KINETICS OF ACID-CATALYZED CYCLIZATION OF SUBSTITUTED HYDANTOINAMIDES TO SUBSTITUTED HYDANTOINS

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The kinetics of acid-catalyzed cyclization of the hydantoinamides type R^3—N(5)H—CO—N(3)R^2—CH_2—CO—N(1)HR^1 (R^1, R^2, R^3 = H and/or CH_3) has been studied in 0·5 to 5 mol l^{-1} hydrochloric acid. The cyclization rate is limited by the rate of the attack of nitrogen atom N(5) on the carbon atom of the protonated amide group. The dissociation constants of the protonated hydantoinamides and rate constants of their cyclizations have been determined. Replacement of hydrogen atom by methyl group at the N(5) nitrogen atom accelerates the cyclization about two times, the same substitution at N(3) accelerates about 50×, whereas at N(1) it results in a 300 fold retardation. With the hydantoinamides having $R^3 = CH_3$, the cyclization rate of the protonated hydantoinamide increases with increasing concentration of hydrochloric acid, whereas with the other derivatives this value is independent of the acid concentration.

Our previous report[1] dealt with the kinetics of base-catalyzed cyclization of hydantoinamides in aqueous and methanolic media. The aim of this present work is a study of kinetics and mechanism of the acid-catalyzed cyclization of hydantoinamides and comparison with the base-catalyzed cyclization. As the phenyl group at the N(5) nitrogen atom and methyl at N(1) strongly retard the cyclization, thus allowing side reactions (especially hydrolysis) to make themselves felt, it was only possible to measure the cyclization rate of the hydantoinamides *Ia*–*Id*:

$$R^3\text{—NH—CO—N}R^2\text{—CH}_2\text{—CO—NH—}R^1$$

Ia, $R^1 = R^2 = R^3 = H$
Ib, $R^1 = R^3 = H$; $R^2 = CH_3$
Ic, $R^1 = H$; $R^2 = R^3 = CH_3$
Id, $R^1 = R^2 = R^3 = CH_3$.

EXPERIMENTAL

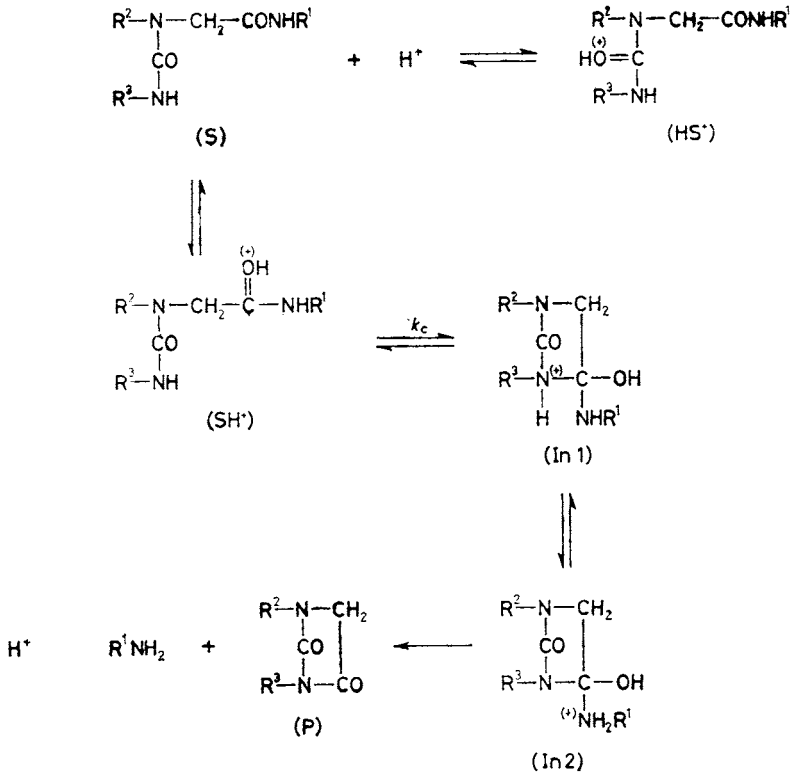
The hydantoinamides *Ia* through *Id* and the corresponding hydantoins were prepared by earlier-described methods[1]. The kinetic measurements were carried out in aqueous solutions of 0·5 to 5 mol l^{-1} hydrochloric acid at 25°C with a VSU 2P spectrophotometer (Zeiss, Jena). Hydrochloric acid (2 ml) was placed in a 1 cm quartz cell, and 20 µl aqueous solution of 10^{-1} to

