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Dedicated to Professor G. I.Koldobskii on occasion of his 75th anniversary

Kinetics and Mechanism of 5-Vinyltetrazole Alkylation

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Abstract—Alkylation of NH-unsubstituted 5-vinyltetrazole with methyl iodide in the presence of triethylamine in acetonitrile solution led to the formation of isomeric 1- and 2-methyl-5-vinyltetrazoles in 1:1 ratio. The reaction rate constants were measured at 25–55°C. According to the thermodynamic parameters of the reaction [$\Delta H^{\neq}$ 66 kJ mol^{-1}, $\Delta S^{\neq}$ –74 J(mol K)$^{-1}$, 298 K] the limiting stage of the reaction consists in the electrophilic attack of methyl iodide on an H-complex of the heterocycle with triethylamine.

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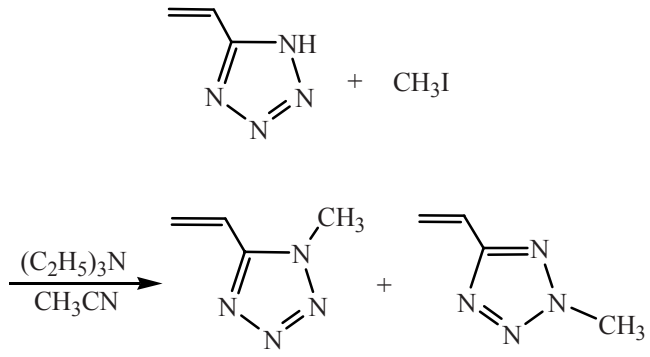
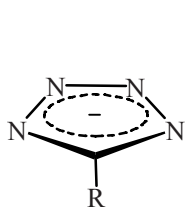
N-Alkyl derivatives of 5-vinyltetrazole (**I**), like 1- and 2-methyl-5-vinyltetrazoles (**II, III**), are regarded as promising vinyl monomers whose polymerization products find application in versatile fields of science and technology [1–4]. Therefore the problem of the study of 5-vinyltetrazole (**I**) reactivity and the search for a rational procedure for preparation of monomers **II** and **III** is urgent [2]. The known methods of the synthesis of compounds **II** and **III** are based on multistage processses involving the formation of the tetrazole ring (1,3-dipolar cycloaddition of ammonium azides or alkylammonium to the corresponding nitriles), the alkylation of thus obtained 5-substituted tetrazoles with dimethyl sulfate or with the corresponding alkyl halide, the regeneration of a double bond (the dehydrohalogenation or the Hofmann cleavage of trimethylammonium salts) etc. [1]. The overall yield of target tetrazoles **II** and **III** did not exceed in these events 50%. We believe that a promising procedure consists in a direct alkylation of NH-unsubstituted 5-vinyltetrazole (**I**) with electrophilic reagents. Actually, this method would provide in one stage the corresponding isomeric *N*-alkyl-5-vinyltetrazoles **II** and **III**. However this route to isomeric *N*-alkyl-5-vinyl-tetrazoles was practically absent from the publications. In the present study we investigated the methylation kinetics of 5-vinyltetrazolea (**I**) with methyl iodide in acetonitrile in the temperature range 25–55°C in the presence of triethylamine.

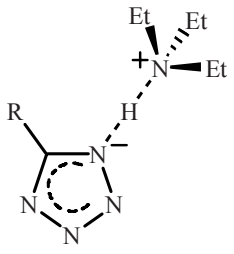
The NH-acidity of the tetrazole ring is known to be high [1], for instance, the pK_a value of 5-vinyltetrazole (**I**) is 4.1 [3], therefore this heterocyclic compound evidently reacts in the form of tetrazolide **A**. The kinetics and mechanism of alkylation were studied for reaction of 5-aryltetrazoles potassium salts with dimethyl sulfate and ethyl bromoacetate in acetonitrile [5–8], and also for the reaction of 5-aryltetrazoles with methyl vinyl ketone in DMF in the presence of triethylamine [9, 10]. 5-Aryl-

Scheme.





A



B

R = Ar, Vin.

