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Influence of pH of an Aqueous–Organic Solvent on the Kinetics of N-Acylation of α-Amino Acids with Benzoic Acid Esters

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Abstract — The pH dependence of the apparent rate constants and activation parameters (enthalpy, entropy) of N-acylation of α-amino acids with benzoic acid esters in water–2-propanol solvent was studied.

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The reactivity of organic molecules largely depends on their acid–base interaction with the medium. The strongest effect can be observed at protonation (or deprotonation) of functional groups. In particular, various agents that acylate nonprotonated amino groups in aromatic and aliphatic amines do not acylate protonated amino groups [1–4]. Protonation of functional groups in substituents can also affect the reaction rate constants.

In this connection, it is of doubtless interest to compare the acid–base properties of such bifunctional compounds as α-amino acids with their reactivity as influenced by pH. In our previous studies [5, 6] we examined the thermodynamics of dissociation of α-amino acids in the water–2-propanol solvent. Acid dissociation of α-amino acids in an aqueous-organic solvent involves reactions (1)–(4):

$$\overset{+}{N}H_3CHRCOOH \overset{K_1}{\rightleftarrows} \overset{+}{N}H_3CHRCOO^- + H^+, \quad (1)$$

$$\overset{+}{N}H_3CHRCOOH \overset{K_2}{\rightleftarrows} NH_2CHRCOOH + H^+, \quad (2)$$

$$\overset{+}{N}H_3CHRCOO^- \overset{K_3}{\rightleftarrows} NH_2CHRCOO^- + H^+, \quad (3)$$

$$NH_2CHRCOOH \overset{K_4}{\rightleftarrows} NH_2CHRCOO^- + H^+, \quad (4)$$

where K_1, K_2, K_3, and K_4 are the equilibrium constants of the corresponding reactions and R is a hydrocarbon substituent.

The fractions of the anionic (α_-), neutral (α_0), cationic (α_+), and zwitterionic ($\alpha_\pm$) forms of an α-amino acid depend on pH of the solution. These fractions can be determined as follows:

$$\alpha_+ = \frac{K_2^{-1}K_3K_4^{-1}C_{H^+}}{1 + K_3C_{H^+}^{-1} + K_3K_4^{-1} + K_2^{-1}K_3K_4^{-1}C_{H^+}}, \quad (5)$$

$$\alpha_\pm = \frac{1}{1 + K_3C_{H^+}^{-1} + K_3K_4^{-1} + K_2^{-1}K_3K_4^{-1}C_{H^+}}, \quad (6)$$

$$\alpha_- = \frac{K_4C_{H^+}^{-1}}{1 + K_3C_{H^+}^{-1} + K_3K_4^{-1} + K_2^{-1}K_3K_4^{-1}C_{H^+}}, \quad (7)$$

$$\alpha_0 = \frac{K_3K_4^{-1}}{1 + K_3C_{H^+}^{-1} + K_3K_4^{-1} + K_2^{-1}K_3K_4^{-1}C_{H^+}}, \quad (8)$$

where C_{H^+} is the hydrogen ion concentration.

Only the nonprotonated amino group of α-amino acids (anionic and neutral species) participates in the N-acylation [5].

The rate of N-acylation of α-amino acids with esters follows a second-order rate equation:

$$-\partial C_{app}/\partial\tau = k_{app}C_{aa}C_{est}, \quad (9)$$

where C_{aa} and C_{est} are the running concentrations of the α-amino acid and ester, respectively, and k_{app} is the apparent rate constant;

$$k_{app} = k_-\alpha_- + k_0\alpha_0, \quad (10)$$

where k_- and k_0 are the rate constants of N-acylation of the anionic and neutral forms of the α-amino acid.

We found [6] that, at a water content in an aqueous-organic solvent higher than 10 wt %, the reaction occurs exclusivelly through the anionic form of α-amino acids. Hence,

$$k_{app} = k_-\alpha_-. \quad (11)$$

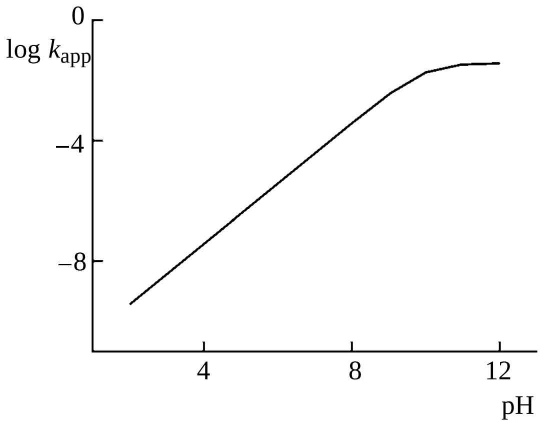

Fig. 1. pH dependence of log k_{app} of N-acylation of glycine with 4-nitrophenyl benzoate in water (40 wt %)–2-propanol; 298 K.

