==

Dedicated to Prof. G.I. Koldobskii
on the 70th Anniversary of His Birth

Thermal Decomposition of 3′-Azidothymidine

V. V. Nedel'ko[1], B. L. Korsunskii[1], N. V. Chukanov[1], T. S. Larikova[1], E. V. Korchevskaya[2], A. A. Malin[2], M. B. Shcherbinin[2], and V. A. Ostrovskii[2]

[1] *Institute of Chemical Physics Problems, Russian Academy of Sciences,*
Chernogolovka, Moscow oblast, 142432 Russia
e-mail: vnedelko@icp.ac.ru

[2] *St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 198013 Russia*

Abstract—The kinetics of thermal decomposition of 3′-azidothymidine (AZT) in melt at 140–201°C were studied by the thermogravimetric and manometric methods. The process follows the first-order kinetics and is decribed by the Arrhenius equation: $k = 10^{14.7 \pm 0.5} \exp[-(38\,100 \pm 900)/RT]$ (1/s). The kinetic and activation parameters are typical of thermal decomposition of aliphatic azides; they suggest that decomposition of the azido group is the rate-determining stage. The formation of nitrogen (1 mol per mole of AZT), furan, methyl alcohol, water, and carbon dioxide was confirmed by mass spectrometry. Thymine was found to be one of the condensed products of thermal decomposition of 3′-azidothymidine.

3′-Azidothymidine (AZT) is an efficient inhibitor of the HIV reverse transcriptase. Despite the fact that some new inhibitors of the reverse transcriptase and protease have appeared in the pharmaceutical market, the significance of AZT as the most important anti-HIV drug has not been reduced [1].

In the recent publications, considerable attention is given to kinetic studies of processes leading to formation of AZT [2, 3]. These studies are important from the viewpoint of understanding the mechanisms of some key reactions in nucleoside synthesis, as well as for solving a number of technological problems. Nevertheless, the available data cannot be regarded as sufficient without information on thermal decomposition of products and intermediates of the above reactions. Quantitative data on their thermal transformations may be useful for interpretation of biological activity of AZT and its metabolism.

In the present work we studied the kinetics of thermal decomposition of AZT and proposed possible ways and mechanism of this process. A molecule of AZT contains two fragments whose thermal decomposition may initiate profound decomposition of the entire molecule. These are the azido group and nucleoside moiety. Thermal decomposition of alkyl and aryl azides has been well documented [4, 5].

Thermal decomposition of nucleosides was studied in [6–8]. Comparison of the activation parameters typical of these processes makes it possible to substantiate a probable mechanism of thermal decomposition of 3′-azidothymidine.

When a sample of AZT was heated in air at a rate of 4 deg/min, no decomposition was observed up to 180°C (Fig. 1). Above that temperature, stepwise decomposition occurred. The first stage was accompanied by a weight loss of ~20% (up to 230°C). The subsequent decomposition (230–260°C) was slow.
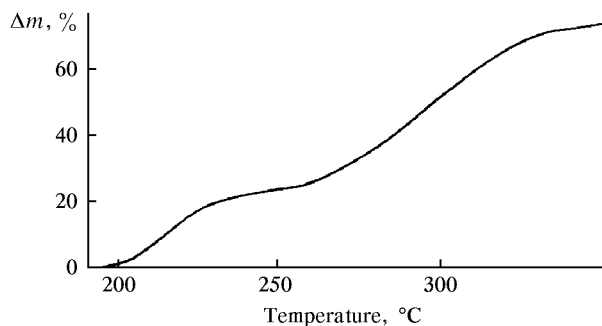

