Syntheses of Novel Catalytic Polyelectrolytes from Poly(*N*-(2,4-dinitrophenyl)-4-vinylpyridinium chloride) and Amines or Amino Acids and Their Rate-Enhancing Effects in Ester Hydrolyses[1]

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Abstract: Polymers catalyzing the hydrolysis of nitrophenyl esters were studied using polyelectrolytes (II) synthesized by reacting poly(*N*-(2,4-dinitrophenyl)-4-vinylpyridinium chloride) (I) with histamine or histamine mixed with other amino derivatives. I was obtained by quaternization of poly(4-vinylpyridine) [or poly(4-vinylpyridine) partially quaternized with alkyl halide] with 2,4-dinitrochlorobenzene. The kinetics of the reactions of I with amines or amino acids were investigated in water and 2.5% ethanol–water at 25° using the rapid-scan stopped-flow technique. The formation of II was characterized by two relaxation times, namely an amine-independent fast process (40–50 sec^{-1}) and an amine-dependent slow process (4–9 × 10^{-2} sec^{-1}). II was prepared by reacting I with histamine or histamine mixed with *n*-butylamine, *n*-cetylamine, β-hydroxyethylamine, and/or β-carboxyethylamine. The hydrolyses of neutral and anionic esters, i.e., *p*-nitrophenyl acetate, *p*-nitrophenyl propionate, and 3-nitro-4-acetoxybenzoic acid with the polyelectrolytes (II) above obtained followed saturation kinetics in alkaline regions. The catalyses by the polyelectrolytes (II) were discussed in terms of the two contributions, i.e., (1) catalysis by imidazolyl group and (2) electrostatic catalysis for the *alkaline* hydrolysis. It was demonstrated that the polyelectrolytes catalyzed the ester hydrolysis largely by the first factor.

Recently, a variety of esterolytic catalyses by polymers containing imidazole groups or other nucleophiles have been investigated as α-chymotrypsin models.[2-14] In common with almost all enzymes, the reactions catalyzed by α-chymotrypsin are characterized by a saturation phenomenon, which implies that the enzyme binds the substrate before the catalytic reaction occurs. Attempts, therefore, have been made to construct synthetic polymers by introducing binding groups besides catalytic sites.

In the present paper, we report novel catalytic polyelectrolytes (II) prepared from poly(4-vinylpyridine) partially quaternized with 2,4-dinitrochlorobenzene which can react with a variety of amino derivatives RNH_2 at room temperature in water or other polar solvent (methanol, ethanol, dimethylformamide, etc.) to yield 2,4-dinitroaniline and polyvinylpyridine quaternized with R group. In 1904, Zincke[15] and König[16] reported independently that *N*-(2,4-dinitrophenyl)pyridinium ions reacted with amines to give a reddish adduct, and detailed studies of this reaction were reported later.[17,18] Our polymer preparation was analogous to these procedures.

Experimental Section

Materials. Poly(4-vinylpyridine) was prepared by bulk polymerization of 4-vinylpyridine with benzoyl peroxide, as described before.[19] The degree of polymerization was 3800. β-Hydroxyethylamine, l-tryptophan, and histamine were obtained from Fluka AG, and l-β-phenyl-α-alanine and tyrosine were obtained from Sigma Chemicals Co. The other amines and amino acids were commercially available. 3-Nitro-4-acetoxybenzoic acid (NABA) was prepared by the method of Overberger et al.[5] and Kunitake et al.[8] *p*-Nitrophenyl acetate (PNPA) obtained from Nakarai Chemicals Co., Kyoto, was further purified by recrystallization (mp 78°). *p*-Nitrophenyl propionate (PNPPR) obtained from Sigma Chemicals Co. was used without further purification. Dimethylformamide and dioxane used were spectral grade reagents. Deionized water distilled using a Yamato auto still (Model WAG-21) and spectroscopic grade ethanol were used for the preparation of the solutions of esters and polymer catalysts.

