KINETICS AND MECHANISM OF BASE-CATALYZED CYCLIZATION OF SUBSTITUTED AMIDES AND NITRILES OF HYDANTOIC ACID

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Dedicated to Prof. J. Klikorka on the occasion of his 65th birthday.

Rates of base-catalyzed cyclizations of 8 substituted derivatives of hydantoic acid amide type R^3—NH(5)—CO(4)—NR^2(3)—CH_2(2)—CO(1)—NHR^1 and 9 nitriles type R^3—NH(5)—CO(4)—NR^2(3)—CHR^1(2)—CN have been measured in aqueous and methanolic media. The cyclization of the amides in aqueous medium is also accompanied by hydrolysis of the hydantoins formed. In some cases the hydrolysis rate constant is greater than the corresponding cyclization reaction rate constant. With the least reactive amides, the cyclization is also accompanied by hydrolysis of the amide group. The rate of the cyclization reactions in water is higher than that in methanol (at the same concentration of the lyate ions) by the factor of 10—100. Substitution of hydrogen at 3 and 5 positions by methyl or phenyl groups causes an acceleration of the cyclization reaction, whereas a substitution in the amide group causes a considerable retardation. The greatest acceleration of the cyclization (by as much as 4 orders) is caused by introduction of phenyl group to the N(5) position, which is due to a substantial increase of concentration of the reactive anion.

Studies of intramolecular reactions are very important for elucidation of many types of reaction mechanisms, especially mechanisms of enzymatic catalysis[1,2]. The increase in reaction rates by many orders of magnitude, which is typical for intramolecular reactions[3], makes it possible to study such reactions which — while taking an intermolecular course — would necessitate high temperatures and long reaction times or would even be overshadowed by other competing reactions. In the previous paper[4] we described the effects of substituents and medium on the kinetics and mechanism of base-catalyzed cyclizations of esters of substituted hydantoic and thiohydantoic acids giving the respective substituted hydantoins and thiohydantoins. The aim of the present paper is a study of cyclization of substituted amides (*I*) and nitriles (*II*) of hydantoic acid.

EXPERIMENTAL

Reagents

The procedures described in literature were used for preparations of the hydrochlorides of glycinamide[5], N-methylglycinamide[6], glycine methylamide[6], and N-methylglycine methylamide[7]. The melting points of the substances prepared agreed with the literature data[5–7].

Hydantoinamides Ia—Id. A saturated aqueous solution of 20 mmol KCNO was treated with a saturated aqueous solution of 20 mmol hydrochloride of substituted glycinamide. The products separated on standing were recrystallized from water.

Hydantoinamides Ie—Ih. A solution of 1 mol l^{-1} sodium methoxide was added drop by drop to a saturated methanolic solution of the respective substituted glycinamide hydrochloride until alkaline reaction (phenolphthalein). Methanol was distilled off in vacuum, and the substituted glycinamide was extracted with chloroform. After addition of equimolar amount of methyl isocyanate or phenyl isocyanate, the product separated on standing. The structure of all the compounds prepared was verified by ^{1}H NMR spectra (Tables I and II).

Methylaminoacetonitrile. A solution of 67 g (1 mol) methylammonium chloride and 50 ml c. 30% aqueous methylamine (about 0·5 mol) in 50 ml water was cooled and treated with 30 g paraformaldehyde (corresponding to 1 mol formaldehyde). The suspension was cooled to 0°C, and a solution of 65 g (1 mol) potassium cyanide in 60 ml water was added thereto within 3 h. The mixture was left to stand in a refrigerator overnight, and the next day it was extracted with 5 portions of ether (1 l total). The combined extracts were dried with calcium sulphate, the solvent was distilled off, and the product was distilled in vacuum under argon. B.p. 61—65°C/ /2·67 kPa (ref.[8] gives b.p. 65°C/2·67 kPa), yield 9·2 g (13%). ^{1}H NMR spectrum (C^2HCl_3): $\delta(CH_2)$ 3·56 (singlet, 2 H); $\delta(CH_3N)$ 2·54 (singlet, 3 H); δ(NH) 1·5 (broad signal, 1 H).

Aminoacetonitrile and its hydrogensulphate were prepared by known procedures[9].

Hydrochloride of α-aminophenylacetonitrile was prepared from benzaldehyde, sodium cyanide, and ammonium chloride in aqueous methanol[10]. Recrystallization from an ethanol–chloroform mixture gave the product with m.p. 166—169°C (decomp.) (ref.[11] gives m.p. 173°C with decomp.), yield 49%.

Nitriles IIa *and* IIg were prepared from salts of aminoacetonitrile or α-aminophenylacetonitrile in the same way as the amides *Ia—Id.*

Nitrile of 3-methylhydantoic acid (IId). A solution of methylaminoacetonitrile in the minimum volume of water was treated with equimolar amount of acetic acid and equimolar amount of potassium cyanate dissolved in the minimum volume of water. The product separated on standing of the solution was recrystallized from water.

Nitriles IIb, IIc, IIe, *and* IIf were prepared by the reaction of aminoacetonitrile or methylaminoacetonitrile with equimolar amount of methyl or phenyl isocyanate in dry ether.

Nitriles IIh *and* IIi. A methanolic solution of α-aminoacetonitrile hydrochloride was treated with equimolar amount of sodium methoxide (as 1 mol l^{-1} solution). Methanol was distilled off in vacuum, and α-aminophenylacetonitrile was extracted with ether from the evaporation residue. The extract was treated with equimolar amount of methyl or phenyl isocyanate.

