BASE CATALYZED CYCLIZATION OF SUBSTITUTED ESTERS OF HYDANTOIC AND THIOHYDANTOIC ACIDS

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Base catalyzed cyclization rates have been measured of 22 derivatives of hydantoic and thiohydantoic acid esters in water and methanol. The cyclization of methyl and ethyl esters of hydantoic and 5-methylhydantoic acids is accompanied by hydrolysis of the ester group, whereas with the other derivatives the hydrolysis does not take place. Hydrolysis of the cyclization products (hydantoin and thiohydantoin derivatives) is not significant under the kinetic conditions. The cyclization of methyl ester of 5-phenylhydantoic acid in methanol is reversible; the equilibrium mixture contains 30% of the starting ester. In all the cases the cyclization is subject to specific base catalysis; exceptions are esters of 5-phenylthiohydantoic and 5-phenyl-2-methylthiohydantoic acids whose cyclizations are subject to general base catalysis. Substituents always accelerate the cyclization. The 3-substituents have the greatest effects, the cyclization rate being considerably increased with bulk of the substituents; similarly large effect of 5-phenyl group consists mainly in its polar effects on the pre-equilibrium. The cyclizations are slower in methanol at the same concentration of the lyate ion: the greatest difference (up to 3 orders of magnitude) is observed with the 5-phenyl derivatives.

Studies of intramolecular reactions are important for elucidation of mechanisms of many reaction types especially in enzymatic catalysis[1,2]. The huge increase in reaction rate which is characteristic of intramolecular reactions[3] enables investigation of such reactions (under normal conditions) which when taking the intermolecular course necessitate extremely high temperatures and long reaction time or even cannot make themselves felt in competition with the other reactants present (inclusive of the solvent). The present paper deals with a study of effects of substituents and medium on kinetics and mechanism of base catalyzed cyclization of esters of substituted hydantoic and thiohydantoic acids type $R^1NH—CX—NR^2—CHR^3—COOR^4$ which involves a nucleophilic attack of the ester group by the nitrogen atom of ureide group and formation of the corresponding hydantoins and thiohydantoins.

Although hydantoins find applications in a number of industrial branches, and considerable attention has been paid to their preparation[4], only few papers are available which deal with kinetics and mechanism of acid catalyzed cyclization of hydantoic acids[5–7], and one paper describes kinetics of base catalyzed cyclization of 2,2,3,5-tetramethylhydantoic acid[8].

EXPERIMENTAL

Reagents

Methyl isothiocyanate and ethyl bromomethanoate were prepared by known procedures[9]. Hydrochlorides of methyl aminoethanoate, ethyl 2-aminopropanoate, ethyl aminoethanoate, and ethyl 2-methylaminoethanoate were prepared by introducing hydrogen chloride into a mixture of the respective amino acid and alcohol[10,11]. The free bases of these esters were obtained from the corresponding hydrochlorides by reaction with aqueous sodium hydroxide and potassium carbonate[10] or methanolic triethylamine[12]. Ethyl butylaminoethanoate and ethyl benzylaminoethanoate were prepared from ethyl bromoethanoate and the respective amine[13]. Ethyl phenylaminoethanoate was prepared from ethyl chloroethanoate and aniline[14].

Ethyl and methyl esters of substituted hydantoic acids ($R^1NHCONR^2CHR^3COOR^4$). The ureidoethanoates *I*—*III* (Table I) were prepared by reaction of hydrochlorides of amino acid esters with potassium cyanate in water[15]. In the case of the ureidoethanoates *IV* and *V*, the respective amino acid ester (instead of its hydrochloride) reacted with the equivalent amount of hydrochloric acid. After the reaction was finished, water was distilled off under reduced pressure, the residue was treated with methanol, and potassium chloride was removed by filtration. Methanol was distilled off, and the compound *IV* was recrystallized from benzene; the compound *V* was isolated in the form of an oil. The ureidoethanoates *VI* and *VII* were prepared by reaction of hydrochloride of the respective amino acid ester with equivalent amount of triethylamine and excess (10%) methyl isocyanate in benzene at room temperature. After the reaction was finished, a five-fold volume of ether was added, the mixture was left to stand 2 h, triethylamine hydrochloride was removed by filtration, the solvent was distilled off under reduced pressure, and the residue was recrystallized from ethanol (compound *IV*) or methanol (compound *VII*).

Ureidoethanoates VIII—XII. A solution of the respective amino acid ester in benzene was treated with excess (10%) methyl isocyanate (the compound *X* without the solvent). After 2 h, the crystalline solid was collected and recrystallized from benzene or benzene–cyclohexane mixture. The compound *XII* was isolated as an oil after removal of benzene.

Ureidoethanoates XIII—XIV. A solution of hydrochloride of the respective amino acid ester in benzene was mixed with equivalent amount of triethylamine and phenyl isocyanate. Triethylamine hydrochloride was extracted with water, the benzene solution was dried with sodium sulphate, and a part of the benzene was distilled off. The precipitated crystalline solid was collected by filtration and recrystallized from ethyl ethanoate (compound *XIII*) or methanol (compound *XIV*).

Ureidoethanoates XV—XIX. The respective amino acid ester was mixed with the equivalent amount of phenyl isocyanate in benzene. After 1 h (24 h for *XVII*) the crystalline solid was collected by filtration and recrystallized from benzene or benzene–cyclohexane mixture.

Ethyl or methyl esters of thiohydantoic acid XX—XXIII. The compounds *XX*—*XXII* were prepared by reaction of the corresponding ester with methyl (*XX*) or phenyl isothiocyanates (*XXI* and *XXII*) in benzene or cyclohexane (*XXII*). The compounds *XXI* and *XXII* were isolated as crystalline solids, the compound *XX* as an oil. The compound *XXIII* was prepared from the respective hydrochloride and phenyl isothiocyanate in the same way as the compounds *XIII* and *XIV*. The yields and analyses of compounds *I*—*XXIII* are given in Table I.

