KINETICS AND MECHANISM OF THE ACID CYCLIZATION OF N-SUBSTITUTED N-NITROSO-α-AMINOACETONITRILES TO SYDNONEIMINES

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The cyclization of N-nitrosoaminonitriles was studied by a kinetic method with spectrophotometric recording. It is shown that the reaction rate increases as the electron-donor properties of the substituent increase and as the size of the substituent increases. The rate-determining step is detachment of a proton from the C_4 atom in the 4H-1,2,3-oxodiazole-5-imine dication.

Up until now, the acid cyclization of N-substituted N-nitrosoaminoacetonitriles Ia-m to sydnoneimines IIa-m has been the only method for the preparation of the sydnoneimine ring. However, its kinetics have not been studied, and some of the views regarding the mechanism of the cyclization [1, 2] are purely speculative in nature.

N-Cyclohexyl-N-nitrosoaminoacetonitrile If was selected for a detailed study, and the trend of the reaction was monitored spectrophotometrically from the absorption of the final product of cyclization of the 3-cyclohexylsydnoneimine cation (IIf) (Fig. 1). The kinetics of the reaction in aqueous hydrochloric and sulfuric acid solutions were studied. It was shown that the reaction is first-order (Fig. 2) in N-nitrosoaminoacetonitrile If and that the rate constants calculated from the decrease in the starting product and the development of the final product were found to be equal; this constitutes evidence for the absence of appreciable side transformations of nitrosonitrile If and for the stability of sydnoneimine cation IIf under the experimental conditions, i.e., for the unambiguous character of the direction of the investigated processes. The equality of the rate constants and the presence of an isopiestic point (Fig. 1) also prove that none of the intermediates, the absorption of which differs from that of the starting material and the final product, accumulates appreciably. We also showed that the reaction rate depends substantially on the proton concentration and is independent of the nature of the anion: the reaction rates are practically identical in hydrochloric and sulfuric acid solutions with the same proton activities (Fig. 3). Analysis of the dependence of the rate constant on the proton concentration in logarithmic coordinates (Fig. 3) showed that the reaction is second-order in protons – the slope of the line in these coordinates is 2.1.

The effect of temperature on the cyclization rate was investigated, and the activation parameters were determined (Fig. 4). Analysis of the graph with respect to the equation (Fig. 5)

$$k=\frac{RT}{Nh}\cdot e^{\frac{\Sigma\Delta S}{R}}\cdot e^{\frac{-\Sigma\Delta H}{RT}},$$

where $\Sigma\Delta S$ and $\Sigma\Delta H$ are the total changes in the entropy and enthalpy for the processes that determine the rate, makes it possible to calculate $\Sigma\Delta H=-16$ kcal/mole and $\Sigma\Delta S=-6.0$ cal/mole·deg. The negative change in the entropy constitutes evidence that the transition state is more rigid, i.e., it has a lower degree of freedom in the starting molecule. This is not surprising if one takes into account the fact that we are studying a transition from a linear molecule to a cyclic molecule, during which cyclic transfer of electrons is possible in one of the steps. This fact makes it possible to assume that the transition state is closer in a steric respect to the final product and that the cyclic compound is closer to the starting compound, and this may attest to "compression" of the substituents attached to the "amine" nitrogen and α-carbon atom (in starting nitrosonitrile I these atoms

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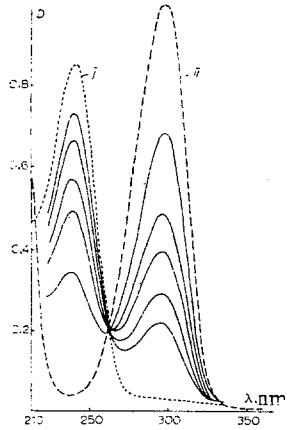


Fig. 1

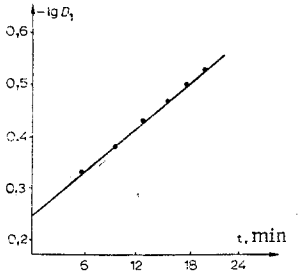


Fig. 2

Fig. 1. Kinetics of the cyclization of If to IIf in aqueous 0.6 N HCl solution. The spectra were recorded every 5 min, and the starting If concentration was $1 \cdot 10^{-4}$ mole/liter.