Yields, physical properties, and ^{1}H NMR spectra of the nitriles synthetized (*IIa—IIi*) are presented in Tables III and IV.

Substituted hydantoins IIIa—IIIf were prepared by cylization of the hydantoic acid esters according to ref.[4]. The physical properties of the hydantoins synthetized (*IIIa—IIIi*) are given in Table V.

5-*Phenylhydantoin* (IIIg) was prepared by the cyclization of 2-phenyl-2-ureidoacetonitrile (*IIg*) in 1 mol l^{-1} sodium methoxide solution and subsequent hydrolysis of the imino derivative by 30 min refluxing with 0·1 mol l^{-1} hydrochloric acid on a boiling water bath. Analogous procedures were applied to the preparations of hydantoins *IIIh* and *IIIi* from the respective nitriles *IIh* and *IIi*. In the case of the nitrile *IIi* the cyclization was carried out in 10^{-3} mol l^{-1} methoxide solution and the hydrolysis in 1 mol l^{-1} hydrochloric acid.

TABLE I

The synthetized substituted hydantoinamides $R^3—NH—CO—NR^2—CH_2—CO—NH—R^1$

Amide	R^1	R^2	R^3	Crystallized from	Yield %	M.p. °C	M.p. (ref.) °C	Calculated			Found		
								% C	% H	% N	% C	% H	% N
Ia	H	H	H	H_2O	73	199—202	204(12)	—	—	—	—	—	—
Ib	CH_3	H	H	H_2O	85	181—183	180—181(13)	—	—	—	—	—	—
Ic	H	CH_3	H	H_2O	79	228—230	—	36·64	6·92	32·05	36·91	6·89	31·70
Id	CH_3	CH_3	H	H_2O	72	173—174	—	41·37	7·64	—	41·26	7·80	—
Ie	H	CH_3	CH_3	CH_3OH	90	155—157	—	41·37	7·64	28·95	41·08	7·32	28·75
If	CH_3	CH_3	CH_3	$CCl_4 + C_6H_{12}$	96	136—138	—	45·27	8·23	—	45·57	8·55	—
Ig	H	CH_3	C_6H_5	$CH_3OH + C_6H_6$	53	164—166	—	57·95	6·32	20·28	57·98	6·45	20·05
Ih	CH_3	CH_3	C_6H_5	C_6H_6	77	152—154	—	59·71	6·83	—	59·92	6·96	—

The ^1H and ^{13}C NMR spectra were measured at 99·602 and 25·047 MHz, resp., by means of a JEOL JNM-FX 100 spectrometer. For the ^1H NMR spectra, hexamethyldisiloxane was used as the internal standard (δ 0·05), the ^{13}C NMR spectra are related to the middle signal of the multiplet of hexadeuteriodimethyl sulphoxide (δ 39·6) or of deuteriochloroform (δ 77·0).

Measurements

The kinetic measurements were carried out at 25°C. The reaction course was recorded by means of a Specord UV VIS (Zeiss, Jena) spectrophotometer in the wavelength range of 220 to 350 nm. The kinetic measurements proper were carried out with the same apparatus and with a VSU 2P (Zeiss, Jena) spectrophotometer at a constant wavelength. The pH values of the buffers used were measured with an MV 870 Digital pH Messgerät using a glass and a silver chloride electrodes. The nitriles and amides were used in the form of stock solutions (concentration 10^{-2} and 0·1 mol l^{-1}, resp.) in acetonitrile, water, or methanol. In the kinetic runs proper, 1 drop of the stock solution was added to 2 ml solution of sodium methoxide or hydroxide or buffer placed in the cell of the spectrophotometer and kept at a constant temperature. The rate constants were determined graphically from the equation $k_{obs}t = -2{\cdot}3 \log (A_t - A_\infty) + \text{const}$. The rate constants of very slow reactions were determined by the method of initial concentrations from the relation $v = \Delta c/\Delta t = k_{obs}c$. The concentrations were estimated from the absorbances, the molar absorption coefficient was determined from the absorbance of a solution of separately prepared product in the same medium. The evaluation of the rate constants in the more complicated cases is described in the discussion.

The composition of aqueous reaction solution containing sodium hydroxide and products of hydrolysis and cyclization of the respective amide was analyzed by acidimetric titration with the use of the MV 870 Digital Messgerät pH-meter.

Determination of the extent of hydrolysis of the amides. About 1 mmol amide *Ia*—*Ic* was accurately weighed and dissolved in 1·2 equivalents of 0·2 mol l^{-1} NaOH. After 2 h, the solution was retitrated with 1 mol l^{-1} HCl with potentiometric indication. In the case of amides *Ia* and *Ic*,

TABLE II

^1H NMR spectra of substituted hydantoinamides R^3—NH—CO—NR^2—CH_2—CO—NH—R^1 in hexadeuteriodimethyl sulphoxide[a]

Amide	$\delta(R^1)$	δ(NH(1))	$\delta(CH_2)$	$\delta(R^2)$	δ(NH(3))	$\delta(R^3)$	δ(NH(5))
Ia	7·04 (b)	7·31 (b)	3·58 (d)	—	6·23 (bt)	5·74 (b)	5·74 (b)
Ib	2·61 (d)	7·75 (b)	3·59 (d)	—	6·24 (bt)	5·71 (b)	5·71 (b)
Ic	6·77 (b)	7·22 (b)	3·72 (s)	2·77 (s)	—	5·87 (b)	5·87 (b)
Id	2·57 (d)	7·70 (b)	3·75 (s)	2·77 (s)	—	5·92 (b)	5·92 (b)
Ie	7·00 (b)	7·27 (b)	3·78 (s)	2·80 (s)	—	2·55 (d)	6·30 (bq)
If	2·61 (d)	7·72 (bq)	3·80 (s)	2·64 (s)	—	2·61 (d)	6·33 (bq)
Ig	[b]	[b]	3·91 (s)	2·99 (s)	—	6·8—7·8 (m)	8·36 (b)
Ih	2·69 (d)	7·85 (b)	3·94 (s)	3·00 (s)	—	6·9—7·6 (m)	8·38 (b)

[a] (s) — singlet, (d) — doublet, (t) — triplet, (q) — quartet, (b) — broad; [b] overlapped by the proton multiplet of phenyl group.

