Kinetic and quantum chemical studies of the mechanism of formation of 1,2-dialkyldiaziridines

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The regularities of AlkNHBr consumption in the reaction of formation of 1,2-dialkyldiaziridines in aqueous media were studied for the first time by UV spectrometry. The rate constants of particular steps of the reaction were estimated starting from the possibility of formation of the precursor of 1,2-dialkyldiaziridine, *N*-halogenaminal, due to the amination of the intermediate iminium cation along with the parallel halogenation of the intermediate *gem*-diamine. The quantum chemical calculations (DFT, B3LYP, 6-31++G(d,p) and 3-21G basis sets) were performed for the spatial and electronic structures of the compounds and indices of the local reactivity and global electrophilicity of the key intermediates of the reactions. The results of the calculations allowed us to explain the retardation of the reaction when using EtNHBr instead of MeNHBr.

Key words: 1,2-dialkyldiaziridines, *N*-brominealkylamines, synthesis, kinetics, quantum chemical calculations, density functional theory (DFT), B3LYP functional, mechanism of formation.

The development of new methods for the synthesis of diaziridines and the study of the mechanism of diaziridine cycle formation have been an area of our scientific interest during several years.^{1a-f} In the recent years these studies were actively stimulated by the use of the synthesized diaziridines in the ring extension reactions under the action of electrophilic reagents, ketenes, isocyanates, and isothiocyanates, ^{2a-g} as well as dipolarophiles in ionic liquids.^{3a-f}

It is known that the diaziridine derivatives can exert a directed effect on the central nervous systems, manifesting different types of neutrotropic activity, mainly antidepressive one.^{4a-d} Under normal conditions, diaziridines have a stable pyramidal configuration of the nitrogen atoms and, hence, are among a few convenient objects for studying stereochemistry of nitrogen-containing organic compounds.^{5a-d} Therefore, new studies of the regularities of the mechanism of diaziridine cycle formation, which yet remains unclear, are urgent and can favor the enhancement of the efficiency of the synthesis of the diaziridine derivatives.

The mechanism earlier proposed 1a,b,e,f for the formation of 1,2-dialkyldiaziridines (1) in the reactions of formaldehyde with primary aliphatic amines (2) and *N*-halogenalkylamines (3) in weakly basic aqueous media assumed the possibility of formation of the diaziridine precursor, *N*-halogenaminal (4), due to the amination of the iminium cation (5) of the Mannich type, when aminating agent 3 acts as an N—H-acidic component (Scheme 1, route *A*). At the same time, it was shown^{1a,b,e,f,6} that in addition to route *A* there is a possible route of formation of *N*-halogenaminals 4 by the halogenation of *gem*-diamine (6) synthesized by the condensation of 1 mole of formaldehyde and 2 moles of primary aliphatic amine (Scheme 1, route *B*).

The regularities of consumption of *N*-bromoalklylamines **3a**,**b** in their reactions with formaldehyde and methyl- or ethylamine (**2a**,**b**) when synthesizing 1,2-dialkyldiaziridines **1a**,**b** were studied for the first time by UV spectrometry (Scheme 2) and the ratios of rate constants of the formation of final product **1** *via* possible routes were estimated by the calculation method.

The use of *N*-bromoalkylamines **3a**,**b** in the study is related to the fact that the absorption maximum of these compounds ($\lambda_{max} = 290-300 \text{ nm}$),⁷ unlike similarly substituted *N*-chloroalklylamines ($\lambda_{max} = 240-250 \text{ nm}$),⁷ lies in a longer-wavelength region of the UV spectrum and is considerably less overlapped with absorption bands of other

Published in Russian in Izvestiya Akademii Nauk. Seriya Khimicheskaya, No. 6, pp. 1112–1118, June, 2012.

^{1066-5285/12/6106-1121 © 2012} Springer Science+Business Media, Inc.





i. RNH₂ (excess), H₂O, pH (optimum).