Fig. 1. Plot of the weight loss (Δm) versus temperature in the nonisothermal decomposition of AZT in air (sample weight 10 mg, heating rate 4 deg/min).
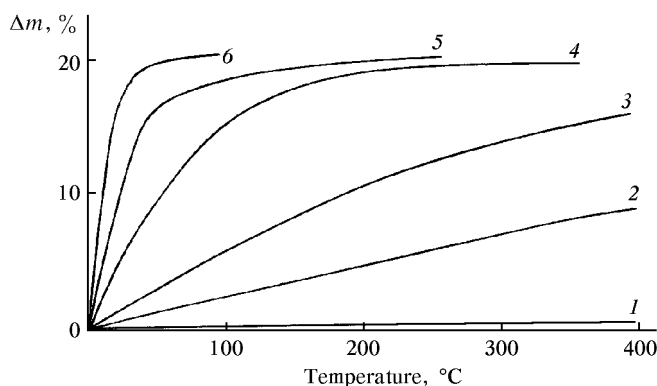
Fig. 2. Kinetics of thermal decomposition of AZT in air at (*1*) 140°C, (*2*) 158°C, (*3*) 169°C, (*4*) 183°C, (*5*) 192°C, and (*6*) 201°C; thermogravimetry, sample weight 40 mg.
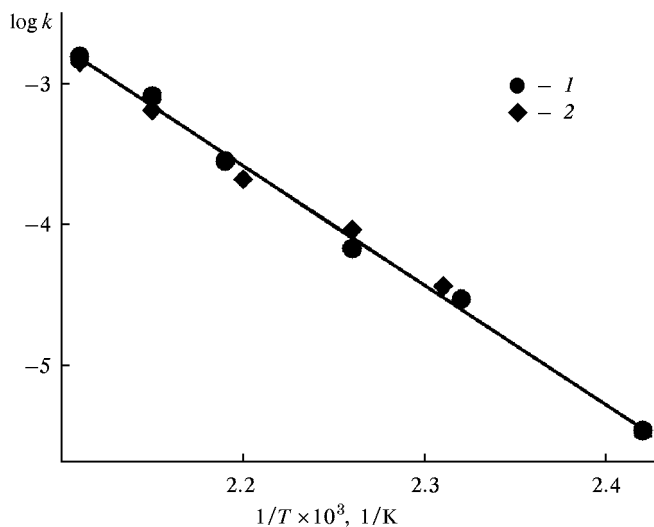

Fig. 3. Arrhenius plot for the first-order rate constant of thermal decomposition of AZT according to (*1*) thermogravimetric and (*2*) manometric measurements.

The rate of thermolysis increases on further heating, presumably as a result of thermooxidative processes. It seems to be important that the kinetic curve for wieght loss of AZT almost does not change up to 250°C on replacement of air by argon (1 atm). This means that the first decomposition stage is a purely thermal process which is not accompanied by oxidation. Under conditions of a dynamic vacuum (continuous evacuation of the reaction vessel) above 170°C, the contribution of sample evaporation becomes appreciable. Taking the above stated into account, the subsequent termogravimetric study of AZT decomposition under isothermal conditions was performed in air at temperatures above the melting point.

Figure 2 shows kinetic curves for thermal decomposition of AZT. The process follows the first-order kinetics, as indicated by the linear plots in the coordinates $\ln(m_\infty - m)\,\tau$, where m_∞ is the total weight loss in the first decomposition stage (20% of the initial weight), and m is the weight loss by a time moment τ. The rate constants $k_1 \times 10^5$ at 140, 158, 169, 183, 192, and 201°C are, respectively, 0.35, 2.9, 6.8, 28, 81, and 147 s^{-1}. Manometric study of the first decomposition stage in the temperature range from 160 to 201°C also revealed the first-order kinetics. The rate constants $k_1' \times 10^5$ at 160, 170, 181, 191, and 201°C, are, respectively, 3.6, 9.2, 21, 64, and 146 s^{-1}. The rate constants for thermal decomposition of AZT, determined by the thermogravimetric (k_1) and manometric methods (k_1'), are very similar. The above listed values fit a common Arrhenius equation (Fig. 3):

$$k \ = \ 10^{14.7 \pm 0.5} \exp[-(38\,100 \pm 900)/RT]\ \ (\text{s}^{-1});$$

$$r \ = \ 0.997, \ \ s \ = \ 0.063, \ \ n \ = \ 11.$$

In thermogravimetric experiments decomposition of AZT occurs in an open reaction system, whereas manometric experiments are carried out in a vessel with a limited volume. Therefore, the similarity between the rate constants obtained in the two series of experiments suggests that there is no appreciable effect of AZT decomposition products on the kinetics of the process. On the other hand, comparison of the thermogravimetric (in air) and manometric kinetic data (in a vacuum) indicates once more that the reaction under study is not accompanied by thermooxidative processes.

