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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 75th anniversary

Kinetics of Azidation of Isomeric Benzenedicarbonitriles

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Abstract—Rate constants and activation parameters of two-step azidation of isomeric dicyanobenzenes with dimethylammonium azide in DMF at 70–100°C were determined. Tetrazole rings are formed from cyano groups in dicyanobenzenes in a stepwise mode following the 1,3-dipolar cycloaddition pattern. The rate of azidation of isomeric dicyanobenzenes is considerably higher than the rate of subsequent azidation of intermediate cyanophenyltetrazolides. The azidation rate constant decrease in going from *m*-dicyanobenzene to its *para* and *ortho* isomers.

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Dinuclear tetrazole-containing compounds are important due to their possible application as bidentante ligands for complex formation with various metal ions and starting materials for the preparation of macrocyclic compounds [1]. Benzene derivatives having two tetrazole rings as substituents attract considerable interest from both theoretical and practical viewpoints. However, no systematic studies have been performed so far on such compounds. There are no published data on the kinetics of formation of ditetrazolylbenzenes, which hinders search for optimal methods of their preparation.

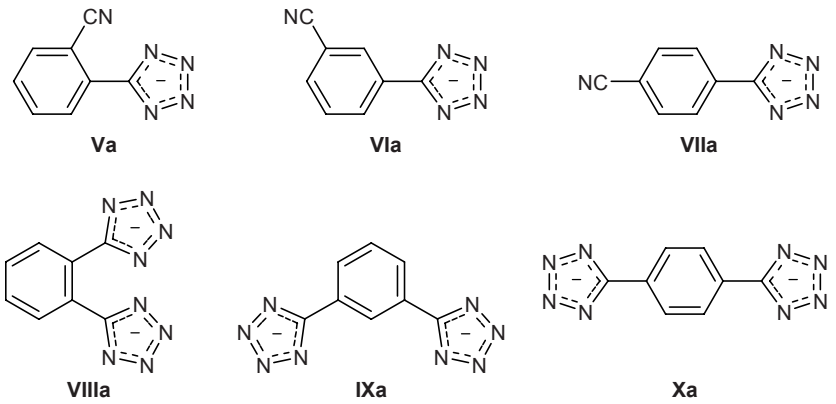
5-Aryltetrazoles are generally synthesized by reaction of substituted benzonitriles with hydrazoic acid salts [1–4]. Azidation of benzonitriles leads to the formation of the corresponding 5-aryltetrazolides, and subsequent acidification yields 5-aryl-1(2)*H*-tetrazoles. Theoretically, the process can follow two alternative paths. The first of these implies addition of azide ion at the cyano group activated by proton or Zn^{2+} ion, followed by cyclization of intermediate azidoazomethine [1]. The second path is 1,3-dipolar cycloaddition of azide to nitrile [1, 3].

In the present work we examined the kinetics and mechanism of azidation of *o*-, *m*-, and *p*-dicyanobenzenes **I**–**III** with dimethylammonium azide in DMF. The kinetic measurement were performed using high-performance liquid chromatography (HPLC). We also used benzonitrile (**IV**) as model substrate; the corresponding azidation rate constants were determined by us previously by gas chromatography, $k^{II} \times 10^4$: 0.78, 1.61, 3.44, 7.88, and 16.40 l mol^{-1} s^{-1} at 80, 90, 100, 110, and 120°C, respectively [4].

The kinetics of azidation of nitriles **I**–**IV** were studied under pseudofirst-order conditions with respect to the substrate in the temperature range from 70 to

Table 1. Rate constants for azidation of isomeric dicyanobenzenes **I**–**III**, benzonitrile **IV**, and isomeric cyanophenyltetrazolides **Va**–**VIIa** in DMF

Temperature, °C	I	II	III	IV	Va	VIa	VIIa
	$k_1^{II} \times 10^3$, l mol^{-1} s^{-1}			$k^{II} \times 10^4$, l mol^{-1} s^{-1}	$k_2^{II} \times 10^5$, l mol^{-1} s^{-1}		
70	1.1	2.2	2.0	0.3	1.2	4.5	2.9
80	2.4	4.1	4.0	0.8	2.4	9.1	5.4
90	4.1	7.7	7.1	1.5	4.8	17.0	10.6
100	8.0	13.3	12.1	3.5	9.0	31.7	17.2