Conductance Measurements. The quaternization of poly(4-vinylpyridine) with 2,4-dinitrochlorobenzene was followed in an electrolytic cell of the Jones-Ballinger type (cell constant = 7.64 cm^{-1}) using an autobalance precision bridge (Wayne Kerr, Model B331 MKII) with a recorder (Riken Denshi Co., Ltd, Model SP-H). The precision of the bridge is claimed to be ±0.01% according to the manufacturer.

Kinetic Measurements. Kinetic measurements of the reaction of I with amine or amino acid were carried out spectrophotometrically by using a Hitachi rapid scan spectrophotometer (Model RSP-2) equipped with thermostated cell holder and a Union stopped-flow spectrophotometer (Model RA1100), a product of the Union Engineering, Hirakata, Osaka-fu. The details of the RSP-2 spectrophotometer were described elsewhere.[19,20] The RA1100 photometer consists of a four-jet mixer and an observation cell with a 1-cm optical path length. The dead time of the apparatus was 1.0 msec by the flow-speed measurements. The hydrolyses of esters were followed using a pH-stat potentiometer (Model 101), a product of the Hiranuma Industry Co., Mito, Ibaraki, by detecting acid released. The initial hydrolysis rate, v_0, was determined by a linear extrapolation of the rate within 10% conversion. The rate of hydrolysis by polymer catalyst,[21] v_{cat}, was defined as $v_{cat} = v_0 - v_0^*$, where v_0^* indicates the rate in the absence of the catalyst. The hydrolyses of all esters studied showed saturation phenomena with respect to the substrate concentration, and the Michaelis–Menten kinetics were applied:

$$C + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C{\cdot}S \xrightarrow{k_3} P + C \qquad (1)$$

where C, S, CS, and P denote the catalytic moiety (imidazolyl group) of the polymer catalyst, the substrate, the complex of the catalytic moiety and the substrate, and the hydrolyzed product, respectively. The rate of the hydrolysis is expressed as shown in eq 2 and 3, where K_m is the Michaelis–Menten constant, and $[C]_0$ and

$$v_{cat} = \frac{k_3[C]_0[S]_0}{K_m + [S]_0} \qquad (2)$$

$$K_m = \frac{k_2 + k_3}{k_1} \qquad (3)$$

$[S]_0$ are the initial concentrations of the imidazolyl group and of the substrate.

Results and Discussion

Syntheses of Polycations (I). The syntheses of the polycation (I) were followed by the time dependence of the specific conductance (κ) of the reaction mixture, i.e., poly(4-vinylpyridine) + 2,4-dinitrochlorobenzene + dimethylfor-

Table I. Composition of Partially Quaternized Polycations (I)

Code	Mole fraction of 2,4-dinitrophenyl groups	Mole fraction of alkyl or benzyl groups	Mole fraction of unquaternized pyridyl groups	Solvent used in quaternization with 2,4-dinitrochlorobenzene
RP3	0.18	0	0.82	Methanol
RP4	0.072	0	0.93	DMF[a]
RP5	0.23	*n*-Butyl 0.72	0.05	Nitromethane
RP7-10	0.24	0	0.76	DMF
RP7-20	0.30	0	0.70	DMF
RP7-40	0.53	0	0.47	DMF
RP7-70	0.62	0	0.38	DMF
RP81	0.12	*n*-Butyl 0.75	0.13	Methanol
RP9	0.13	Benzyl 0.70	0.17	DMF
RP11-3	0.15	*n*-Butyl 0.62 *n*-Cetyl 0.08	0.15	Nitromethane

[a] Dimethylformamide.

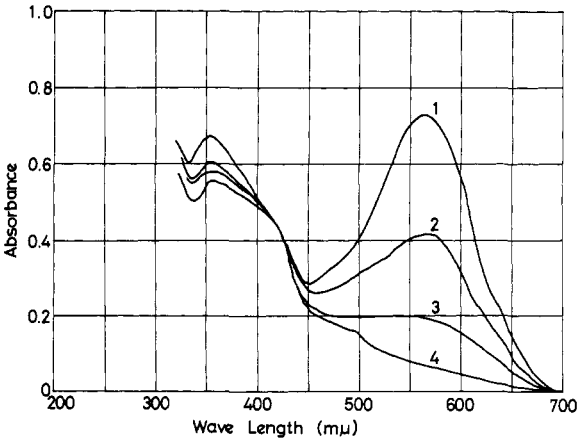


Figure 1. Reaction of RP81 with octylamine at 25°. [RP81] = 10^{-3} equiv $l.^{-1}$, [octylamine] = 2.5×10^{-3} *M*, in 2.5% EtOH–H_2O. Curve 1, 1 sec; curve 2, 10 sec; curve 3, 30 sec; curve 4, 100 sec.