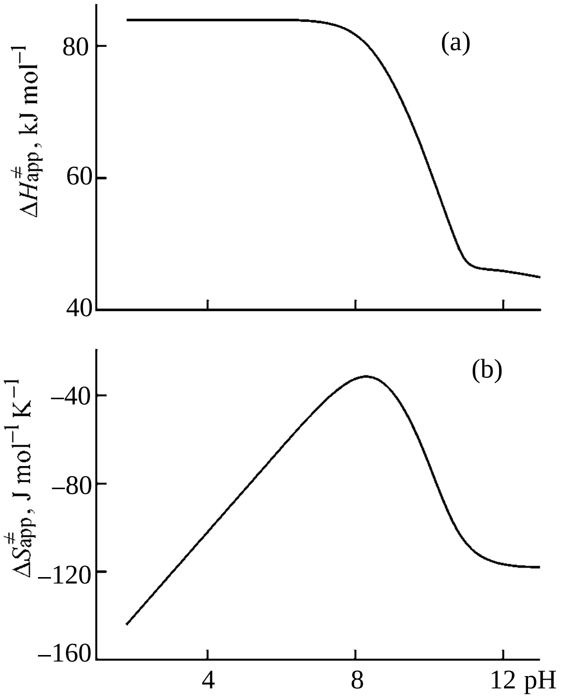

Fig. 2. pH dependences of (a) $\Delta H^{\neq}_{app}$ and (b) $\Delta S^{\neq}_{app}$ of N-acylation of glycine with 4-nitrophenyl benzoate in water (40 wt %)–2-propanol; 298 K.

The quantity α_- is related to the equilibrium constant of Eq. (7) (transformation of the zwitterionic form to the anionic form, constant K_3) as follows (taking into account that at pH 4–10 $K_3K_4^{-1}$ and $K_2^{-1}K_3K_4^{-1}C_{H^+} \ll K_3C_{H^+}^{-1}$):

$$\alpha_- = K_3/(C_{H^+} + K_3). \qquad (12)$$

Thus, the apparent rate constant of N-acylation of α-amino acids with esters depends on C_{H^+} or, in other words, on the pH of the medium:

$$k_{app} = k_-K_3/(C_{H^+} + K_3). \qquad (13)$$

The rate constant of the reaction of glycine with 4-nitrophenyl benzoate in water (40 wt %)–2-propanol solvent, k_- 0.0368 l mol^{-1} s^{-1}, was determined spectrophotometrically by the procedure described in [7]; the equilibrium constant K_3 under the same conditions was determined previously: $K_3 = 9.77 \times 10^{-11}$ mol l^{-1} [5].

The rate constant k_{app} was calculated by Eq. (13); the pH dependence of $\log k_{app}$ is shown in Fig. 1. It is seen that $\log k_{app}$ increases with pH, flattening out in alkaline medium.

It follows from Eqs. (7) and (13) that the apparent activation energy and entropy as functions of pH are described by Eqs. (14) and (15):

$$\Delta H^{\neq}_{app} = \Delta H^{\neq}_{-} + \frac{\Delta H_3}{1 + K_3C_{H^+}}, \qquad (14)$$

$$\Delta S^{\neq}_{app} = R\ln\frac{k_{app}h}{k_BT} + \frac{\Delta H^{\neq}_{app}}{T}, \qquad (15)$$

where $\Delta H^{\neq}_{-}$ and ΔH_3 are, respectively, the activation enthalpy and the thermal effect of dissociation by reaction (3); k_B, Boltzmann constant; h, Planck constant. The pH dependences of $\Delta H^{\neq}_{app}$ and $\Delta S^{\neq}_{app}$ of the reaction of glycine with 4-nitrophenyl benzoate in water (40 wt %)–2-propanol at 298 K are plotted in Fig. 2; ΔH_3 = 38 kJ mol^{-1} [8].

Figure 2 shows that the dependence $\Delta H^{\neq}_{app} = f(\text{pH})$ has an inflection point, and $\Delta S^{\neq}_{app} = f(\text{pH})$, a maximum. The inflection point of the former dependence corresponds to pH = pK_3, and the maximum of the latter dependence, to pH = pK_3 + $\log[RT/(\Delta H_3 - RT)]$. Since the p$K_3$ values for other α-amino acids are approximately equal, the pH dependences of their apparent kinetic characteristics should also be similar.

We believe that the dependence of the apparent rate constant k_{app} on the hydrogen ion concentration that we obtained is associated neither with the catalytic effect of H$^+$ or OH$^-$ ions not with changes in the reaction mechanism and is exclusively due to the pH dependence of the fraction of the reactive species (α_-).

An increase in the concentration of the nonaqueous component of an aqueous-organic solvent in N-acylation of α-amino acids with esters should lead to higher contribution of the reaction pathway through the neutral α-amino acid species; however, kinetic experiments in organic media with a low water content are complicated by low solubility of α-amino acids. Presumably, the rate of N-acylation of α-amino acids in these media should be considerably lower.

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