

Mechanisms of 5'-O-Benzoyl-2,3'-anhydrothymidine Reactions with Nucleophiles:

IV.* Kinetics and Thermodynamics of Azidation with Dimethylammonium Azide in DMF–1,4-Dioxane**

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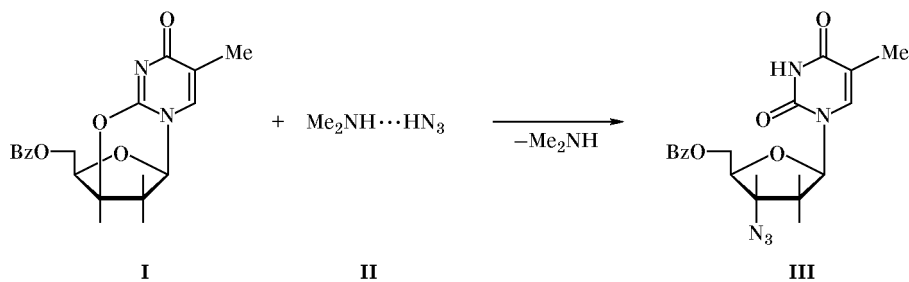
Abstract—The reaction of 5'-O-benzoyl-2,3'-anhydrothymidine with dimethylammonium azide in the system DMF–1,4-dioxane in the temperature range from 80 to 100°C follows the overall second-order kinetics and first-order kinetics with respect to each reactant. The activation parameters in the systems containing 30, 40, and 50 vol % of dioxane are, respectively: ΔH_{298}^\ddagger 99, 85, and 79 kJ/mol; ΔS_{298}^\ddagger –46, –83, and –101 J mol⁻¹ K⁻¹. A refined model of the transition state for the rate-determining stage was proposed, which takes into account specific interaction with 1,4-dioxane.

We previously reported [2] on the kinetics of the reaction of 5'-O-benzoyl-2,3'-anhydrothymidine with dimethylammonium azide in the system DMF–1,4-dioxane at 100°C, which leads to formation of 3'-azido-5'-O-benzoyl-3'-deoxythymidine (Scheme 1). It was found that the reaction is described by the overall second-order kinetic equation, being of first order in each of the reactants. The order of the reaction does not depend on the dioxane concentration in the system (up to 50 vol %). Increase of the fraction of weakly polar dioxane accelerates the reaction, and the dependence $\log k = f[(\epsilon - 1)/(2\epsilon + 1)]$ is nonlinear.

Addition of large amounts of dioxane increases the reaction rate to a lesser extent than it might be expected from the linear Kirkwood dependence. The observed anomaly was explained in terms of specific solvation by nucleophilic solvents. However, additional studies are necessary to get a deeper understanding of the process.

The goal of the present work was to determine and analyze activation parameters of the reaction of 5'-O-benzoyl-2,3'-anhydrothymidine (I) with dimethylammonium azide (II). For this purpose, the kinetic measurements were performed in a binary

Scheme 1.



* For communication I, see [1].

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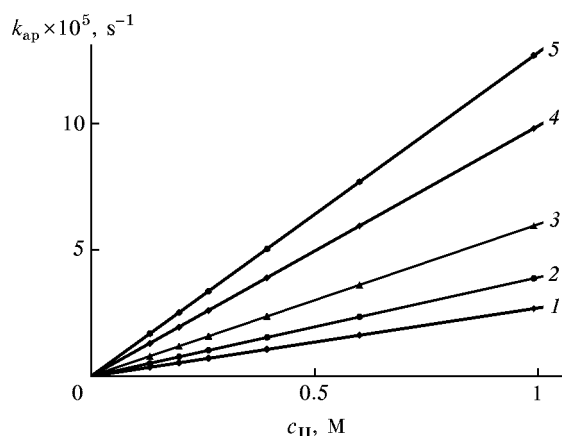


Fig. 1. Dependences of the apparent rate constants for azidation of 5'-*O*-benzoyl-2,3'-anhydrothymidine (**I**) with dimethylammonium azide (**II**) on the concentration of the latter in the system DMF–1,4-dioxane containing 40 vol % of dioxane at (1) 80, (2) 85, (3) 90, (4) 95, and (5) 100°C.

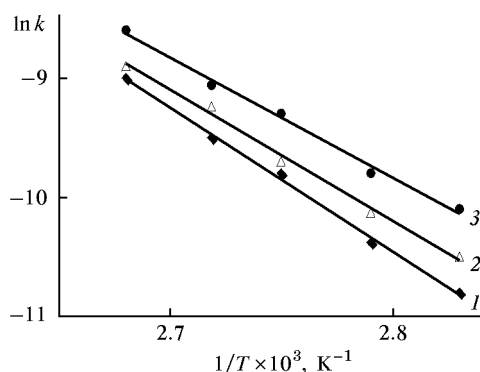


Fig. 2. Temperature dependence of the rate of azidation of 5'-*O*-benzoyl-2,3'-anhydrothymidine (**I**) with dimethylammonium azide (**II**) in the systems DMF–1,4-dioxane containing (1) 30, (2) 40, and (3) 50 vol % of dioxane.