TABLE III

The synthetized substituted nitriles of hydantoic acid $R^3—NH—CO—NR^2—CHR^1—CN$

Nitrile	R^1	R^2	R^3	Crystallized from	Yield %	M.p. °C	M.p. (ref.) °C	Calculated			Found		
								% C	% H	% N	% C	% H	% N
IIa	H	H	H	CH_3OH	48	136–138	138(14)	—	—	—	—	—	—
IIb	H	H	CH_3	$CH_3OH + CHCl_3$	94	118–120	—	42·47	6·24	37·15	42·15	6·23	37·45
IIc	H	H	C_6H_5	CH_3OH	87	155–157	154–155(15)	—	—	—	—	—	—
IId	H	CH_3	H	H_2O	72	116–118	216, decomp. (16)	42·47	6·24	37·15	42·71	6·51	37·28
IIe	H	CH_3	CH_3	C_6H_6	88	80–83	83–83·5(17)	—	—	—	—	—	—
IIf	H	CH_3	C_6H_5	C_2H_5OH	92	89–92	83(18)	—	—	—	—	—	—
IIg	C_6H_5	H	H	$H_2O + CH_3OH$	85	177–180	178, decomp. (19)	—	—	—	—	—	—
IIh	C_6H_5	H	CH_3	$CH_3OH + CHCl_3$	43	168–169	—	63·47	5·86	22·21	63·83	6·23	22·50
IIi	C_6H_5	H	C_6H_5	C_2H_5OH	48	157–159	—	71·69	5·21	16·73	71·35	5·13	16·33

TABLE IV

^{1}H NMR spectra of substituted nitriles of hydantoic acid R^3—NH—CO—NR^2—CHR^1—CN

Nitrile	Solvent	δ(CH(2))	δ(R^1)	δ(NH(3))	δ(R^2)	δ(NH(5))	δ(R^3)
IIa	[a]	4·00 (d)	4·00 (d)	6·70 (bt)	—	6·00 (b)	6·00 (b)
IIb[c]	[a]	4·02 (d)	4·02 (d)	6·56 (bt)	—	6·25 (bq)	2·60 (d)
IIc[d]	[a]	4·16 (d)	4·16 (d)	6·74 (bt)	—	8·95 (b)	6·75—7·50 (m)
IId[e]	[a]	4·31 (s)	4·31 (s)	—	2·91 (s)	6·35 (b)	6·35 (b)
IIe	[b]	4·29 (s)	4·29 (s)	—	2·99 (s)	5·61 (b)	2·80 (d)
IIf	[b]	4·27 (s)	4·27 (s)	—	3·05 (s)	8·22 (b)	6·8—7·6 (m)
IIg	[a]	5·85 (d)	7·40 (b)	7·20 (bt)	—	5·78 (b)	5·78 (b)
IIh	[b]	5·91 (d)	7·40 (b)	6·95 (d)	—	5·71 (bq)	2·72 (d)
IIi	[a]	5·91 (d)	7·0—7·7 (m)	7·00 (d)	—	8·30 (b)	7·0—7·7 (m)

[a] Hexadeuteriodimethyl sulphoxide; [b] deuteriochloroform; [c] ^{13}C NMR spectrum: δ(CO) 158·42, δ(CN) 119·04, δ(CH_2) 28·74, δ(CH_3) 26·68; [d] ^{13}C NMR spectrum: δ(CO) 155·33, δ(C_6H_5) 138·98, 118·79, 129·11, 122·44, δ(CN) 118·88, δ(CH_2) 28·78; [e] ^{13}C NMR spectrum: δ(CO) 158·61, δ(CN) 117·68, δ(CH_2) 36·92, δ(CH_3) 34·92.

ammonia was formed by both the hydrolysis and the cyclization. In the first procedure, ammonia was distiled over in vacuum at room temperature before the titration, in the second procedure, the solution was kept in a closed flask until the titration. The hydrolysis extent of the amide *Ib*, where methylamine is released, was only determined by the second procedure.

TABLE V

The synthetized substituted hydantoins

Hydantoin	R^1	R^2	R^3	Crystallized from	Yield %	M.p. °C	M.p. (ref.) °C
IIIa	H	H	H	$C_2H_5OH + H_2O$	85	216–218	217–218(20)
IIIb	H	CH_3	H	$C_2H_5OH + H_2O$	72	156–158	157–158(21)
IIIc	H	H	CH_3	H_2O	72	181–183	184–185(22)
IIId	H	CH_3	CH_3	C_2H_5OH	78	42–43	44–45(23)
IIIe	H	H	C_6H_5	H_2O	79	154–156	159(24)
IIIf	H	CH_3	C_6H_5	C_2H_5OH	89	109–111	108–110(25)
IIIg	C_6H_5	H	H	CH_3OH	30	181–183	181–182(19)
IIIh	C_6H_5	H	CH_3	CH_3OH	40	160–162	161–162(26)
IIIi [a]	C_6H_5	H	C_6H_5	CH_3OH	55	186–187	–

[a] For $C_{15}H_{12}N_2O_2$ (252·3) calculated: 71·41% C, 4·79% H, 11·10% N; found: 71·34% C, 4·72% H, 11·16% N. ^{1}H NMR spectrum (deuteriochloroform): δ(NH) 8·69 (b), $\delta(C_6H_5)$ 7·41 (m), δ(CH) 5·16 (s).

