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Mechanisms of 5'-*O*-Benzoyl-2,3'-anhydrothymidine Reactions with Nucleophiles: II.* Kinetics of the Reaction with Triethylammonium Tetrazolide in DMF**

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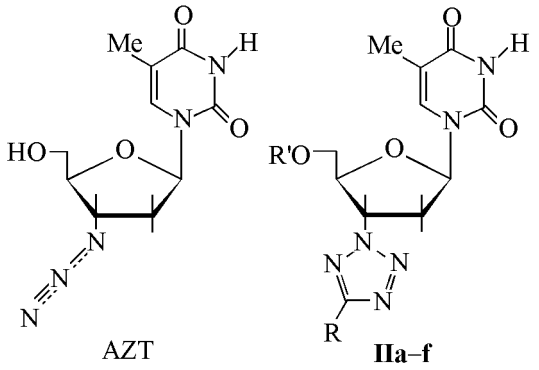
Abstract—The reaction of 5′-*O*-benzoyl-2,3′-anhydrothymidine with triethylammonium tetrazolide in DMF at 100–120°C is described by a second-order kinetic equation, following the first-order kinetics in each of the reactants. On the basis of the experimental activatin parameters, $\Delta H^{\neq}_{298}$ = 80 kJ/mol, $\Delta S^{\neq}$ = –116 J × mol^{-1} K^{-1}, a mechanism was proposed, according to which in the rate-determining stage of S_N2 reaction triethylammonium tetrazolide attacks the C^3′ atom of 5′-*O*-benzoyl-2,3′-anhydrothymidine with simultaneous loosening of the C^3′–O^2 anhydro bond.

We previously studied the kinetics of the reaction of 5'-*O*-benzoyl-2,3'-anhydrothymidine (**I**) with dimethylammonium azide in DMF and in the system DMF–1,4-dioxane [1, 2]. As a result, the rate constants and activation parameters were determined and a mechanism was proposed, according to which heterolytic dissociation of the C^3′–O^2 anhydro bond in the nucleoside molecule occurs in the rate-determining stage [1, 2]. These data elucidate specific features of the azidation of substrate **I**, which is the key stage in the synthesis of 3'-azido-2',3'-dideoxythymidine (AZT), an inhibitor of the HIV reverse transcryptase [3].

Modified nucleosides **IIa–IIf** containing a tetrazolyl substituent (a cyclic analog of the azido group) in position *3′* were recently synthesized [3]. These compounds showed an anti-HIV activity.

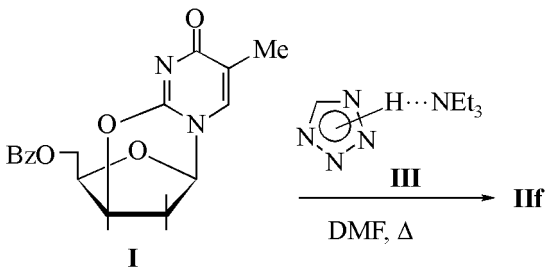
Compounds **II** were obtained by reactions of **I** with the corresponding triethylammonium tetrazolides, followed by removal of the 5'-*O*-benzoyl protection via reaction with dimethylamine in methanol. Regardless of the substituent in position *5* of the tetrazole ring, only the N^2-isomer was formed. No data are available on the mechanism of this process.

The goal of the present work was to reveal and analyze quantitative kinetic relations which could elucidate the mechanism of introduction of tetrazolyl group into position *3′* of 5'-*O*-benzoyl-2,3'-anhydrothymidine. As model nucleophile we selected one of the simplest reperesentatives, triethylammonium tetrazolide (**III**), which has no substituent in position *5* of the tetrazole ring (Scheme 1).



R' = H, R = H (**a**), Me (**b**), Ph (**c**), Bzl (**d**), 4-FC_6H_4 (**e**); R = H, R' = Bz (**f**).

Scheme 1.



* For communication II, see [1].