Substituted hydantoins and thiohydantoins were prepared by cyclization of the esters *I*—*XXIII* by two procedures in the yields of 70—85%. Procedure *a*: The substituted hydantoic acid ester was dissolved in methanol, and a catalytic amount of sodium methoxide was added thereto (the

TABLE I

The synthetized esters of hydantoic acid derivatives (X = O) *I*—*XIX* and thiohydantoic acid derivatives (X = S) *XX*—*XXIII* of general formula $R^1NH—CX—NR^2—CHR^3—COOR^4$

Ester (yield, %)	R^1	R^2	R^3	R^4	M.p., °C m.p. (ref.)	Calculated/Found		
						% C	% H	% N
I (90)	H	H	H	C_2H_5	135—137 135 (15)	—	—	—
II (54)	H	H	H	CH_3	97—99 97 (17)	—	—	—
III (68)	H	H	CH_3	C_2H_5	96—98 94 (15)	—	—	—
IV (80)	H	CH_3	H	C_2H_5	96—97	44·99 44·78	7·55 7·56	17·49 17·62
V[a] (43)	H	C_4H_9	H	C_2H_5	oil	—	—	—
VI (40)	CH_3	H	H	C_2H_5	82—83·5	44·99 45·09	7·55 7·90	17·49 17·80
VII (38)	CH_3	H	H	CH_3	102—103	41·09 41·06	6·90 6·64	19·17 19·70
VIII (63)	CH_3	CH_3	H	C_2H_5	62—65	48·26 48·39	8·10 8·32	16·08 16·30
IX (87)	CH_3	H	CH_3	C_2H_5	92—94	48·26 47·96	8·10 8·40	16·08 16·22
X (53)	CH_3	C_6H_5	H	C_2H_5	72—73	61·00 60·96	6·83 6·86	11·86 11·80
XI (88)	CH_3	$C_6H_5CH_2$	H	C_2H_5	83—85	62·38 62·55	7·25 7·26	—
XII[b] (50)	CH	C_4H_9	H	C_2H_5	oil	—	—	—
XIII (70)	C_6H_5	H	H	C_2H_5	110—111 110 (18)	—	—	—
XIV (75)	C_6H_5	H	H	CH_3	139—141 143 (19)	—	—	—
XV[c] (73)	C_6H_5	CH_3	H	C_2H_5	84—85 75 (20)	61·00 61·33	6·83 6·58	11·86 12·12
XVI (70)	C_6H_5	H	CH_3	C_2H_5	84—86	61·00 61·05	6·83 7·00	—
XVII (64)	C_6H_5	C_6H_5	H	C_2H_5	109—111	68·44 68·53	6·08 6·12	—

TABLE I
(*Continued*)

Ester (yield, %)	R^1	R^2	R^3	R^4	M.p., °C m.p. (ref.)	Calculated/Found		
						% C	% H	% N
XVIII (82)	C_6H_5	$C_6H_5CH_2$	H	C_2H_5	88–91	69·21 68·98	6·45 6·21	—
XIX (45)	C_6H_5	C_4H_9	H	C_2H_5	77–79	64·75 65·04	7·97 8·09	—
XX[d] (66)	CH_3	H	H	C_2H_5	oil	—	—	—
XXI (70)	C_6H_5	H	H	C_2H_5	83–85 85 (10)	—	—	—
XXII (55)	C_6H_5	H	CH_3	C_2H_5	79–81	57·12 56·93	6·39 6·60	—
XXIII (50)	C_6H_5	H	H	CH_3	84–85	53·55 53·86	5·39 5·23	12·49 12·58

[a] ^{1}H NMR spectrum (C^2HCl_3, 25 °C): $\delta(OCH_2)$ 4·19 (2 H, quartet); $\delta(CH_2)$ 3·86 (2 H, singlet); $\delta(NCH_2CH_2)$ 3·25 (2 H, distorted triplet); $\delta((CH_2)_2)$ about 1·27 (4 H, broad band); $\delta(OCH_2CH_3)$ 1·27 (3 H, triplet); $\delta((CH_2)_3CH_3)$ 0·91 (3 H, distorted triplet). [b] $\delta(OCH_2)$ 4·17 (2 H, quartet); $\delta(CH_2)$ 4·00 (2 H, singlet); $\delta(NCH_2CH_2)$ 3·21 (2 H, distorted triplet); $\delta(CH_3NH)$ 2·76 (3 H, doublet); $\delta((CH_2)_2)$ about 1·41 (4 H, broad band); $\delta(OCH_2CH_3)$ 1·25 (3 H, triplet); $\delta((CH_2)_3.CH_3)$ 0·91 (3 H, distorted triplet). [c] $\delta(OCH_2)$ 4·20 (2 H, quartet); $\delta(CH_2)$ 4·10 (2 H, singlet) $\delta(NCH_3)$ 3·06 (3 H, singlet); $\delta(CH_2CH_3)$ 1·26 (3 H, triplet); $\delta(C_6H_5)$ 7·49–6·94 (5 H, multiplet). [d] $\delta(CH_2NH)$ 4·38 (2 H, doublet); $\delta(OCH_2CH_3)$ 4·23 (2 H, quartet); $\delta(NHCH_3)$ 3·01 (3 H, doublet); $\delta(CH_2CH_3)$ 1·31 (3 H, triplet).

final methoxide concentration varied from 10^{-3} to 1 mol l^{-1} according to reactivity of the ester). After the cyclization was finished (which was checked by electronic spectra), the mixture was acidified with diluted hydrochloric acid, methanol was distilled off, and the cyclizate was recrystallized from a water–ethanol mixture. Procedure *b*: The ester was heated on water bath in aqueous hydrochloric acid 1 h, cooled, and the cyclizate was collected by filtration and recrystallized. Melting points of the cyclizates agreed with published data. The following six compounds have not been described so far:

1-*Butyl*-3-*methylhydantoin* was prepared by the procedure *a*; a colourless oil; ^{1}H NMR spectrum (C^2HCl_3, 25°C): $\delta(CH_2)$ 3·86 (2 H, singlet), $\delta(NCH_2)$ 3·39 (2 H, triplet), $\delta(NCH_3)$ 3·00 (3 H, singlet), $\delta((CH_2)_2)$ 1·46 (2 × 2 H, multiplet), $\delta((CH_2)_3CH_3)$ 0·95 (3 H, distorted triplet); (hexadeuteriodimethyl sulphoxide, 25°C): $\delta(CH_2)$ 3·80 (2 H, singlet), $\delta(NCH_2)$ 3·39 (2 H, broadened triplet), $\delta(N—CH_3)$ 3·00 (3 H, singlet), $\delta((CH_2)_2)$ 1·46 (4 H, broadened band), $\delta((CH_2)_3CH_3)$ 0·95 (3 H, distorted triplet).