TABLE VI

The rate constants k_2[a] (1 mol^{-1} s^{-1}) of base-catalyzed cyclization of hydantoinamides *I* in aqueous sodium hydroxide and methanolic sodium methoxide solutions at 25°C

Amide	R^1	R^2	R^3	k_2 (water)	k_2 (methanol)
Ia	H	H	H	$4{\cdot}3 \cdot 10^{-4}$	$2{\cdot}4 \cdot 10^{-5}$
Ib	CH_3	H	H	$6{\cdot}9 \cdot 10^{-5}$	–
Ic	H	CH_3	H	$1{\cdot}2 \cdot 10^{-2}$	$1{\cdot}1 \cdot 10^{-3}$
Id	CH_3	CH_3	H	$2{\cdot}5 \cdot 10^{-3}$	$1{\cdot}4 \cdot 10^{-4}$
Ie	H	CH_3	CH_3	$1{\cdot}6 \cdot 10^{-1}$[b]	$7{\cdot}6 \cdot 10^{-3}$
If	CH_3	CH_3	CH_3	$1{\cdot}1 \cdot 10^{-2}$[b]	$1{\cdot}4 \cdot 10^{-3}$[b]
Ig	H	CH_3	C_6H_5	4·45	$2{\cdot}9 \cdot 10^{-2}$
Ih	CH_3	CH_3	C_6H_5	$4{\cdot}3 \cdot 10^{-1}$[b]	$4{\cdot}7 \cdot 10^{-3}$

[a] If not otherwise stated, the maximum error in k_2 is ±10%; [b] the maximum error in k_2 is ±20%.

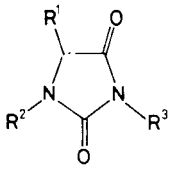
Determination of pK_A *of substituted* 4-*iminohydantoins.* The imino derivatives were prepared by cyclization of 0·01 mol l^{-1} solutions of the ureidonitriles *II* in 0·01 mol l^{-1} methoxide. The cyclization course was followed spectrophotometrically by means of the Specord UV VIS. When the reaction was finished, the solution was neutralized with hydrochloric acid (phenolphthalein). A drop of the obtained c. 0·01 mol l^{-1} solution of the imino derivative was added to 2 ml of citrate-phosphate buffer (pH 4–8) in a 1 cm quartz cell; the ionic strength of the buffer was adjusted at $I = 1$ mol l^{-1} by addition of 2 mol l^{-1} KCl. The absorbance A of the solutions thus prepared was measured with the VSU 2P spectrophotometer. The absorbance A_2 of the protonated form of the imino derivative was measured in 0·1 mol l^{-1} hydrochloric acid, and that of the neutral form (A_1) in 0·1 mol l^{-1} NaOH. The $\log((A_1 - A)/(A - A_2))$ values were plotted against the pH values of the buffers.

R^3—NH—CO—NR^2—CH_2—CO—NHR^1

Ia: $R^1 = R^2 = R^3 = H$
Ib: $R^1 = CH_3$; $R^2 = R^3 = H$
Ic: $R^1 = R^3 = H$; $R^2 = CH_3$
Id: $R^1 = R^2 = CH_3$; $R^3 = H$
Ie: $R^1 = H$; $R^2 = R^3 = CH_3$
If: $R^1 = R^2 = R^3 = CH_3$
Ig: $R^1 = H$; $R^2 = CH_3$; $R^3 = C_6H_5$
Ih: $R^1 = R^2 = CH_3$; $R^3 = C_6H_5$

R^3—NH—CO—NR^2—CHR^1—CN

IIa: $R^1 = R^2 = R^3 = H$
IIb: $R^1 = R^2 = H$; $R^3 = CH_3$
IIc: $R^1 = R^2 = H$; $R^3 = C_6H_5$
IId: $R^1 = R^3 = H$; $R^2 = CH_3$
IIe: $R^1 = H$; $R^2 = R^3 = CH_3$
IIf: $R^1 = H$; $R^2 = CH_3$; $R^3 = C_6H_5$
IIg: $R^1 = C_6H_5$; $R^2 = R^3 = H$
IIh: $R^1 = C_6H_5$; $R^2 = H$; $R^3 = CH_3$
IIi: $R^1 = R^3 = C_6H_5$; $R^2 = H$



