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Kinetics of Addition of Alcohols to 3-Aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones

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Abstract—The kinetics of the reaction of 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with aliphatic alcohols in toluene at 25°C were studied by spectrophotometry. The effects of electronic and steric factors in the nucleophile and substrate were estimated by treatment of the kinetic results by the Hammett and Taft equations.

We previously studied the kinetics of hydration of 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-1,2,4-triones **I**–**V** [1] in comparison to monocyclic 2,3-dihydropyrrole-2,3-diones [2]. We found that in both cases [1, 2] the reaction with water involves formation of a favorable six-membered cyclic transition state. Here, nucleophilic addition to carbon atom in position *5* of the pyrroledione system is facilitated by general base catalysis despite considerable steric shielding of C^5. In the present work we made an attempt to analyze on a quantitative level the effects of electronic and steric factors in the addition of aliphatic alcohols. For this purpose we examined the kinetics of the reaction of 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*]-[1,4]benzoxazine-1,2,4-triones **I**–**V** with a number of aliphatic alcohols. The process involves nucleophile addition at the activated vinylic center, carbon atom in position *5* of the pyrroledione fragment, and leads to formation of 3a-alkoxy-3-aroyl-2-hydroxy-3a,4-di-hydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,4-diones **VI**–**X** (Scheme 1).

Monocyclic pyrrolediones having similar substituents in the aroyl fragment are characterized by a higher reactivity in the hydration process than their fused analogs [2]. In the addition of alcohols, the reverse pattern is observed: the rate of the reaction with pyrrolobenzoxazinetriones **I**–**V** is higher by an order of magnitude than the rate of alcohol addition to monocyclic pyrrolediones [3]. Therefore, some new factors favoring the reaction appear in nucleophilic addition of aliphatic alcohols.

Table 1 contains the rate constants for noncatalytic addition of water [1] and a series of aliphatic alcohols to 2,3-dihydropyrrole-2,3-diones fused through the *a* bond to 1,4-benzoxazine system. The experimental data given therein are satisfactorily described by the Hammett and Taft equations (Table 2). The rate of addition gradually increases in going from MeOH to *n*-BuOH, which may be due to increase in the positive inductive effect of the R^2 substituent (Table 2). However, this tendency is not typical of all the examined alcohols. The values of $\log k_0$ for isropopyl and *tert*-

Scheme 1.
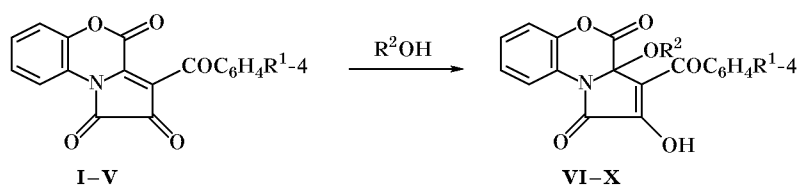
I, **VI**, R^1 = OMe; **II**, **VII**, R^1 = Me; **III**, **VIII**, R^1 = H; **IV**, **IX**, R^1 = Cl; **V**, **X**, R^1 = NO$_2$; **1**, R^2 = H; **2**, R^2 = Me; **3**, R^2 = Et; **4**, R^2 = *n*-Pr; **5**, R^2 = *n*-Bu; **6**, R^2 = *i*-Pr; **7**, R^2 = *t*-Bu.

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[†] Deceased.

Table 1. Rate constants (k_0, l mol^{-1} s^{-1}) of noncatalytic addition of water and aliphatic alcohols R^{2}OH **1–7** to 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **I–V**

Reagent no.	R^2	R^1 = OMe	R^1 = Me	R^1 = H	R^1 = Cl	R^1 = NO$_2$
1	H	5.51×10^{-3}	3.95×10^{-3}	4.18×10^{-3}	6.27×10^{-3}	1.58×10^{-2}
2	Me	4.72	3.44	2.60	2.96	3.78
3	Et	5.07	4.00	3.36	3.72	4.58
4	*n*-Pr	5.36	4.20	3.44	3.82	4.74
5	*n*-Bu	5.43	4.26	3.56	3.89	4.82
6	*i*-Pr	1.4	1.05	1.06	1.169	1.563
7	*t*-Bu	0.032	0.024	0.02	0.025	0.039

Table 2. Parameters of the correlation $\log k_0$—σ^* for noncatalytic addition of aliphatic alcohols to 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **I–V**

Comp. no.	R^1	ρ^*	r	S
I	OMe	–0.458	0.951	0.007
II	Me	–0.763	0.985	0.004
III	H	–1.079	0.989	0.002
IV	Cl	–0.962	0.988	0.003
V	NO$_2$	–0.458	0.952	0.007

Table 3. Parameters of the correlation $\log k_0$—E_s for noncatalytic addition of aliphatic alcohols to 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **I–V**
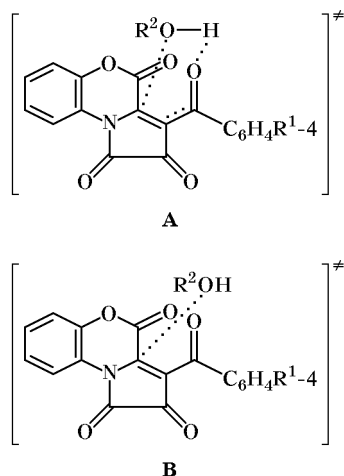
Comp. no.	R^1	δ	r	S
I	OMe	1.451	0.998	0.060
II	Me	1.459	0.997	0.074
III	H	1.443	0.993	0.109
IV	Cl	1.411	0.994	0.099
V	NO$_2$	1.349	0.994	0.094

butyl alcohol deviate from the general dependence, indicating a significant contribution of steric factor. Furthermore, the reaction under study is weakly sensitive to inductive effect of the R^2 substituent. This follows from the low absolute value of ρ^*. The above data suggest that steric effects of substituents play the determining role in the addition of alcohols to 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **I–V**. The $\log k_0$ values satisfactorily correlate with the steric constants E_S of substituents in the alcohols, which take into account hyperconjugation between C–H and C–C bonds in the substituents [4]. The correlation parameters are given in Table 3.