1-*Butyl*-3-*phenylhydantoin* was prepared by the procedure *b* and recrystallized from cyclohexane, m.p. 65–66°C. For $C_{13}H_{16}N_2O_2$ (232·3) calculated: 67·22% C, 6·94% H, 12·06% N; found: 67·12% C, 6·88% H, 11·80% N.

1-*Butylhydantoin* was prepared by the procedure *b* and recrystallized from ethanol, m.p. 91–92·5°C. For $C_7H_{12}N_2O_2$ (156·2) calculated: 53·83% C, 7·74% H; found: 53·43% C, 7·53% H.

3,5-*Dimethylhydantoin* was prepared by the procedure *a* and recrystallized from water, m.p. 109–111°C. For $C_5H_8N_2O_2$ (128·1) calculated: 46·87% C, 6·29% H, 21·86% N; found: 46·84% C, 6·57% H, 21·55% N.

1-*Benzyl*-3-*phenylhydantoin* was prepared by the procedure *a* and recrystallized from methanol, m.p. 64·5–66°C. For $C_{16}H_{14}N_2O_2$ (266·3) calculated: 72·17% C, 5·30% H; found: 72·43% C, 5·53% H.

1-*Benzyl*-3-*methylhydantoin* was prepared by the procedure *b* and recrystallized from water, m.p. 75–76·5°C. For $C_{11}H_{12}N_2O_2$ (204·2) calculated: 64·69% C, 5·92% H; found: 64·82% C, 5·74% H.

Kinetic measurements were carried out photometrically at 25°C. First the reaction course was recorded with a Specord UV VIS spectrophotometer (Zeiss, Jena) in the region of 200–350 nm. The proper kinetic experiments were mainly measured with a VSU 2P spectrophotometer (Zeiss, Jena), fast reactions were followed with a Durrum D 110 apparatus. The pH values were measured with a Precision Digital pH Meter, OP 208 Radelkis using a combined glass and saturated calomel electrode or with an MV 870 Digital pH Messgerät using an indication glass electrode and AgCl reference electrode.

The compounds measured were dissolved in acetonitrile or methanol to make 10^{-1} to 10^{-2} mol l^{-1} stock solutions. For the kinetic experiment one drop of the stock solution was added to 2 ml temperated buffer, sodium methoxide or hydroxide solution in 1 cm quartz cell. If the reaction was of pseudo-first-order kinetics, the rate constant was determined graphically from the equation $k_{obs}\, t = -2{\cdot}303 \log (A_t - A_\infty) + \text{const.}$, where A_t and A_∞ are the absorbances measured at the time t and after six half-lives, respectively. The reactions with half-lives above 2 h were measured and evaluated by the Guggenheim method[16]. The evaluation of the rate constants of cyclization of esters *XIII*–*XIX* in methanol is described in Discussion. The composition

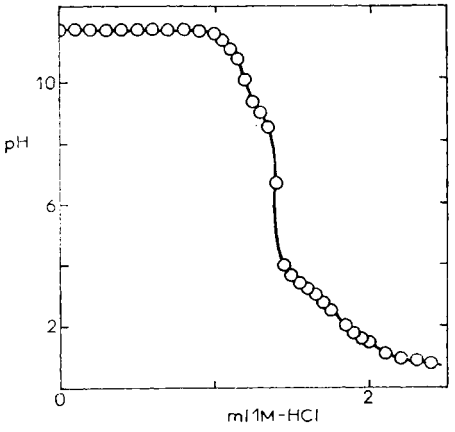


FIG. 1

Potentiometric titration of the products formed by 15 min action of 0·1 mol l^{-1} sodium hydroxide solution on the methyl hydantoate *II*

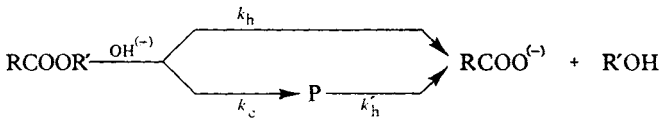
of the reaction mixture (methyl ester *XIV* in equilibrium with the cyclizate — 3-phenylhydantoin) was determined spectrophotometrically. Spectra were recorded of methanolic solutions of the cyclizate and methyl ester (both at $6 . 10^{-5}$ mol l^{-1} concentrations) and of their mixture (of the same concentration) in 10^{-2} mol l^{-1} sodium methoxide. The ratio of absorbance differences of the compounds in methanol and the equilibrium mixture in methoxide at 4 various wavelength values was used for calculation of the concentration ratio: cyclizate to methyl ester *XIV* = 7 : 3.

Determination of the hydrolysis extent of the esters during their cyclization in aqueous sodium hydroxide was carried out by potentiometric titration: About 10^{-3} mol ester was precisely weighed and dissolved in 1·1 equivalents of 10^{-1} mol l^{-1} sodium hydroxide. After about 15 min the reaction solution was titrated with 1 mol l^{-1} hydrochloric acid, and the pH change was plotted against the amount of the titrant (Fig. 1). Amounts of the respective hydantoic acid and hydantoin were calculated from the distance of inflection points. In the case of the esters *VI* and *VII* the solution of the compound and 1·2 equivalents of 10^{-2} mol l^{-1} sodium hydroxide was titrated after 3 min. The ^{1}H NMR spectra were measured with a JNM-FX 100 JEOL apparatus at 99·602 MHz in solutions in deuteriochloroform and hexadeuteriodimethyl sulphoxide with hexamethyldisiloxane as the internal standard.

RESULTS AND DISCUSSION

Base Catalyzed Cyclization of Hydantoates and Thiohydantoates in Water

The reactions taking place in aqueous solutions are represented in Scheme 1, where RCOOR', $RCOO^{(-)}$, and P mean the starting hydantoate, salt of the hydantoic acid, and the hydantoin or thiohydantoin formed by the cyclization, respectively.