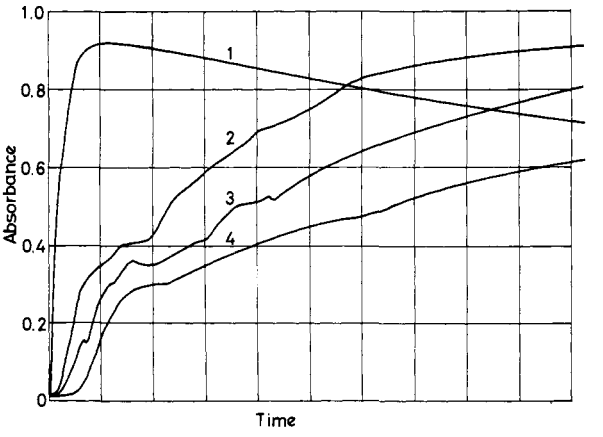


Figure 2. Reaction of RP81 with tryptamine at 25°. [RP81] = 2.5×10^{-4} equiv $l.^{-1}$, pH 10.3, at 570 nm. [Tryptamine] = 2.5×10^{-3} *M*, in 2.5% EtOH–H_2O. Curve 1, 160 msec/div; curve 2, 8 msec/div; curve 3, 4 msec/div; curve 4, 1.6 msec/div.

mamide. The solution became reddish blue after 1 hr and turned to dark blue after 3 hr under the experimental conditions employed. I obtained by the quaternization was soluble in methanol, ethanol, dimethylformamide, and other polar solvents, but insoluble in water. Water-soluble polycation was easily obtained by partial quaternization of poly(4-vinylpyridine) with alkyl or benzyl halide before the quaternization with 2,4-dinitrochlorobenzene.

The preparative procedures of a polycation (code RP-2) were as follows. Benzyl chloride (14.1 ml) was added dropwise into a solution of poly(4-vinylpyridine) (16.2 g) in 300 ml of nitromethane. The solution was kept at 45° for 3 days. The solvent and unreacted benzyl chloride were then eliminated by heating in vacuo. The residue was dissolved into water and then precipitated in dioxane. The dried product was hygroscopic, slightly yellow powder, 18 g yield. The degree of quaternization determined from the chloride ion analysis was 70%. The poly(4-vinylpyridine) partially quaternized with benzyl chloride was dissolved into 100 ml of ethanol. The solution was mixed with an ethanolic solution (50 ml) of 2,4-dinitrochlorobenzene and kept at 35° for 2 hr, the reaction mixture turning a reddish color. The solution was then poured into a large quantity of dioxane. Decantation was twice carried out with dioxane. The dried product was slightly yellow powder, 13.5 g yield and 28% degree of quaternization with 2,4-dinitrochlorobenzene. Anal. Calcd for $(C_7H_7N)_{0.02}(C_{13}H_{10}N_3O_4Cl)_{0.28}$-$(C_{14}H_{14}NCl)_{0.70}$: C, 65.12; H, 5.09; N, 8.73; Cl, 13.90. Found: C, 65.5; H, 5.2; N, 8.6; Cl, 13.9.

In Table I, other typical polycations synthesized in the present paper are listed. Halide ion analyses were conducted after each quaternization with dinitrochlorobenzene and alkyl halide to determine the composition of the polymers. The elementary analyses were also carried out.

