, *VIII*) and hexadeuteriodimethyl sulfoxide (for *VII*) with a JNM FX-100 (JEOL) apparatus at 99·602 MHz at 25°C with hexamethyldisiloxane as the internal standard (δ 0·05).

Preparation of the Substances

Methyl glycolate[3], 3-(methoxycarbonyl)propionyl chloride[4], and succinic anhydride[5] were prepared by the procedures described earlier.

3-(*Methoxycarbonyl*)*propionanilide* (I). Aniline (7·5 g, 40 mmol) was added dropwise to a solution of 3 g (20 mmol) 3-(methoxycarbonyl)propionyl chloride in 100 ml benzene with stirring.

After 3 h, the precipitated anilinium chloride was filtered off, the filtrate was concentrated under reduced pressure, the precipitated raw product was collected by suction and recrystallized from methanol. Yield 2·85 g (69%), m.p. 97—99°C in accordance with ref.[6].

O-(*Methoxycarbonylmethyl*)-N-*phenylcarbamate* (II). A solution of 2·9 g (30 mmol) methyl glycolate in 50 ml tetrachloromethane was treated with 1 drop triethylamine and 3·6 g (30 mmol) phenyl isocyanate added with stirring and cooling. After several minutes the solution began to separate crystals which were collected by suction. Yield 5·2 g (83%), after recrystallization from methanol m.p. 70—72°C (ref.[7] gives m.p. 73·5—74°C). ^{1}H NMR (C^2HCl_3): 7·66 b, 1 H (NH); 6·85—7·56 m, 5 H (C_6H_5); 4·66 s, 2 H (CH_2); 3·75 s, 3 H (OCH_3).

1-*Phenyl*-2,5-*pyrrolidinedione* (III) was prepared by a known procedure[8] from succinic anhydride and aniline. Yield of the raw product 71%, m.p. 152—154°C after recrystallization from methanol (in accordance with refs[8,9]).

3-*Phenyl*-2,4-*oxazolidinedione* (IV). A solution of 2·1 g (10 mmol) compound *II* in 18 ml benzene was treated with 1 drop of triethylamine, and the mixture was refluxed 3 h. Benzene was distilled off, and the residue was recrystallized from a mixture of benzene and cyclohexane. Yield 0·53 g (30%), m.p. 121—122°C (ref.[10] gives m.p. 126°C). ^{1}H NMR (CCl_4): 7·45 s, 5 H C_6H_5); 4·85 s, 2 H (CH_2).

O-(*Methoxycarbonylmethyl*)-N-*methylcarbamate* (V). A solution of 3 g (33 mmol) methyl glycolate in 15 ml tetrachloromethane was treated with 1 drop of triethylamine, cooled with stirring, and treated with 2 ml methyl isocyanate added drop by drop. Tetrachloromethane was distilled off at room temperature under reduced pressure and 4 g of oily product (80%) was obtained. The attempts at its purification by means of the vacuum distillation or column chromatography resulted in the cyclization of this product. According to ^{1}H NMR spectrum the substance is pure. ^{1}H NMR (CCl_4): 5·69 bq, 1 H ($NHCH_3$); 4·49 s, 2 H (CH_2); 3·72 s, 3 H (OCH_3); 2·76 d, 3 H ($NHCH_3$).

3-(*Methoxycarbonyl*)*propionamide* (VI). A solution of 3 g (20 mmol) 3-(methoxycarbonyl)propionyl chloride in 50 ml acetone was saturated with gaseous ammonia. The separated ammonium chloride was filtered off, and the filtrate was distilled until dry. The residue was recrystallized from methanol. Yield 1·43 g (55%), m.p. 85—87°C (ref.[11] gives m.p. 89—91°C).

-(*Methoxycarbonyl*)*propionic acid methylamide* (VII). A benzenic solution of 3 g 3-(methoxycarbonyl)propionyl chloride was mixed with two equivalents of methylamine dissolved in chloroform. The methylammonium chloride precipitated by addition of acetone was filtered off, and acetone was distilled from the filtrate to leave 1·8 g (62%) yellowish liquid which crystallized on standing in refrigerator overnight. The substance melts at 49—51°C (benzene). For $C_6H_{11}NO_3$ (145·2) calculated: 49·65% C, 7·64% H; found: 49·52% C, 7·87% H. ^{1}H NMR (hexadeuteriodimethyl sulfoxide): 7·84 b, 1 H (NH); 3·62 s, 3 H (OCH_3); 2·60 d, 3 H ($NHCH_3$)- 3·62 s, 3 H; (OCH_3); c. 3·59 m, 2 × 2 H (CH_2–CH_2).