I – *XXIII*

SCHEME 1

Both the competition reactions (cyclization and hydrolysis of the ester) are 1. order in hydroxyl ion, so the ratio of their rates is pH independent, and

$$k_{obs} = k_c + k_h . \qquad (1)$$

Substituent polar effects on the ester hydrolysis are small. Predominantly they are alkyl groups and substituents far away from the reaction centre. Steric effects of the substituents usually retard the hydrolysis[21]. As all the substituents increase the cyclization rate (Table II), the competitive hydrolysis is most significant with the least substituted hydantoates which undergo the slowest cyclization. Therefore, we determined the ratio of the cyclizate to the anion of acid in the reaction products of the

esters *I*–*IV*, *VI*, and *VII*. Both the products could be determined by potentiometric titration with respect to the considerable difference in the pK_a values of the two compounds (hydantoin 9·04; 3-methylhydantoin 13·06, ref.[22]; hydantoic acid 3·52, ref.[5]). With the methyl derivatives *III* and *IV* the potentiometry only detected the cyclizates, which indicates that the hydrolysis is practically insignificant. With the ethyl hydantoate *I* we found 38 ± 3% of the hydantoin, with the methyl derivative *II* the amount of hydantoin was 37 ± 3%, therefore, it is $k_c = 0{\cdot}38 \,.\, k_{obs}$ and $0{\cdot}37 \,.\, k_{obs}$, respectively. With the hydantoates *VI* and *VII* the found cyclizate amounts were 80 ± 6%. The date is loaded with greater error, because the acid was only determined potentiometrically, and ring opening takes place to a small extent during the experiment. At the conditions of kinetic experiments, on the contrary, the subsequent hydrolysis of hydantoin (k_h') almost did not take place, because in all the cases it is

TABLE II

The rate constants k (1 mol^{-1} s^{-1}) of base catalyzed cyclization of esters *I*–*XXII* in aqueous solutions of sodium hydroxide or aqueous buffers (a) and in methanolic solutions of sodium methoxide or methanolic buffers (b)

Ester	k (water)	k (methanol)
I	$(3{\cdot}2 \pm 0{\cdot}2) \,.\, 10^{-1}$	$(1{\cdot}2 \pm 0{\cdot}2) \,.\, 10^{-2}$
II	$(3{\cdot}6 \pm 0{\cdot}3) \,.\, 10^{-1}$	$(1{\cdot}3 \pm 0{\cdot}1) \,.\, 10^{-2}$
III	$(3{\cdot}2 \pm 0{\cdot}2)$	$(4{\cdot}9 \pm 0{\cdot}5) \,.\, 10^{-2}$
IV	$(1{\cdot}2 \pm 0{\cdot}1) \,.\, 10^{1}$	$(5{\cdot}5 \pm 0{\cdot}4) \,.\, 10^{-1}$
V	$(2{\cdot}8 \pm 0{\cdot}3) \,.\, 10^{1}$ (a)	$1{\cdot}4 \pm 0{\cdot}6$
VI	$1{\cdot}8 \pm 0{\cdot}2$	$(4{\cdot}6 \pm 0{\cdot}3) \,.\, 10^{-2}$
VII	$3{\cdot}0 \pm 0{\cdot}3$	$(5{\cdot}5 \pm 0{\cdot}2) \,.\, 10^{-2}$
VIII	$(2{\cdot}4 \pm 0{\cdot}2) \,.\, 10^{1}$	$1{\cdot}3 \pm 0{\cdot}1$
IX	$(1{\cdot}4 \pm 0{\cdot}04) \,.\, 10^{1}$	$(1{\cdot}6 \pm 0{\cdot}1) \,.\, 10^{-1}$
X	$(1{\cdot}1 \pm 0{\cdot}1) \,.\, 10^{2}$	$6{\cdot}8 \pm 0{\cdot}4$
	$(1{\cdot}6 \pm 0{\cdot}1) \,.\, 10^{2}$ (a)	
XI	$(1{\cdot}5 \pm 0{\cdot}1) \,.\, 10^{2}$ (a)	$8{\cdot}3 \pm 0{\cdot}3$
XII	$(9{\cdot}1 \pm 3{\cdot}6) \,.\, 10^{1}$ (a)	$4{\cdot}8 \pm 0{\cdot}7$
XIII	$(2{\cdot}4 \pm 0{\cdot}1) \,.\, 10^{2}$	$(8{\cdot}6 \pm 1{\cdot}0) \,.\, 10^{-1}$
	$(3{\cdot}9 \pm 0{\cdot}06) \,.\, 10^{2}$ (a)	
XIV	$(6{\cdot}4 \pm 0{\cdot}4) \,.\, 10^{2}$ (a)	$4{\cdot}3 \pm 0{\cdot}4$
XV	$(1{\cdot}2 \pm 0{\cdot}03) \,.\, 10^{5}$ (a)	$(4{\cdot}6 \pm 0{\cdot}4) \,.\, 10^{2}$
XVI	$(4{\cdot}3 \pm 0{\cdot}9) \,.\, 10^{3}$ (a)	$3{\cdot}5 \pm 0{\cdot}09$
XVIII	$(2{\cdot}1 \pm 0{\cdot}2) \,.\, 10^{5}$ (a)	$(1{\cdot}5 \pm 0{\cdot}1) \,.\, 10^{3}$ (b)
XIX	$(1{\cdot}9 \pm 1{\cdot}0) \,.\, 10^{5}$ (a)	$(1{\cdot}2 \pm 0{\cdot}1) \,.\, 10^{3}$
XX	$(2{\cdot}2 \pm 0{\cdot}1) \,.\, 10^{4}$ (a)	$(2{\cdot}9 \pm 0{\cdot}4) \,.\, 10^{2}$
XXI	$(4{\cdot}1 \pm 0{\cdot}1) \,.\, 10^{3}$ (a)	$(1{\cdot}0 \pm 0{\cdot}2) \,.\, 10^{1}$
XXII	$(8{\cdot}4 \pm 0{\cdot}7) \,.\, 10^{4}$ (a)	$(1{\cdot}2 \pm 0{\cdot}1) \,.\, 10^{2}$

$k_c \gg k'_h$, and the cyclization takes a simple pseudomonomolecular course. The great difference between both the rate constants was verified by comparison of the k_c measured with the k'_h measured or published, or in other way by following the hydrolysis (with the Specord spectrophotometer) after the cyclization was finished and the hydroxyl ion concentration in the reaction solution increased.

