Russian Journal of General Chemistry, Vol. 71, No. 5, 2001, pp. 763–766. Translated from Zhurnal Obshchei Khimii, Vol. 71, No. 5, 2001, pp. 814–817.

Hydrolysis of *N*-Cyanoazoles

S. V. Pan'kov, N. A. Belyakova, V. V. Vishnyakov, and P. P. Purygin

Samara State University, Samara, Russia

Received June 23, 1999

Abstract—The hydrolysis kinetics of *N*-cyanoazoles in alkaline solutions is described by a first-order kinetic equation with respect to the substrate and concentration of hydroxide ions. The hydrolysis rate constants increase with increasing number of nitrogen atoms in the heterocyclic moiety and decrease with introduction of the annelated benzene ring.

1-Cyanoazoles show promise as water-soluble condensing agents. They can be successfully used to effect formation of phosphodiester [1–4] and amide (peptide) bonds [5, 6] in organic and aqueous solutions. However, no data are available on stability of these compounds in aqueous solutions, which limits their use as water-soluble condensing agents.

In this work we studied the hydrolysis kinetics of 1-cyanoazoles in aqueous solutions at pH 8–11 with the aim to obtain new data on the influence of pH and structure of 1-cyanoazoles on their stability.

We have studied the hydrolysis kinetics of 1-cyanoimidazole (**I**), 1-cyanobenzimidazole (**II**), 1-cyano-1,2,4-triazole (**III**), 1-cyanobenzotriazole (**IV**), and 2-methyl-1-cyanoimidazole (**V**) in tetraborate aqueous buffer solutions containing 5.71 vol % 1,4-dioxane. The reaction progress was monitored by electronic spectroscopy.

Hydrolysis of *N*-cyanoazoles **I**–**V** was performed under pseudo-first-order conditions. Variation of the concentration of **I**–**V** in time at constant pH is well described by an equation for an irreversible first-order reaction. The dependence in the coordinates $\ln(1/c_{az}) = f(t)$ is linear up to 85–95% conversion for **I** and **III**–**V** and up to 70% conversion for **II**. Figure 1 shows as example the kinetic curves of hydrolysis (in semilog coordinates) of nitrile **I** at various pH.

These data suggest that hydrolysis of **I**–**V** is first-order with respect to the substrate. The kinetic equation of the reaction is as follows:

$$-dc_{az}/dt = k_{app}c_{az},$$

$$k_{app} = k_{H_2O} + k_{HO^-}c_{HO^-},$$

where c_{az} is the cyanoazole concentration, k_{app} is the apparent rate constant of hydrolysis, k_{H_2O} is the rate constant of spontaneous hydrolysis, and k_{HO^-} is the rate constant of base hydrolysis.

The calculated apparent rate constants of hydrolysis of *N*-cyanoazoles **I**–**V** (k_{app}) at 30°C and various pH are listed in the table.

The linearity of the dependences in the coordinates $k_{app} = f(\text{HO}^-)$ (Fig. 2) suggests that the reaction is first-order with respect to hydroxide ions and that the hydrolysis of *N*-cyanoazoles **I** and **III**–**V** mainly occurs by the pathway involving hydroxide ions.

From data in Fig. 2, we calculated the rate constants of base hydrolysis k_{HO^-}, l mol^{-1} s^{-1}: **I**, 171 ± 13; **II**, 2.21 ± 0.10; **III**, 3000 ± 170; **IV**, 4.40 ± 0.01; **V**, 29.8 ± 0.5; and **VI**, 3730 ± 280.