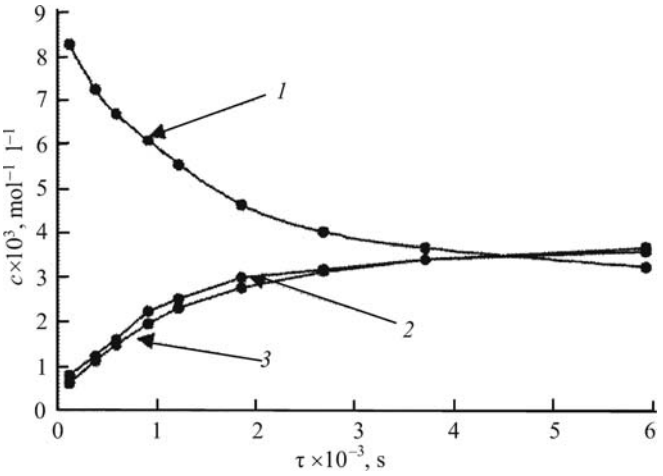


Fig. 1. Dependence on time of concentrations of reagent and alkylation products at 30°C: (*1*) 5-vinyltetrazole (**I**); (*2*) 1-methyl-5-vinyltetrazole (**II**); (*3*) 2-methyl-5-vinyltetrazole (**III**).

tetrazoles potassium salts dissociated under the conditions of the experiment to free tetrazolides **A** that were the species reacting with the electrophiles [11]. In the presence of proton-containing reagents like triethylamine the tetrazoles are involved into the reaction in the form of complexes with a hydrogen bond. Thus, in the alkylation of 5-aryltetrazoles with methyl vinyl ketone (R = Ar) in the presence of triethylamine, and also in the reaction of 5'-O-benzoyl-2,3'-anhydrothymidine with triethylammonium tetrazolide in aprotic dipolar solvents apparently the reacting species is complex **B** [11–13].

We presume that the alkylation of 5-vinyltetrazole (**I**) with methyl iodide in the presence of triethylamine also occurs involving complex **B** (R = Vin). No information exists on the reactivity of complex **B** and on the regioselectivity of its reaction with electrophiles.

In this study we established experimentally both the kinetic parameters and the ratio of the isomeric products of the reaction under consideration. The monitoring of the reagents conversion and the accumulation of the reaction products was performed by HPLC method. This procedure made it possible to follow the variation of the concentrations both by the consumption of the initial substance [5-vinyl-tetrazole (**I**)] and by the accumulation of the reaction products [1- and 2-methyl-5-vinyltetrazoles (**II, III**)] up to the 80% conversion. The reaction was carried out under the conditions of the pseudofirst order of the process: the alkylating agent, methyl iodide, was taken in a 10-fold molar excess with respect to reagent **I**. The dependence of the running concentrations of 5-vinyltetrazolea (**I**), 1- and 2-methyl-5-vinyltetrazoles (**II, III**) on time are typical kinetic curves of the first order reactions (Fig. 1). In the course of the process we did not observe a formation of additional products involving the reaction at the double bond.

The analysis of kinetic data using equations of parallel reactions showed that the process under study is well described by the equation of the pseudofirst order [14]. The second order constant was obtained by dividing the pseudofirst order constant by the concentration of methyl iodide.

The values of the rate constants in the temperature range 25–55°C calculated both from the consumption of 5-vinyltetrazole (**I**) ($k_{\mathrm{I}}^{\mathrm{I}}$, $k_{\mathrm{II}}^{\mathrm{I}}$) and from the accumulation of 1-methyl- (**II**) ($k_{\mathrm{I}}^{\mathrm{II}}$, $k_{\mathrm{II}}^{\mathrm{II}}$) and 2-methyl-5-vinyltetrazoles (**III**) ($k_{\mathrm{I}}^{\mathrm{III}}$, $k_{\mathrm{II}}^{\mathrm{III}}$) (see the table) were utilized for the calculation of the activation parameters of the studied reaction ($\Delta H^{\neq}$, $\Delta S^{\neq}$). We assumed that in the studied range of concentrations and temperatures the structure of complex **B** remained unchanged. In this case we can estimate the thermodynamic values of the activation parameters from the temperature dependence of rate constants found from the consumption of 5-vinyltetrazole

Rate constants of alkylation of 5–vinyltetrazole (**I**) with methyl iodide in acetonitrile[a]

Temperature, °C (K)	5-Vinyltetrazole (**I**)		1-Methyl-5-vinyltetrazole (**II**)		2-Methyl-5-vinyltetrazole (**III**)	
	$k^{\mathrm{II}}\times 10^4$, s^{-1}	$k_{\mathrm{II}}^{\mathrm{I}}\times 10^3$, l $mol^{-1}s^{-1}$	$k_{\mathrm{I}}^{\mathrm{II}}\times 10^4$, s^{-1}	$k_{\mathrm{II}}^{\mathrm{II}}\times 10^3$, l $mol^{-1}s^{-1}$	$k_{\mathrm{I}}^{\mathrm{III}}\times 10^4$, s^{-1}	$k_{\mathrm{II}}^{\mathrm{III}}\times 10^3$, l $mol^{-1}s^{-1}$
25 (298)	0.85	1.94	0.48	1.09	0.40	0.90
30 (303)	1.83	4.15	0,93	2.11	0.90	2.04
35 (308)	2.79	6.34	1.41	3.19	1.34	3.03
45 (318)	6.16	13.88	3.20	7.21	3.15	7.11
55 (328)	11.74	26.67	5.82	13.21	5.65	12.82