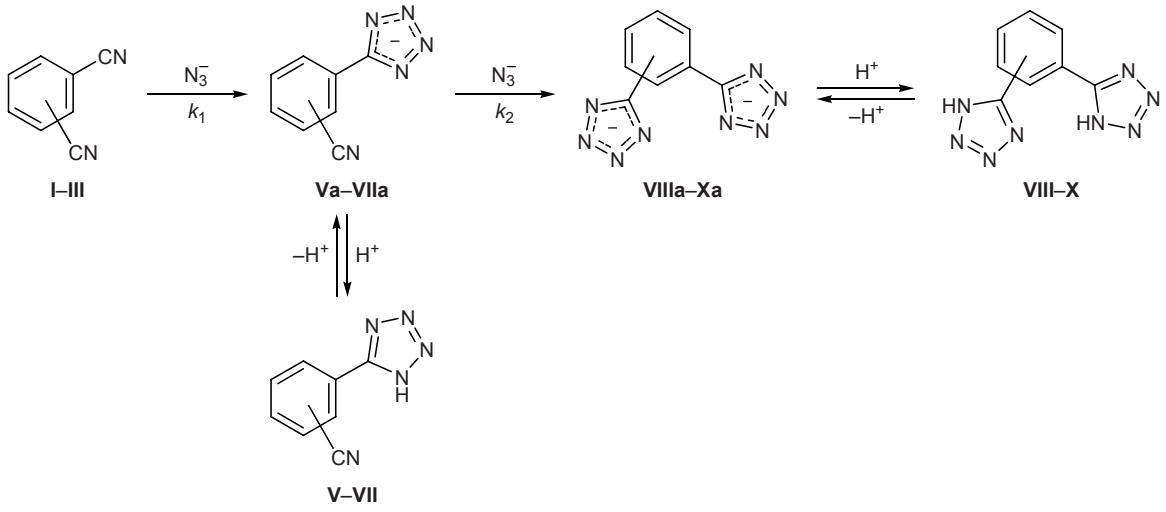
100°C. As azidating agent we used dimethylammonium azide (10 equiv per cyano group). It is known that dimethylammonium azide at a concentration of about 0.1 M reacts with nitriles in the form of H complex $Me_2N^+H_2\cdots N_3^-$ which is capable of reacting as 1,3-dipole [4, 5].

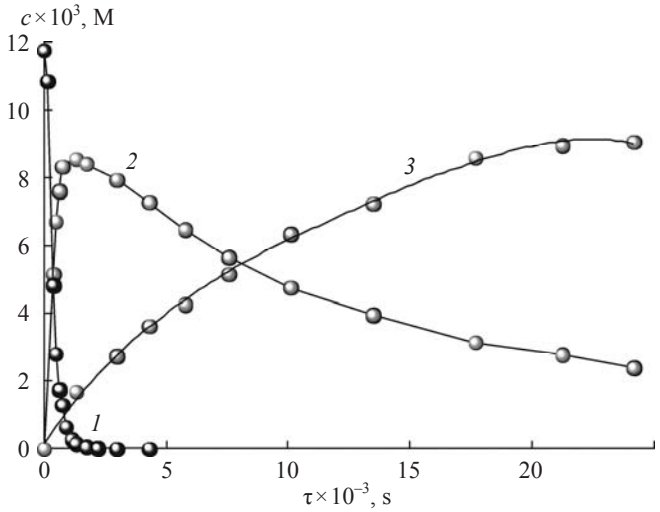
The concentrations of the initial reactants and intermediate and final products were monitored by HPLC (UV detector). Unlike GLC used previously, this technique allowed us to trace variations in the concentration of all main components of the reaction mixture with time. The rate constants k^{II} for azidation of benzonitrile (**IV**), determined in the present work (Table 1), were very consistent with the data reported previously [4], which demonstrated suitability of the developed procedure for kinetic measurements. Within the examined range of reactant concentrations, the rate constants did not depend on equilibrium dissociation processes, so that they can be used to compare the reactivity of substrates, as well as to determine activation parameters.