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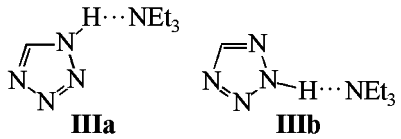
Enthalpies of formation, dipole moments, $N_{Ht}-H$ and $H\cdots NEt_3$ bond lengths (l_1 and l_2) and orders (W_1 and W_2), and charges on atoms in N^1- and N^2-triethylammonium tetrazolides **IIIa** and **IIIb**

Comp. no.	Medium	Calculation method	ΔH_f, kcal/mol	μ, D	l_1, Å	W_1	l_2, Å	W_2	$q(N^1)$, a.u.	$q(N^2)$, a.u.
IIIa	Gas	MNDO	40.29	6.08	1.00	0.882	4.22	0	–0.221	–0.027
	Gas	MNDO/M	39.57	6.44	1.02	0.872	2.60	0.001	–0.218	–0.032
	DMF	MNDO/M	22.28	7.69	1.03	0.859	2.58	0.002	–0.198	–0.038
IIIb	Gas	MNDO	44.77	2.59	1.01	0.869	4.12	0	–0.106	–0.150
	Gas	MNDO/M	43.71	2.96	1.03	0.856	2.58	0.002	–0.107	–0.150
	DMF	MNDO/M	36.53	3.73	1.04	0.850	2.59	0.002	–0.111	–0.131

Initially, we performed quantum-chemical calculations of the electronic structure and geometry of nucleophile **III** and estimated the effect of solvation on the calculated parameters. The calculations were performed in terms of the MNDO approximation which is known to reproduce well charges on atoms in nitrogen-containing compounds [4]; its modification MNDO/M is one of the best methods for studying complexes formed via hydrogen bonding [5] (software package from [6] was used). Hydrogen bonding is a very important factor determining specific structure of ammonium salts derived from azoles, which are stable just as H-complexes [7]. Nonspecific solvation was taken into account in terms of the point dipole method [8]; the boundary energy of solvent disordering, $\varepsilon_p = 0.016$ kcal mol^{-1} Å^{-3}, was estimated on the assumption that the bond energy between DMF molecules is equal to 2 kcal/mol; the density, dipole moment, and dielectric constant of DMF were taken from [9]; and its polarizability was calculated by the Clausius–Mossoti formula. Table contains some parameters of two possible forms **IIIa** and **IIIb** of the triethylammonium tetrazolide molecule (with coordination of the ammonium fragment at N^1 and N^2) and charges on atoms, which determine the reactive centers and structure of the transition state in the reaction with substrate **I**.



IIIa **IIIb**

It is seen that 1*H*- and 2*H*-isomers of triethylammonium tetrazolide both in the gas phase and in DMF are stable as H-complexes rather than as salt-like structures. Comparison of the bond lengths and bond orders shows that the complex formation leads, on the one hand, to some loosening of N^1-H and N^2-H bonds and, on the other, to formation of hydrogen bonds whose length and energy are close to the corresponding standard parameters, 2.5–2.6 Å and 0.5–1 kcal/mol, respectively. Our results are consistent with those reported in [6] for ammonium salts derived from pyrazoles and imidazoles.

As follows from the gas-phase enthalpies of formation, the most stable is H-complex **IIIa** which is formed with participation of the electron-donor N^1 atom. In addition, this complex is more polar than **IIIb**, which gives rise to stronger stabilization in a dipolar solvent. The N^2 atom in **IIIa** has a smaller negative charge than N^1. However, the latter is sp^3-hybridized, and it cannot be a reaction center, for structural rearrangement necessary for the attack on $C^{3'}$ of the substrate requires a considerable energy. Therefore, the N^2 atom is the active center in the reaction of triethylammonium tetrazolide with benzoylanhydrothymidine **I**.

The reaction kinetics (Scheme 1) were studied in the range of substrate concentrations from 0.026 to 0.10 M and nucleophile **III** concentrations from 0.2 to 0.5 M. The concentrations of the reactants and the products were monitored by spectrophotometry in the temperature range from 100 to 120°C. The latter was chosen for the following reasons: below 100°C the conversion of the reactants is too low to ensure proper determination of the rate constants, while at temperatures exceeding 120°C the process is complicated by side reactions including decomposition of nucleoside components and thermal decomposition of DMF. The procedure for kinetic measurements was analogous to that described in [1, 2].

Preliminary experiments showed that the UV spectra of compounds **I** and **IIf** in the range of concentrations from 10^{-5} to 10^{-3} M fit the Bouguer–Lambert–Beer law. In addition, 5'-*O*-benzoyl-3'-(2-tetrazolyl)-2',3'-dideoxythymidine (**IIf**) was found to be stable in DMF at 100°C for a long time.