3-*Methyl*-2,4-*oxazolidinedione* (VIII). A solution of 1 g (7 mmol) compound *V* in 5 ml 10^{-3} mol l^{-1} sodium methoxide was left to stand until it separated an oily phase which crystallized. The solid was collected by suction and washed with water. Yield 0·56 g (72%), m.p. 134 to 134·5°C (after vacuum sublimation). For $C_4H_5NO_3$ (115·1) calculated: 41·75% C, 4·38% H, 12·17% N; found: 41·65% C, 4·46% H, 12·30% N. ^{1}H NMR (CCl_4): 4·66 s, 2 H (CH_2); 3·01 s, 3 H (NCH_3).

N-*Methyl*-2,5-*pyrrolidinedione* (IX). Succinic anhydride (2 g, 18 mmol) was added to 5 ml aqueous methylamine solution (40%, i.e. c. 60 mmol). After an exothermic reaction the mixture

was cooled and the excess methylamine was distilled off under reduced pressure. The ammonium salt was transformed into the acid by the titration with 5 mol l^{-1} hydrochloric acid (Methyl Orange). Simultaneously the cyclization took place, too. The crystalline methylammonium chloride separated after a while of standing was filtered off. The filtrate gave 0·3 g (13·8%) product *IX*, m.p. 68—70°C in accordance with ref.[12]

Kinetic and Equilibrium Measurements

The kinetic measurements were carried out spectrophotometrically at 25°C. The spectral changes during the reaction course were recorded in the region of 210—350 nm using a Specord UV-VIS apparatus (Zeiss). For the kinetic measurements we used a VSU-2P spectrophotometer (Zeiss) at the wavelengths chosen according to the spectra of the starting substances and product. A 1 cm quartz cell was filled with 2 ml buffer (ionic strength 0·5 mol l^{-1} adjusted by addition of potassium chloride) or sodium methoxide solution, and 20 µl methanolic solution of ester *I* (or *II*) or cyclizate *III* (or *IV*) was injected therein, whereupon the absorbance was measured. The rate coefficient was calculated graphically from the equation $k_{obs}t = -2{\cdot}3 \log (A_t - A_\infty) +$ const.

When measuring the cyclization rate of amide *I* in phosphate buffers (where the subsequent hydrolysis of the cyclizate *III* is slower only by the factor of 30) we used, instead of the A_∞ value, the absorbance value extrapolated from the linear absorbance–time dependence to the time t after six half-lives of the cyclization reaction.

The rate of the reverse reaction $II \rightleftarrows IV$ in methoxide solutions was measured by the stopped-flow technique using the Durrum D 110 apparatus. The reaction was realized by mixing equal volumes of methoxide solution from one syringe (10^{-3}—10^{-2} mol l^{-1}) and methanolic solution of ester *II* or its cyclization product *IV* (10^{-4} mol l^{-1}) from the other syringe.

The composition of equilibrium mixtures of the cyclizates *III* and *IV* with the methyl esters *I* and *II*, respectively, was determined spectrophotometrically with the Specord UV-VIS apparatus. First the spectra were recorded of the methanolic solution of the cyclizate and methyl ester ($6 \cdot 10^{-5}$ mol l^{-1}), and then the spectrum of the equilibrium mixture of the same concentration in $2 \cdot 10^{-3}$ mol l^{-1} methoxide was measured. The concentration ratios [*III*]/[*I*] and [*IV*]/[*II*] were calculated from the ratio of the absorbance differences between the solutions of the compounds in methanol and those of the equilibrium mixture (in methoxide).

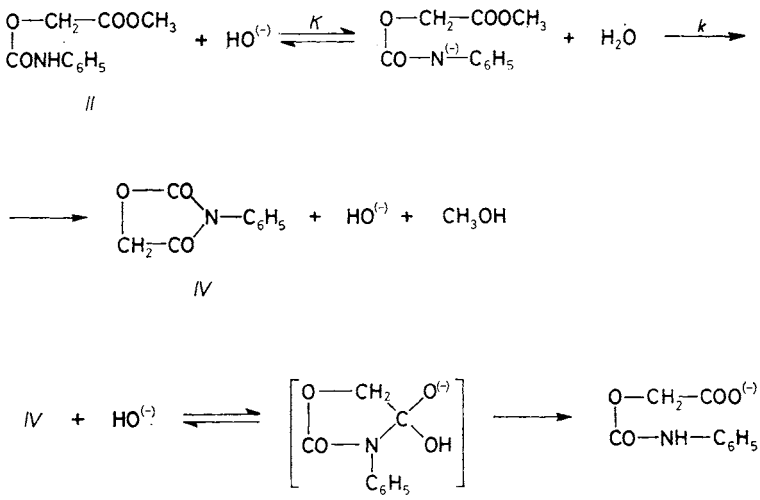
The pH values were measured with a Precision Digital pH Meter and OP 208 Radelkis apparatus using the glass indication electrode and the calomel or silver chloride reference electrodes.