By cooling the gaseous AZT thermolysis products in the Bourdon gage from 25°C to –196°C (liquid nitrogen) we found that the volume fraction of nitrogen among these products is 95.2%. According to the mass spectrometric data, nitrogen is the major gaseous product formed in the first stage of thermal decomposition of AZT (190°C, 10 h); also, carbon dioxide (no more than 3 vol. %), methanol, and furan were detected: m/z (I_{rel}, %): 68 (1.0) [CH=CHOCH=CH]$^+$; 44 (3.9), 42 (0.3) [CO$_2$]$^+$; 40 (0.3), 39 (1.4), 32 (0.4), 31 (0.7), 29 (1.3), 28 (100) [N$_2$]$^+$, 18 (3.2) [H$_2$O]$^+$, 17 (1.2), 16 (0.5), 15 (0.3), 14 (5.2), 12 (0.2).

The solid residue obtained after complete decomposition of AZT in the temperature range 140–201°C has a dark color. Its weight fraction is about 80%. The yield of volatile products approaches 20%, i.e., it is almost twice as large as the theoretical weight

Scheme 1.
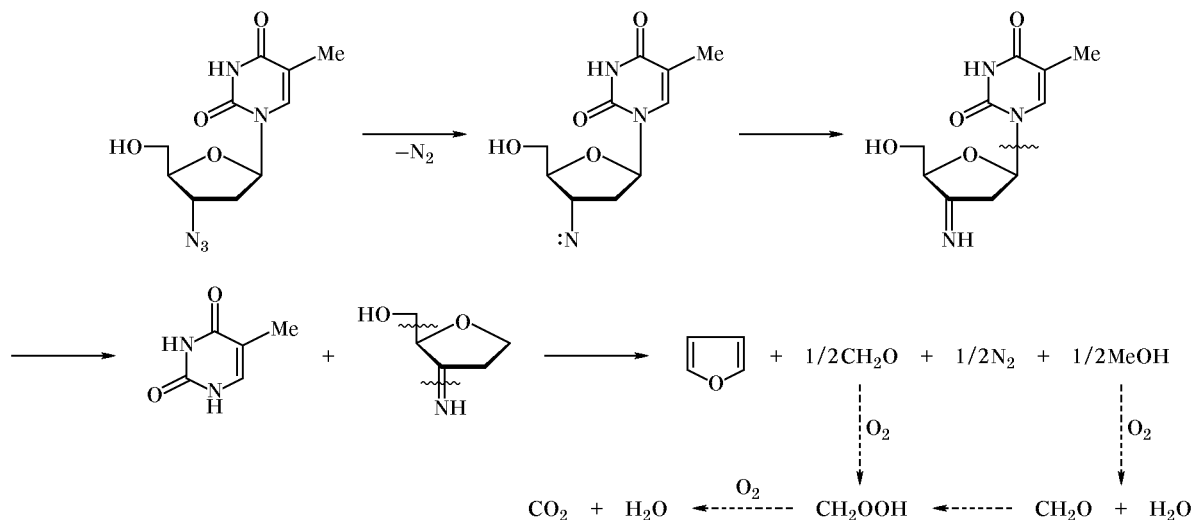
fraction of nitrogen (10.5%) provided that each azido group of AZT gives rise to one nitrogen molecule. Thus the formation of nitrogen by decomposition of the azido group is accompanied by degradation of the molecular structure of AZT. Analysis of the IR spectrum of the solid residue obtained by decomposition of AZT at 158°C (48 h) shows strengthening of hydrogen bonds involving hydroxy group (a shoulder at 3350 cm^{-1}). Treatment of the solid residue with water and subsequent evaporation of the extract gave yellowish crystals which became colorless on washing with carbon tetrachloride. The colorless crystalline product was identified as a pyrimidine base (thymine) by TLC on silica gel (Silufol) using an authentic sample. Their identity was also proved by the IR spectra and melting test: no depression of the melting point was observed on mixing with an authentic sample (Aldrich, mp 316°C).

