Polymer Concentration-Controlled Substrate Specificity in Solvolysis of *p*-Nitrophenyl Alkanoates Catalyzed by 4-(Dialkylamino)pyridine-Functionalized Polymer in Aqueous Methanol Solution

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Abstract: The substrate specificity in solvolysis reactions of *p*-nitrophenyl alkanoates **2** ($n = 2-18$) catalyzed by 4-(dialkylamino)pyridine-functionalized polymer **1** can be controlled by the concentration of **1** in 50:50 (v/v) methanol−aqueous phosphate buffer solution at pH 8.0 and 30 °C. Below 1.0×10^{-5} unit mol L^{-1}, macromolecule **1** exhibits substrate specificity for **2** ($n = 14$). As the concentration of **1** increases to 2.5×10^{-5} unit mol L^{-1}, the substrate preference changes from **2** ($n = 14$) to **2** ($n = 12$). The substrate specificity changes again from **2** ($n = 12$) to **2** ($n = 10$) when the concentration of **1** increases further to 7.5×10^{-5} unit mol L^{-1}. The control of substrate specificity by polymer catalyst concentration is believed to be unprecedented for catalysis of ester solvolysis.

Introduction

The hydrophobic effects, which are a principal force in determining the structures of proteins and nucleic acids and the binding of substrates to enzymes, play a pivotal role in many chemical phenomena in aqueous solution. Small-molecule amphiphiles are well-known to form aggregates of various morphologies in aqueous solution.[1] Depending on the copolymer composition and the surrounding medium, amphiphilic macromolecules can also form aggregates with multiple morphologies.[2] Extensive studies have shown that the increase of hydrophobic effects of amphiphilic macromolecules, i.e., the increase in ratio of hydrophobic to hydrophilic components and the addition of salting-out agents, leads to changes of aggregate morphology from spheres to rods, and to vesicles in appropriate solvents.[2,3] 4-(Dialkylamino)pyridine-functionalized polymers have been regarded as useful and simple model systems for obtaining a better understanding of the origins of enzymic efficiency and selectivity.[4−6] Recently, we have reported ion-induced substrate specificity in solvolysis of *p*-nitrophenyl alkanoates **2** ($n = 2-18$) catalyzed by polymer **1** containing the 4-(dialkylamino)pyridine functionality and a bis(trimethylene)disiloxane backbone (Scheme 1).[7] The tris(hydroxymethyl)-methylammonium ion as a salting-in ion induces the same substrate specificity for **2** ($n = 6$) in aqueous Tris buffer solution that is obtained with cholesterol esterase for the same hydrolysis reaction.[8] The addition of salting-out agent NaCl induces a substrate specificity change from **2** ($n = 14$) to **2** ($n = 12$) in 50:50 (v/v) methanol−aqueous phosphate buffer solution.[7c] However, control of substrate specificity by the concentration of catalyst has not been reported to date for catalysis of solvolysis reactions.

In this report we describe the first example of substrate specificity controlled by a polymer catalyst concentration in solvolysis reactions of **2** ($n = 2-18$) catalyzed by **1** in 50:50 (v/v) methanol−aqueous phosphate buffer solution. By changing the concentration of **1**, we are able to change the substrate preference in **1**-catalyzed solvolysis of **2** ($n = 2-18$) in methanol−water medium. These results are unprecedented for catalysis of ester solvolysis. Furthermore, we report a detailed kinetic characterization of the effects of polymer concentration on the **1**-catalyzed solvolysis of **2** ($n = 10-16$) in different

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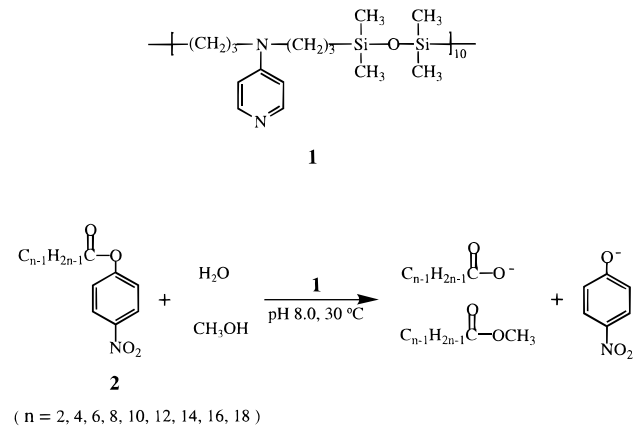
Scheme 1



compositions of methanol−aqueous phosphate buffer solution, which provides significant new insight into the mechanism of catalytic ester solvolysis.