HPLC analysis of the reaction mixtures showed that azidation of isomeric dicyanobenzenes **I**–**III** occurs in succession at each cyano group. Cyanophenyltetrazolides **Va**–**VIIa** are formed initially, and their subsequent azidation yields ditetrazolides **VIIIa**–**Xa** (Scheme 1). Monitoring of the current concentrations of the initial reactants and intermediate and final products revealed no any by-products. It is important that the sum of the concentrations of dicyanobenzenes, cyanophenyltetrazolides, and phenyleneditetrazolides in the reaction mixture remains constant during the process. These data indicate high conversion of the initial reactants and the absence of by-products.

The plots of the concentrations of compounds **I**–**III** and **Va**–**Xa** in the reaction mixture versus time are typical kinetic curves for consecutive first-order reactions (see figure). The pseudofirst-order rate constants (k_1^I, k_2^I) for azidation of isomeric dicyanobenzenes **I**–**III** and cyanophenyltetrazolides **Va**–**VIIa** were determined from the kinetic equations for consecutive first-order reactions [6, 7]. The pseudofirst order of the

Scheme 1.





Plots of the concentration of compounds (*1*) **II**, (*2*) **VIa**, and (*3*) **IXa** versus time in the azidation of benzene-1,3-dicarbonitrile (**II**) in DMF at 100°C.

reaction with respect to dimethylammonium azide was confirmed by linearity of the apparent azidation rate constants k_1^I and k_2^I in the concentration of dimethylammonium azide. The second-order rate constants k_1^{II} and k_2^{II} were determined from the slopes of the above linear dependences (Table 1). It is seen that the rate of the first step of azidation of dicyanobenzenes **I–III** is considerably higher than the rate of azidation of benzonitrile (**IV**) (Table 1). This may be due to electron-withdrawing effect of the second cyano group. It is known that electron-withdrawing substituents considerably increase the reactivity of nitriles toward alkylammonium azides [4]. The azidation of isomeric cyanophenyltetrazolides **Va–VIIa** is a much slower process than the azidation of nitriles **I–IV**. The reason is the presence of negatively charged tetrazolide substituent in the benzene ring of **Va–VIIa**. This substituent exerts no pronounced electron-acceptor effect ($\sigma_I = 0.12$, $\sigma_m = 0.09$ [8]) and hence does not accelerate azidation of **Va–VIIa**.

Table 2. Activation parameters of azidation of isomeric dicyanobenzenes **I–III** and cyanophenyltetrazolides **Va–VIIa** in dimethyldormamide

Substrate no.	E_a, kJ/mol	$\Delta H^{\neq}$, kJ/mol	$-\Delta S^{\neq}$, J mol^{-1} K^{-1}
I	68	66	112
II	65	62	117
III	63	60	123
Va	72	69	139
VIa	69	67	137
VIIa	64	62	154

Comparison of the rate constants k_1^{II} and k_2^{II} for the azidation of isomeric dicyanobenzenes **I–III** shows that 1,3-dicyano isomer **II** is the most reactive in the first step. The rate constants for the azidation of compounds **II** and **III** are fairly similar and are almost twice as high as that for 1,2-dicyanobenzene (**I**). The differences in the rates of azidation of isomeric cyanophenyltetrazolides **Va–VIIa** are even more appreciable. The rate of azidation of 5-(3-cyanophenyl)tetrazolide (**VIa**) is considerably higher than those found for compounds **Va** and **VIIa**. Presumably, the tetrazolide group in the *meta* position with respect to the cyano group stabilizes the transition state (chelation effect), which is impossible in the reaction with *para* isomer **VIIa**. Steric hindrances in *ortho* isomer **Va** slow down the reaction.