Reaction of Polycations (I) with Amines or Amino Acids. In Figure 1, the absorption changes are shown for the reactions of a polycation, RP81, with *n*-octylamine (in 2.5% EtOH–H_2O), which were obtained by the rapid-scan stopped-flow technique. The absorption peak at λ_{max} 570 nm appeared within 1 sec and then gradually disappeared. On the other hand, the absorption peak at 360 nm due to 2,4-dinitroaniline increased monotonically. The time dependence of the absorption at 570 nm for the reaction of RP81 with tryptamine is shown in Figure 2, where a rapid increase in the absorbance (relaxation time, τ_{fast} = 25.6 msec) followed by a comparatively slow decrease (τ_{slow} = 11.5 sec) was observed.[22] The overall reaction mechanism of the polycation *I* with amine is believed to be given by Scheme I, by analogy with the monomeric chloride [*N*-(2,4-dinitrophenyl)pyridinium chloride] with amine.[17,18] The rate-determining steps of the formation of the colored intermediate (I_c) and the N-substituted poly(vinylpyridinium) salt (II) are also believed to be that from I_a to I_b and that from I_d to II, respectively, by analogy with *N*-(2,4-dinitrophenyl)pyridinium chloride with amine.[17,18] The first-order rate constants of the both steps (τ^{-1}_{fast} and τ^{-1}_{slow}, respectively) are compiled in Table II. The reactions were carried out in water or in 2.5% ethanol-water.

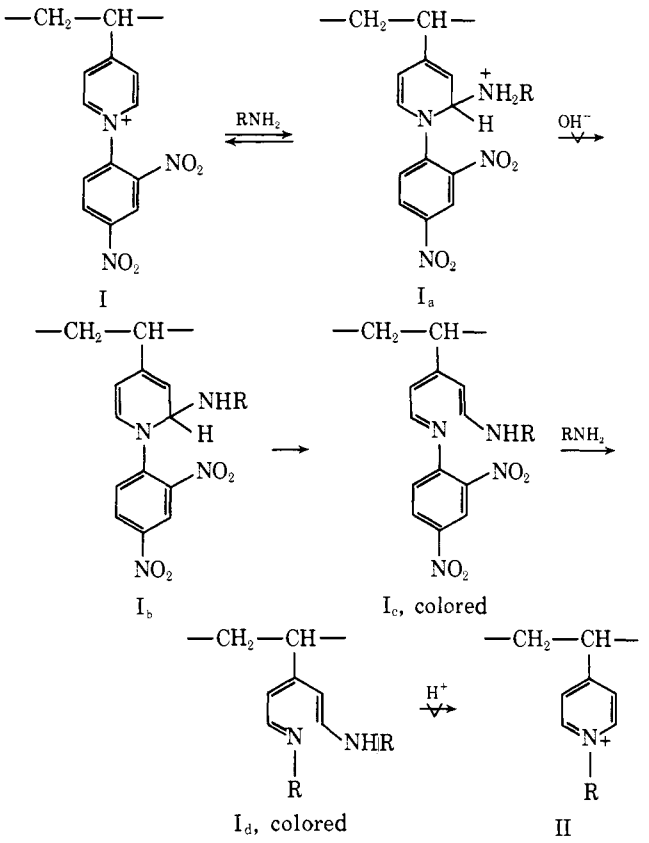
The τ^{-1}_{fast} was slightly dependent on pH. In the case of the *N*-(2,4-dinitrophenyl)pyridinium chloride reaction, the τ^{-1}_{fast} depended very strongly on pH. Therefore, though the τ^{-1}_{fast} values for the polymer and for *N*-(2,4-dinitrophenyl)pyridinium ion were comparable at high pH, the former became much faster than the latter at lower pH. This can be interpreted in terms of the electrostatic attractive forces

Table II. The τ^{-1}_{fast} and τ^{-1}_{slow} Values of Reactions of RP81 with Amines and Amino Acids at 25°[a]

Amine or amino acid	Concentration of amine or amino acid	pH	τ^{-1}_{fast}, sec^{-1}	$\tau^{-1}_{slow} \times 10^2$, sec^{-1}
Ethylamine	2.5	10.7	50	7.4
Monoethanolamine	2.5	9.8	39	5.3
Diethylamine	2.5	10.4	50	
Hexylamine[b]	5.0	10.9	83	8.7
Octylamine[b]	5.0	11.3	100	8.7
Phenethylamine	2.5	10.9	37	5.3
Benzylamine	2.5	10.0	37	4.1
Aniline	2.5	8.4	Very slow and faint	
Tryptamine[b]	2.5	10.6	39	8.7
β-Alanine	2.5	11.2	40	7.2
α-Alanine	2.5	11.2	38	7.1

[a] [RP81] = 10^{-3} equiv $l.^{-1}$ in H_2O. [b] In 2.5% ethanol–water.