Scheme 2

$$H_{H} C=0 + RNH_{2} + RNHBr \xrightarrow{i}$$

$$H 2a,b 3a,b$$

$$H H_{H} H_{NR} + RNH_{2} \cdot HBr$$

$$h H_{H} H_{NR} + RNH_{2} \cdot HBr$$

$$h H_{R} H_{R} H_{R}$$



i. RNH₂ (excess), H₂O, pH (optimum), 20 °C.

participants of the reaction. The reaction was carried out directly in the cell of the UV spectrometer, measuring the absorbance of the reaction mixture at a constant analytical wavelength of 320 nm. This made it possible to maximally exclude the influence of the final reaction products on the measured absorbance of the reaction solutions and to significantly increase the accuracy of the measurement results.

Since the yield of formed 1,2-dialkyldiaziridines **1a**,**b** in the reaction *via* Scheme 2 depended substantially on the pH of the reaction medium, ^{1a,b,e} to achieve the maximum yield, the reaction was carried out in a threefold excess of the initial primary aliphatic amine **2**, which provided the necessary value of pH (optimum) of the reaction medium in the range from 12.0 to 11.6. The yield of diaziridines **1a**,**b** determined by the iodometric titration of the reaction mixture^{8a,b} was 92.0–96.3% under these conditions. Quartz cells with a thickness of 0.5 (Fig. 1, curves 1 and 3) and 1.0 cm (Fig. 1, curves 2 and 4) were used for the possibility of variation of the initial concentrations of the starting compounds at the optimum level of absorbance detection.



Fig. 1. Decrease in the concentrations of *N*-bromoalkylamines in time: curves *I* and *2* for *N*-bromoethylamine (**3b**), *3* and *4* for *N*-bromomethylamine (**3a**) at the initial concentrations 6.25 (*1*), 11.25 (*2*), 5.75 (*3*), and 12.05 mmol L^{-1} (*4*).

Figure 1 presents the curves of decreasing the concentrations of starting compounds 3a,b attributed to their initial values and obtained in four most successful experiments. It is seen from Fig. 1 that *N*-bromomethylamine (**3a**) considerably more actively enters into the reaction, which ceases for it mush more rapidly than for *N*-bromoethylamine (**3b**).

When composing the kinetic model of the synthesis of dialkyldiaziridines, we took into account the following circumstances. According to the assumption advanced and indirectly confirmed,^{8a} we believe that the equilibrium indicated in Scheme 1 and established upon mixing of solutions of formaldehyde and an excess of primary aliphatic amine is completely shifted towards aminal 6. Therefore, its initial concentration was accepted to be equal to the initial concentration of formaldehyde. In this case, because of amine excess and, hence, the absence of free protons in the reaction mixture (pH of the medium ~ 12.0) that play the role of an acidic catalyst for the amine elimination from aminal 6, we accepted that iminium cation 5 is absent in the reaction medium at the first stage of the reaction. As RNHBr (3) was added to the reaction mixture and diaziridine 1 was formed, HBr evolved, due to which the formation of cation 5 is catalyzed. The latter rapidly reacts with the deprotonated form of aminating agent 3 (see Scheme 1, intermediate 7). Therefore, the possible reversibility of the reaction between products 6 and 5 was ignored in the calculations. In addition, to simplify the calculations, we accepted the rates of backward reactions between products 5–4 and 6–4 to be considerably lower than the rates of forward reactions. The order of all reactions with respect to the reactants was accepted to be 1.0.

Kinetic scheme 3 (routes *I* and *II*) formally corresponds to the above assumptions.

The following system of mathematical equations corresponds to Scheme 3:

	$dc_6/dt = -k_3c_6 - k_2c_6c_3,$
ł	$dc_5/dt = -k_3c_6 - k_1c_5c_3,$
	$dc_3/dt = -k_2c_6c_3 - k_1c_5c_3$

where k_1 , k_2 , and k_3 are the reaction rate constants and c_3 , c_5 , and c_6 are the concentrations of reactants 3, 5, and 6.

The kinetic calculations were performed using the Mathcad-14 mathematical system. The dependences of



the concentrations of bromoalkylamines 3a,b on the reaction duration found by the integration of these equations were compared with the experimental values. Thus obtained rate constants for particular steps and standard approximation errors (sd) in relative units are given in Table 1.