The cyclization rate of more reactive esters was measured in buffers, and simultaneously followed was the dependence of k_{obs} on the buffer concentration. Except for the phenylthiohydantoates *XXI* and *XXII*, no influence or only small changes in k_{obs} were observed with increasing concentration of phosphate buffers (due obviously to different solvation properties of the solution with high buffer concentration and low content of potassium chloride as compared with those of buffers of lower concentrations with higher content of chloride).

With the phenylthiohydantoates *XXI* and *XXII* we observed a large linear increase in k_{obs} with increasing concentration of the basic buffer component (Fig. 2), which means that the cyclization of these compound is subject to general base catalysis (Eq. (2)). The k_{OH} values defined by Eq. (3)

$$k_{obs} = k_B[B] + k_{OH} \cdot a_{OH} \qquad (2)$$

$$k_{obs} = k_{OH}[OH^{(-)}] \quad \text{or} \quad k_{obs} = k_{OH} \cdot a_{OH} \qquad (3)$$

were found graphically from the dependence of k_{obs} on the OH^- ion concentration or activity, respectively.

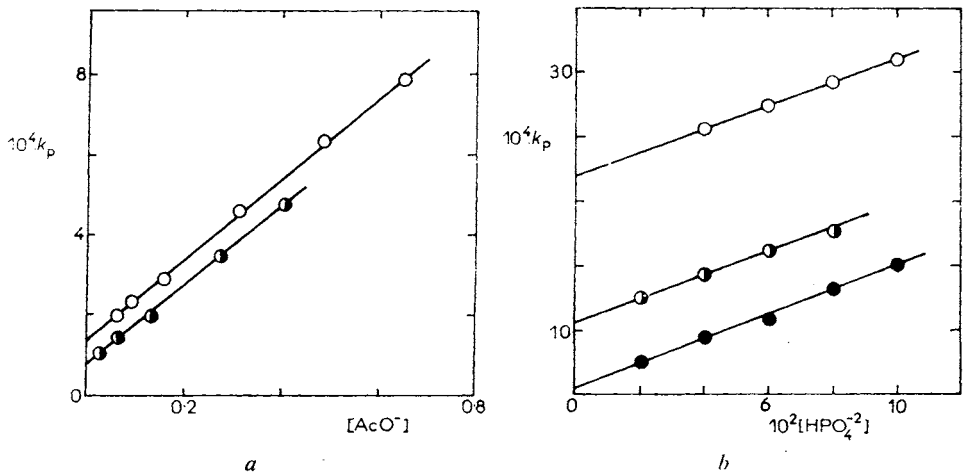
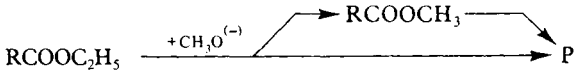


FIG. 2

Dependence of the observed rate constants k_{obs} (s^{-1}) of the cyclization of ester *XXII* on concentration of *a* [AcO^-] : [AcOH] = 4 (○), 2 (◑); *b* [$H_2PO_4^-$] : [HPO_4^{-2}] = 4 (●), 2 (◑), 1 (○)

Base Catalyzed Cyclization of Hydantoates and Thiohydantoates in Methanol

In methanolic solutions the cyclizate P is formed by the reactions given in Scheme 2.



SCHEME 2

For the competitive reactions (cyclization, transesterification) the situation is analogous here as in aqueous solutions. The transesterification can be considered (with respect to cyclization) in the case of the least reactive esters. Three limit cases can be considered: *1*) The transesterification is far slower than the cyclization. *2*) The transesterification is far faster than the cyclization. In these two cases the time dependence of logarithm of absorbance change ($\log \Delta A$) is linear within the whole range. *3*) The rates of cyclization and transesterification are comparable. Then the time dependence of $\log \Delta A$ is not linear except for cases when the cyclization rate constants of both the esters are approximately the same. In all the cases except ethyl phenylhydantoate *XIII* (see below) the dependences found were linear in the whole range measured.

The compounds *II*, *VII*, *XIV*, and *XXIII* are methyl esters. Their cyclization rate constants in aqueous and methanolic solutions are presented in Table II. The ratio of the cyclization to hydrolysis products was practically the same with the methyl ester *VII* as with the ethyl ester *VI*. The cyclization rate constant ratio of the corresponding methyl and ethyl esters for the non-substituted esters *I* and *II* equals 1·0 within experimental error both in water and in methanol, that of the 5-methylhydantoates *VI* and *VII* is 1·6 in water and 1·2 in methanol, and that of the phenylhydantoates *XIII* and *XIV* is 2·7 in water and 3·6 in methanol. For comparison it can be mentioned that the hydrolysis rate constant ratio of methyl and ethyl ethanoates is 1·7 (ref.[23]).

As the cyclization rates of the two esters are the same in water for the non-substituted compounds *I* and *II* (no transesterification can take place in aqueous solutions), we presume the cyclization rate constants of the two esters to be the same in methanolic solutions, too. With the methyl ester *VII* the cyclization rate constant is somewhat higher than that of the ethyl ester *VI* both in water and in methanol. The difference between the rate constants in methanol is, however, much too small, which prevents any conclusion to be made from kinetic experiments about the cyclization of ethyl ester *VI*, *i.e.* whether it takes the direct pathway or the two paths given in Scheme 2. Even in the latter case (two pathways) the k_{obs} would not be substantially different from k_c of the ethyl ester itself.

A much greater difference between the cyclization rates of the methyl and ethyl esters was found with the phenylhydantoates *XIII* and *XIV*. Obviously the reason

lies in the large steric effect of phenyl group and greater stability of the anion which results in greater selectivity of the proper cyclization reaction. It can be stated that the cycilzation rate constants measured in methanol correspond to the cyclization of the ethyl esters, even though in the case of the unsubstituted ethyl ester *I* or methyl derivative *VI* transesterification can also partially operate (in analogy to aqueous solutions where partial hydrolysis takes place).