Fig. 2. Changes in the optical density of If ($\lambda = 237$ nm) with time.

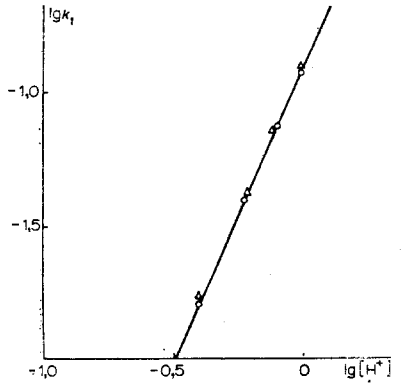


Fig. 3

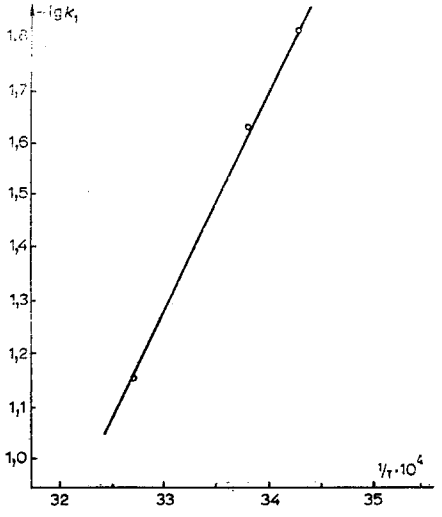
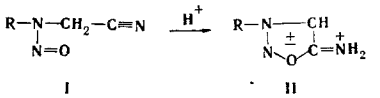


Fig. 4

Fig. 3. Dependence of the rate constant for cyclization of N-nitrosoaminoacetonitrile on the proton concentration in logarithmic coordinates: O) HCl; Δ) H_2SO_4.

Fig. 4. Effect of the temperature on the rate of cyclization of N-nitrosoaminoacetonitrile If in 0.4 N aqueous HCl.

have a nonplanar configuration, whereas in the sydnoneimine molecule they have a practically planar configuration). If these assumptions are true, one should observe the so-called "steric facilitation" of cyclization as the volume of the substituents attached to the "amine" nitrogen atom increases and as substituents are introduced at the α-carbon atom in nitrosonitrile I.



I II

The quantitative effect of substituent R in nitrosonitrile I on the rate of acid cyclization to sydnoneimine II was verified by means of the Taft equation [3]. The rate constants for this process were measured for nitrosonitrile I with various substituents attached to the nitrogen atom at 30° in 0.9 N hydrochloric acid (Table 2); the Taft inductive and steric (E_S^C) constants with allowance for hyperconjugation [4] are known for nine of them (Ia-i). It is apparent from Table 2 that substituents have a substantial effect on the cyclization rate – the rate increases

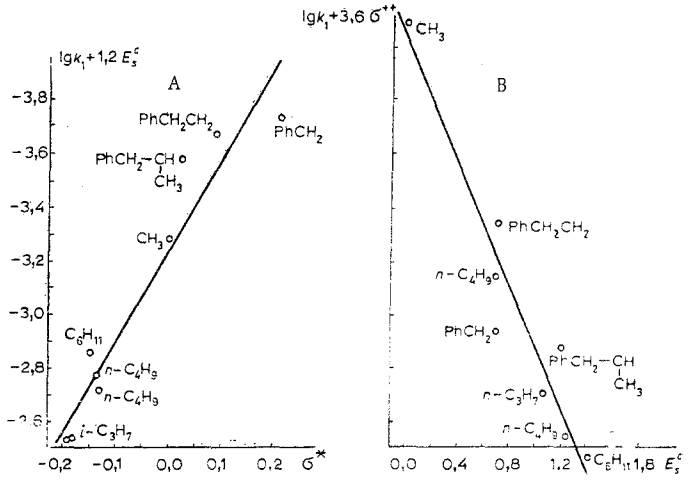


Fig. 5. Effect of structural factors in the rate of cyclization of N-nitrosoaminoacetonitriles to sydnoneimines in 0.9 N HCl: A) dependence of log k after subtraction of the component of the steric effect (1.2 E_S^c) on the Taft inductive constants (σ^*); B) dependence of log k after subtraction of the component of the inductive effect (−3.6 σ^*) on the steric substituent constants (E_S^c).