[a] The values of rate constants remained constant (within ±1%) at various concentrations of 5-vinyltetrazole (**I**) [(4.4–13.2) × 10^{-3} mol l^{-1}]. Concentration of methyl iodide 22.6 mol l^{-1}.

(**I**) ($\ln k_{II}^{I}$) and from the accumulation of 1-methyl- (**II**) ($\ln k_{II}^{II}$) and 2-methyl-5-vinyltetrazole (**III**) ($\ln k_{II}^{III}$) [equations (1–3)].

$$\ln k_{II}^{I} = (21.6 \pm 0.1) - (8250 \pm 11)1/T,$$
$$r\ 0.99,\ n\ 5,\ s\ 0.02, \quad (1)$$
$$\ln k_{II}^{II} = (20.1 \pm 0.2) - (7970 \pm 12)1/T,$$
$$r\ 0.99,\ n\ 5,\ s\ 0.01, \quad (2)$$
$$\ln k_{II}^{III} = (21.3 \pm 0.1) - (8380 \pm 13)1/T,$$
$$r\ 0.98,\ n\ 5,\ s\ 0.02. \quad (3)$$

The enthropy and enthalpy values were calculated from the parameters of equations (1–3) by Arrhenius and Eyring methods [15]. The calculation results obtained by these methods were for 5-vinyltetrazolea (**I**) $\Delta H^{\neq}$ 66 kJ mol^{-1}, $\Delta S^{\neq}$ –74 J mol^{-1} K^{-1}; for 1-methyl-5-vinyltetrazole (**II**) $\Delta H^{\neq}$ 64 kJ mol^{-1}, $\Delta S^{\neq}$ –87 J mol^{-1} K^{-1}; for 2-methyl-5-vinyltetrazole (**III**) $\Delta H^{\neq}$ 70 kJ mol^{-1}, $\Delta S^{\neq}$ –76 J mol^{-1} K^{-1}. The small positive enthalpy values and negative entropy values of the process indirectly suggest that the limiting stage is bimolecular [16]. Apparently this stage consists in an electrophilic attack of methyl iodide on complex **B**.

It should be noted that the activation parameters calculated from the consumption of 5-vinyltetrazolea [equation (1)] and from the accumulation of 1- and 2-methyl-5-vinyltetrazoles (**II, III**) [equations (2, 3)] are well consistent. This fact indicates that for the process the stationarity principle is valid [17].

The regioselectivity of the process is closely connected with the establishment of the reaction mechanism of heterocyclic compounds with the electrophilic agents [18]. In this study the regioselectivity of 5-vinyltetrazole (**I**) alkylation was measured by HPLC procedure (Fig. 2). The criterion of the regioselectivity in this case might serve the selectivity factor $F=S_{III}/S_{II}$, where S_{III} and S_{II} were the areas under the chromatographic peaks of the corresponding isomers **II** and **III**.

It follows from the data obtained (Fig. 2) that the alkylation provided the regioisomers **II** and **III** in the ratio 1:1, $F = 1$. Formerly by an example of reactions of 5-aryltetrazoles the variation of factor F with the temperature was studied and permitted the identification of the mechanism of the corresponding reactions [5–7]. In reactions involving tetrazolides of **A** type the increase in the temperature led to the decrease in the F factor and consequently to the higher yield of N^{1}-isomer [5]. This fact was interpreted within the concept of two-stage reaction mechanism presuming the formation as a result

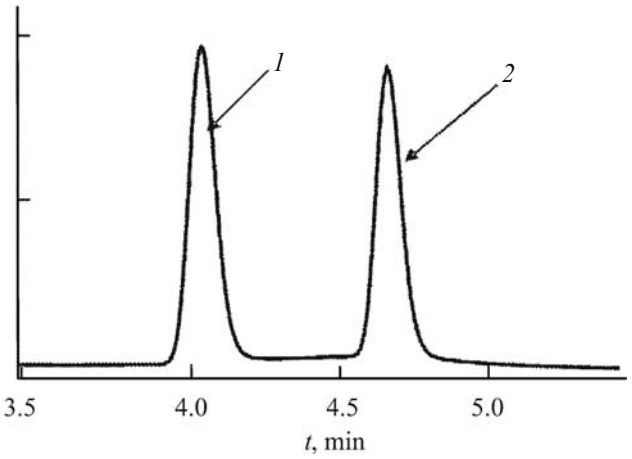


Fig. 2. Chromatogram of products of 5-vinyltetrazole (**I**) alkylation with methyl iodide at 30°C: *1,* 1-methyl-5-vinyltetrazole (**II**); *2,* 2-methyl-5-vinyltetrazole (**III**).