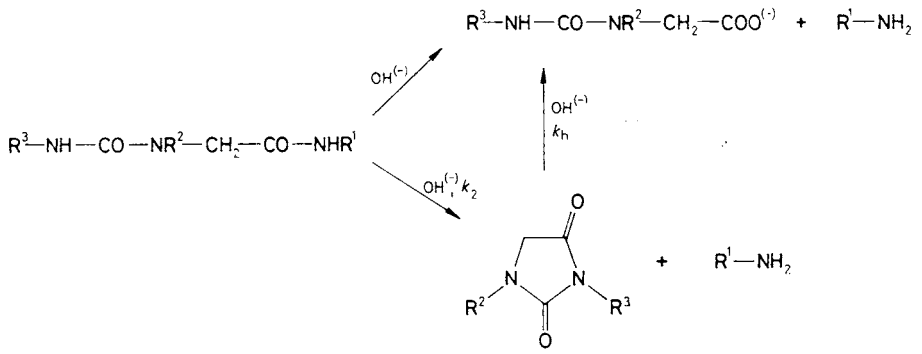
IIIa: $R^1 = R^2 = R^3 = H$
IIIb: $R^1 = R^3 = H$; $R^2 = CH_3$
IIIc: $R^1 = R^2 = H$; $R^3 = CH_3$
IIId: $R^1 = H$; $R^2 = R^3 = CH_3$
IIIe: $R^1 = R^2 = H$; $R^3 = C_6H_5$
IIIf: $R^1 = H$; $R^2 = CH_3$; $R^3 = C_6H_5$
IIIg: $R^1 = C_6H_5$; $R^2 = R^3 = H$
IIIh: $R^1 = C_6H_5$; $R^2 = H$; $R^3 = CH_3$
IIIi: $R^1 = R^3 = C_6H_5$; $R^2 = H$

RESULTS AND DISCUSSION

Cyclization of Hydantoinamide in Aqueous Solutions of Sodium Hydroxide

The following reactions (Scheme 1) can be presumed during the cyclization of amides *I*. The hydrolysis is significant, as it was also the case with esters of substituted hydantoic acids[4], in the cyclizations of the most slowly cyclizing compounds. This result was confirmed by analysis of the reaction products of the cyclization of com-

pounds *Ia–Ic*. In the case of amide *Ia*, 66 ± 4% yield of hydantoin *IIIa* is obtained. from the amide *Ib* the yield is 75 ± 10% *IIIa*. This means that methyl group at 1 position of the hydantoinamide molecule retards the cyclization as much as its hydrolysis (Table VI). No hydrolysis was observed in the cyclization of amide *Ic*,



SCHEME 1

Amides of hydantoic acid undergo the cyclization more slowly than the corresponding esters (by several orders of magnitude), hence the hydrolysis of the primary hydantoin is far more significant. The hydantoin *IIIb* has pK_A 9, so that already in mildly basic medium it is transformed into the anion, which is hydrolyzed very slowly. The hydrolysis rate of hydantoin *IIIb* is slower than the cyclization rate of amide *Ic* by at least one order in all the cases. The same is true of the other hydantoins, which have the proton at the N(3) atom (the hydantoins formed by the cyclization of amides *Ia–Id*).

The hydrolysis rate of 1,3-dimethylhydantoin (*IIId*) increases with the square of hydroxyl ion concentration, whereas the cyclization rate only increases linearly. Hence the ratio of rates of the two reactions depends on hydroxyl ion concentration. In the case of 3,5-dimethylhydantoinamide (*Ie*), which undergoes relatively fast cyclization, the cyclization rate was measured at low concentrations of hydroxyl ion (0·01 – 0·03 mol l^{-1}), when the hydrolysis rate is lower than the cyclization rate by about one order of magnitude. 3,5-Dimethylhydantoinmethylamide (*If*) is cyclized about 15 times more slowly, that is why its cyclization rate was measured at higher hydroxyl ion concentrations (above 0·1 mol l^{-1}). In this medium, the hydrolysis rate is several times higher than the cyclization rate. This is a system of consecutive reactions, and the absorbance change is defined by Eq. (*1*). The cyclization rate constant k_2 was determined from the linear section of the time dependence of log $(A_t - A_\infty)$ (ref.[27]) and the hydrolysis rate constant k_h from the initial non-linear section of the dependence (Fig. 1). The rate constant found for the hydrolysis (k_h = 0·28 l^2 mol^{-2} s^{-1}) is – within experimental error – identical with that found

for the hydrolysis of the separately prepared 1,3-dimethylhydantoin (*IIId*) (k_h = = 0·24 l² mol⁻² s⁻¹).

$$A_t - A_\infty = \alpha \cdot e^{-k_h t} + \beta \cdot e^{-k_2 t} \qquad (I)$$

The hydrolysis rate of 3-phenylhydantoins *IIIe* and *IIIf* exhibits a linear increase with increasing hydroxyl ion concentration and so does also the cyclization rate of amides *Ig* and *Ih*, hence the rate constant ratio cannot be affected by the hydroxyl ion concentration. In the case of 3-methyl-5-phenylhydantoinamide (*Ig*), the hydrolysis rate constant of its cyclization product (hydantoin *IIIf*) is about 5 times lower than the cyclization rate constant. The rate constants of these consecutive reactions were determined in the same way as those in the previous case. The hydrolysis rate constant of the hydantoin *IIIf* determined by the above-described way from the cyclization kinetics of amide *Ig* is k_h = 0·84 l² mol⁻² s⁻¹; ref.[28] gives for the same reaction the rate constant value k_h = 0·9 l² mol⁻² s⁻¹. In the case of the cyclization of amide *Ih*, the difference between the cyclization rate constant and the hydrolysis rate constant of the hydantoin formed was so small, that it was impossible to obtain a reliable value of the hydrolysis rate constant from the non-linear section of the time dependence of log $(A_t - A_\infty)$ (the rate constant values varied from 0·7 to 1·3 l² . . mol⁻² s⁻¹).