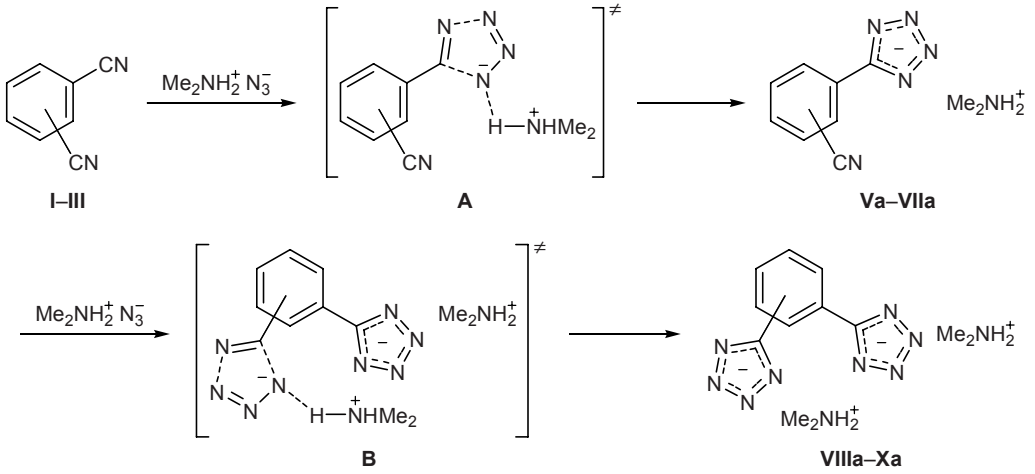
The activation parameters for each step of azidation of isomeric dicyanobenzenes **I–III** were determined on the basis of the kinetic data according to Arrhenius–Eyring [9] (Table 2). Relatively small positive enthalpies of activation (<85 kJ/mol) and negative entropies of activation suggest that the rate-determining steps in the azidation of dicyanobenzenes **I–III** and cyanophenyltetrazolides **Va–VIIa** are bimolecular reactions [9]. The activation parameters determined for the first and second azidation steps are typical of transition states in 1,3-dipolar cycloaddition [4, 10]. A probable reaction mechanism is illustrated by Scheme 2.

In the first step, azidation of one cyano group through activated complex **A** gives cyanophenyltetrazolides **Va–VIIa**. In the second step, azidation of the second cyano group, which also follows 1,3-dipolar cycloaddition pattern, yields the corresponding ditetrazolides **VIIIa–Xa** through activated complex **B**.

EXPERIMENTAL

The UV spectra were recorded on a Shimadzu UV-2401 PC spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured from solutions in DMSO-d_6 on a Bruker DPX-300 instrument at 300 and 75 MHz, respectively, using tetramethylsilane as internal reference. The kinetic measurements were performed using a Shimadzu LC-10Avp liquid chromatograph equipped with a UV detector; Supelco C_{18} reversed-phase column, 250×4.6 mm, grain size 5 μm; temperature 30°C; eluent acetonitrile–0.1% H_3PO_4, 40:60; working wavelengths: λ 238 nm for benzonitrile (**IV**), λ 237 nm for

Scheme 2.



1,2- and 1,4-dicyanobenzenes **I** and **III**, and λ 226 nm for 1,3-dicyanobenzene (**II**).

Kinetic experiments were carried out in a glass reactor equipped with an effective reflux condenser, magnetic stirrer, and fittings for sample withdrawal and dosage. The corresponding dicyanobenzene and dimethylammonium azide were dissolved in dimethylformamide, and the solution was transferred into the reactor preliminarily heated to a temperature close to the required one. The temperature was maintained with an accuracy of ±0.2°C. The moment corresponding to attainment of stationary temperature was taken as reaction start. The overall concentration of the substrate and products was about 0.01 M. Accurately measured samples of the mixture were withdrawn and diluted with acidified eluent to an analytical concentration of about 10^{-5} M. Under these conditions, tetrazolides **Va**–**Xa** were completely converted into neutral NH forms **V**–**X**. Samples were introduced into the injection loop (20 μl) using a microsyringe.