by more than two orders of magnitude on passing from methyl derivative Ia to cyclohexyl derivative Ie. Correlation analysis of the data within the framework of the LFE principle leads to the equation

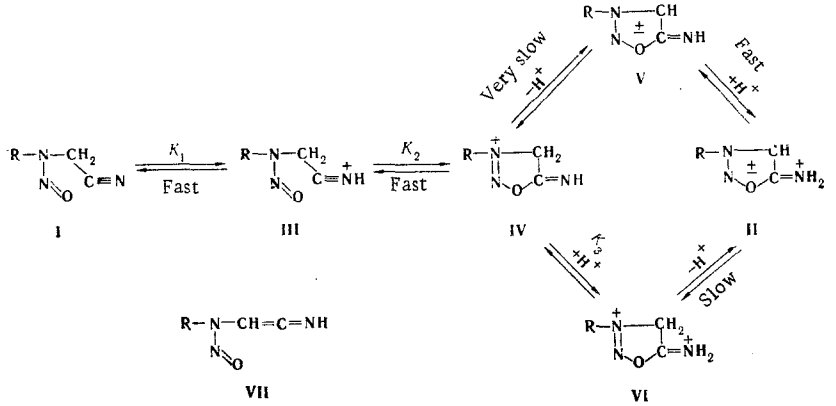
$$\lg k_1 = -3.2 - 3.6\sigma^* - 1.2E_s^c \quad (r=0.97;\ s=0.12). \qquad (3)^*$$

It follows from this equation that the reaction rate increases as the electron-donor properties of substituent R increase ($\rho^* = -3.6$) and, as we assumed, with an increase in the volume of this substituent ($\delta_c = -1.2$), i.e., as the σ^* value decreases and the absolute value of the negative E_S^c value increases. For the available set of substituents the contribution to the log k_1 value of "steric facilitation" ($\Delta S = \delta_c \cdot E_S^c = 0.4$–$1.7$ logarithmic units) is even somewhat greater than the contribution of the electronic (in this case, inductive) effect ($\Delta I = \rho^*\sigma^* = -0.8$ to $+0.7$ logarithmic units).

It may similarly be assumed that the considerable acceleration of cyclization (by a factor greater than 10) when a methyl group is present at the α-carbon atom (compare nitrosonitriles Ih and Il) is explained primarily by the "steric facilitation" effect.

The data on the formation of a sydnoneimine ring make it possible to state an assumption regarding the mechanism of this process. In a study of the kinetics of the equilibrium reaction of alkaline ring opening [5-7] it was established that the reaction is second-order in hydroxide ions, and it was assumed that the first step is the formation of sydnoneimine base V, which exists in equilibrium with the other noncyclic tautomeric form — N-nitrosonitrile I.

The proposed mechanism of the acid cyclization is depicted by the scheme



I $\Delta E = -2,9$, II $\Delta E = -16,1$, III $\Delta E = -9,9$, IV $\Delta E = -15,4$, V $\Delta E = 0,00$, VII $\Delta E = 4,2$ eV.

*See the experimental section for Eqs. (1) and (2).

TABLE 1. Rate Constants for the Cyclization of Nitrosonitrile Ic to Sydnoneimine IIc (min^{-1})

	Acid cyclization	Alkaline cyclization
pH 8,75 $C_{OH^-}=5,6\cdot10^{-6}$ $C_{H^+}=1,8\cdot10^{-9}$	$k_1^{H^+}=18\cdot10^{20}$ $k_{-1}^{H^+}=4,3\cdot10^{18}$	$k_1^{OH^-}=3\cdot10^{4}$ $k_{-1}^{OH^-}=73\cdot10^{4*}$
1 N. HCl $C_{OH^-}=10^{-14}$ $C_{H^+}=1$	$k_1^{H^+}=9,5\cdot10^{2*}$ $k_{-1}^{H^+}=3,3\cdot10^{9}$	$k_1^{OH^-}=4,7\cdot10^{11}$ $k_{-1}^{OH^-}=1,6\cdot10^{20}$

* This is the experimental value.