of the electrophilic attack on tetrazolide **A** of an unstable intermediate that further unimolecularly decomposed along two parallel routes giving the alkylation products **II** and **III**. According to this mechanism the factor F value is proportional to the difference between the partial activation energies of the formation of regioisomers.

In the reaction under investigation within 25–55°C the temperature did not affect the selectivity factor. Therefore we cannot state that the alkylation of 5-vinyltetrazole (**I**) proceeds by a two-stage mechanism formerly suggested for tetrazolides of **A** type [11]. We cannot exclude the possibility of a dual reactivity of complex **B** with respect to electrophilic reagents. Then the formation of isomers **II** and **III** should result from the occurrence of two parallel reactions: the attack of the alkylating agent on atoms N^{1} and N^{2}. Additional research is required to distinguish the two alternatiove mechanisms. First of all the electronic and geometric structure of complex **B** should be investigated.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker WM-400 at operating frequency 400 MHz, from solution in $CDCl_3$, internal reference TMS. The chromatographic studies were performed on a liquid chromatograph Shimadzu LC-10Avp equipped with an UV detector, a column 250 × 4.6 mm with a reverse phase Supelco C_{18}, particles diameter 5 μm, column at 30°C, eluent acetonitrile–0.1% H_3PO_4, 1:9.

The kinetic experiments were carried out in a temperature-controlled (±0.2°C) glass reactor equipped with

a reflux condenser with an efficient surface of heat exchange, magnetic stirrer, and adapters for sampling and dosage of reactants. 5-Vinyltetrazole (**I**) was dissolved in triethylamine, and the solution of methyl iodide in acetonitrile was added. The prepared solution was charged into the reactor preliminary heated to the temperature of the experiment. As the time of start of the reaction was taken the moment of the device achievement of the stationary temperature regime. The sum of the concentrations of the substrate reagent and the reaction products was ~4×10^{-3} mol l^{-1}. For the chromatographic measurements a precise sample of the reaction mixture was taken, diluted with eluent to the analytical concentration ~1×10^{-5} mol l^{-1}, and charged into the chromatograph with a microsyringe (20 μl).

Commercial reagents: triethylamine, acetonitrile, dimethyl sulfate, dichloromethane, and methyl iodide were additionally purified by known procedures [19, 20]. 5-Vinyltetrazole (**I**) and 5-(2-dimethylamino-ethyl)-tetrazole were prepared and purified by the known methods [21, 22]. The properties of the compounds were consistent with the published data.

1-Methyl-5-vinyltetrazole (II). To a solution of 10 g (70.8 mmol) of 5-(2-dimethylaminoethyl)tetrazole in 50 ml of water was added dropwise 16 ml (163 mmol) of freshly distilled dimethyl sulfate, maintaining pH 10 of the solution by the addition of 30% water solution of NaOH. The reaction mixture was stirred for 4 h at 40°C (pH 9–11). Further 0.1 g of hydroquinone was added for stabilization, and at stirring concn. NaOH was added to pH 12. The reaction mixture was additionally stirred for 1 h at room temperature, and then concn. H_2SO_4 was added to pH 3. The solution obtained was extracted with dichloromethane (8 × 40 ml). The combined extract was dried over $MgSO_4$, and evaporated. The residue, a mixture of isomers **II** and **III**, was separated by fractional distillation using as a stabilizer 2,2,6,6-tetramethyl-4-oxopiperidine 1-oxide. Compound **II** was additionally purified by a vacuum distillation. Yield 1.56 g (20%), bp 116–119°C (1 mm Hg), n_D^{20} 1.5025 [3]. ^{1}H NMR spectrum, δ, ppm: 3.88 (3H, CH_3), 5.67, 6.01, 6.53 (3H, Vin).

2-Methyl-5-vinyltetrazole (III) was isolated from the isomers mixture (see above) by a vacuum distillation. Yield 2.4 g (30%), bp 80°C (20 mm Hg), n_D^{20} 1.4850 [3]. ^{1}H NMR spectrum, δ, ppm: 4.11 (3H, CH_3), 5.48, 6.18, 6.60 (3H, Vin).

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