10^{-2} mol l^{-1} amide was added thereto, whereupon the absorbance increase was measured at 230 nm. The cyclization rate constant k_{exp} was obtained graphically from the relation $k_{exp}t = -2{\cdot}3 \log (A_\infty - A_t) + \text{const}$, the Guggenheim method[2] being used for the slow reactions.

RESULTS AND DISCUSSION

In all the cases the cyclization was a pseudo-first-order reaction, and the absorbance of the reaction product did not change after the cyclization had finished.

The dependence of k_{exp} on hydrochloric acid concentration is given in Fig. 1 for the hydantoinamide *Ia*. At the beginning the increase of k_{exp} with increasing hydrochloric acid concentration is progressive (gradually steeper and steeper), which is due to the fact that the acidity of medium increases faster than the proton concentration. At higher concentrations of hydrochloric acid the slope is gradually diminished, because the protonated amide *Ia* begins to predominate in the reaction mixture. The cyclization reaction mechanism is presented in Scheme 1.



In the last reaction step, plus between H^+ and $R^1 NH_2$ is missing.

SCHEME 1

The intermediate In 1 is a much stronger acid than the intermediate In 2, so the proton transfer is energetically favourable. The intermediate In 2 rapidly splits off ammonia or methylamine to give the product P. The rate-limiting step of the product formation consists in the attack of the N(5) nitrogen atom on the carbon atom of the protonated amide group. From the Scheme 1 it is possible to derive Eqs (*1*) and (*2*) for the cyclization rate with the presumption of equality of the activity coefficients γ_{SH^+} and γ_{HS^+}. The K_a value denotes the overall equilibrium constant of formation of the protonated forms HS^+ and SH^+ from the substrate S. The protonation of both amide and ureide group follows the amidic H_a acidity function[3], where $H_a = -\log h_a$, and the proton becomes attached to carbonyl oxygen atom in both cases.

$$v = k_{exp} c_S = k_c[SH^+] = k_T([SH^+] + [HS^+]) = k_T h_a c_S/(K_a + h_a) \qquad (1)$$

$$K_a = [S]\,\gamma_S a_{H^+}/([HS^+]\,\gamma_{HS^+} + [SH^+]\,\gamma_{SH^+}) =$$
$$= ([S]/([SH^+] + [HS^+]) \,.\, (a_{H^+}\gamma_S/\gamma_{SH^+}) =$$
$$= h_a[S]/([HS^+] + [SH^+]) \qquad (2)$$

The dependence of the cyclization rate constant k_T on medium is given by Eq. (*3*).

$$k_T = k_T^0 \gamma_{SH^+}/\gamma^* = k_T^0 h^*/h_a \qquad (3)$$

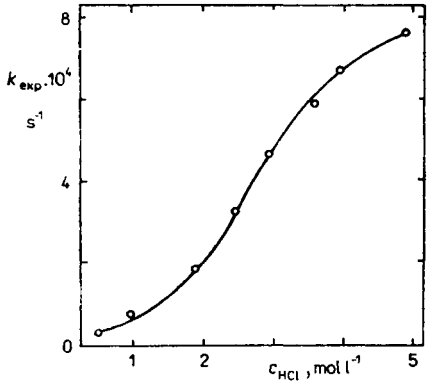


FIG. 1

The dependence of the rate constant k_{exp} (s^{-1}) of the cyclization of 3,5-dimethylhydantoinamide (*Ia*) on concentration of hydrochloric acid