TABLE 2. Quantitative Evaluation of the Effect of Substituents on the Rate of Cyclization of N-Nitrosoaminoacetonitriles

I	R	R'	$k_1\cdot10^3$ min^{-1}	Exptl.– log k_1	σ*	E_s^c	$\Delta I=$ $=-3,6\sigma^*$	$\Delta s=$ $=-1,2E_s^c$	Calc.– log k_1
a	CH_3	H	0,53	3,3	0,00	0,00	0,00	0,00	3,2
b	C_2H_5	H	11,00	2,0	−0,10	−0,38	0,36	0,45	2,4
c	*i*-C_3H_7	H	61,00	1,2	−0,19	−1,08	0,68	1,30	1,2
d	*n*-C_4H_9	H	13,40	1,9	−0,13	−0,70	0,47	0,84	1,9
e	*i*-C_4H_9	H	53,00	1,3	−0,125	−1,24	0,45	1,49	1,3
f	*cyclo*-C_6H_{11}	H	75,00	1,1	−0,15	−1,40	0,54	1,65	1,0
g	C_6H_5—CH_2	H	1,25	2,9	0,215	−0,69	−0.77	0,83	3,1
h	C_6H_5—CH_2CH_2	H	1,50	2,8	0,08	−0,71	−0,28	0,85	2,7
i	C_6H_5—$CH_2CH(CH_3)$	H	7,20	2,1	0,02	−1,20	−0,07	1,44	1,9
j	1'-Adamantyl	H	800,00	0,1	(−0,30)	(−1,7)	1,08	2,04	0.1
k	1'-Adamantylmethyl	H	6,00	2,2					
l	C_6H_5—CH_2CH_2	CH_3	17,00	1,8					
m	C_6H_5—CH_2CH_2	C_6H_5	11,00	2,0					

In the proposed scheme the first process is protonation of the nitrogen of the nitrile group. Judging from the molecular models, in cation III and in starting nitrosonitrile I the distance between the electron-surplus oxygen atom and the electrophilic carbon atom of the nitrile group in one of the conformations is very small, on the order of 1.6 Å.* This makes it possible to assume a fast reaction between these atoms to give a new C–O covalent bond of the type involved in the formation of imino esters in acidic media – as a result, cyclic imino ester diazotate IV is obtained. This ring is a tautomer of sydnoneimine cation II of the type involved in imine–amine tautomerism, and sydnoneimine base V can, in principle, therefore be formed with detachment of a proton from the C_4 atom. Protonation of the highly active imino group in the sydnoneimine base cannot determine the reaction rate as a whole, since this process takes place immeasurably more rapidly than cyclization, and one would observe a reaction that is first-order in protons in this case. Detachment of a proton from the C_4 atom evidently proceeds extremely slowly, and the prototropic isomerization of imino ester IV to base V is catalyzed by acid: imino ester IV adds a proton to the imino group, and in dication VI the proton is detached substantially more rapidly from the C_4 atom. One can then explain the second-order in protons in the investigated interval, which attests to the accelerating participation of two protons in equilibrium prototropic processes that precede the step that determines the reaction rate as a whole. Thus the rate-determining step is detachment of a proton from the C_4 atom of dication VI.

One should immediately note that all of the intermediate processes between nitrosonitrile I and sydnoneimine cation II should be equilibrium processes, for otherwise the principle of microscopic reversibility would be violated.