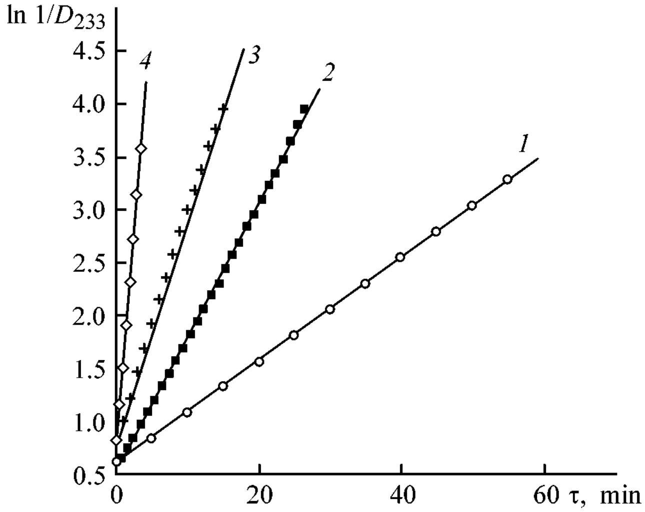


Fig. 1. Kinetic curves of hydrolysis of 1-cyanoimidazole **I** (in semilog coordinates) at 30°C and pH (*1*) 8.35, (*2*) 8.74, (*3*) 9.14, and (*4*) 9.70.

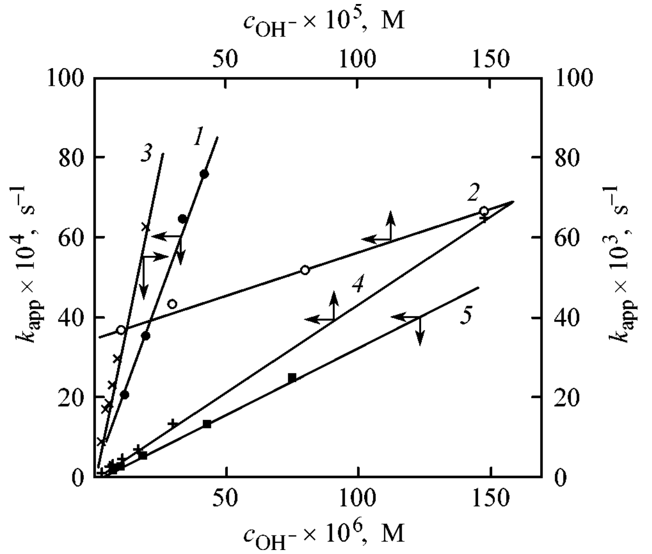
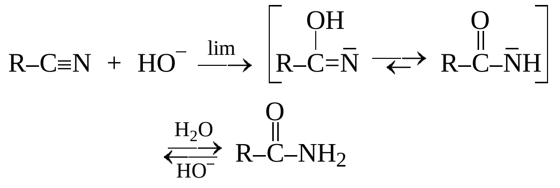


Fig. 2. Apparent rate constants of hydrolysis (k_{app}) of cyanoazoles **I**–**V** at 30°C as functions of the concentration of hydroxide ions at 30°C: (*1*) 1-cyanoimidazole **I**, (*2*) 1-cyanobenzimidazole **II**, (*3*) 1-cyano-1,2,4-triazole **III**, (*4*) 1-cyanobenzotriazole **IV**, and (*5*) 1-cyano-2-methylimidazole **V**.

To construct the schemes of hydrolysis of **I**–**V**, we analyzed, along with the kinetic data, also published data on the mechanism of hydrolysis of compounds containing the cyano group and studied the intermediate and final products of hydrolysis of **I**–**V**.

Published data [7] on base hydrolysis of the cyano group in molecules of various organic compounds suggest the following mechanism:



$$R\text{–}C{\equiv}N + HO^- \xrightarrow{\text{lim}} \left[R\text{–}\overset{OH}{\overset{|}{C}}{=}\bar{N}^- \rightleftarrows R\text{–}\overset{O}{\overset{\|}{C}}\text{–}\bar{N}H^-\right] \underset{HO^-}{\overset{H_2O}{\rightleftarrows}} R\text{–}\overset{O}{\overset{\|}{C}}\text{–}NH_2 \qquad (1)$$

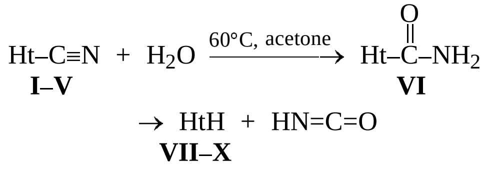
R = Alk, ArO, ArS, R_2N.