Experimental Section

Materials and Reagents. Synthesis of the poly(siloxane-bis-(trimethylene)) supported 4-(dialkylamino)pyridine (**1**) has been described previously.[6c] *p*-Nitrophenyl alkanoates **2** ($n = 2-18$) and 1,4-dioxane were purchased from Sigma Chemical Co. Methanol and aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution were used as received from Aldrich and Fisher. Stock solutions (2.5×10^{-2} M) of *p*-nitrophenyl alkanoates **2** ($n = 2-18$) were prepared in 1,4-dioxane. The fresh catalyst solutions for kinetic experiments were made up in methanol−aqueous phosphate buffer solution.

Kinetic Measurements. The cuvette was filled with 2.5 mL of a fresh solution containing catalyst in methanol−aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution and the solution was equilibrated for 10 min at 30 °C in the thermostated cell compartment of a Hewlett-Packard Model 8450 spectrophotometer. A fresh stock solution (5 μL) of *p*-nitrophenyl alkanoates **2** ($n = 2-18$, 2.5×10^{-2} M) in dioxane was added by microsyringe. The reaction mixture was quickly mixed by shaking and the absorbance at 400 nm was recorded as a function of time. The reactions were performed for 4−5 half-lives and the pseudo-first-order rate constants (k_{obsd}) were obtained as slopes of plots of $\ln[A_\infty/(A_\infty - A_t)]$ vs time, where A_∞ and A_t are the absorbance at infinite time and time t, respectively. The first-order rate constants (k_{obsd}) represent the average of three runs and experimental error is less than ±5%.

Results and Discussion

The macromolecule **1** is an amphiphilic polymer containing distinct hydrophobic and hydrophilic regions. The catalytic center of macromolecule **1** is the 4-(dialkylamino)pyridine group and the hydrophobic association of substrate to catalyst in the reaction medium is responsible for the rate enhancements observed in the **1**-catalyzed solvolysis reaction of **2**.[4-7]

We have measured pseudo-first-order rate constants for the **1**-catalyzed solvolysis of **2** ($n = 2-18$) with different concentrations of **1** as a function of alkanoate chain length in 50:50 (v/v) methanol−aqueous phosphate buffer solution at pH 8.0 and 30 °C. The results are presented in Figure 1 and Table 1. Without **1**, the solvolysis rate of **2** ($n = 2-18$) is very slow and no substrate specificity is observed in methanol−water solution. In fact, an increase of the alkanoate chain length in **2** causes small decreases in the solvolysis rates. The rates for **1**-catalyzed solvolysis of **2** ($n = 2-18$) increase significantly with increasing concentration of **1**. Surprisingly, we find that macromolecule **1** demonstrates different substrate preferences as its concentration increases from 5.0×10^{-6} to 1.0×10^{-4} unit mol L^{-1} (Table 1). At 5.0×10^{-6} unit mol L^{-1}, the macromolecule **1** exhibits a preference for **2** ($n = 14$). As the concentration of **1** increases to 1.0×10^{-5} unit mol L^{-1}, the substrate preference is still for **2** ($n = 14$) (Table 1). However, when the concentration of **1** increases to 2.5×10^{-5} unit mol L^{-1}, the substrate specificity changes from **2** ($n = 14$) to **2** ($n = 12$) (Figure 1). For 5.0×10^{-5} unit mol L^{-1}, the substrate specificity also favors **2** ($n = 12$) (Table 1). As the concentration of **1** increases further to 7.5×10^{-5} unit mol L^{-1}, the substrate specificity changes again from **2** ($n = 12$) to **2** ($n = 10$). The latter substrate specificity is also observed for 1.0×10^{-4} unit mol L^{-1} **1** (Table 1). Apparently, the substrate specificity for the **1**-catalyzed solvolysis of **2** is controlled by the concentration of **1** in 50:50 (v/v) methanol−aqueous phosphate buffer solution. Although both enzymes and synthetic catalysts exhibit substrate specificity for the same solvolysis reactions,[5,8-10] we are not aware of any catalytic systems that show substrate specificity controlled by the concentration of catalyst for catalysis of ester solvolysis.

