MICELLAR EFFECTS IN THE ACYLATION OF N-SUBSTITUTED IMIDAZOLES BY p-NITROPHENYL ESTERS OF CARBOXYLIC ACIDS

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The imidazole group is contained in the active sites of many enzymes [1-3]; therefore, the investigation of micellar [4, 5] and polymeric [6] effects in imidazole catalysis is of great interest. We studied the influence of micelles of surface-active substances (surfactants) on the acylation of imidazole (IM) and its N-alkyl derivatives by p-nitrophenyl esters of aliphatic carboxylic acids:

\[ \text{N}^+\text{O} + \text{R}_2^+ \rightarrow \text{R}^- + \text{N}^+\text{O} \]

where \( R_1 = \text{H, CH}_3, (\text{CH}_2)_2\text{CH}_3, (\text{CH}_2)_6\text{CH}_3 \) and \( R_2^+ = \text{CH}_3, (\text{CH}_2)_2\text{CH}_3, (\text{CH}_2)_6\text{CH}_3, (\text{CH}_3)_2\text{CH}_3 \). Cetyltrimethylammonium bromide (CTAB) and sodium dodecylsulfate (SDS) were used as surfactants.

The basic observations were the following: 1) CTAB and SDS change the rate of reaction (1) by no more than 2-3-fold (Figs. 1 and 2). 2) The nature and magnitude of the observed effects practically do not depend on the sign of the charge of the micelle (see Figs. 1 and 2). 3) An increase in the hydrophobic character of the nucleophile (IM derivative) has a positive effect on the reaction rate. From Fig. 1 it is evident that the inhibiting influence of surfactants on the acylation by p-nitrophenylacetate decreases with increasing length of the N-aliphatic chain \( R_1 \) in the N-alkylimidazole, while in the case of N-heptylimidazole or N-benzylimidazole, an addition of surfactant promotes reaction (1). 4) On the contrary, an increase in the hydrophobic character of the acylating agent has a negative effect on the reaction rate. From Fig. 2 it is evident that the promoting influence of surfactants on the reaction in which N-heptylimidazole participates decreases with growth of the \( R_2^+ \) chain in the ester molecule.

In a discussion of the causes of the change in the rate of the second order reaction in the presence of surfactant micelles

\[ A + B \xrightarrow{k_{\text{app}}} \text{Products} \]

we should separately consider: a) the contribution to the acceleration of the reaction on account of the concentration of the reagents in the micelle and b) the change in the reactivity of the reagents in the micellar medium in comparison with aqueous medium. The kinetic theory of micellar catalysis [7] gives the following expression for the apparent rate constant \( k_{\text{app}} \)

\[ k_{\text{app}} = \frac{k_m K_A K_B C / F + k_{aq}}{(1 + K_A C)(1 + K_B C)} \]

where \( k_m \) and \( k_{aq} \) are the true rate constants of the reaction in the micellar and aqueous "phases", respectively; \( K_A \) and \( K_B \) are the constants of binding of the reagents to the micelles, equal to \((P-1)V\), where the distribution constant \( P \) is equal to the ratio of the reagent concentrations in the micellar and aqueous "phases"; \( C \) is the concentration of the surfactant, reduced by the value of the critical concentration
Fig. 1. Dependence of the apparent rate constant of the acylation by p-nitrophenylacetate on the concentration of the surfactants for: 1) N-heptylimidazole; 2) N-propylimidazole; 3) N-methylimidazole; 4) N-benzylimidazole; 5) imidazole. A) CTAB; B) SDS. 30°, 1 vol. % DMSO, 0.02 M borate buffer: pH 8.5 (A), 9.6 (B).

Fig. 2. Dependence on the surfactant concentration of the apparent rate constant of acylation of N-heptylimidazole: 1) by p-nitrophenyl acetate; 2) by p-nitrophenyl butyrate; 3) by p-nitrophenyl heptanoate. A) CTAB; B) SDS. Curves 2 and 3 in Fig. 2A were constructed according to Eq. (4), using the values of the constants indicated in Table 1. 30°, 1 vol. % DMSO, 0.02 M borate buffer: pH 8.5 (A), 9.6 (B).

To resolve the questions posed, we should find the constants $K_A$ and $K_B$ and compare the true rate constants ($k_{aq}$ and $k_m$) in the aqueous and micellar "phases." We analyzed the experimental results (see Figs. 1 and 2), using linear plots of Eq. (3) [7]. As an example, Table 1 cites the constants obtained in the treatment of the data of Fig. 2A. Since the reagents exhibit strong bonding to the micelles, it should have been expected that the concentration of the reagents in the micelles should have a significant influence on the reaction rate. From Eq. (7) (see Experimental Method) it follows that concentration of the reagents in micelles should lead to an acceleration of reaction (1) by at least 10–100-fold (at $k_m = k_{aq}$ and $\bar{V} = 0.35$ liter/mole [8]). However, in the presence of surfactants there is only a negligible change in $k_{app}$ (see Figs. 1 and 2). This is due to the fact that the transfer of reaction (1) from water to the micellar medium leads to a substantial decrease in the true second-order rate constant ($k_m \ll k_{aq}$, see Table 1). To explain the result observed, let us indicate that an increase in the concentration of the organic component in an aqueous ethanol mixture leads to a substantial inhibition of the reaction of acylation of derivatives of IM by p-nitrophenyl carboxylates [9]. The transition state of the reaction is probably more polar than the initial compounds (possibly because the transition state is close to a tetrahedral adduct with separated charges [1, 2]); in such a case the reaction rate should decrease with decreasing dielectric permeability and solvating ability of the medium [10, 11]. The value of the dielectric permeability not only within the micelles but also in their surface layer is substantially lower than in water [7, 12], and the water content in the micelle decreases sharply with increasing distance from the surface layer to the hydrophobic...