The calculations performed made it possible to estimate the ratio (r) of the amount of substance 1 formed in route *II* to its amount formed *via* route *I*. The changes in the value of *r* in time in various experiments are presented in Fig. 2.

The data obtained suggests that the replacement of the methyl radical by the ethyl radical at the N atom in initial reactant **3** noticeably decreases the rate of formation of final product **1**. The nature of the alkyl substituent mainly affects the rates of both steps of route *II*.

To explain this fact, we performed the quantum chemical calculations of the geometric and electronic structures and indices of reactivity of the key intermediates of the reactions shown in Scheme 1. The calculations were performed using the Gaussian 98 program package⁹ in the framework of the DFT method with the B3LYP hybrid functional in the 6-31++G(d,p) standard split-valence basis set for compounds containing no Br atom and in the 3-21G basis set with the Br atom. The calculations were performed for the gas phase only, because we failed to optimize the structures of intermediates **7a** and **7b** with allowance for their solvation by water by the PCM method in the Gaussian 98 program, it might be due to these compounds contain the Br atom.

Table 1. Kinetic parameters of RNHBr (3a,b) consumption in the formation of 1,2-dimethyl(diethyl)diaziridines 1a,b via Scheme 3

R	$c_0 \cdot 10^{-2} / \text{mol } \text{L}^{-1}$	k_1	<i>k</i> ₂	<i>k</i> ₃	sd	Correlation	Yield (%)	Diaziridine
			min ⁻¹			coefficient		
Me	1.205	0.430	0.05	0.46	0.009	0.99948	92.0	1a
	0.575	0.250	0.05	0.30	0.007	0.99745	93.6	1a
Et	1.125	0.057	0.11	0.05	0.025	0.99645	96.3	1b
	0.625	0.059	0.11	0.08	0.038	0.99825	94.1	1b



Fig. 2. Changes in time in the ratios (*r*) of amounts of 1,2-dialkyldiaziridines formed *via* routes *II* and *I*: curves *I* and *2* for *N*-bromomethylamine (**3a**), *3* and *4* for *N*-bromoethylamine (**3b**) at the initial concentrations 5.75 (*I*), 12.05 (*2*), 6.25 (*3*), and 11.25 mmol L⁻¹ (*4*).

At the first stage, the global minimum on the potential energy surface (PES) was searched for each compound by the Hartree-Fock nonempirical method in the STO-3G basis set. Based on the obtained geometry, the subsequent optimization was performed in the framework of DFT with the B3LYP functional and the corresponding basis set. The positions of stationary points on the PES were fixed on the basis of the Hesse matrix by the absence of imaginary frequencies and the transition state was determined by the presence of one imaginary frequency. Using the NPA method,¹⁰ the indices of reactivity and local Fukui indices f_i (see Ref. 11) were estimated as the most informative ones for the studied reactions. These indices were approximated by the final electron density differences. The indices of local electrophilicity $\omega_i = \omega f_i$ for a particular atom were obtained by the multiplication of the Fukui index by the index of global electrophilicity ω (see Ref. 12), which was calculated from the energies of frontier orbitals.

According to the calculations (Tables 2–5), the most reactive center in the anions of *N*-bromoalkylamines **7a** and **7b** (nucleophilic reagents) is the N(1) atom for which the highest values of the Fukui index were obtained: $f^- = 0.436$ and 0.446, respectively (see Tables 4 and 5). In iminium cations **5a** and **5b** (electrophilic reagents), the C(5) atom is most reactive, since the highest Fukui indices f^+ correspond to it: 0.500 and 0.488, respectively (see Tables 2 and 3).