Furthermore, we find that the solutions of **1** show appreciable turbidity when the concentration of **1** is increased beyond 1.0

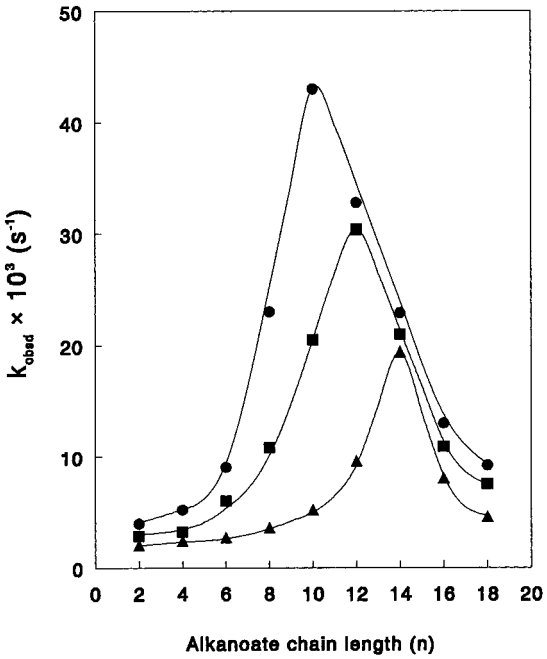


Figure 1. Pseudo-first-order rate constants (k_{obsd}) for the solvolysis of *p*-nitrophenyl alkanoates **2** ($n = 2-18$, 5.0×10^{-5} M) catalyzed by **1** as a function of alkanoate chain length (n) in 50:50 (v/v) methanol−aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution at 30 °C: (●) 7.5×10^{-5} unit mol L^{-1} **1**; (■) 2.5×10^{-5} unit mol L^{-1} **1**; (▲) 5.0×10^{-6} unit mol L^{-1} **1**.

Table 1. Summary of the Effect of Concentration of **1** on the Substrate Specificity of **1**-Catalyzed Solvolysis of **2** ($n = 2-18$) in Aqueous Methanol Solution at 30 °C[a]

concn of **1** (unit mol L^{-1})[b]	substrate specificity
5.0×10^{-6}	**2** ($n = 14$)
1.0×10^{-5}	**2** ($n = 14$)
2.5×10^{-5}	**2** ($n = 12$)
5.0×10^{-5}	**2** ($n = 12$)
7.5×10^{-5}	**2** ($n = 10$)
1.0×10^{-4}	**2** ($n = 10$)

[a] **2**, 5.0×10^{-5} M. [b] In 50:50 (v/v) methanol−aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution.

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Table 2. The Decrease of Length of Alkanoate Chain (D_L) of **2** Associated with Substrate Specificity Changes from **2** ($n = 14$) to **2** ($n = 12$) and **2** ($n = 10$) and the Decrease of Stretching of Hydrophobic Chains (D_S) of Amphiphilic Macromolecules Associated with Aggregate Morphology Changes from Sphere to Rod and Vesicle[a]

change of substrate specificity	D_L[b]	change of aggregate morphology	D_s[c]
2 ($n = 14$) → **2** ($n = 14$)	0%	sphere → sphere	0%
2 ($n = 14$) → **2** ($n = 12$)	14%	sphere → rod	11%
2 ($n = 14$) → **2** ($n = 10$)	29%	sphere → vesicle	29%

