NITROSOALKYLUREAS WITH QUATERNARY NITROGEN ATOM. COMMUNICATION 3. STUDY OF REACTION KINETICS OF DECOMPOSITION OF CHOLINE-LIKE NITROSOALKYLUREAS IN AN AQUEOUS MEDIUM

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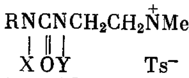
UDC 541.127:542.92:547.495.4

The antitumorigenic action of nitrosoalkylureas (NAU) is due to the ability of these compounds to decompose under the organism conditions to form reactive cytotoxic particles, which are derivatives of isocyanates and carbocations with carbamoylating and alkylating action, respectively [1].

In the present work, we studied the reaction kinetics of the decomposition of a new group of choline-like NAU (I)-(III) [2] under nearly physiological conditions at different temperatures and pH values of the medium



$$R\underset{X}{\underset{|}{N}}\underset{O}{\underset{\|}{C}}\underset{Y}{\underset{|}{N}}CH_2CH_2\overset{+}{N}Me_3 \qquad Ts^-$$

(I)—(III)

R = Me, X = NO, Y = H (I); R = CH_2CH_2Cl, X = NO, Y = H (II); R-cyclo-C_6H_{11},
X = H, Y = NO (III).

The reactions were carried out in 1/15 M phosphate buffer solutions. The dependence of the spectrophotometrically determined analytical concentration of (I)-(III) $[NAU_{anal}]$ on time (τ) is linear in ln $([NAU_{anal}]/[NAU_{anal}]_0)$ vs τ coordinates (Fig. 1), where $[NAU_{anal}]_0$ is the initial concentration of NAU. Table 1 lists the rate constants of the pseudofirst-order reaction k_{obs} for reactions of (I)-(III) in a weakly alkaline medium at different pH values of the buffer solution at 37°C. In their order of magnitude, the k_{obs} values are close to those for 1-methyl-1-nitrosourea [3], 1,3-bis-(2-chloroethyl)-1-nitrosourea [4], and aromatic NAU [5].

The coefficients of Eq. (1) (Table 2), which can be rewritten in the form of (2), were found from the dependence of log k_{obs} on pH (Fig. 2). The coefficient m

$$\lg k_{obs} = m\mathrm{pH} + b \tag{1}$$

$$k_{obs} = 10^{(m\mathrm{p}K_w+b)} \cdot [OH^-]^m \tag{2}$$

represents the order of the decomposition reaction with respect to the hydroxyl ion. From Eq. (2) and the expression for the rate constant of a bimolecular reaction k

$$\kappa = k_{obs}/[OH^-]^m = 10^{(m\mathrm{p}K_w+b)} \tag{3}$$

the corresponding values of k can be obtained (see Table 2). The overall course of the reaction in the pH 7.08-7.57 range is described by the equation

$$d[NAU_{anal}]/d\tau = -k[NAU_{anal}][OH^-]^m \tag{4}$$

The experimental data agree well with the process proceeding by the ElcB mechanism

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Institute of Chemistry, Ural Scientific Center, Academy of Sciences of the USSR, Sverdlovsk. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 553-557, March, 1985. Original article submitted January 5,1984.

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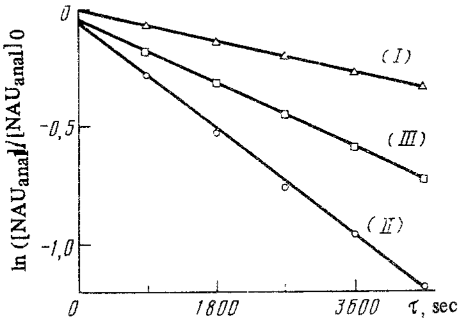


Fig. 1

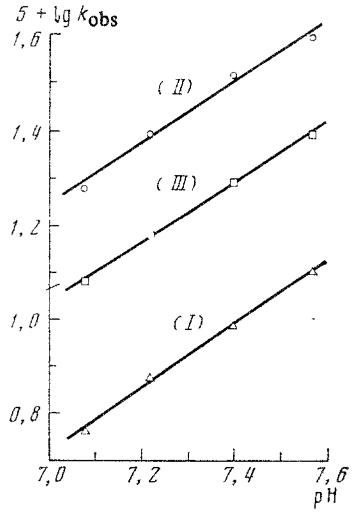


Fig. 2

Fig. 1. Kinetic curves of decomposition of (I)-(III), pH 7.22.