The activation parameters for thermal decomposition of AZT fall into a narrow range typical of decomposition of aliphatic azides [4, 5]. This fact, as well as the formation of nitrogen as the major gaseous product, indicate that the rate-determining stage in the thermolysis of AZT is decomposition of the azido group. Presumably, next follows rupture of the glycoside bond to form thymine and products of decomposition of the carbohydrate moiety (Scheme 1). All these reactions constitute the first macroscopic stage of the thermolysis process, and the kinetics of just that stage have been studied in the present work. On the other hand, as follows from Fig. 1, more profound thermal transformations are possible at higher temperatures.

EXPERIMENTAL

Thermogravimetric experiments were performed with the use of an ATV-14M automatic electronic thermobalance which was designed and manufactured at the Institute of Chemical Physics Problems, Russian Academy of Sciences [9]. This device allowed us to perform kinetic measurements in a vacuum, in air, and in an inert atmosphere (krypton, argon, 1 atm) both under isothermal conditions and in the temperature-programming mode. A Bourdon tube pressure gage was used in manometric measurements. The residual pressure before decomposition did not exceed 0.1 torr. Gaseous and condensed thermolysis products were identified by IR spectroscopy using a Specord 75IR spectrophotometer and mass spectrometry using an MI-1201-V mass spectrometer (70 eV, 25°C).

Initial 3'-azidothymidine was synthesized by the procedure described in [10] and was purified by sublimation; it contained no less than 99.4% of the main substance (HPLC; Perkin–Elmer 200; UV detector, λ 260 nm; 4.6×250 nm column packed with Nucleosil C_{18}; eluent acetonitrile–0.1 M potassium dihydrogen phosphate).

REFERENCES

1. Malin, A.A. and Ostrovskii, V.A., *Russ. J. Org. Chem.,* 2001, vol. 37, p. 759; Pathak, T., *Chem. Rev.,* 2002, vol. 102, p. 1623.

2. Malin, A.A., Shcherbinin, M.B., Poplavskii, V.S., Kononov, A.V., and Ostrovskii, V.A., *Russ. J. Org. Chem.,* 1997, vol. 33, p. 549.

3. Korchevskaya, E.V., Malin, A.A., Shcherbinin, M.B., and Ostrovskii, V.A., *Russ. J. Org. Chem.,* 2000, vol. 36, p. 1369.

4. Geiseler, G. and Konig, W., *Z. Phys. Chem.* (Leipzig), 1964, vol. 227, p. 81.

5. Stepanov, R.S., Kruglyakova, L.A., and Buka, E.S., *Kinet. Katal.,* 1986, vol. 27, p. 479.

6. Tanaka, Y., Takeda, N., and Fujita, D., *Thermochim. Acta,* 1987, vol. 115, p. 281.

7. Lopez, R., Gutierrez, M.D., Quijano, M., Nogueras, M., and Sanchez, A., *Thermochim. Acta,* 1989, vol. 153, p. 113.

8. Olafsson, P.G., Bryan, A.M., Davis, G.C., and Anderson, S., *Can. J. Biochem.,* 1974, vol. 52, p. 997.

9. Gal'perin, L.N. and Kolesov, Yu.R., *Izm. Tekhn.,* 1981, no. 4, p. 23.

10. Ostrovskii, V.A., Poplavskii, V.S., Shcherbinin, M.B., Malin, A.A., Koshtaleva, T.M., Khokhryakova, N.R., Bezklubnaya, E.V., and Kononov, A.V., Russian Patent no. 2 135 512, 1997; *Byull. Izobret.,* 1999, no. 24.