[a] Stretching of hydrophobic chains in aggregate morphology (ratio of the core radius of aggregate to the hydrophobic chain end-to-end distance in the unperturbed state): 1.40 for spheres, 1.25 for rods, and 1.00 for vesicles (see ref 3a,c). [b] $D_L = (L_{2(n=14)} - L_{2(n=12 \text{ or } 10)})/L_{2(n=14)}$, where L is the length of alkanoate chains of substrates. [c] $D_S = (S_{\text{sphere}} - S_{\text{rod or vesicle}})/S_{\text{sphere}}$, where S is the stretching of hydrophobic chains of aggregate morphology ($S_{\text{sphere}} = 1.40$, $S_{\text{rod}} = 1.25$, and $S_{\text{vesicle}} = 1.00$).[3a]

$\times 10^{-4}$ unit mol L^{-1} in 50:50 (v/v) methanol−aqueous phosphate buffer solution. These results suggest that changes of the aggregate morphology of **1** from spheres to rods, and to vesicles may accompany the increases of concentration of **1** from 5.0×10^{-6} to 1.0×10^{-4} unit mol L^{-1} in 50:50 (v/v) methanol−aqueous phosphate buffer solution.[3] A phenomenon well-known for small-molecule amphiphiles is that increases of their concentrations are accompanied by the transition from spherical micelles to micellar rods and vesicles in solution.[11] Very recently, changes of aggregate morphology of polystyrene-*b*-poly-2-vinylpyridine copolymers from spheres to rods, and to vesicles have also been observed with increasing polymer concentration.[12] The continual changes in aggregate morphology are governed solely by the polymer concentration in the solutions.[12] The stretching of hydrophobic chains of macromolecular amphiphiles is known to be greatest when they are located within spherical aggregates, and stretching decreases as the aggregate morphology changes from spheres to rods and decreases further as vesicles are formed.[3] Thus, spherical aggregates tend to provide the strongest hydrophobic binding to lipophilic substrates among the common aggregate morphologies in the reaction medium.

We have made an attempt to compare the decreases of alkanoate chain length (D_L) of **2** associated with substrate specificity changes from **2** ($n = 14$) to **2** ($n = 12$) and **2** ($n = 10$) with the decreases of stretching of hydrophobic chains (D_S) of amphiphilic macromolecules associated with aggregate morphology changes from spheres to rods and vesicles[3] (Table 2). As indicated by Eisenberg et al.,[3] the kinetics of exchange between aggregates and single chains in solution are slow due to the high viscosity of the insoluble chains within the aggregates of polymers. On a reasonable time scale, the aggregates of polymers may be regarded as "frozen" structures with no dynamic equilibrium between aggregates and single chains.[3] Therefore, an application of theoretical models for such systems requires the assumption that a dynamic equilibrium does exist at some stage of aggregate formation even though the final result is a frozen aggregate.[3] These considerations are also adopted in our calculations. Interestingly, the values of D_L and D_S are almost the same for both processes. The 3% difference between values of D_L and D_S for the change from **2** ($n = 14$) to **2** ($n = 12$) and the change from spheres to rods seems to be reasonable when probable measurement error in the studies of morphological structures by transmission electron microscopy is taken into consideration.[3] These results suggest that a parallel and equivalent decrease in hydrophobic effects is involved in both processes. Therefore, the substrate specificity changes that accompany an increase in the concentration of **1** may be caused by an energetically favorable matching of hydrophobicities of substrate **2** and aggregates of **1** leading to enhanced stabilization of **1·2** complexes. We suggest that the substrate specificity change from **2** ($n = 14$) to **2** ($n = 12$) may result from a change of aggregate morphology of **1** from spheres to rods leading to decreased hydrophobic binding and increased access of **1·2** complexes to the nucleophilic medium that is optimum for **2** ($n = 12$), whereas the specificity change from **2** ($n = 12$) to **2** ($n = 10$) may be attributed to further change of aggregate morphology of **1** from rods to vesicles leading to further decreased hydrophobic binding compensated by more rapid turnover that is optimum for **2** ($n = 10$). The matching of hydrophobicities of substrate and aggregate of catalyst is believed to be responsible for the molecular discrimination described by the term hydrophobic interactions at active sites of enzymes and catalysts in controlling substrate specificity for biological and chemical catalysis. Moreover, we find that increasing the concentration of **1** has a parallel effect on the substrate specificity, as does increasing the concentrations of NaCl in 50:50 (v/v) methanol−aqueous phosphate buffer solution,[7a,c] which is consistent with the notion that the hydrophobic effect is at work controlling the substrate specificity in the **1**-catalyzed solvolysis of **2** ($n = 2-18$). We suggest further that the distribution of both **1** and **2** among solution and aggregate phases controlled by polymer concentration and reaction medium may also be a major factor affecting the solvolysis rates of **2** in methanol−aqueous phosphate buffer solution.