If the reaction is not stopped at the stage of the amide derivative, its final product is the carboxy derivative [7].

Study of the hydrolysis products of **I**–**V** by UV and IR spectroscopy and by TLC showed that the reaction products are the H forms of azoles rather than their carbamoyl or carboxy derivatives as in scheme (1).

To find in what stage the functional group is eliminated, we have studied the reactions of **I**–**V** with an equivalent amount of water in acetone.

We found that cyanoazoles **I**, **II**, **IV**, and **V** give azoles **VII**–**X**, and compound **III** gives 1-carbamoyl-1,2,4-triazole **VI** [scheme (2)]. Compound **VI** was also prepared in [8] by reaction of 1,2,4-triazole with cyanogen bromide in water, presumably via formation of 1-cyano-1,2,4-triazole.



$$\underset{\textbf{I–V}}{Ht\text{–}C{\equiv}N} + H_2O \xrightarrow{60°\text{C, acetone}} \underset{\textbf{VI}}{Ht\text{–}\overset{O}{\overset{\|}{C}}\text{–}NH_2} \rightarrow \underset{\textbf{VII–X}}{HtH} + HN{=}C{=}O \qquad (2)$$

Ht = imidazol-1-yl (**I**, **VII**), benzimidazol-1-yl (**II**, **VIII**), 1,2,4-triazol-1-yl (**III**, **VI**), benzotriazol-1-yl (**IV**, **IX**), and 2-methylimidazol-1-yl (**V**, **X**).

Apparent rate constants of hydrolysis (k_{app}, s^{-1}) of 1-cyanoazoles **I**–**V** and 1-carbamoyl-1,2,4-triazole **VI** at 30°C

Comp. no.	pH	$k_{app} \times 10^4$	Comp. no.	pH	$k_{app} \times 10^4$
I	8.35	8.08 ± 0.06	**IV**	9.30	1.18 ± 0.01
	8.74	20.9 ± 0.2		9.59	2.55 ± 0.02
	9.14	35.4 ± 0.8		9.70	3.00 ± 0.05
	9.36	64.5 ± 0.9		9.88	4.47 ± 0.04
	9.45	75.7 ± 2.0		10.31	13.2 ± 0.2
II	9.88	36.6 ± 0.2		11.00	65.0 ± 0.6
	10.31	43.3 ± 3.5	**V**	8.58	1.61 ± 0.06
	10.73	51.8 ± 4.1		8.80	2.75 ± 0.04
	11.00	66.3 ± 2.6		9.08	5.58 ± 0.33
III	8.25	87.2 ± 0.8		9.45	13.2 ± 0.1
	8.49	169 ± 6		9.70	24.9 ± 0.4
	8.58	185 ± 3	**VI**	7.85	60.2 ± 0.36
	8.65	230 ± 5		8.26	130.38 ± 0.40
	8.80	298 ± 14		8.50	197.7 ± 5.1
	9.13	626 ± 23		8.65	270.3 ± 8.7

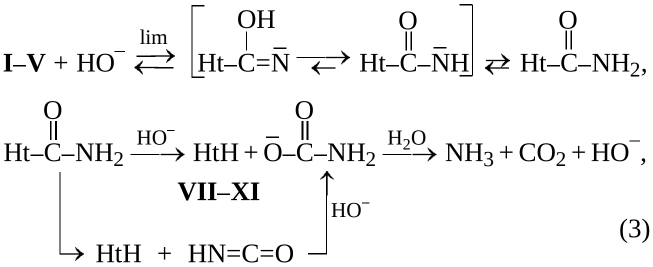
Formation of amide **VI** suggests that hydrolysis of cyanotriazole **III** follows scheme (1). From the other cyanoazoles **I**, **II**, **IV**, and **V**, 1-carbamoyl derivatives are probably also formed, but, as shown in [9], they are extremely unstable and spontaneously decompose to azole and isocyanic acid.