Figure 1 displays a considerable difference in the molar absorption coefficients of **I** and **IIf** at λ 230 and 270 nm. The rate constants determined from the substrate consumption and accumulation of product **IIf** were identical, indicating that no stable intermediate species is formed during the process. It should be noted that measurements of the product **IIf** concentration ensured substantially higher accuracy in the determination of the kinetic parameters; therefore, λ 270 nm as taken as analytical wavelength.

The reaction is described by the first-order equation with respect to the substrate, and the semilog kinetic plots remain linear up to a substrate conversion of 80–85%; the rate constant calculated by the classical first-order kinetic equation [10] does not depend on the substrate concentration in the range from 0.026 to 0.10 M. The order of the reaction with respect to nucleophile **III** was determined from the dependence of the first-order rate constant on its concentration. As is seen from Fig. 2, the corresponding plots are linear, and intercepts on the *y* axis are negligible. These findings suggest that the order of the reaction in the nucleophile is also first. The second-order rate constants k, $l\,mol^{-1}\,s^{-1}$, determined from the slopes of the straight lines shown in Fig. 2 are given below:

Temperature, °C	100	105	110	115	120
$k\times10^5$	1.28 ± 0.05	2.2 ± 0.1	3.0 ± 0.1	4.6 ± 0.2	5.2 ± 0.2

The temperature dependence of the second-rate constant is described by the Arrhenius equation

$$\log k_2 = (4.33\pm0.51)10^3/T + (6.77\pm1.21);$$

$$r = 0.98,\ n = 5,\ s = 0.07.$$

The thermodynamic activation parameters, calculated from the slope and the free term of the Arrhenius equation are as follows: $\Delta H^{\neq}_{298} = 80\ kJ\,mol^{-1}$ and $\Delta S^{\neq} = -116\ J\,mol^{-1}\,K^{-1}$. These values fall into the range typical of bimolecular nucleophilic substitution reactions (S_N2) [11].

Taking into account the above data on the structure of triethylammonium tetrazolide, some details of the reaction mechanism can be proposed (Scheme 2). In the rate-determining stage a bond is formed between the N^2 atom of heterocycle **IIIa** and $C^{3'}$ atom of substrate **I**; simultaneously, dissociation of the $C^{3'}-O^2$ bond occurs. The charge localized on the oxygen atom in intermediate **A** favors fast proton transfer from triethylammonium ion $Et_3\overset{+}{N}H$ to the oxygen atom attached to the pyrimidine fragment. Intermediate **B**

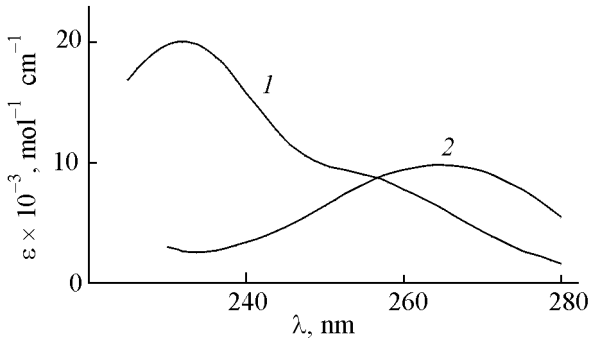


Fig. 1. UV spectra of 5′-*O*-benzoyl-2,3′-anhydrothymidine (**I**) and 5′-*O*-benzoyl-3′-(2-tetrazolyl)-2′,3′-dideoxythymidine (**IIf**) in ethanol.

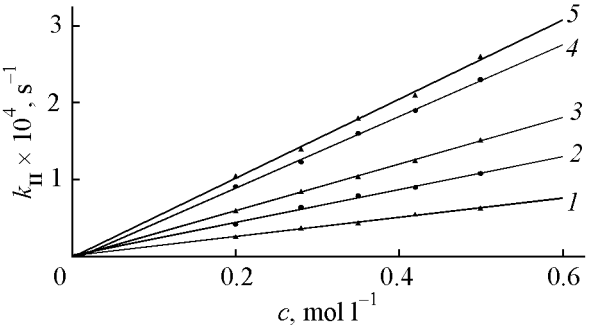


Fig. 2. First-order rate constants of the reaction of benzoylanhydrothymidine **I** with triethylammonium tetrazolide (**III**) in DMF versus nucleophile concentration at (*1*) 100, (*2*) 105, (*3*) 110, (*4*) 115, and (*5*) 120°C.