RESULTS AND DISCUSSION

The cyclization and solvolysis of carbamate *II* were followed either in aqueous phosphate and borax buffers or methanolic sodium methoxide solutions. In the phosphate buffers we measured the rate constants of the base-catalyzed ring closure of ester *II* into oxazolidinedione *IV*. The rate constants of the base-catalyzed hydrolysis of the cyclizate *IV* formed, which are two orders lower than those of its formation (Table I), were determined at higher pH values in the borax buffers.

The same values for the hydrolysis rate constants (Table I) were obtained from the measurements of the absorbance–time changes of the cyclizate *IV* as well as from

those of the starting ester *II* in the borax buffers. The ester *II* underwent the ring closure in the borax buffers within several seconds.



SCHEME 1

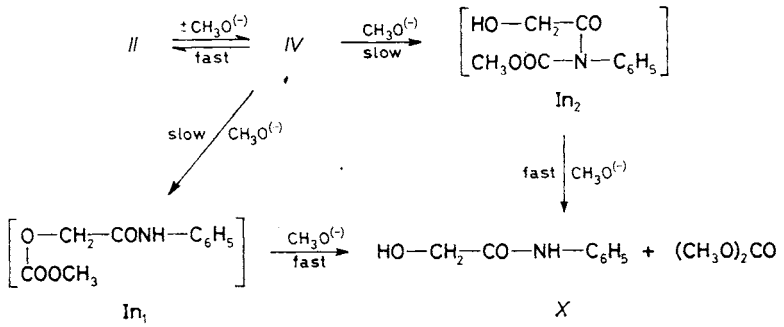
The overall reaction course is represented in Scheme 1, and the cyclization (v_c) and solvolysis rates (v_s) are described by Eqs (*1*) and (*2*), respectively.

$$v_c = k_{obs}[II] = k_c[OH^-][II] \quad (1)$$

$$v_s = k_{obs}[IV] = k_s[OH^-][IV] \quad (2)$$

The base-catalyzed reaction of ester *II* in methanol proceeded anomalously. After addition of sodium methoxide to the methanolic solution of ester *II*, a very fast (small) absorbance decrease was observed indicating that the reversible cyclization $II \leftrightarrows IV$ proceeded to a small extent. The rate coefficient of formation of the equilibrium mixture ($II + IV$) is $k_{eq} = 116\ l\ mol^{-1}\ s^{-1}$ (it was measured at the sodium methoxide concentrations from $5 . 10^{-4}$ to $2 . 10^{-3}$ mol l^{-1}). Thereafter, there followed a much slower transformation of compound *IV* into glycolic acid anilide (*X*): its rate of formation was $(4{\cdot}27 \pm 0{\cdot}11) . 10^{-1}\ l\ mol^{-1}\ s^{-1}$. The rate coefficient of this slow reaction $IV \rightarrow X$ was the same as the separately measured rate coefficient of the methanolysis of compound *IV* in the methoxide of the same concentration.

The equilibrium constant of cyclization determined from the absorbances of ester *II*, cyclizate *IV*, and their equilibrium mixture is $K = 0{\cdot}1$. Table I gives the rate coefficients calculated from these values. The overall reaction course can be represented as in Scheme 2.

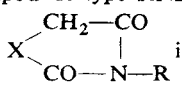


SCHEME 2

The first step consists in a rapid, methoxide-catalyzed establishing of the equilibrium between ester *II* and cyclizate *IV*. The ester *II* predominates in the equilibrium mixture. The slow, rate-limiting step consists in the ring opening by means of methoxide ion to give the intermediate In_1 or In_2 which are very rapidly split to the anilide *X* and dimethyl carbonate.

The rate coefficients of cyclization of ester *I* to the pyrrolidinedione *III* were measured in phosphate and borax buffers, too. The hydrolysis rate coefficient is c. 1·5 orders of magnitude smaller than the cyclization rate constant (Table I). As with the carbamate *II* – in this case, too, the equilibrium mixture $I \leftrightarrows III$ is formed (in methoxide), the ester *I* being predominant. However, the absorbance of the mixture (*I* + *III*) formed does not further change with time. Table I gives the rate

TABLE I

The rate coefficients of cyclization (k_c, s^{-1}) of the compounds type $RNHCOXCH_2COOCH_3$ and those of the solvolyses (k_s, s^{-1}) of the cyclizates type  in water and methanol at 25°C