Under conditions of the kinetic experiments on hydrolysis of **I**–**V**, we did not observe accumulation of the carbamoyl intermediate, which suggests its higher reactivity as compared to the 1-cyano precursor. To confirm this conclusion, we studied the hydrolysis kinetics of **VI** in the range pH 8–11 (see table).

Similar to cyanoazoles **I**–**V**, the kinetic equation for hydrolysis of **VI** is first-order with respect to the concentrations of **VI** and hydroxide ions.

Comparison of the rate constants of base hydrolysis (k_{HO^-}) of cyanotriazole **III** and amide **VI** (see table) shows that the 1-carbamoyl derivative is more reactive and therefore cannot accumulate in the course of hydrolysis of the 1-cyano derivative.

Based on our kinetic data, studies of hydrolysis products, and published data, we suggest the following scheme of hydrolysis of **I**–**V** with the participation of hydroxide ions:



$$\mathbf{I{-}V} + HO^- \overset{lim}{\rightleftarrows} \left[Ht{-}\overset{OH}{\overset{|}{C}}{=}\bar{N} \rightleftarrows Ht{-}\overset{O}{\overset{\|}{C}}{-}\bar{N}H \right] \rightleftarrows Ht{-}\overset{O}{\overset{\|}{C}}{-}NH_2,$$

$$\begin{tikzcd}[column sep=small] \underset{\mathbf{VII{-}XI}}{Ht{-}\overset{O}{\overset{\|}{C}}{-}NH_2} \arrow[r, "HO^-"] \arrow[d] & HtH + \bar{O}{-}\overset{O}{\overset{\|}{C}}{-}NH_2 \arrow[r, "H_2O"] & NH_3 + CO_2 + HO^-, \\ HtH + HN{=}C{=}O \arrow[ur, "HO^-"'] & & \end{tikzcd} \qquad (3)$$

Ht = imidazol-1-yl (**I**, **VII**), benzimidazol-1-yl (**II**, **VIII**), 1,2,4-triazol-1-yl (**III**, **XI**), benzotriazol-1-yl (**IV**, **IX**), and 2-methylimidazol-1-yl (**V**, **X**).

The calculated rate constants of base hydrolysis k_{HO^-} (see table) show that the reactivity of cyanoazoles **I**–**V** decreases in the order **III** > **I** > **V** > **IV** > **II**, which is fully consistent with the order of reactivities of *N*-acetyl azole derivatives in hydrolysis [10]. The different susceptibility to nucleophilic attack is due to the fact that the residues of azole-containing heterocycles exhibit acceptor properties which increase with increasing number of nitrogen atoms in the ring and decrease in going from the five-membered ring to the annelated system. This trend is also consistent with the trend in variation of the acid dissociation constants of the H forms of the corresponding azoles [11].

EXPERIMENTAL

The rate of hydrolysis of **I**–**VI** in aqueous buffer solutions containing 5.71 vol % dioxane was determined from the variation of the concentration of the initial cyanoazole, monitored spectrophotometrically. The optical densities of the reaction mixtures D_λ were measured with an SF-46 spectrophotometer at the following wavelengths, nm: **I** and **V**, 233.0 ± 0.5; **II**, 287.0 ± 0.5; **III**, 217.0 ± 0.5; **IV**, 308.0 ± 0.5; and **VI**, 215.0 ± 0.5.

Tetraborate buffer solutions with definite pH were prepared according to [12]. Before hydrolysis and after its completion, their pH was checked with a pH-673M pH meter.