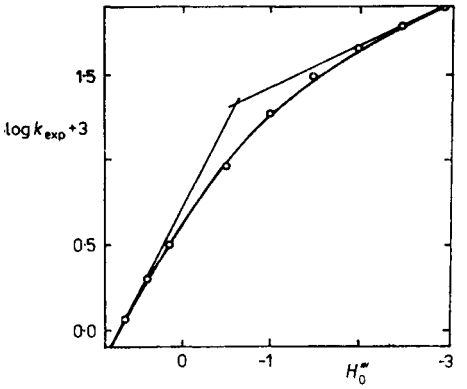


FIG. 2

The dependence of $\log k_{exp}$ of the acid-catalyzed cyclization of 3,5-dimethylhydantoinamide (*Ic*) on the acidity funcion H_0'''. The curve was calculated from Eq. (*4*) and the values of Table I. The asymptotes represent the limit cases calculated according to Eqs (*5*) and (*7*)

The acidity functions of the activated complex and of the protonated amide are defined as $h^* = a_{H^+}\gamma_S/\gamma^*$ and $h_a = a_{H^+}\gamma_S/\gamma_{SH^+}$, respectively. Introduction into Eq. (*1*) gives Eq. (*4*) for the rate constant k_{exp}.

$$k_{exp} = k_T^0 h^*/(K_a + h_a) \tag{4}$$

Equation (*5*) applies to the region of $h_a \ll K_a$, and the cyclization rate increases linearly with the proton concentration: $v = k_2[H^+][S]$. The bimolecular rate constant k_2 of the proton-catalyzed cyclization is given by Eq. (*6*). If $h_a \gg K_a$, then the rate constant k_{exp} is given by Eq. (*7*).

$$k_{exp} = k_T^0 h^*/K_a = k_T^0[H^+]/K_a \tag{5}$$

$$k_2 = k_{exp}/[H^+] = k_T^0/K_a \tag{6}$$

$$\log k_{exp} = \log k_T^0 + H_a - H^* \tag{7}$$

Structure of the activated complex of the cyclization rate-limiting step resembles that of the intermediate In 1 (Scheme 1). For $R^3 = H$ (amides *Ia*, *Ib*) the intermediate has a character of the protonated secondary amine, for $R^3 = CH_3$ that of the protonated tertiary amine. The protonation of substituted N-methylanilines follows the H_0 acidity function[4] and that of substituted N,N-dimethylanilines the H_0''' function[5]. The experimental values of the rate constants k_{exp} showed a very good accordance with the calculated ones, if the h_0 and h_0''' values (instead of h^*) were used for the amide *Ia*, *Ib* and amides *Ic*, *Id* (Fig. 2), respectively, in Eq. (*4*). The calculated values of the rate constants k_2 and k_T^0 and the pK_a values are given in Table I.

As the acidity functions H_a and H_0 are almost identical in the concentration range of hydrogen chloride from 0·5 to 5 mol l^{-1}, the k_T values of the amides *Ia* and *Ib*

TABLE I

The pK_a values of protonated hydantoinamides *Ia*—*Id* and the rate constants k_2 (l mol^{-1} s^{-1}), k_T^0 (s^{-1}), and k_c^0 (s^{-1}) of their cyclization in aqueous solutions of hydrochloric acid at 25°C

Amide	pK_a	$10^5 . k_2$	$10^5 . k_T^0$	$10^3 . k_c^0$
Ia	−1·4	5·3	130	3·7
Ib	−0·7	11	56	8·0
Ic	−0·35	550	1 200	360
Id	−0·35	1·8	4·0	1·6

do not practically change with the acid concentration. In the case of the hydantoinamides *Ic* and *Id*, the k_T values rapidly increase with the acid concentration (the change in log k_T is determined by the difference $H_a - H_0'''$). Therefore, the cyclization rate of these amides increases with hydrogen chloride concentration even in the media where the predominant part of the substrate is present in the protonated form.