The proposed scheme is in agreement with the experimental data. It is apparent from the scheme that the rate-determining step (k_{rds}) is related to the observed reaction rate (k_1) by the equation

$$k_1 = k_{rds}\cdot[H^+]^2\cdot K_1\cdot K_2\cdot K_3 \quad (4)$$

or

$$\lg k_1 = \lg k_{rds} - pK_1 - pK_2 - pK_3 + 2\lg[H^+]. \quad (4a)$$

In addition to the fact that the reaction is second-order in protons, it follows from Eq. (4a) that the effect of structural factors, temperature, solvent, etc., is an overall effect and is made up of the effect not only on the

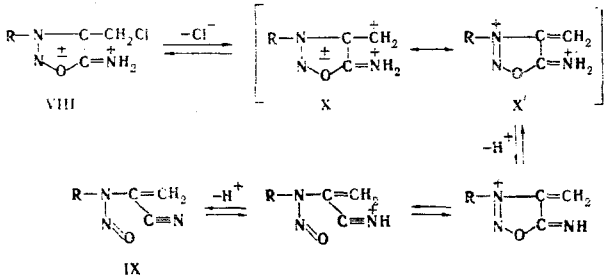
* For comparison, the O_1–C_5 bond length in the sydnone ring is 1.407 Å [8].

slowest step (on k_{rds}) but also on the basicities of nitrosonitrile I and imino ester IV, as well as on the position of the equilibrium between products III and IV. Consequently, the negative entropy factor $\Sigma\Delta S = -6.0$ cal/mole · deg constitutes evidence for the determining effect of the negative change in the entropy of the reaction during equilibrium conversion of the linear molecule of cation III to cyclic structure IV; in all likelihood, $\Delta S \cong 0$ for the other processes in the scheme presented above. One's attention is drawn to the fact that the rate-determining step is, in principle, slowed down when the electron-donor properties of substituent R increase, i.e., $\rho^*_{lim} > 0$, whereas $\rho^* < 0$ is observed. This may be possible if $\Sigma\rho^*_i > 0$ and $|\Sigma\rho^*_i| > |\rho^*_{lim}|$ for K_1, K_2, and K_3. In this case it is clear for basicity constants K_1 and K_3 that $\rho^*_1 > 0$ and $\rho^*_3 > 0$; a positive value is also most likely for the equilibrium between cation III and structure IV, since the donor properties of R facilitate the formation of imino ester IV with a positive charge on the nitrogen atom adjacent to R. Insofar as steric facilitation of the reaction as the volume of R increases is concerned, this effect is evidently realized at the cation III⇌imino ester IV stage. The addition of a substituent to the C_4 atom facilitates detachment of a proton from the tertiary C_4 atom in imino ester VI (the strength of C acids increases in the order primary < secondary < tertiary C atom), and, in addition, one will observe steric facilitation because of "expansion" of the substituent on passing from the tetragonal sp^3 C_4 atom in imino ester VI to the planar sp^2 C_4 atom in sydnoneimine cation II.

The completely satisfactory correlation of the logarithms of the rate constants of the investigated reactions with the Taft steric constants is worthy of attention. Not many reactions of this sort have been described in the literature, and there have not been any examples at all until recently of a negative coefficient of E_S. In contrast to the Taft inductive constants (σ^*), the steric constants are not universal, and, as a rule, satisfactorily describe the steric effects only when these effects are manifested in processes that are similar to the process from which they are determined: the E_S constants are determined during acid hydrolysis of esters ($RCOOC_2H_5$), and "compression" of the substituents, which is associated with transition from the planar sp^2 carbon to the tetragonal sp^3-hybridized carbon atom, occurs in the rate-determining step; this explains the steric hindering of hydrolysis [9].

In conformity with the proposed scheme of the reaction under investigation, "expansion" of the substituents attached to the nitrogen atom from the tetragonal configuration in the nitrosoamine to the planar configuration in the case of the sp^2-hybridized N_3 atom in the imino ester occurs in the cyclization of nitrosamine III to imino ester IV, and we observe steric facilitation of the reaction. Thus the fact of the satisfactory description of the steric effect in the reaction under consideration may serve as an additional confirmation of the proposed mechanism.