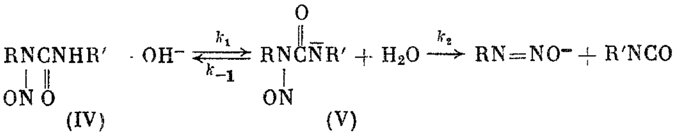
Fig. 2. pH-Dependence of log k_{obs} on decomposition reaction of (I)-(III).

TABLE 1. Rate Constants of First-Order Reaction k_{obs} for Decomposition of (I)-(III) at 37°C

Compound	pH	$k_{obs}\cdot10^4$, sec^{-1}	Compound	pH	$k_{obs}\cdot10^4$, sec^{-1}
(I)	7,08	0,588±0,006	(II)	7,40	3,3±0,2
	7,22	0,751±0,005		7,57	3,9±0,1
	7,40	0,975±0,007	(III)	7,08	1,22±0,01
	7,57	1,27±0,01		7,22	1,515±0,009
(II)	7,08	1,90±0,05		7,40	1,96±0,09
	7,22	2,50±0,08		7,57	2,46±0,04

TABLE 2. Rate Constants of Bimolecular Reaction and Coefficients of Equation (1), m, b

Compound	k, $liter^m\cdot sec^{-1}\cdot mole^{-m}$	m	b
(I)	2,40±0,03	0,67±0,01	9,0±0,1
(II)	4,6±0,2	0,64±0,05	8,3±0,3
(III)	2,29±0,02	0,62±0,01	8,32±0,08



$$\underset{\mathrm{(IV)}}{\mathrm{RN(NO)C(=O)NHR'}} + \mathrm{OH^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathrm{(V)}}{\mathrm{RN(NO)C(=O)\bar{N}R'}} + \mathrm{H_2O} \xrightarrow{k_2} \mathrm{RN{=}NO^-} + \mathrm{R'NCO}$$

The spectrophotometrically determined concentration of $[NAU_{anal}] = [NAU\text{–}H] + [NAU^-]$ is the sum of concentrations of the neutral form of nitrosoalkylurea [NAU–H] (IV) and its conjugate base $[NAU^-]$ (V). The sum of the rates of change in [NAU–H] (5) and $[NAU^-]$ (6) is equal to the rate of change in $[NAU_{anal}]$ (7). By comparing the kinetic equations and equilibrium conditions at the first stage (8), the dependence of k_{obs} on $[OH^-]$ (9) could be found.

$$d[\mathrm{NAU}-\mathrm{H}]/d\tau = -k_1[\mathrm{NAU}-\mathrm{H}][\mathrm{OH}^-] + k_{-1}[\mathrm{NAU}^-][\mathrm{H_2O}] \tag{5}$$

$$d[\mathrm{NAU}^-]/d\tau = -k_{-1}[\mathrm{NAU}^-][\mathrm{H_2O}] + k_1[\mathrm{NAU}-\mathrm{H}][\mathrm{OH}^-] - k_2[\mathrm{NAU}^-] \tag{6}$$

$$d[\mathrm{NAU_{anal}}]/d\tau = d[\mathrm{NAU}-\mathrm{H}]/d\tau + d[\mathrm{NAU}^-]/d\tau = -k_2[\mathrm{NAU}^-] \tag{7}$$

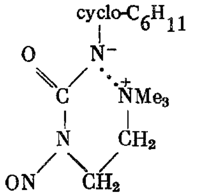
$$K_1^{eq} = [\mathrm{NAU}^-][\mathrm{H_2O}]/[\mathrm{NAU}-\mathrm{H}][\mathrm{OH}^-] \tag{8}$$

$$k_{obs} = k_2K_1^{eq}[\mathrm{OH}^-]/(K_1^{eq}[\mathrm{OH}^-] + [\mathrm{H_2O}]) \tag{9}$$

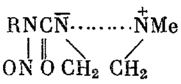
The first order with respect to the hydroxyl ion, previously observed in similar reactions [3, 5], is a particular case, when $K_1^{eq} \cdot [OH^-] << [H_2O]$. With increase in $K_1^{eq} \cdot [OH^-]$, the order of reaction with respect to the hydroxy ion should decrease, and at $K_1^{eq} \cdot [OH^-] >> [H_2O]$, it tends to zero, while k_{obs} asymptotically approaches k_2. This type of dependence was observed for the alkaline hydrolysis of O-aryl-N-phenylthiocarbamates [6].

