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NITROSOALKYLUREAS WITH A QUATERNARY NITROGEN ATOM.

6. STUDY OF REACTION KINETICS OF THE DECOMPOSITION IN AQUEOUS MEDIUM OF NITROSOALKYLUREAS BASED ON MONOQUATERNARY ALKYLAMMONIUM SALTS

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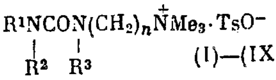
UDC 541.127:542.92:547.495.4

We have previously studied the reaction kinetics of the decomposition of choline-like dialkyl-substituted nitrosoalkylureas (NAU) (I)-(III) in aqueous medium [1]. The data obtained for the decomposition reactions of these compounds conform with the ElcB mechanism. In the present work, we studied the kinetics of the decomposition of NAU over a wide range of pH, and also the kinetics of decomposition of its analogs with a longer alkyl chain between the quaternary N atom and the urea-grouping (IV)-(VII), and the trialkyl substituted NAU (VIII) and (IX), having no amide proton, and therefore not decomposable by the ElcB mechanism



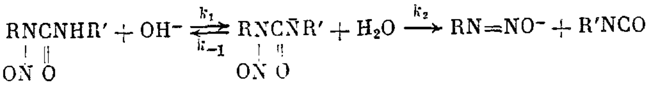
$$\mathrm{R^1\underset{\substack{|\\ R^2}}{N}CO\underset{\substack{|\\ R^3}}{N}(CH_2)_n\overset{+}{N}Me_3\cdot TsO^-}$$

(I)—(IX)

$R^1 = Me$, $R^2 = NO$, $R^3 = H$, $n = 2$ (I); $R^1 = (CH_2)_2Cl$, $R^2 = NO$, $R^3 = H$, $n = 2$ (II); $R^1 =$ cyclo-C_6H_{11}, $R^2 = H$, $R^3 = NO$, $n = 2$ (III); $R^1 = Me$, $R^2 = NO$, $R^3 = H$, $n = 3$ (IV); $R^1 =$ cyclo-C_6H_{11}, $R^2 = H$, $R^3 = NO$, $n = 3$ (V); $R^1 = Me$, $R^2 = NO$, $R^3 = H$, $n = 4$ (VI); $R^1 =$ cyclo-C_6H_{11}, $R^2 = H$, $R^3 = NO$, $n = 4$ (VII); $R^1 = R^3 = Me$, $R^2 = NO$, $n = 2$ (VIII); $R^1 = (CH_2)_2Cl$, $R^2 = NO$, $R^3 = Me$, $n = 2$ (IX).

The reactions were carried out in 1/15 M phosphate buffer solutions. As in [1], the dependence of the spectrophotometrically determined analytical concentration of (I)-(IX) $[NAU_{anal}]$ on time (τ) is linear in the $\ln([NAU_{anal}]/[NAU_{anal}]_0)$ vs. τ coordinates at all pH values ($[NAU_{anal}]_0$ is initial concentration of NAU). The pseudofirst order reaction rates k_{obs} for the reactions of (I)-(IX) at 37°C were calculated by the method of least squares (Table 1). With increased distance between the quaternary N atom and the nitrosoureido group, the stability of NAU (IV)-(VII) increases compared with (I)-(III), clearly due to the weakening of the electron-acceptor action of N^+. The trialkyl-substituted NAU (VIII) and (IX) are 20-100 times more stable than the corresponding disubstituted compounds (I) and (II).

The pH dependence of $\log k_{obs}$ for dialkyl-substituted (I)-(VII) is in general nonlinear; over the whole pH range, the tangent of the angle of slope of the tangential line to the curve (m), i.e., the order of the reaction with respect to OH^- [1], is equal to 0.5-0.7 on an average, and does not exceed 0.8. As well as the composition of the decomposition products of the dialkyl-substituted NAU, [2], these data do not contradict the ElcB mechanism



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

The realization of the following equation has been shown previously [1]

$$k_{obs} = \frac{k_2\cdot K_1^{eq}\ [OH^-]}{K_1^{eq}\ [OH^-] + [H_2O]} \tag{1}$$