The cyclization of phenylhydantoate *XIII* in methanol exhibits the following time dependence of log ΔA: the first non-linear steeper decrease is followed by slower linear decrease. The final absorbance of the solution is substantially higher than the absorbance of the product alone. With the methyl ester *XIV* the time dependence of log ΔA is linear in the whole range measured, and its slope is about 5 times greater than that of the linear section of the ethyl ester *XIII*. The final absorbance is the same as in the cyclization of the ethyl ester *XIII*. If the same amount of the cyclizate was added to methanolic solution of the same methoxide concentration (*i.e.* the same conditions as those in the cyclization, the only exception being in that the cyclizate was added instead of the ester), the absorbance was increased. The final absorbance was practically the same as in the previous cases, and the time dependence of log ΔA was linear with the same slope as in the case of the methyl ester *XIV*. The facts found can be explained by Scheme 3. The formation of the cyclizate P from the methyl ester represents a reversible reaction, hence Eq. (*4*) is true. The ratio expressed by Eq. (*5*)

$$k_{obs} = k'_c + k_v \tag{4}$$

$$k'_c/k_v = [P]/[RCOOCH_3] \tag{5}$$

and found from the absorbance of methyl ester, cyclizate P, and the reaction mixture (after the reaction is finished) is 7 : 3, *i.e.* $k'_c = 0{\cdot}7k_{obs}$. The base catalyzed cyclization of the ethyl esters irreversibly produces the cyclizate which is transformed into an equilibrium mixture of the cyclizate and methyl ester.

$$RCOOC_2H_5 + CH_3O^{(-)} \xrightarrow{k_c} P + C_2H_5O^{(-)} + CH_3OH \rightleftharpoons$$

$$\rightleftharpoons P + C_2H_5OH + CH_3O^{(-)}$$

$$P + CH_3OH \underset{k_c'}{\overset{CH_3O^{(-)}\, k_v}{\rightleftharpoons}} RCOOCH_3$$

SCHEME 3

The rate constant of establishing of the equilibrium is 5 times greater than that of the cyclization of ethyl ester *XIII*. From kinetic equations for consecutive reactions[24] we can derive Eq. (*6*), where k_1 means the rate constant of transformation

of the ethyl ester to the cyclizate and is given by the linear section

$$A_t - A_\infty = a \cdot e^{-k_1 t} + b \cdot e^{-(k_2+k_3)t} \qquad (6)$$

of the time dependence of $\log(A_t - A_\infty)$, $(k_2 + k_3)$ is the sum of rate constants of the reversible transformation P ⇄ methyl ester, and it can be obtained either from the non-linear section of the time dependence of $\log(A_t - A_\infty)$ (from the differences of the absorbances measured and those extrapolated from the linear section to the same time interval), or – more precisely – by direct measurement of the absorbance changes of the methyl ester *XIV* or cyclizate (3-phenylhydantoin).

A measurable equilibrium was only established with 3-phenylhydantoin. With all the other esters the cyclizate is formed practically quantitatively. The high proportion of the ester *XIV* in the equilibrium mixture with the cyclizate in methoxide – in contrast to aqueous solution and other derivatives – is due to the following factors: Acyl derivatives of aniline are much less stable than those of aliphatic amines, so the solvolysis is easier. The stability difference is approximately given by the difference in the dissociation constants of the amines (in this case about 5 orders of magnitude). With the N(3)- and C(2)-methylsubstituted hydantoates the cyclization rate is more than 20× higher as compared with the unsubstituted phenylhydantoate, whereas the solvolysis rate[25] is approximately the same. Therefore, the amount of ester in the reaction mixture is negligible after the cyclization is finished. In aqueous solution the cyclizate si substantially more solvated than the ester (as compared with the methanolic solution), so the equilibrium is shifted completely to the cyclizate.

In all the cases the rate constant k_{obs} depends linearly on methoxide concentration, *i.e.* Eq. (7) is true.

$$k_{obs} = k_{CH_3O^{(-)}}[CH_3O^{(-)}] \qquad (7)$$

Again the $k_{CH_3O^-}$ values were determined graphically from the dependence of k_{obs} on methoxide concentration and are given in Table III.

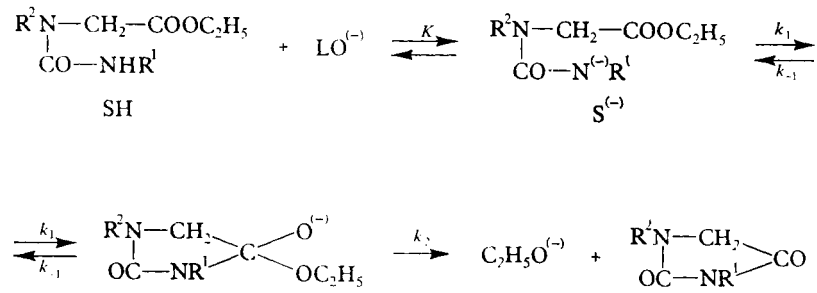
Reaction Mechanism of the Base Catalyzed Cyclization

The cyclization reaction mechanism is given in Scheme 4, where K means the equilibrium constant of the reaction of ester SH with the lyate ion $LO^{(-)}$, and concentration of the ester anion $S^{(-)}$ is given by Eq. (8).

$$[S^{(-)}] = c_{SH}/(1 + (K[LO^{(-)}])^{-1}) \qquad (8)$$

If it is $K[LO^{(-)}] \ll 1$ (such $LO^{(-)}$ concentration that $[S^{(-)}]$ is negligibly small as compared with the concentration of the starting compound), Eq. (8) is transformed into Eq. (9).