The buffer solution was charged to a cell placed in the temperature-controlled unit of the spectrophotometer. The cell was sealed with a tight lid to prevent uptake of CO_2 from air. After attaining the required temperature, a freshly prepared solution of cyanoazole **I**–**V** in 1,4-dioxane was added in amount necessary to obtain the concentrations of cyanoazoles **I**–**V** and amide **VI** ($c \times 10^4$, M) of 3.0, 4.4, 5.1, 3.3, 1.5, and 6.5, respectively, and the concentration of 1,4-dioxane of 5.71 vol %. The optical density of the solution was measured at regular intervals. The error in determination of the kinetic characteristics was calculated by the formulas of the mathematical statistics [13].

Cyanoazoles **I**–**V** prepared according to [14] were preliminarily sublimed in a vacuum (1 mm Hg). Analytically pure grade 1,4-dioxane was purified to eliminate impurities absorbing at $\lambda > 213$–215 nm according to [15]. Tetraborate buffer solutions were prepared from hydrochloric acid, sodium hydroxide, and sodium tetraborate (all chemically pure grade); the latter was recrystallized two times from water.

1-Carbamoyl-1,2,4-triazole VI. A solution of 0.2 g of cyanotriazole **III** in 10 ml of acetone containing 0.077 g of water was brought to reflux and kept at this temperature for 5 min. Then the solvent was distilled off, and the residue was recrystallized from 1,4-dioxane. Compound **VI** was obtained in a yield of 0.167 g (70%); its physicochemical properties agreed with the published data [8].

Hydrolysis of **I**, **II**, **IV**, and **V** under similar conditions results in regeneration of the corresponding azoles (IR and TLC data).

REFERENCES

1. Ferris, P., Huang, C., and Hagan, W.Y., *Nucleosides Nucleotides*, 1985, vol. 3, no. 3, pp. 407–414.

2. Eiko, K. and Hiroshi, Y., *Symp. Nucl. Acids Chem.*, 1986, vol. 14, no. 30, pp. 101–104.
3. Li, T., Weinstein, D.S., and Nicolaou, K.C., *Chem. Biol.*, 1997, vol. 4, no. 3, pp. 209–214.
4. Zuber, G. and Behr, J.P., *Biochemistry*, 1994, vol. 33, no. 26, pp. 8122–8127.
5. Purygin, P.P. and Pan’kov, S.V., *Zh. Org. Khim.*, 1996, vol. 32, no. 6, pp. 903–905.
6. Pan’kov, S.V. and Purygin, P.P., *Zh. Org. Khim.*, 1996, vol. 32, no. 6, p. 950.
7. March, *J., Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, New York: McGraw-Hill, 1968. Translated under the title *Organicheskaya khimiya. Reaktsii, mekhanizmy i struktura*, Moscow: Mir, 1987, vol. 3, p. 331.
8. Beser, H.G.O. and Eisenschmidt, V., *J. Pr. Chem.*, 1973, vol. 315, no. 4, pp. 640–648.
9. Staab, H.A., *Angew. Chem.*, 1962, vol. 74, no. 12, p. 418.
10. Staab, H.A., *Angew. Chem.*, 1962, vol. 74, no. 12, pp. 407–409.
11. *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*, Barton, D. and Ollis, W.D., Eds., Oxford: Pergamon, 1979. Translated under the title *Obshchaya organicheskaya khimiya*, Moscow: Khimiya, 1985, vol. 8, p. 437.
12. *Spravochnik khimika*, Nikol’skii, B.P., Ed., Moscow: Khimiya, 1964, vol. 3, p. 175.
13. Spiridonov, V.P. and Lopatkin, A.A., *Matematicheskaya obrabotka fiziko-khimicheskikh dannykh* (Mathematical Processing of Physicochemical Data), Moscow: Mosk. Gos. Univ., 1970, pp. 94–100.
14. Purygin, P.P. and Pan’kov, S.V., *Zh. Org. Khim.*, 1995, vol. 31, no. 6, pp. 934–936.
15. Gitis, S.S., Glaz, A.I., and Ivanov, M.K., *Praktikum po organicheskoi khimii* (Practical Course of Organic Chemistry), Moscow: Vysshaya Shkola, 1991, p. 48.