Commercial acetonitrile and dimethylformamide were additionally purified by standard procedures [11, 12]. Dimethylammonium azide was prepared from dimethylamine hydrochloride and sodium azide in DMF according to the procedure described previously [4]. Isomeric dicyanobenzenes **I**–**III** were commercial products (Merck) containing no less than 98% of the main substance and were used without additional purification.

2-(1*H*-Tetrazol-5-yl)benzonitrile (V). Sodium azide, 0.76 g (11.7 mmol), and dimethylamine hydrochloride, 0.95 g (11.7 mmol), were added to a solution of 3 g (23.4 mmol) of benzene-1,2-dicarbonitrile (**I**) in 40 ml of DMF, and the mixture was stirred for 5 h at 100°C. The precipitate of sodium chloride was filtered off, the filtrate was evaporated under reduced pressure, the solid residue was dissolved in 200 ml of water, and the solution was adjusted to pH 8 by adding 1% aqueous sodium hydroxide. Unreacted compound **I** was filtered off, the filtrate was acidified to pH 2 with concentrated hydrochloric acid, and the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.65 g (41%), colorless crystals, mp 224°C. ^{1}H NMR spectrum, δ, ppm: 7.53–8.06 m (4H, H_{arom}), 16.14 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 110.3, 127.6, 129.7, 131.3, 133.7, 134.9 (C_{arom}); 117.2 (CN); 155.6 (C^5). Found, %: C 56.37; H 3.14; N 40.51. $C_8H_6N_8$. Calculated, %: C 56.14; H 2.92; N 40.94.

3-(1*H*-Tetrazol-5-yl)benzonitrile (VI) was synthesized in a similar way. Yield 1.81 g (45%), colorless crystals, mp 156°C. ^{1}H NMR spectrum: δ 7.79–8.34 ppm, m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 112.9, 126.3, 130.7, 131.1, 131.8, 134.9 (C_{arom}); 118.4 (CN); 155.4 (C^5). Found, %: C 56.26; H 3.18; N 40.57. $C_8H_6N_8$. Calculated, %: C 56.14; H 2.92; N 40.94.

4-(1*H*-Tetrazol-5-yl)benzonitrile (VII) was synthesized in a similar way. Yield 1.60 g (40%), colorless crystals, mp 194°C. ^{1}H NMR spectrum: δ 7.83–8.23 ppm, m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 113.8, 129.2, 128.0, 133.7 (C_{arom}); 118.6 (CN); 155.6 (C^5). Found, %: C 56.13; H 2.99; N 41.01. $C_8H_6N_8$. Calculated, %: C 56.14; H 2.92; N 40.94.

Isomeric phenyleneditetrazoles **VIII**–**X** were synthesized by reaction of the corresponding dicyanobenzenes **I**–**III** with triethylamine hydrochloride and sodium azide in toluene as described in [13].

5,5′-(1,2-Phenylene)bis(1*H*-tetrazole) (VIII). mp 227°C. ^{1}H NMR spectrum, δ, ppm: 7.80–7.90 m

(4H, H_{arom}), 16.52 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 124.6, 130.8, 131.4 (C_{arom}), 154.8 (C^5). Found, %: C 44.90; H 2.51; N 52.83. $C_8H_6N_8$. Calculated, %: C 44.86; H 2.80; N 52.34.

5,5′-(1,3-Phenylene)bis(1*H*-tetrazole) (IX). mp 260°C. ^1H NMR spectrum, δ, ppm: 7.82–8.77 m (4H, H_{arom}), 16.47 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 125.3, 125.6, 129.3, 130.6 (C_{arom}); 155.5 (C^5). Found, %: C 44.42; H 2.84; N 52.65. $C_8H_6N_8$. Calculated, %: C 44.86; H 2.8; N 52.34.

5,5′-(1,4-Phenylene)bis(1*H*-tetrazole) (X). mp 300°C. ^1H NMR spectrum: δ 8.22 ppm, m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 126.7, 127.9 (C_{arom}); 155.4 (C^5). Found, %: C 45.14; H 3.27; N 52.86. $C_8H_6N_8$. Calculated, %: C 44.86; H 2.8; N 52.34.

The properties of compounds **V**–**X** were consistent with published data [14, 15].

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