We have also examined the effects of polymer concentration on the **1**-catalyzed solvolysis of **2** ($n = 10-16$) in different compositions of methanol−aqueous phosphate buffer solution at pH 8.0 and 30 °C in order to detect the relationships between the rate of model reaction and changes of concentration of **1** in the reaction medium. The data in Figure 2 on the pseudo-first-order rate constants for the **1**-catalyzed solvolysis of **2** ($n = 10$) as a function of concentration of **1** show that the solvolysis rates increase strongly with an increase in the concentration of **1** in 45:55 and 50:50 (v/v) methanol−water but modestly with an increase in the concentration of **1** in 55:45 and 60:40 (v/v) methanol−water, and tend to level off at the later stage. Strikingly, below 2.5×10^{-5} unit mol L^{-1} **1**, the order of reactivity for **2** ($n = 10$) is 45:55 > 50:50 > 55:45 > 60:40 (v/v) methanol−aqueous phosphate buffer solution. However, above 5.0×10^{-5} unit mol L^{-1} **1**, the reactivity order is 50:50 > 45:55 > 55:45 > 60:40 (v/v) methanol−aqueous phosphate buffer solution.

The pseudo-first-order rate constants for the **1**-catalyzed solvolysis of **2** ($n = 12$) as a function of the polymer concentration in different compositions of methanol−aqueous phosphate buffer solution are plotted in Figure 3. We find that the pseudo-first-order rate constants increase by a factor of about 35 when the concentration of **1** is increased to 2.5×10^{-5} unit mol L^{-1} and then stay at plateau values up to 1.0×10^{-4} unit

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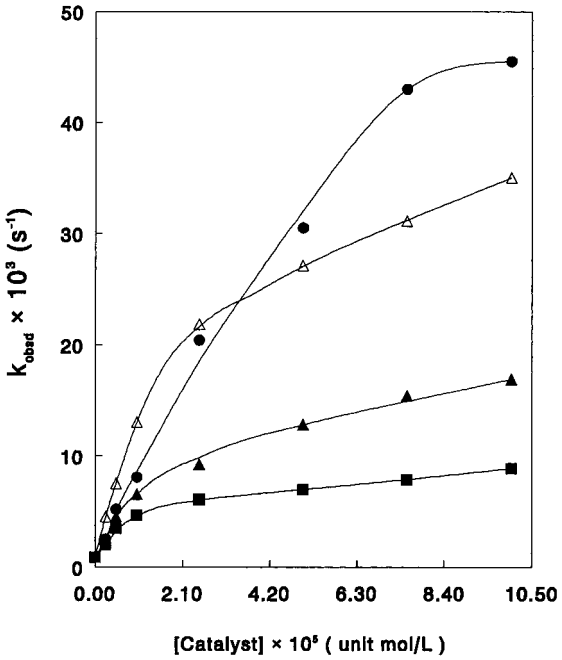

Figure 2. Pseudo-first-order rate constants (k_{obsd}) for the **1**-catalyzed solvolysis of **2** (n = 10, 5.0 × 10^{-5} M) as a function of polymer concentration in different compositions of methanol−aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution at 30 °C: (△) in 45:55 (v/v) CH_3OH-H_2O; (●) in 50:50 (v/v) CH_3OH-H_2O; (▲) in 55:45 (v/v) CH_3OH-H_2O; (■) in 60:40 (v/v) CH_3OH-H_2O.