The quantum chemical calculations of the geometric (Fig. 3) and electronic structures (Fig. 4) of iminium cations **5a** and **5b**, having the methyl and ethyl substituents, respectively, at the N atom, revealed no substantial difference in charges on the C(5) atom: 0.097 and 0.092

Table 2.	Fukui	indices	f^+	and	f^{-}	for
H ₂ C-+1	NHMe	(5a)				

Atom	f^+	f^{-}
N(1)	0.185	0.135
C(2)	-0.028	0.095
H(3)	0.060	0.159
H(4)	0.032	0.058
C(5)	0.500	0.238
H(6)	0.060	0.043
H(7)	0.059	0.053
H(8)	0.071	0.053
H(9)	0.061	0.166

Table 3. Fukui indices f^+ and f^- for $H_2C^{-+-}NHEt$ (5b)

Atom	f^+	f^-
N(1)	0.188	0.016
C(2)	-0.017	0.039
H(3)	0.056	0.160
H(4)	0.027	0.090
C(5)	0.488	0.146
C(6)	-0.013	0.114
H(7)	0.051	0.063
H(8)	0.017	0.157
H(9)	0.025	0.114
H(10)	0.058	0.028
H(11)	0.057	0.044
H(12)	0.062	0.032

Table 4. Fukui indices f^+ and f^- for Me–N[–]–Br (7a)

Atom	f^+	f^-
N(1)	0.281	0.436
C(2)	-0.020	-0.086
H(3)	0.118	0.123
H(4)	0.117	0.119
H(5)	0.093	0.071
Br(6)	0.412	0.336

(see Fig. 4). At the same time, the difference in charges on the N(1) atom in anions **7a** and **7b** is substantial: -0.634 and -0.563. It is most likely that this is a reason for decreasing reaction rate constant k_1 on going from MeNHBr (**3a**) to EtNHBr (**3b**).

Although the index of local electrophilicity ω_i of the N atom is 0.004 eV higher in anion **7b** than that in anion **7a**, the index of local electrophilicity ω_i of the C(5) atom is 0.107 eV lower in cation **5b** than in cation **5a**. Thus, the relative decrease in the index of local electrophilicity of the reaction center in compound **5** is $|-0.107/0.004| \approx 27$

Table 5.	Fukui	indices	f^+	and	f^{-}	for
Et-N ⁻ -	-Br (7b)				

Atom	f^+	f^-
N(1)	0.245	0.446
C(2)	-0.023	-0.079
H(3)	0.094	0.111
H(4)	0.092	0.109
Br(5)	0.373	0.321
C(6)	-0.017	-0.019
H(7)	0.141	0.049
H(8)	0.048	0.031
H(9)	0.047	0.031

when the methyl substituent is replaced by ethyl one, which can also be a reason for the observed retardation of the reaction *via* route A when EtNHBr (**3b**) is used instead of MeNHBr (**3a**).

The global indices of electrophilicity ω , chemical potentials μ , and chemical hardness η (see Ref. 13) for compounds **5a,b** and **7a,b** characterizing their reactivity as a whole are given in Table 6. A comparison of global indices ω shows that anion **7a** exhibits a higher nucleophilic character compared to anion **7b**, since the lower value of ω corresponds to this anion. At the same time, this characteristic remains almost unchanged on going from cation **5a** to cation **5b**. It should be mentioned that chemical hardness η (energy gap between the frontier molecular orbitals) does not indicate a decrease in the reactivity on

Table 6. Global electrophilicity indices ω , chemical potentials μ , and chemical rigidities η of compounds **5a**,**b** and **7a**,**b**

Compound	ω	μ	η	
		eV		
5a	9.234	-0.438	0.283	
5b	9.235	-0.415	0.253	
7a	0.158	-0.040	0.139	
7b	0.164	-0.041	0.137	

going both from anion 7a to anion 7b and from cation 5a to cation 5b: in the both cases, this value decreases rather than increases. This indicates that the reactions of anions 7a and 7b with cations 5a and 5b are not orbital-controlled but are charge-controlled.

In order to analyze the regularities of consumption of N-bromoalkylamines **3a** and **3b** via route B and to determine the rate-determining step of the formation of intermediate **4**, we calculated the heat effects of the reactions and activation barriers of the consecutive steps leading to intermediates **4** and **6** (see Scheme 1). Figure 5 exemplifies the transition state for the formation of halogenaminal **4a** through N-bromomethylamine (**3a**).