Cyclization of Substituted Hydantoinamides in Methanolic Solution of Sodium Methoxide

The reaction described in Scheme 2 can take place in this cyclization. The methanolysis rate of amides *I* is independent of polar effects of the R^2 and R^3 substituents, sterical effects of these substituents cause a decrease in the methanolysis rate and an increase of the cyclization. The ratio of the cyclization rate constants in water and in methanol at the same concentration of the lyate ions (*i.e.* $k_{OH^-}/k_{CH_3O^-}$) is almost

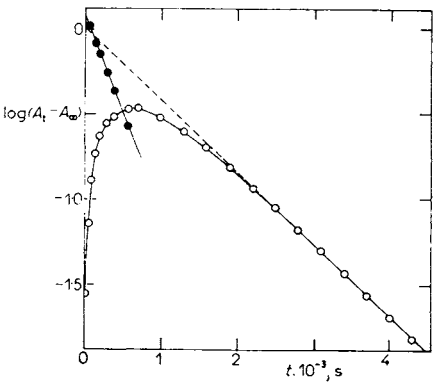
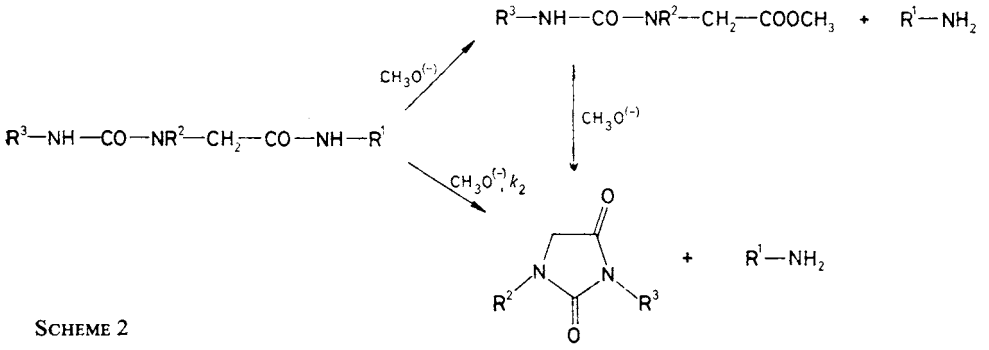


FIG. 1

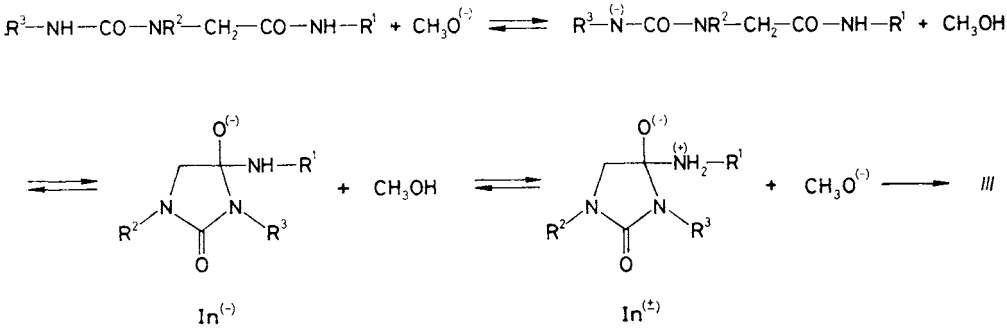
Estimation of the rate constants of slow cyclization of amide *If* to hydantoin *IIId* (k_2, ○) and of subsequent fast hydrolysis of hydantoin *IIId* (k_h, ●) in 0·1 mol l⁻¹ sodium hydroxide solution

constant for the amides *Ia–If* (Table VI), although the reactivity difference of the amides almost makes 2·5 orders of magnitude. Therefrom it can be inferred that the methanolysis can only make itself felt with the least reactive amides and to a small extent only. The rate constants found thus correspond to the cyclization rate constants of the amides.



SCHEME 2

The rate and way of splitting off of the ureido or amino group from the tetrahedral intermediate are decisive for the course of the cyclization reactions of amides *I* both in water and in methanol. The ureido group is split off relatively easily in the form of anion, whereas splitting off of amino group in the form of anion requires high energy. Therefore, amino group is split off as neutral. On the basis of this consideration it is possible to suggest the cyclization reaction mechanism (Scheme 3). This conclusion is also supported by the results of studies of the base-catalyzed hydrolysis of substituted formanilides[29], where 4-nitroaniline was split off with only slight assistance of water, whereas in the case of the far more basic non-substituted formanilide the proton transfer is practically complete in the transition state of the splitting off of aniline.



SCHEME 3

The pK_A value of dissociation of the tetrahedral intermediate $In^{\pm}$ (Scheme 3) can be calculated on the basis of structure-reactivity correlations[30,31]: for dissociation of aliphatic ammonium ions it is $\varrho_I = -8{\cdot}4$; methylammonium ion has pK_A 10·66; gradual substitution of protons in methyl group of the methylammonium ion by the groups $-CH_2NHCONH_2$ ($\sigma_I = 0{\cdot}07$), $-NHCONH_2$ ($\sigma_I = 0{\cdot}23$), $-OH$ ($\sigma_I = 0{\cdot}24$) and correction for the presence of $-O^{(-)}$ group instead of the $-OH$ group ($\sigma_I = -0{\cdot}35 \pm 0{\cdot}05$; the value is assessed from the difference between the dissociation constants of the structures $=C(O^{(-)})NH_3^{(+)}$ and $=C(OH)NH_3^{(+)}$ from ref.[32]) finally gives the pK_A value of the intermediate $In^{\pm}$ about 11·0, *i.e.* this intermediate is stable enough to be able of existence.