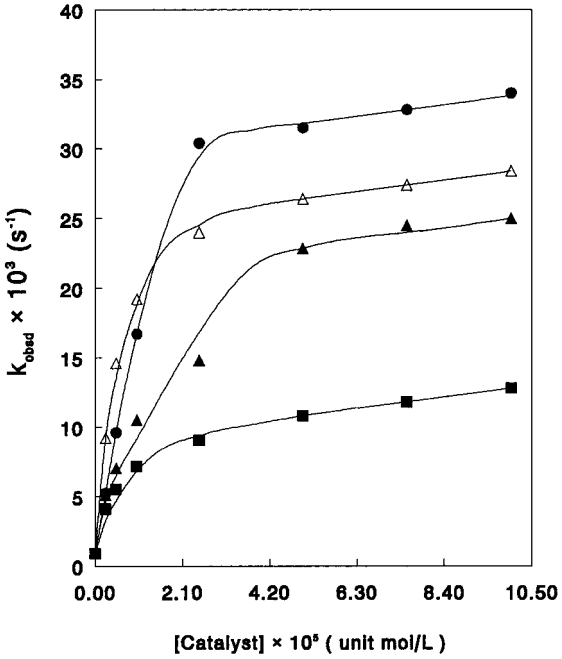

Figure 3. Pseudo-first-order rate constants (k_{obsd}) for the **1**-catalyzed solvolysis of **2** (n = 12, 5.0 × 10^{-5} M) as a function of polymer concentration in different compositions of methanol−aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution at 30 °C: (△) in 45:55 (v/v) CH_3OH-H_2O; (●) in 50:50 (v/v) CH_3OH-H_2O; (▲) in 55:45 (v/v) CH_3OH-H_2O; (■) in 60:40 (v/v) CH_3OH-H_2O.

mol L^{-1} in 50:50 (v/v) methanol−aqueous phosphate buffer solution. Similar types of kinetic behavior for **2** (n = 12) have also been observed in 45:55, 55:45, and 60:40 (v/v) methanol−aqueous phosphate buffer solution. Significantly, below 1.0 × 10^{-5} unit mol L^{-1} **1**, the catalytic efficiency for **2** (n = 12) is 45:55 > 50:50 > 55:45 > 60:40 (v/v) methanol−aqueous

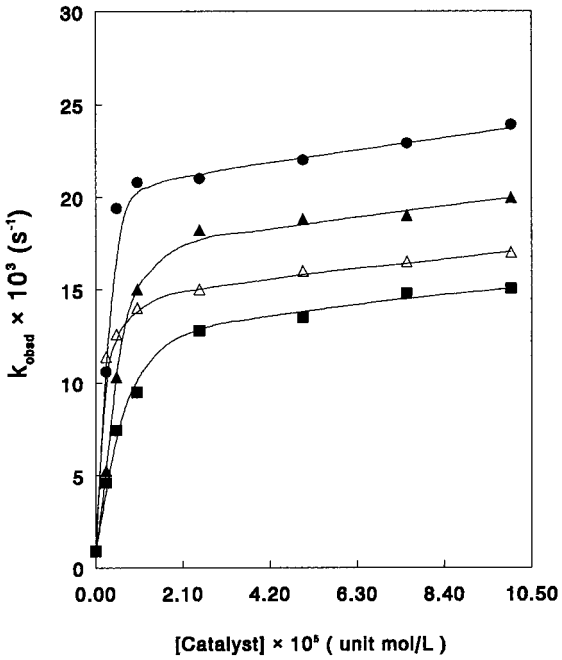

Figure 4. Pseudo-first-order rate constants (k_{obsd}) for the **1**-catalyzed solvolysis of **2** (n = 14, 5.0 × 10^{-5} M) as a function of polymer concentration in different compositions of methanol−aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution at 30 °C: (△) in 45:55 (v/v) CH_3OH-H_2O; (●) in 50:50 (v/v) CH_3OH-H_2O; (▲) in 55:45 (v/v) CH_3OH-H_2O; (■) in 60:40 (v/v) CH_3OH-H_2O.