$$[S^{(-)}] = K[LO^{(-)}] \cdot c_{SH} \qquad (9)$$



SCHEME 4

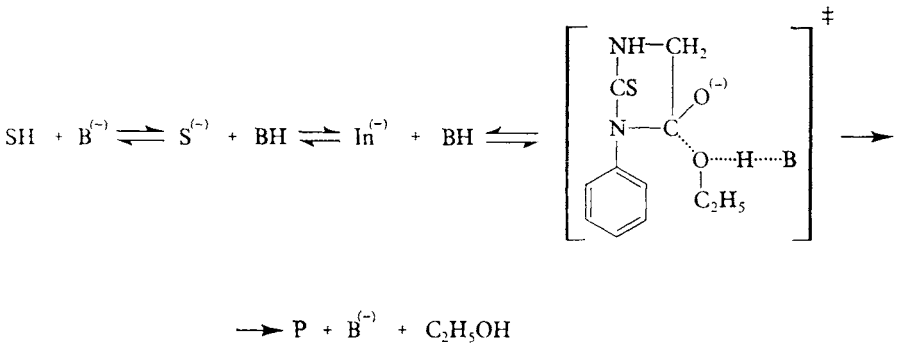
In all the cases the k_{obs} value increased linearly with concentration of the lyate ion, *i.e.* in the equilibrium mixture an only negligible amount of the anion $S^{(-)}$ was present, so it is possible to use the simplified expression (*9*). Then the rate is given by Eq. (*10*) and k_{obs} by Eq. (*11*). In aqueous buffers

$$k_{obs} \cdot c_{SH} = k_1 k_2 [S^{(-)}]/(k_{-1} + k_2) = k[S^{(-)}] = kKc_{SH}[LO^{(-)}] \qquad (10)$$

$$k_{obs} = kK[LO^{(-)}] = k_{LO^-}[LO^{(-)}] \qquad (11)$$

in all the cases except for the esters *XXI* and *XXII*, k_{obs} only depends on the activity a_{OH^-} and does not depend on the buffer concentration, hence the reaction is subject to specific base catalysis. With the compounds *XXI* and *XXII* the k_{obs} value increased linearly with increasing buffer concentration, hence in these cases the cyclization is subject to general base catalysis. So the rate-limiting step is different here from that of the other esters. The rate-limiting step can consist either in formation of the intermediate (Scheme 4) or in splitting off of $C_2H_5O^{(-)}$ group, *i.e.* decomposition of the intermediate into products. The decisive factor is the ratio of the rate of reverse transformation of the intermediate to the anion $S^{(-)}$ to that of its decomposition into products with splitting off of $C_2H_5O^{(-)}$. The rate ratio will predominantly depend on the relative tendencies to C—O and C—N bond splitting. As a criterion of these tendencies we can consider the basicities of $S^{(-)}$ and $C_2H_5O^{(-)}$ or the pK_a values of the substrate SH and ethanol. The pK_a value of ethanol in water is 16 (ref.[26]). For SH it is impossible to find the pK_a value, because in the region of the hydroxyl ion concentrations corresponding to the equilibrium constant the cyclization proceeds much too fast. An approximate estimate of pK_a can be made on the basis of the published dissociation constants of substituted phenylureas and thioureas[27]. The pK_a values of phenylthiourea are 16·95 in methanol and 13·0 in water (calculated from the Hammett equation) and those of phenylurea are about 20 (methanol) and 16 (water). The pK_a values of the alkyl derivatives and unsubstituted urea are still greater by several orders of magnitude. From the pK_a values given it

can be concluded: All the oxygen derivatives and the thio derivative *XX* have substantially higher basicity at the amino group than at ethoxy group. Therefore, the trend to split off the amino group from the intermediate will be far lower than that of the ethoxy group, and the rate-limiting step will consist in formation of the intermediate. This fact agrees with the cyclization of these compounds being subject to specific base catalysis; the formation of the intermediate from anion $S^{(-)}$ (Scheme 5) needs no catalysis.



SCHEME 5

With the phenylthio derivatives *XXI* and *XXII* the rate of decomposition of the intermediate into the anion is much greater than that of its transformation into products, and the rate-limiting step begins to consist in the transformation of the intermediate into product. This step must be catalyzed, and as the first step (formation of $S^{(-)}$ in Scheme 5) involves specific base catalysis, this step must be catalyzed with an acid (general acid catalysis), because the result of specific base catalysis and general acid catalysis is general base catalysis. Mechanism of this general base catalysis can be expressed by Scheme 5. The rate-limiting step is changed, if $pK_a^{SH} \doteq \doteq pK_a^{EtOH}$.

Effect of Medium on the Cyclization Reactions of Esters

The cyclization of the methyl substituted and unsubstituted esters *I*, *II*, *VI*, *VII* in methanol proceeds 20–30× slower than in water at the same concentrations of the lyate ion (the retardation is still greater (about 3×) in the case of the alanine derivative *III* and *IX* and thio derivative *XX*), whereas with the phenylhydantoates *XIII*, *XIV* and thio derivative *XXI* the retardation is still greater (by one order of magnitude). The effect of the change of medium makes itself felt on the equilibrium constant *K* (Scheme 4) as well as on the rate constant of the cyclization reaction (or also of the transformation of the intermediate into product). The pK_a values

of substituted phenylureas and thioureas in methanol are lower than in water by 4 units[27], and as pK_a of methanol is higher than pK_a of water by 3 units[28], the equilibrium constant K (Scheme 4) will be about one order of magnitude lower in methanol than in water.

Another factor consists in the effect of medium on energy of the activated complex of the rate-limiting step. Its structure is close to that of tetrahedral intermediate (closest probably with the phenyl derivatives, which are the weakest nucleophiles). Therefrom it follows that the negative charge is considerably localized at the oxygen atom and is more stabilized by solvation in water than in methanol.

Substituent Effects on Rate of the Cyclization Reaction

If the oxygen atom of the carbonyl group is replaced by sulphur, pK_a values of substituted ureas are increased by 3 units[27], and practically the same increase is observed with carbamates[29]. From these findings it can be concluded that the anion concentration of thiohydantoates will be about 3 orders higher than that of the oxygen analogues at the same concentration of the lyate ions.

The cyclization rate constant of the methyl thiohydantoate *XX* is by 4 orders higher than that of the oxygen analogue *VI*; both the esters react by the same mechanism. This means that the cyclization rate increase is due mainly to the increase in the equilibrium constant. The substitution of oxygen by sulphur atom has little effect in this case on the rate constant of formation of the intermediate from the anion. With the phenylhydantoates *XIII*, *XIV*, *XXI*, and *XXIII* the thio derivative reacts 10× and 20× faster, resp., than the oxygen analogue. The relatively small increase in the rate constant also confirms a change in the rate-limiting step. The resulting k_{LO^-} is even lower than that of the methylthio derivative *XX*. The greater tendency to cyclization observed with methyl thiohydantoates makes itself felt in preparation of these compounds, too. Several attempts were made at preparation of sulphur analogue of the hydantoate *VIII*, but soon after mixing the reactants the reaction solution quantitatively deposited the cyclizate (3,5-dimethyl-2-thiohydantoin) even if the mixture was cooled with ice.