The pK_a values measured represent the acidity of both protonated forms of the substrate (SH^+ and HS^+, Scheme 1). For determination of the cyclization rate constant k_c^0 related to the concentration of the SH^+ form being cyclized it is necessary to know the population of this SH^+ form in the equilibrium mixture of the protonated substances. The dissociation constant of the SH^+ form of the protonated hydantoinamide can be assessed by means of LFER. From the values of the dissociation constants of the protonated acetamide (−0·93), chloroacetamide (−2·80), and cyanoacetamide (−3·69) (ref.[6]) and the values of σ_I substituent constants of the substituents —$NHCONH_2$ (0·23), —Cl (0·47), and —CN (0·63) (ref.[7]) it can be calculated $pK_a = -1·9$ for the cyclized protonated form of hydantoinamide *Ia* (SH^+). From the measured overall dissociation constant of protonation (Table I) and pK_a value of SH^+ form it is then possible to calculate $pK_a = -1·6$ for the HS^+ form and population (36%) of the SH^+ form (being cyclized) in its mixture with the HS^+ form. In the case of 3-methylhydantoinamide (*Ib*) the HS^+ form has $pK_a = -0·75$ and the population of the SH^+ form is 7%, for the amide *Ic* it is $pK_a = -0·35$ and the population of SH^+ is 3%. All these calculations are correct under the presumption that the basicity of amidic group does not change on substitution of hydrogen atoms by methyl groups at the N(3) and N(5) nitrogen atoms. The last column of Table I presents the cyclization rate constant values k_c^0 of the reactive form SH^+ in the tautomeric mixture. Practically the same k_c^0 constants can be obtained from Eq. (7), if the pK_a value calculated for the reactive SH^+ form

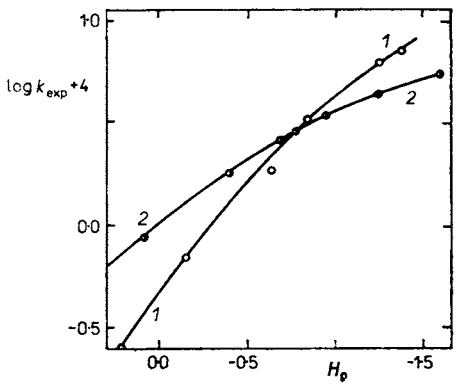


FIG. 3

The dependence of log k_{exp} of the acid-catalyzed cyclization of the hydantoinamides *Ia* (*1*) and *Ib* (*2*) on the acidity function H_0. The curves were calculated from Eq. (*4*) and the values of Table I

(−1·9) is used instead of the pK_a values found for the tautomeric mixtures of SH^+ and HS^+ forms.

At low concentrations of hydrogen chloride, 3-methylhydantoinamide (*Ib*) reacts twice as fast as the non-substituted amide *Ia*; at the highest HCl concentration used (5 mol l^{-1}), however, it reacts more slowly by the factor of 2·5 (Fig. 3). Replacement of hydrogen atom at N(3) atom by methyl group facilitates the cyclization in similar way as in the case of the base-catalyzed cyclization[1], but the acceleration is substantially less in the case of the acid catalysis. The methyl group at N(3), at the same time, increases the basicity of ureide group which is, therefore, protonated predominantly. At high hydrogen chloride concentrations, when the main part of the substrate is protonated, the population of the SH^+ reactive substrate form is about five times lower than that of the hydantoinamide *Ia* and, therefore, the cyclization of the amide *Ib* is slower. The proportion of the reactive SH^+ form in protonated 3,5-dimethylhydantoinamide (*Ic*) is still lower, nevertheless, the amide *Ic* cyclizes far faster than *Ia* and *Ib* in the whole range of hydrogen chloride concentrations. The methyl group at N(5) nitrogen atom stabilizes, by its polar effect, the positive charge in the activated complex and thus accelerates the cyclization. As compared with the amide *Ib*, the amide *Ic* cyclizes about 50 times faster in dilute hydrochloric acid.

When the hydrogen atom of the amidic group is replaced by methyl group ($R^1 = CH_3$), the reaction is slowed down by the factor of 300. This is a deceleration which is by about one order of magnitude greater than that caused by the same substitution in the base-catalyzed cyclization[1]. The reason can be either in a more energy-demanding formation of the activated complex than in the case of the attack of negatively charged nitrogen atom of ureide group on the amidic carbon atom (so the structure of the activated complex is closer to that of the tetrahedral intermediate, and sterical effects of both the methyl groups, R^1 and R^2, are more significant) or in a less easy approach of solvating water molecules to the negatively charged nitrogen atom in the activated complex.

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