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TABLE 1. Rate Constants of the Pseudofirst Order Decomposition Reaction $k_{obs} \cdot 10^4$, sec^{-1}, for (I)-(IX) at 37°C

Compound	pH						
	6.33	6.74	7,16	7,40	7,96	8,37	8,50
(I)	0,153±0,001	0,346±0,003	0,751±0,005*	0,975±0,007†	2,75±0,03	5,4±0,1	
(II)	1,00±0,01	1,66±0,01	2,50±0,08*	3,3±0,2†		7,5±0,5	
(III)	0,254±0,007	0,663±0,002	1,52±0,01*	1,96±0,09†	4,39±0,01	5,8±0,2	
(IV)	0,067±0,001	0,160±0,009	0,295±0,007	0,504±0,002	1,10±0,031	1,75±0,01	
(V)	0,148±0,002	0,37±0,02	0,68±0,02	1,01±0,01	1,9±0,1	2,0±0,1	
(VI)	0,038±0,003	0,081±0,003	0,190±0,002	0,306±0,003	0,838±0,005	1,42±0,01	
(VII)	0,098±0,004	0,23±0,01	0,425±0,009	0,719±0,005	1,36±0,04	1,56±0,04	
(VIII)					0,013±0,002	0,028±0,001‡	0,046±0,001
(IX)	0,175±0,005	0,172±0,003	0,169±0,005	0,176±0,002	0,169±0,002	0,167±0,006	

*pH 7.22 [2].

†Data from [2].

‡ pH 8.21.

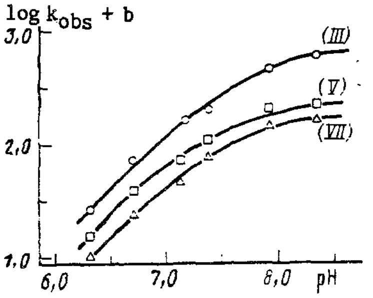


Fig. 1

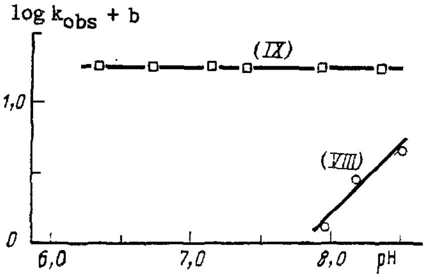


Fig. 2

Fig. 1. Dependence of the rate of decomposition of cyclohexylnitrosoureas (III), (V), (VII) on pH. The curves were plotted according to Eq. (1) and from data in Table 2.

Fig. 2. Dependence of rate of decomposition of trialkyl-substituted NAU (VIII), (IX) on pH.

TABLE 2. Decomposition Rate Constants of a Conjugate Base k_2, Equilibrium Constants K_1^{eq} and Acidity Constants K_A of Cyclohexylnitrosoureas

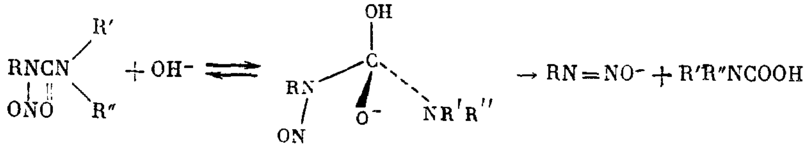
Compound	$k_2 \cdot 10^4$, sec^{-1}	$K_1^{eq} \cdot 10^{-8}$	$K_A \cdot 10^8$, mole/liter
(III)	6±2	1,0±0,2	1.9±0.4
(V)	2.3±0.3	1,8±0.3	3.2±0,5
(VII)	1,7±0,1	1.54±0,09	2.8±0,2

Equation (1) well describes the pH dependence of $\log k_{obs}$ of the decomposition reaction of the cyclohexyl derivatives (III), (V), and (VII) (Fig. 1). In the case of methyl and 2-chloroethylnitrosoureas, the dependence also has the form of a plateau in the alkaline region, but with decrease in pH, the experimental points deviate from the curve described by Eq. (1).