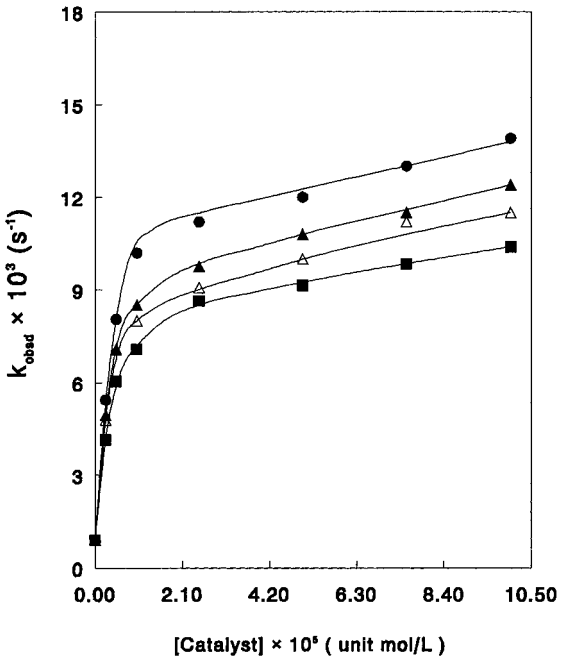

Figure 5. Pseudo-first-order rate constants (k_{obsd}) for the **1**-catalyzed solvolysis of **2** (n = 16, 5.0 × 10^{-5} M) as a function of polymer concentration in different compositions of methanol−aqueous buffer (0.05 M $H_2PO_4^-/HPO_4^{2-}$, pH 8.0) solution at 30 °C: (△) in 45:55 (v/v) CH_3OH-H_2O; (●) in 50:50 (v/v) CH_3OH-H_2O; (▲) in 55:45 (v/v) CH_3OH-H_2O; (■) in 60:40 (v/v) CH_3OH-H_2O.

phosphate buffer solution. But, the magnitude of catalytic effects is 50:50 > 45:55 > 55:45 > 60:40 (v/v) methanol−aqueous phosphate buffer solution over 2.5 × 10^{-5} unit mol L^{-1} **1**.

The dependence of the pseudo-first-order rate constants on the concentration of **1** for the **1**-catalyzed solvolysis of **2** (n = 14) in different compositions of methanol−aqueous phosphate

buffer solution is presented in Figure 4. The solvolysis reactions exhibit rapid enhancements of the pseudo-first-order rate constants at low concentrations of **1**, followed by gradual levelling off with increasing concentrations of **1**. Finally, the rate constants reach plateau values. It is noted that the reactivity order of **2** ($n = 14$) is 45:55 > 50:50 > 55:45 > 60:40 (v/v) methanol−aqueous phosphate buffer solution below 5.0×10^{-6} unit mol L^{-1} **1**, and the order of reactivity is 50:50 > 45:55 > 55:45 > 60:40 (v/v) methanol−aqueous phosphate buffer solution between 5.0×10^{-6} and 1.0×10^{-5} unit mol L^{-1} **1** and 50:50 > 55:45 > 45:55 > 60:40 (v/v) methanol−aqueous phosphate buffer solution above 1.0×10^{-5} unit mol L^{-1} **1**.

Relevant plots of the pseudo-first-order rate constants vs polymer concentrations for the **1**-catalyzed solvolysis of **2** ($n = 16$) in different compositions of methanol−aqueous phosphate buffer solution are graphically shown in Figure 5. The solvolysis rates for **2** ($n = 16$) increase rapidly with increasing concentration of **1** up to 1.0×10^{-5} unit mol L^{-1}. But the effects of polymer concentration on the solvolysis rates are very small with further increase in the concentration of **1**. Interestingly, the catalytic efficiency is found to be in the order 50:50 > 55:45 > 45:55 > 60:40 (v/v) methanol−aqueous phosphate buffer solution in the concentration range of **1** investigated.

These results demonstrate that the substrate specificity of catalysis of ester solvolysis can be controlled by the concentration of polymer catalyst in the reaction medium, and provide a new approach to the control of chemical reactivity that can be useful in understanding the fundamental basis of controlling substrate specificity at the molecular level in biological and chemical catalysis. The demonstration of polymer concentration-controlled substrate specificity establishes this system as a potential guide to synthetic receptors which can mimic the biological systems in terms of molecular recognition and selective interactions with hydrophobic drugs.

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