The heat effect of the non-barrier formation of N, N-dimethylmethanediamine (**6a**) from iminium cation **5a** and methylamine is 18.7 kcal mol⁻¹ and that of N, N-diethylmethanediamine (**6b**) from iminium cation **5b** and ethyl-



Fig. 3. Molecular structures and bond lengths of compounds 5a, b and 7a, b (according to the B3LYP/3-21G and B3LYP/6-31++G(d,p) calculations, respectively).



Fig. 4. NPA charges of atoms in compounds 5a,b and 7a,b (according to the B3LYP/3-21G and B3LYP/6-31++G(d,p) calculations, respectively).

amine is 22.7 kcal mol⁻¹. The activation barrier for the formation of the corresponding *N*-halogenaminal **4a** through *N*-bromomethylamine (**3a**) is 32.3 kcal mol⁻¹ and that of *N*-halogenaminal **4b** through *N*-bromoethylamine (**3b**) is 35.4 kcal mol⁻¹. This suggests that the rate-determining step of formation of intermediate **4** via route **B** is the second of the considered processes. It is important to mention an increase in the calculated energy barrier of



Fig. 5. Structure of the transition state upon the formation of halogenaminal **4a** through *N*-bromomethylamine (**3a**) (distances are given in Å, and angles are given in deg).

formation of N-halogenaminal **4b** compared to N-halogenaminal **4a** when the methyl substituent in N-bromoalkylamine **3** takes the place of the ethyl substituent, which can also retard the reaction when EtNHBr(3b) is used instead of MeNHBr(**3a**).

Experimental

Bromine Br₂ (2.6 mL, 0.05 mol) was added dropwise with vigorous stirring at 0-5 °C to a solution of methyl(ethyl)amine (0.4 mol) in water (~200 mL). The yield and concentration of formed MeNHBr (3a) or EtNHBr (3b) in solution were determined by iodometric titration. The yield was ~97-99%. When a quartz cell with the working layer thickness 10 and 5 mm was used, the obtained solution (2.5 and 5 mL, respectively) was dissolved in water (100 mL), and the absorbance of the solution was measured with a KFK-3 digital spectrometer (photoelectron colorimeter) at the analytical wavelength $\lambda = 320$ nm $(\lambda_{max}(MeNHBr) = 345 \text{ nm}, \lambda_{max}(EtNHBr) = 350 \text{ nm}).$ Then the initial absorption intensity was determined: $A_0 = 0.810 - 0.902$ for MeNHBr and $A_0 = 0.881 - 0.907$ for EtNHBr. The accuracy of determination of absorbance E depending on the reaction conditions and quickness of analysis was at least $E_{\text{work}} = 0.004 - 0.019$. Formaldehyde (0.05 mol) in water (6 mL) was added with vigorous stirring to the initial (undiluted) reaction mixture at T = -1-5 °C, and the temperature was increased to 20 °C (pH₀~11.8) as soon as possible. This moment was considered the time of reaction onset ($\tau = 0$). A portion of the dilute reaction mixture was rapidly placed in a cell of the photoelectron colorimeter, and the absorbance of the solution was measured during the reaction course. The time interval from $\tau = 0$ to the first measurement of the absorbance of the sample was ~1.5 min.

Further the absorbance was measured at an interval of 15-20 s for the subsequent 1-3 min and then at an interval of 0.5-2 min until the zero absorbance of the sample was attained. Diaziridines were isolated as follows: an undiluted reaction mixture was saturated with NaOH, and the upper layer was separated and dried above NaOH. Diaziridines were distilled above NaOH under atmospheric pressure collecting the fraction with b.p. 48-50 °C for 1,2-dimethyldiaziridine (1a) and the fraction with b.p. 98-100 °C for 1,2-diethyldiaziridine (1b). The obtained physicochemical characteristics for 1,2-dimethyldiaziridine (1a) almost coincided with those given in refs 6 and 14 and for 1,2-diethyldiaziridine (1b) they coincided with those published earlier. 14.6

The calculated and experimental data were compared by the "corr" functions incorporated into the Mathcad-14 system.

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Received October 24, 2011; in revised form March 15, 2012