As compared to monocyclic 2,3-dihydropyrrole-2,3-diones [3], the addition of alcohols to their fused analogs is characterized by a considerably higher sensitivity to steric effect of the alcohols. Presumably, there is no additional steric effect of substituents in positions *1* and *5* of the pyrrole ring, for they are fixed in the fused system (in monocyclic analogs, rotation of substituents in these positions is possible). Therefore, steric effects of substituents in the alcohols become determining. The value of δ is minimal for the most reactive substrate (**V**); in this case, the transition state is reagent-like. On the whole, values of δ weakly depend on R^1.

Figure shows the correlation between $\log k_0$ for the examined alcohols and constants σ of R^1 substituents in the aroyl fragment of pyrrolobenzoxazinetriones. The addition of nucleophiles to both monocyclic and fused substrates is characterized by nonlinear dependence [1, 2, 3]. In the reaction under study, the plot of $\log k_0$ versus σ has a minimum which corresponds to a nearly zero value of σ (R^1 = H). This may be explained in terms of the existence of two reaction paths which are characterized by different ρ values [5]. In the addition of water and alcohols to pyrrolobenzoxazinetrione, apart from cyclic transition state **A** [2], transition state **B** is also possible. In the latter case, the rate-determining stage does not involve proton transfer.
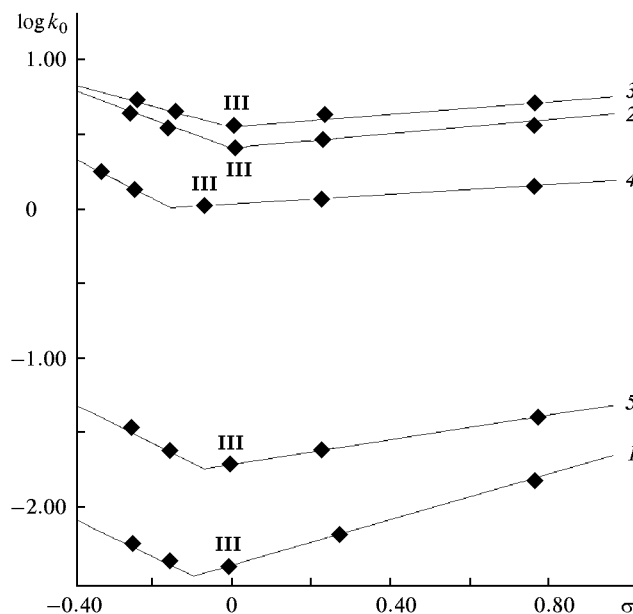
The reaction rate increases ($\rho > 0$) on introduction of electron-withdrawing substituents into the substrate. Provided that steric hindrances are absent, the rate of addition is directly proportional to the nucleophilicity of the reagent. In the reaction with strong nucleophiles, the main process is formation of the C–O bond without preliminary association and proton transfer (transition state **B**). This follows from increase in the rate constants in the series MeOH < EtOH < PrOH < BuOH < *i*-PrOH < *t*-BuOH ($\log k_0$ 0.205, 0.172, 0.178, 0.179, 0.218, and 0.369, respectively).

A

B

Correlations of $\log k_0$ with R^1 substituent constants σ for the reaction of pyrrolobenzoxazinetriones **I**–**V** with nucleophiles in toluene at 25°C: (*1*) H_2O, (*2*) MeOH, (*3*) EtOH, (*4*) *i*-PrOH, (*5*) *t*-BuOH.

For substrates having electron-donor substituents ($\rho < 0$), the contribution of preliminary association of the reactants and initial formation of O–H bond are significant. As a result, the nucleophilicity of the reagent increases, favoring formation of cyclic transition state like **A**. Here, the absolute values of ρ decrease in the series of nucleophiles MeOH > EtOH > PrOH > BuOH (–0.939, –0.693, –0.651, and –0.658, respectively) due to decrease in the degree of O–H bonding, which is explained by increased steric hindrances and reduction in the acidity of the alcohols. The largest value (–1.39) was found for the reaction with water, where both electronic and steric factors favor the process.

Thus, unlike the addition of alcohols to monocyclic pyrroledions studied previously [3], for the reaction with 3-aroyl-2,4-dihydro-1*H*-pyrrolo[5,1-*c*][1,4]benzoxazine-1,2,4-triones we obtained satisfactory correlations between $\log k_0$ and Taft constants σ^* and E_S. Moreover, we succeeded in establishing that the sensitivity of this reaction to steric effects of substituents in the alcohols is considerably higher [3] and that it plays the decisive role. However, as compared to monocyclic analogs, structural variations in compounds **I**–**V** did not produce essential change in the mechanism of addition of water and aliphatic alcohols. On the basis of the obtained results, we can conclude that the mechanism involving transition state like **B** is preferable.

We failed to examine the kinetics of alcohol addition to 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine-1,2,4-triones **I**–**V** under catalysis by carboxylic acids (cf. [3]), for the reaction rate was too high. The procedures for kinetic measurements, processing of the kinetic data, and synthesis and purification of initial compounds were described previously [1, 3, 6].

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