For choline-like NAU, the order of the decomposition reaction of (I)-(III) with respect to the hydroxyl ion $m \approx 0.65$ indicates that $K_1^{eq} \cdot [OH^-]$ and $[H_2O]$ are comparable values; the dependence of log k_{obs} on pH should thus be nonlinear, but, nevertheless over a small range of pH changes, it is described well by Eq. (1). Since the value of $[OH^-]$ did not exceed the values used in the case of other classes of NAU [3, 4, 5], increase in $K_1^{eq} \cdot [OH^-]$ is due to increase in K_1^{eq}.

We used Eq. (8), and from the graph of the $1/k_{obs}$ vs $1/[OH^-] \equiv 10^{(pK_w - pH)}$ dependence and calculated the values of k_2, K_1^{eq}, and also the acidity constants $K_A = K_1^{eq}K_w/[H_2O]$ for (I)-(III) and found that the values of K_A for (I)-(III) are four orders of magnitude higher than those for 1,3-dimethyl-1-nitrosourea [3]. The cyclohexyl derivative (III) is a stronger acid than the methyl and chloroethyl derivatives (I), (II). This can be explained by the formation of a stabilized form of the NAU anion (VI)-(VIII); the stabilization conditions for (VIII) are thus more favorable than for (VI) and (VII).



(VIII)



R = Me (VI); R = CH_2CH_2Cl (VII).

The values of entropy ($\Delta S^{\#}$) and enthalpy of activation ($\Delta H^{\#}$) (see Table 4) could be calculated from a study of the decomposition kinetics of (I)-(III) in phosphate buffer at pH 7.22 at various temperatures (Table 4). The positive value $\Delta S^{\#}$ for (I) and (III) agrees with the fact that the reaction proceeds by the E1cB mechanism [5, 6]. Additional investigation is required to explain the negative values of $\Delta S^{\#}$ in the case of the chloroethyl derivative. It is possible that this is due to an ordered transition as the result of the reaction of the chlorine atom with the reaction center, which to a certain extent is confirmed by the formation of cyclization products during the decomposition of chloroethylnitrosoureas [8].

TABLE 3. Decomposition Rate Constants (k_2), Equilibrium Constants K_1^{eq}, and Acidity Constants of Anions (V)

Compound	$k_2 \cdot 10^4$, sec^{-1}	$K_1^{eq} \cdot 10^{-8}$	$K_A \cdot 10^8$, moles/liter
(I)	2,7±0,1	1,29±0,08	2,3±0,1
(II)	8,6±0,8	1,3±0,2	2,4±0,3
(III)	4,7±0,1	1,63±0,08	2,9±0,1

TABLE 4. Rate Constants of Pseudofirst-Order Reaction k_{obs} and Activation Parameters of Decomposition Reaction of (I)-(III) $\Delta S^{\#}$ and $\Delta H^{\#}$ (pH 7.22)

Compound	Reaction temp., °C	$k_{obs} \cdot 10^4$, sec^{-1}	$\Delta S^{\#}$, e.u.	$\Delta H^{\#}$, kcal/mole
(I)	32	0,33±0,01	7,3±0,4	26,3±0,9
	37	0,751±0,005		
	42	1,46±0,05		
	47	2,7±0,3		
(II)	32	1,44±0,08	−(22±5)	16±2
	37	2,50±0,08		
	42	4,2±0,3		
	47	5,3±0,9		
(III)	32	0,59±0,02	8±1	26±2
	37	1,515±0,009		
	42	3,1±0,1		
	47	4,6±0,4		

EXPERIMENTAL

The buffer solutions were prepared according to [9], the pH was controlled on the OP-208/1 apparatus (Radelkis). The decomposition was carried out in a thermostat U-15C, the change in the NAU concentration was controlled spectrophotometrically on a Specord UV-VIS apparatus from a change in the optical density of the solutions at 395 nm; the measurements were carried out every 15 min for 1.5 h. The experimental data were treated by the method of least squares.

CONCLUSIONS

1. The rate of decomposition of choline-like nitrosoalkylureas (NAU) was measured in aqueous solutions, and the activation parameters of the decomposition reaction were calculated.

2. Acidity constants of NAU and decomposition rate constants of the conjugate base were determined; choline-like NAU are stronger acids than aliphatic and aromatic NAU.

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