Borisov [10] has calculated, by the CNDO/2 (complete neglect of differential overlap) method, the starting, final, and intermediate molecules of the proposed scheme and the total energies of the molecules [they are presented in the above scheme in terms of the symbol $\Delta\bar{E}$ (in electron volts)] as compared with the energy of the sydnoneimine base, for which it was assumed that $\Delta\bar{E} = 0$. A comparison of the $\Delta\bar{E}$ values confirms the ease of cyclization of cation III to imino ester IV; in this process there is a substantial energy gain (+5.5 eV). The results of calculation of the intermediates of a different cyclization pathway in which a proton is detached from the methylene group of cation III ($\Delta\bar{E} = -9.9$ eV) to give imino ketene VII ($\Delta\bar{E} = 4.2$ eV), which is protonated at the imino group, and cation VII H^+ ($\Delta\bar{E} = -7.7$ eV) is cyclized to sydnoneimine cation II, shows that there is an energy loss in this case. However, one cannot completely exclude the possibility of an alternative cyclization mechanism, since kinetic factors rather than thermodynamic factors may prevail in the process. Thus quantum-chemical calculations in general provide evidence in favor of the proposed scheme: cyclization to imino ester IV occurs initially and is followed by detachment of a proton, which is catalyzed by acids. The reversibility of the proposed scheme is confirmed by the experimental fact, presented in [10, 11], of opening of the ring of a dication of the VI type when there is no hydrogen in the α position in the resulting nitrile of the I type. The authors have observed that N-nitroso-N-benzylaminoacrylonitrile IX precipitates very rapidly when 3-benzyl-4-chloromethylsydnoneimine hydrochloride (VIII) is dissolved in water. The mechanism of this process is in complete agreement with the reversible process presented in the scheme for the reaction under consideration.



Carbonium ion X is formed during the dissociation of the chlorine atom in sydnoneimine VIII (as in substitution reactions of the S_N1 type). This carbonium ion can be represented in the form of limiting structure X, which is similar to the structure of dication VI; successive detachment of two protons leads to ring opening to give IX.

Considering the reversible character of the cyclization and ring opening processes and knowing the constants of the equilibrium between nitrosonitrile I and sydnoneimine cation II [12], one can calculate the rate constants of the forward and reverse reactions in alkaline and acidic media. The calculation was performed in the case of compounds with an isopropyl substituent (Ic and IIc). Allowance was made for the fact that acid cyclization for Ic is accelerated as a function of the proton concentration in accordance with the equation $k_1^{H^+} = 0.095\ C_{H^+}^{2}$ (1/min), alkaline ring opening for IIc is accelerated in accordance with the equation [12] $k_{-1}^{OH^-} = 1.6 \cdot 10^8\ C_{OH^-}^{-2}$, and that [12] $K_{eq}/C_{H^+} = k_{-1}^{H^+}/k_1^{H^+} = k_{-1}^{OH^-}/k_1^{OH^-} = 3.4 \cdot 10^{-8}$.

It follows from these data that ring opening of IIc should proceed very slowly in acidic media via an acid catalysis mechanism $k_{-1}^{H^+} = 3.3 \cdot 10^{-9}$ min^{-1} and even more slowly via an alkaline catalysis mechanism $k_{-1}^{OH^-} = 1.6 \cdot 10^{-20}$ min^{-1}. The cyclization also proceeds analogously in alkaline media, and in this case alkaline catalysis is considerably more effective than acid catalysis: $k_{-1}^{OH^-} = 3 \cdot 10^{-4}$ min^{-1}, and $k_1^{H^+}$ $18 \cdot 10^{-20}$ min^{-1}.

N-1-Adamantyl (Ij) and N-1-adamantylmethyl (Ik) derivatives were among the compounds whose rates of formation were measured. The steric constants were not measured for these substituents. It may be assumed that the 1-adamantyl substituent, as a framework system with a quaternary carbon atom at the addition site, is an extremely bulky substituent and will substantially accelerate cyclization in conformity with Eq. (3). In fact, the 1-adamantyl derivative (Ij) is cyclized much more rapidly than the investigated compounds (Table 2). Proceeding from the k_1 value and using the σ^* value for the tert-butyl group ($\sigma^* = -0.30$) as the inductive constant, we calculated the steric constant for the 1-adamantyl group ($E_S^C = -1.7$) from Eq. (3). This value was found to be larger in absolute magnitude than the value obtained for the cyclohexyl group ($E_S^C = -1.4$) but less than the steric constant of the tert-butyl group ($E_S^C = -2.2$). The latter is possibly associated with the absence of free rotation of the individual atoms and groups of atoms of adamantane.