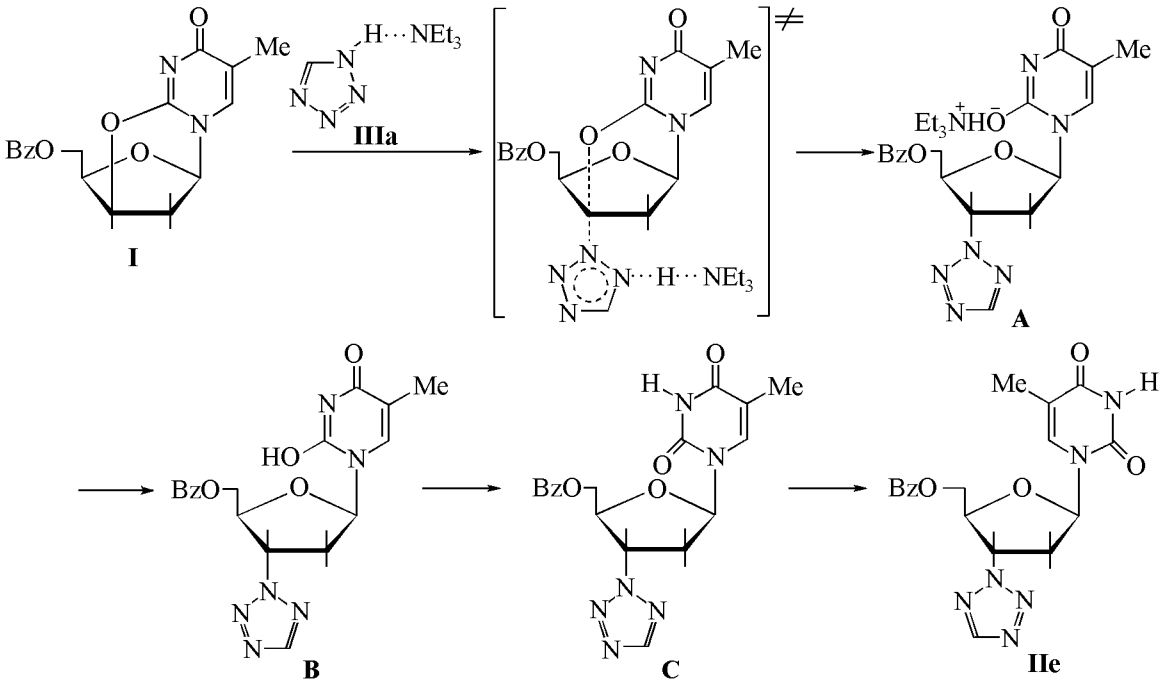
thus formed undergoes fast tautomerization into **C**. Finally, kinetically uncontrollable rotation of the pyrimidine base (glycone) about the glycoside C^1-N bond occurs through an angle of 180°, yielding product **IIf**.

To conclude, it should be noted that the reaction mechanisms of dimethylammonium azide and trimethylammonium tetrazolide with substrate **I** are essentially different, although both nucleophiles exist in DMF as H-complexes. In the first case, the reaction involves a six-center transition state [1, 2], while in the second case the process follows a classical S_N2 scheme. We hope to get a more clear insight into the structure–property relations holding in such transformations by continuing our kinetic studies.

EXPERIMENTAL

Spectrophotometric measurements were performed on an SF-46 instrument using 1-cm quartz cells. Dimethylformamide was purified as described in [9]. 5′-*O*-Benzoyl-2,3′-anhydrothymidine (**I**) and 5′-*O*-ben-

Scheme 2.



zoyl-3'-(2-tetrazolyl)-2',3'-dideoxythymidine (**IIf**) were synthesized and purified by the procedures reported in [12, 13].

Procedure for kinetic measurements. A jacketed reactor equipped with a magnetic stirrer and a powerful reflux condenser was charged with a solution of compound **I** in DMF and adjusted to a required temperature (±0.5°C). Solutions of freshly distilled triethylamine and sublimed tetrazole in DMF were added through calibrated pipettes, and this moment was taken as the reaction onset. Samples of the mixture were withdrawn at specified time intervals, transferred into a receiver, and quickly cooled to room temperature to stop the reaction. A 2 × 10-ml portion of the sample was transferred using a calibrated microsyringe into a volumetric flask filled with ethanol, the mixture was stirred and adjusted to a volume of 25 ml by adding ethanol, and the optical density of the resulting solution was measured against ethanol containing 0.08 vol % of DMF.

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