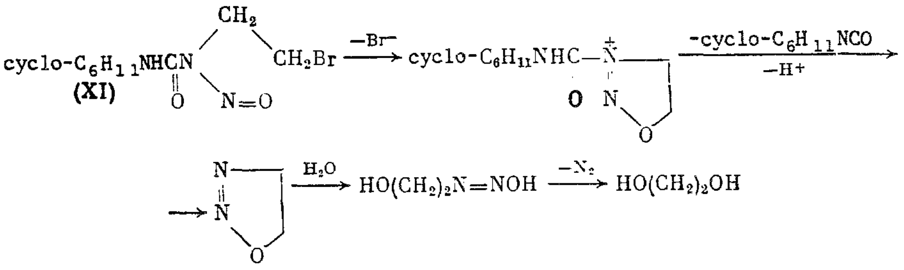
The values of k_2, K_1^{eq}, and also the acidity constants K_A for the cyclohexyl derivatives (III), (V), and (VII) (Table 2) were determined by the method of least squares and from the graph for the dependence $1/k_{obs}$ vs. $1/[OH^-] = 10(pK_w - pH)$, as in [1]. If we substitute the values of K_1^{eq} and OH^- into the tangential equation (2), obtained from expression (1) by differentiation with respect to $\log[OH^-]$, we can calculate the values of m for a given pH

$$m = \frac{[H_2O]}{K_1^{eq}[OH^-] + [H_2O]} \qquad (2)$$

The rate of decomposition of the trisubstituted NAU (VIII), (IX) reveals a further dependence on the concentration of the OH^- ions (Fig. 2). Thus, the order of the decomposition reaction with respect to OH^- for the methyl derivative (VIII) is close to unity which satisfies the BAc2 mechanism



The order with respect to OH^- for chloroethylnitrosourea (IX) is practically equal to zero, which was not observed previously for the decomposition reaction of chloroethylnitrosoureas in neutral and weakly alkaline media. Since the only difference between compounds (VIII) and (IX) consists in the type of the alkyl substituent R^1, it is natural to assume that the reason for the anomalous behavior of (IX) is the specific influence of the 2-chloroethyl grouping. Further investigations must be carried out to clarify the mechanism of this influence. However, the absence of ethylene glycol among the decomposition products of (IX) [2], makes it questionable whether the decomposition can proceed via alkylation by a chloroethyl radical at the O atom of the nitroso group, as has been proposed for the decomposition reaction of 1-(2-bromoethyl)-3-cyclohexyl-1-nitrosourea (XI), which is also of zero order with respect to the OH⁻ ion [3]


(XI)

EXPERIMENTAL

The synthesis of NAU is described in [4]. The buffer solutions were obtained according to [5]. The pH was monitored by using a Radelkis OP-208/1 digital pH meter. The change in the NAU concentration was followed spectrophotometrically on a SF-26 apparatus with a ShCh-1312 digital voltmeter at wavelengths corresponding to the λ_{max} of the compounds in the visible region.

CONCLUSIONS

1. The dependence of the rate of decomposition in aqueous solutions of dialkyl substituted nitrosoureas based on monoquaternary alkylammonium salts on pH conforms to the E1cB mechanism of decomposition.

2. A new compound of the chloroethylnitrosourea class has been discovered. Its rate of decomposition in neutral and weakly alkaline media is independent of pH.

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REPLACEMENT OF HALOGEN IN α-HALONITRO-COMPOUNDS OF THE ALIPHATIC SERIES.

3.* PREPARATION AND PROPERTIES OF SODIUM SALTS OF ESTERS OF NITROSULFOACETIC ACID

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Substitution of halogen atoms in chloronitro- and bromonitroacetic acid (CNA, BNA) by other radicals is a practical problem the solution of which opens up a route to the synthesis of many types of compound including α-aminoacid precursors. There is little information on the properties of the C–Hal bond in these compounds; only the replacement of halogen by hydrogen using catalytic hydrogenation [1], and the action of triphenylphosphine [3] and sodium dithionite [2] are known. Alkyl esters of CNA and BNA do not take part in a Grignard reaction with alkyl bromides nor in a Friedel–Crafts reaction with benzene or toluene in the presence of $AlCl_3$. This is evidence of the inadequate polarization of the C–Hal bond in esters of CNA and BNA.

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*For previous communications, see [1, 2].

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