Except for the amides *Ig* and *Ih*, the rate constant k_{obs} of the cyclization increases linearly with the lyate ion concentration. Hence, the rate-limiting step must consist in the reaction of the negatively charged molecule. In this case, the rate-limiting step is the cyclization of anion of the starting amide to the negatively charged intermediate In^-.

For the amides *Ig* and *Ih* the dependence of $\log k_{obs}$ on $\log [CH_3O^{(-)}]$ was not linear. The decrease of the slope of this dependence with increasing methoxide ion concentration can have two reasons: *a*) with increasing methoxide ion concentration, the concentration of anion of the starting substance begins to exceed that of its neutral form; *b*) the rate-limiting step is gradually changed in favour of the splitting of the intermediate $In^{\pm}$ to the product.

The empirical kinetic equation reads as follows:

$$k_{obs} = a[CH_3O^{(-)}]/(b + c[CH_3O^{(-)}]) . \qquad (2)$$

For the two cases we can derive kinetic equations (*3*)–(*5*), where SH means the substrate.

1.

$$SH + CH_3O^{(-)} \overset{K_1}{\rightleftharpoons} S^{(-)} + CH_3OH \xrightarrow{k_1} \longrightarrow \text{Product} + CH_3O^{(-)} \qquad (A)$$

$$k_{obs} = k_1[CH_3O^{(-)}]/(K_1^{-1} + [CH_3O^{(-)}]) \qquad (3)$$

$$pK_A(SH) = pK(CH_3OH) - \log K_1 . \qquad (4)$$

2.

$$SH + CH_3O^{(-)} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} In^- + CH_3OH \overset{K_2}{\rightleftharpoons} \rightleftharpoons In^{\pm} + CH_3O^{(-)} \xrightarrow{k_2} \text{Product} + CH_3O^{(-)} \qquad (B)$$

$$k_{obs} = k_1k_2K_2[CH_3O^{(-)}]/(k_{-1}[CH_3O^{(-)}] + k_2K_2) . \qquad (5)$$

The second explanation (*i.e.* the change in the rate-limiting step) is more likely, because: *a*) the difference between the pK_A values of amides type *I* in water and methanol is about 4 (ref.[33]); from Eqs (*3*) and (*4*) it was calculated for compound *Ih* in methanolic solution $pK_A = 16{\cdot}8$ to $16{\cdot}9$, hence in water it should be about 13. But, the cyclization of compound Ih in aqueous solutions of hydroxide exhibits no decrease in the slope of dependence $\log k_{obs}$ *vs* $\log [OH^-]$ even at hydroxyl ion concentrations above 0·1 mol l^{-1}; *b*) the pK_A value of 4-nitrophenylurea is 17·9 (ref.[33]), and it is very unlikely that the pK_A of the phenyl derivative *Ih* were by as much as one order of magnitude lower.

Substitution of methyl by phenyl group at the 5 position (the amides *Ig* and *Ih*) results in acceleration of the reverse decomposition of the intermediate In^- (the $—CONC_6H_5^{(-)}$ group is split off more easily than $—CONR^{(-)}$) and in somewhat more difficult protonation of —NHR group in formation of the intermediate $In^{\pm}$. At a sufficiently high methoxide ion concentration, the activated complex of decomposition of the intermediate $In^{\pm}$ into the product will have higher energy than that for the cyclization of the anion of starting amide, and this step (whose rate is independent of methoxide ion concentration) will become rate-limiting.

For the amides *Ia*–*If*, which have the substituent at N(5) nitrogen atom $R^3 = H$ or CH_3, the dependences $\log k_{obs}$ *vs* $\log [CH_3O^{(-)}]$ were linear up to the highest methoxide ion concentration used (about 1 mol l^{-1}). This means that the activity coefficients of the transition state and of the methoxide ion are changing in the same way with increasing concentration of methoxide ion. This fact is obviously due to the negative charge being predominantly localized at oxygen atom in both the transition state of the rate limiting step and the methoxide ion.

Cyclization of Substituted Nitriles of Hydantoic Acids in Aqueous Hydroxide and Methanolic Methoxide Solutions

Substituted 4-iminohydantoins form the cyclization products from the substituted ureidoacetonitriles *IIa*–*IIi* in anhydrous medium. These compounds are hydrolyzed to the corresponding hydantoins[34] in aqueous media below pH 7. The iminohydantoins are considerably unstable and were not prepared in the purity needed for elemental analysis. Two methods were used of identification of iminohydantoins: *1.* Iminohydantoins are relatively strong bases, hence it was possible (in the case of 3-methyl-, 3-phenyl-, 1,3-dimethyl-, and 1-methyl-3-phenyl-4-iminohydantoins, which are formed by cyclization of the nitriles *IIb*, *IIc*, *IIe*, and *IIf*, respectively) to determine the pK_A values of their conjugated acids spectrophotometrically (Table VII). The other iminohydantoins formed exhibit too small differences in spectra of the bases and conjugated acids for the pK_A to be measured. *2.* The ureidonitriles *IIg*–*IIi* were cyclized in diluted solutions of sodium hydroxide or methoxide, and the cyclization course was followed by means of spectrophotometry. After the cyclization was

finished, the reaction mixture was acidified with hydrochloric acid and heated to boiling 20 min. The hydantoins formed were isolated and identified by their mixed melting points with independently prepared samples or by elemental analyses (Table V).

In the case of 3-phenyl-4-iminohydantoin (the cyclization product from the nitrile *IIc*) we studied the hydrolysis kinetics of the imino group in acidic solutions of $10^{-4}-10^{-2}$ mol l^{-1} hydrochloric acid. The observed rate constant $k = (2{\cdot}6 \pm 0{\cdot}2) . 10^{-5}$ s^{-1} is independent of pH of the medium in accordance with the fact that – at the pH values given – iminohydantoin is practically completely protonated, and the hydrolysis goes through the protonated form.