system DMF–1,4-dioxane according to the procedure described in [3]. Dioxane was dried over NaOH and was distilled over metallic sodium [4]. The reaction was carried in the temperature range from 80 to 100°C under conditions of pseudofirst-order with respect to the substrate ($c_{\text{II}} \gg c_{\text{I}}$) in the solvent systems containing 30, 40, and 50 vol % of dioxane. The semilog kinetic plots remained linear in all the examined solvent mixtures up to a conversion of 80–85%. It should also be noted that in all cases the yield of product **III** (determined by spectrophotometry) was nearly quantitative. The pseudofirst-order rate constant k_{ap} was determined from the slope of the semilog dependence

$$\ln(D_{\infty} - D_0) = k_{\text{ap}} \tau - \ln(D_{\infty} - D_{\tau}),$$

where D_0 , D_{∞} , and D_{τ} are, respectively, the optical densities of the reaction solution at λ 270 nm at the initial moment, by the end of the process, and at a moment τ . The parameters of the linear dependence were determined by regression analysis under the constraint that the dispersion of reproducibility is uniform [5]. The general regression parameters were calculated using $\ln(D_{\infty} - D_{\tau})$ values which fall into or lie at the boundary of confident interval defined at a significance level β of 0.05; Fisher test 0.8; number of degrees of freedom 16. The D_0 values determined by extrapolation to the initial moment almost coincided with the optical densities calculated for the initial concentrations of **I**. Thus the linearity of the semilog kinetic plot indicates first order of the reaction in the substrate, 5'-*O*-benzoyl-2,3'-anhydrothymidine (**I**). The order of the reaction with respect to dimethylammonium azide (**II**) was found from the dependence of the first-order rate constants on the concentration of **II** for all DMF–1,4-dioxane systems. As an example, Fig. 1 shows concentration dependences of the apparent rate constants in the solvent system containing 40 vol % of dioxane at 80–100°C.

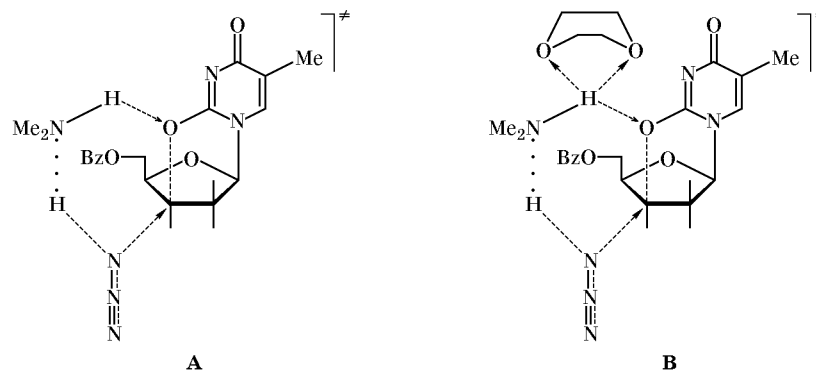
Analogous dependences were obtained for all the examined DMF–1,4-dioxane mixtures. Figure 1 shows that these dependences are linear throughout the temperature range under study and that the intercepts at the y axis are negligible. Taken together, these data also indicate first order of the reaction in dimethylammonium azide.

The second-order rate constants were calculated from the slopes of the above dependences (see table). These values were used to construct temperature dependences which are well described by the Arrhenius equation for all the examined DMF–dioxane mixtures (Fig. 2). The activation parameters were determined from the slopes and intercepts of the straight lines plotted in Fig. 2, in keeping with the Arrhenius–Eyring theory. Their values are given

Rate constants ($k \times 10^5$, $\text{l mol}^{-1} \text{s}^{-1}$) for azidation of 5'-*O*-benzoyl-2,3'-anhydrothymidine (**I**) with dimethylammonium azide (**II**) in DMF–1,4-dioxane

Temperature, °C	30 vol % of dioxane	40 vol % of dioxane	50 vol % of dioxane
80	2.0	2.7	4.0
85	2.7	3.9	5.4
90	5.6	6.0	9.0
95	7.5	9.9	11.4
100	11.9	12.8	17.7

Scheme 2.



below together with the activation parameters for azidation of 5'-O-benzoyl-2,3'-anhydrothymidine with dimethylammonium azide in 100% DMF, which were determined by us previously [3].

Concentration of dioxane, vol %	ΔH_{298}^\ddagger , kJ/mol	$-\Delta S_{298}^\ddagger$, J mol ⁻¹ K ⁻¹
0	126	33
30	99	46
40	85	83
50	79	101

These data indicate that addition of dioxane leads to decrease of both the entropy and the enthalpy of activation. We tried to interpret the observed pattern by correcting the transition state model proposed previously [3]. When the azidation is carried out in DMF, cyclic complex **A** (Scheme 2) is formed in the rate-determining stage. Here, protonation of O², nucleophilic azidation at C^{3'}, and loosening of the C^{3'}-O² bond occur simultaneously. In going to the binary DMF-1,4-dioxane system, the transition state may be stabilized due to reduced polarity of the medium (as a result of addition of weakly polar dioxane). Therefore, the enthalpy of activation decreases and the reaction rate increases as the concentration of dioxane in the system rises [2]. Reduction of the entropy of activation may be explained using model **B** which includes 1,4-dioxane molecule. According to [6], 1,4-dioxane is a more basic solvent than DMF and it is capable of specifically solvating

the proton which migrates from the amino nitrogen atom to the anhydro oxygen. Such specific interaction increases the degree of ordering of the system, and the entropy of activation decreases as the fraction of dioxane rises. An analogous nucleophilic solvent assistance to stabilization of cyclic transition states was observed previously [7] in the ammonolysis of carbonyl-containing compounds.

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