The effects of alkyl or phenyl substituents at N(3), N(5), and C(2) positions on the cyclization rate can be divided into three factors: *1*) Replacement of hydrogen by a bulkier substituent facilitates (entropically) formation of the intermediate by reduction of the number of possible rotamers; an enthalpic effect is possible, if – at the same time – non-bonding interactions are decreased on formation of the intermediate[5,30–34]. *2*) Near the reaction centre steric effects of substituents will decrease the reaction rate. *3*) Substituents affect (by their polar effects) the equilibrium constant and reactivity of nitrogen atom and ester group in the $S^{(-)}$ anion.

Replacement of hydrogen atom by methyl group at N(5) position causes the factors 1 and 2 to operate; as they cancel out each other to considerable extent, the net

acceleration is small (2–4×). It is an open question whether or not polar effects of methyl group operate. The same substitution at C(2) position is connected with the factor 1 and – to a lesser extent – factor 2; the result is an 10–20 fold acceleration of the cyclization reactions. Replacement of hydrogen by alkyl group at N(3) position of the esters *IV*, *V*, *VIII*, *XII*, *XV*, and *XIX* is only connected with the factor 1 (polar effects are probably negligible), and the acceleration is the greatest in this case, being increased with the bulk of the substituent. Introduction of phenyl group to N(3) position (the compounds *X* and *XVII*) should be also connected with operation of polar effects of phenyl group, but the results show that such influence is small. Introduction of phenyl group to N(5) position (the compounds *XIII*, *XIV*, *XV*, *XVI*, *XVIII*, *XIX*, and *XXIII*) again causes the factors 1 and 2 to operate considerably, but the greatest influence is exercised by polar effect of phenyl group which causes a considerable increase in the equilibrium constant. The anion formed is less reactive than that formed from the alkyl- and non-substituted derivatives, but this effect makes itself felt to a considerably lesser extent, which is seen from the fact that the phenyl derivatives react faster than the other esters by several orders of magnitude. The reactions of phenylhydantoates *XXI* and *XXII* differ in the rate-limiting step, which prevents their comparison with the other esters.

REFERENCES

1. Jencks W. P.: *Catalysis in Chemistry and Enzymology*. McGraw Hill, New York 1969.
2. Page M. I.: Angew. Chem., Int. Ed. Engl. *16*, 449 (1977).
3. Kirby A. J.: Advan. Phys. Org. Chem. *17*, 183 (1980).
4. Ware E.: Chem. Rev. *46*, 403 (1950).
5. Stella V., Higuchi T.: J. Org. Chem. *38*, 1527 (1973).
6. Güler F., Moodie R. B.: J. Chem. Soc., Perkin Trans. 2, *1980*, 1752.
7. Drobnica L.: This Journal *30*, 97 (1965).
8. Blagoeva I. B., Pojarlieff I. G., Kirby A. J.: J. Chem. Soc., Perkin Trans. 2, *1984*, 745.
9. Natelson S., Gottfried S.: Org. Syn., Coll. Vol. III, 381 (1955).
10. Fischer E.: Chem. Ber. 34, 433 (1901).
11. Curtius Th., Goebel F.: J. Prakt. Chem. (2), *37*, 150 (1888).
12. Chambers R. W., Carpenter F. H.: J. Amer. Chem. Soc. *77*, 1522 (1955).
13. Bischoff A. C., Hansdörfer A.: Chem. Ber. *25*, 2270 (1892).
14. Speziale A. J., Javorski E. G.: J. Org. Chem. *75*, 728 (1960).
15. Harries C., Weiss M.: Justus Liebigs Ann. Chem. *327*, 355 (1903).
16. Laidler K. J.: *Chemical Kinetics*, p. 14. McGraw-Hill, New York 1965.
17. Rosen O.: Acta Chem. Scand. *4*, 687 (1950).
18. Bochmann W. E., Maxwell E. Ch.: J. Amer. Chem. Soc. *72*, 2880 (1950).
19. Curtius Th., Leonard W.: J. Prakt. Chem. (2), *70*, 230 (1904).
20. Paal C., Ganser F.: Chem. Ber. *28*, 3234 (1895).
21. Williams A., Jencks W. P.: J. Chem. Soc., Perkin Trans. 2, *1974*, 1753.
22. Blagoeva I. B., Pojarlieff I. G., Dimitrov V. S.: J. Chem. Soc., Perkin Trans. 2, *1978*, 887.
23. Furanto E. K. in the book: *The Chemistry of Carboxylic Acids and Esters* (S. Patai, Ed.), Chapt. 11, p. 518. Wiley, London 1969.

24. Capellos C., Bielski B. H.: *Kinetic Systems*. Interscience-Wiley, London 1972.
25. Blagoeva I. B., Pojarlieff I. G.: Dokl. Bulg. Akad. Nauk *7*, 1043 (1977).
26. Hine J., Koser G. F.: J. Org. Chem. *36*, 1348 (1971).
27. Kaválek J., El Bahaie S., Štěrba V.: This Journal *48*, 1430 (1983).
28. Rochester C. H.: *Acidity Functions*, p. 247. Academic Press, London 1970.
29. Mindl J., Večeřa M., Šilar Z., Balcárek P.: This Journal *45*, 3130 (1980).
30. Capon B., McManus S. P.: *Neighbouring Group Participation*, Vol. 1, Chapt. 2. Plenum Press, New York 1976.
31. Page M. I.: Chem. Soc. Rev. *2*, 295 (1973).
32. Newman M. S.: *Steric Effects in Organic Chemistry*, p. 203. Wiley, New York 1956.
33. Bruice T. C., Pandit U. K.: J. Amer. Chem. Soc. *82*, 5858 (1960).
34. De Tar D., Luthra N. P.: J. Amer. Chem. Soc. *102*, 4505 (1980).

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