The fact that the introduction of a methylene group between the adamantyl group and the nitrogen atom in nitrosonitrile Ik reduced the cyclization rate by a factor greater than 100 was surprising. Judging from the molecular models, in the 1-adamantylmethyl derivative free rotation about the $C-N_3$ bond becomes possible after cyclization of Ik to cation IVk. The most advantageous conformation with a linear orientation of the $C-N_3-C_4$ bonds is forbidden because of considerable overlap of the van der Waals radii of the hydrogen atoms of the methylene group of the ring C_4 atom and the adamantyl methyl substituent. Overlapping of this sort is not observed in the case of the N-1-adamantyl derivative. This steric hindrance evidently shifts the equilibrium between products III and IV to favor product IIIk and reduces the K_2 value; judging from Eq. (4), this should lead to a proportional decrease in the observed k_1 rate constant.

EXPERIMENTAL

The N-substituted N-nitrosoaminoacetonitriles in aqueous solutions have an intense absorption band at 235-240 nm, and the final product of sydnoneiminecations IIa-m absorbs at 295-300 nm. The kinetics of the cyclization were studied in 0.25-1.2 N aqueous hydrochloric and sulfuric acid solutions at 30° in thermostated cuvettes. The concentration of the starting compounds was $1 \cdot 10^{-4}$ mole/liter. The rate constants were calculated from the decrease in the concentration of Ia-f:

$$k_1 = \frac{2{,}303 \lg (D_n^{I} - D_{n+1}^{I})}{t_{n+1} - t_n} \quad (1)$$

and from the appearance of final products IIa-f

$$k_2 = \frac{2{,}303[\lg (D_\infty^{II} - D_n^{II}) - \lg (D_\infty^{II} - D_{n+1}^{II})}{t_{n+1} - t_n}, \quad (2)$$

where D_n^{I}, D_{n+1}^{I}, D_n^{II}, and D_{n+1}^{II} are the instantaneous optical densities of N-nitrosonitriles Ia-f and sydnoneimine cations IIa-f at times t_n and t_{n+1}; D_∞^{II} is the final optical density of sydnoneimine cation II.

N-Nitrosoaminoacetonitriles Ia-i,l,m were obtained by the method in [13] and corresponded to the indicated parameters. Compounds Ij and Ik were kindly provided by Z. A. Olovyanishnikova; they were characterized by elementary analysis and their IR, UV, and PMR spectra.

The study was carried out with a Shimadzu MPS-50L spectrophotometer.

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REACTION OF 4H-1,3-BENZOXAZINE-4-ONIUM SALTS WITH C-NUCLEOPHILIC AROMATIC COMPOUNDS

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UDC 547.867.2.07

A method is proposed for the synthesis of 2-(4-dialkylaminophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-ones and diindolylcyaninemethanes by reaction of 4H-1,3-benzoxazin-4-onium salts with N,N-dialkylanilines and indole.

It follows from the results of a quantum-mechanical calculation of the oxazinium cation* that the positive charge in salts I is localized on the $C_{(2)}$, $C_{(4)}$, and $C_{(6)}$ atoms of the heteroring and that the highest charge is concentrated on the meso-carbon atom. According to the calculation, attack by nucleophilic reagents should be directed to the 2 position of the heteroring; this is actually observed in the reactions of benzoxazinonium salts with activated homo- and heteroaromatic compounds.

It has been shown that, depending on the conditions, benzoxazinonium salts react with dialkylanilines in different ways. For example, dimethylaniline reacts like a tertiary amine at room temperature, and equilibrium I⇌III, which, however, is shifted to the left when the mixture is refluxed, since under these conditions dimethylanilines acts as a C-nucleophilic arylating agent, is established in the reaction mixture as a consequence of this. The previously unknown 2-(4-dialkylaminophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-ones (IIa-f, see Table 1) were obtained by this method by refluxing 4H-1,3-benzoxazin-4-onium perchlorates (I) [1] with N,N-dialkylaniline in acetic acid or nitromethane. The dihydrobenzoxazinone salts formed in some cases can be isolated.

* The quantum-mechanical calculation was performed by V. I. Minkin and R. M. Minyaev.

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