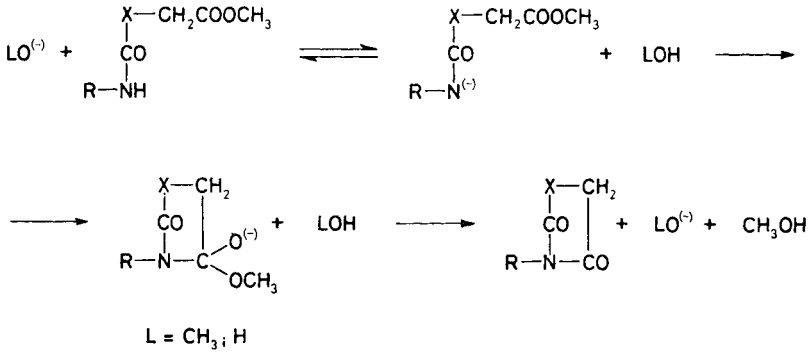
Compound	X	R	k_c		k_s	
			H_2O	CH_3OH	H_2O	CH_3OH
—	NH[a]	CH_3	3·0	$5{\cdot}5 \cdot 10^{-2}$	—	—
—	NH[a]	C_6H_5	637	3·04	0·9	1·3
I	CH_2	C_6H_5	220	0·9	7·4	13·9
II	O	C_6H_5	5 610	10·4	59·1	112
—	S[b]	CH_3	$1{\cdot}5 \cdot 10^4$	$5{\cdot}5 \cdot 10^2$	—	—

[a] Ref.[13]; [b] ref.[2].

coefficients of cyclization and methanolysis (k_c, k_s) calculated from the rate coefficients of formation of the equilibrium mixture (k_{eq} = 14·8 l mol^{-1} s^{-1}) and the equilibrium constant (K = 0·065).

We also tried to measure the cyclization rate coefficients of the methyl carbamate *V* and amides *VI* and *VII*. But the absorbance changes took place at low wavelengths (220 nm) and were indistinct. Therefore, it was impossible to obtain reliable values of the cyclization rate coefficients of these compounds.

The cyclization mechanism of all the compounds given in Table I is the same. The first step is a pre-equilibrium producing a small amount of the conjugated base of the starting substance. The second, rate-limiting step produces the cyclic intermediate (Scheme 3).



SCHEME 3

The effect of the group X on the equilibrium constant can be estimated from the dissociation constants of compounds with similar structure. The effect of replacement of NH by CH_2 group on the equilibrium constant was determined from the difference of the dissociation constants of 4-nitrophenylurea (pK_a = 14·0, ref.[14]) and 4-nitroacetanilide (pK_a = 13·8, ref.[15]).

The dissociation constant of the oxygen analogue, O-methyl-N-(4-nitrophenyl)-carbamate measured in 20% aqueous dioxane is pK_a = 13 (ref.[16]). The pK_a value in water is lower by 0·5, i.e. pK_a ≈ 12·5 (ref.[17]).

The effect of replacement of NH group by sulphur atom on the equilibrium constant can be roughly estimated by comparing the values of the dissociation constants of O-phenyl-N-(*p*-nitrophenyl)carbamate (pK_a = 12·5 in 20% dioxane[16]) and the corresponding S-phenyl-N-(4-nitrophenyl)thiocarbamate (pK_a = 9·3 in the same medium[18]).

The differences in dissociation constants and in rate coefficients given in Table I indicate that the decisive effect of the group X is that on the equilibrium constant of the pre-equilibrium. The same conclusion was made from the comparison of the

cyclization rate coefficients of 5-methylhydantoate and 5-methylthiohydantoate[2,13]. The following conclusions were made from the comparison of the methanolysis rate coefficient (i.e. for the reverse reaction of the cyclizate to ester in methanol) and the hydrolysis rate coefficient:

1. With all three phenyl derivatives (X = NH, CH_2, O) the ratio of rate coefficients of the solvolyses in methanol and in water is approximately the same (1·5 to 1·9).

2. The rate coefficients of methanolysis are higher than those of hydrolysis, although the cyclization rate coefficients are two orders higher in water than in methanol. Therefrom it follows that the cyclizate in methanolic medium is c. three orders less stable than esters in aqueous medium. The methanolysis rate coefficient of the oxygen derivatives (X = O) is two orders higher than that of the nitrogen derivatives (X = NH). This difference obviously is due to the difference between the dissociation constants of the two esters. The methanolysis rate coefficients of the derivatives with X = CH_2 are one order higher than those with X = NH, although the dissociation constants are comparable. This fact could indicate a destabilization of the five-membered ring in some other way beside the effect of the groups X (CH_2, NH, O) on the acidity and, hence, also nucleophilicity of the N(5) atom.

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