The cyclization mechanism of nitriles *II* is described by Scheme 4. The cyclization rate-limiting step consists in the attack of nitrile group by negatively charged nitrogen atom. In all the cases the cyclization proceeded as a pseudomonomolecular reaction, and the rate constant observed (k_{obs}) increased linearly with the concentration of lyate ion of the solvent (Eq. (*6*)). The rate constant values are presented in Table VII.

$$k_{obs} = k_{LO^-}[LO^{(-)}] = k_2 K[LO^{(-)}] \qquad (6)$$

The Effects of Structure of Reactants and of Medium on the Cyclization Rate

The cyclization rate of substituted amides and nitriles of hydantoic acid is lower

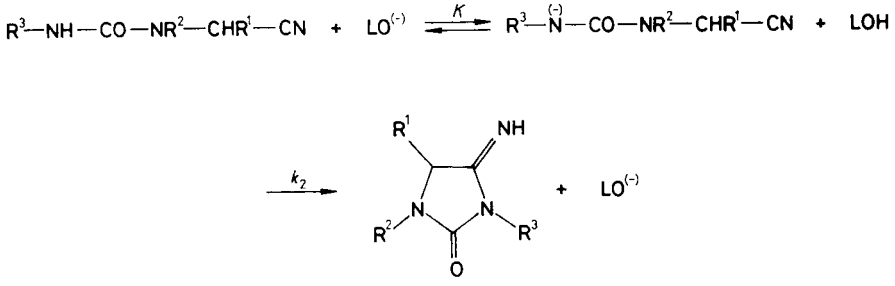
TABLE VII

The rate constants k_2[a] (1 mol^{-1} s^{-1}) of base-catalyzed cyclization of substituted nitriles of hydantoic acid *II* in aqueous sodium hydroxide and methanolic sodium methoxide solutions at 25°C. The pK_A values of the protonated 4-iminohydantoins formed by the cyclization of nitriles *II*

Nitrile	R^1	R^2	R^3	k_2 (water)	k_2 (methanol)	pK_A
IIa	H	H	H	$3{\cdot}92 . 10^{-3}$	$1{\cdot}47 . 10^{-4}$	—
IIb	H	H	CH_3	$7{\cdot}60 . 10^{-2}$	$2{\cdot}40 . 10^{-3}$	6·5
IIc	H	H	C_6H_5	$2{\cdot}38 . 10^{1}$[b]	$3{\cdot}25 . 10^{-1}$	6·1
IId	H	CH_3	H	$7{\cdot}60 . 10^{-2}$	—	—
IIe	H	CH_3	CH_3	1·87	$1{\cdot}58 . 10^{-1}$	6·9
IIf	H	CH_3	C_6H_5	$1{\cdot}24 . 10^{3}$[b]	$7{\cdot}23 . 10^{1}$	6·5
IIg	C_6H_5	H	H	$1{\cdot}57 . 10^{-1}$	$3{\cdot}92 . 10^{-3}$	—
IIh	C_6H_5	H	CH_3	3·13[b]	$4{\cdot}79 . 10^{-2}$	—
IIi	C_6H_5	H	C_6H_5	$1{\cdot}19 . 10^{3}$[b]	$1{\cdot}08 . 10^{1}$	—

[a] The maximum error in k_2 is ±10%; [b] measured in aqueous buffers.

in methanolic solutions of sodium methoxide than in aqueous solutions of sodium hydroxide (at the same lyate ion concentrations) by the factor of 10–100. The greatest differences in the cyclization rates were found for the substrates carrying phenyl group at the N(5) position. The substituents being the same, amides react more slowly than nitriles by the factor of 10–100. Again the greatest difference was found with the 5-phenyl derivatives. As compared with the esters[4], the amides are cyclized more slowly by 3–4 orders of magnitude. Methyl groups at 2 or 3 positions increase 20–50 times the cyclization rate, in the case of nitriles a methyl group at 5 position also causes an about 20 fold acceleration. The acceleration is obviously due to the decreased number of possible conformers in the initial state. The substitution of hydrogen by methyl group at 5 position of the amides *I* causes a smaller acceleration than the same change in the nitriles *II*. The lowest acceleration of the cyclization, caused by introducing methyl group into 5 position, was observed with the substituted methylamides of hydantoic acids (about 5–15×).



SCHEME 4

In addition, the substituents at 5 position also affect (by polar effects) the preequilibrium and formation of the intermediate as well as (by sterical effects) the formation of the tetrahedral intermediate in the case of amides. The substitution of hydrogen by methyl group at 5 position of nitriles *II* causes practically the same acceleration as the introduction of methyl group into 3 position, which could mean a small polar effect of the methyl group. The greatest sterical effect was observed with the methylamides *Id*, *If*, and *Ih* (all adjacent atoms in the tetrahedral intermediate carry substituents) which are cyclized by one order more slowly than the amides *Ic*, *Ie*, and *Ig*.

Introduction of phenyl group instead of hydrogen at 5 position of the amides *I* and nitriles *II* increases the cyclization rates by the factor of 200–400 and about 10^4, respectively. In this case the main reason of the acceleration of cyclization consists in the increase of concentration of the reactive anion due to the polar effect of phenyl group. The lower acceleration effect observed with the amides (as compared with that of nitriles) is obviously due to sterical requirements during formation of the tetrahedral intermediate.

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