Scheme I



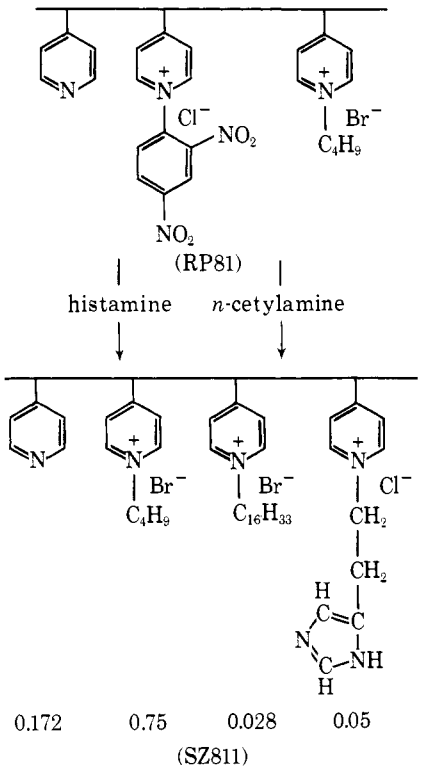
between the highly charged polycation and the OH^- ion in the first reaction step.

The rate of the fading reaction (τ^{-1}_{slow}) measured at 570 nm of the RP81 varied with amines or amino acids, which indicated that the ring-closure reaction rate ($I_d \rightarrow II$) was strongly influenced by the nucleophilicity and electron-donating strength of amine, etc. The features of τ^{-1}_{slow} of the polycation seem to be similar to those of 2,4-dinitrophenyl-3-carbamoylpyridinium cation.[23]

It should be noted that the reaction ($I \rightarrow II$) proceeded in various kinds of polar solvents, for example, water, ethanol, and dimethylformamide.

Esterolytic Activity of the Catalytic Polyelectrolytes. The catalytic polyelectrolytes (II in Scheme I) were synthesized easily by addition of amines to I. The preparative procedures of SZ811, for example, were as follows (see Scheme II); an alcoholic solution of histamine and then an alcoholic solution of *n*-cetylamine were added to an alcoholic solution of RP81. After 24 hr, the solution was poured into a large excess of dioxane. The precipitate thus obtained was dried in vacuo. The residue was dissolved in water and treated with activated charcoal powder. The filtrate was then dialyzed against distilled water. The final polymer thus obtained contained 5% histidyl, 2.8% *n*-cetyl, and 75% *n*-butyl groups.

Scheme II



Elementary analyses were carried out after the substitution with the amine, from which the composition of the product polymers was determined.

The hydrolyses of PNPA, NABA, and PNPPR were carried out in the presence of SZ811. The saturation kinetics were observed for the three esters. The values of K_m and k_3 obtained from the Lineweaver-Burk plots[24] are listed in Table III. SZ811 having *n*-cetyl group is considered to be very hydrophobic. Thus the comparatively small values were observed for K_m.

Next, we synthesized other catalytic polyelectrolytes, namely, SZ11-3-1, SZ11-3-3, and SZ11-3-7 from RP11-3 and various amines, i.e., histamine, β-carboxyethylamine or ethanolamine, and tested their efficiency in catalyzing the hydrolyses of PNPA at pH 8.0. The Michaelis-Menten and Lineweaver-Burk profiles of the hydrolyses by SZ11-3-1 are shown in Figure 3. The values of K_m and k_3 are compiled in Table III. The fractions of the quaternized groups are shown in the parentheses.

As is apparent from the table, the k_3 value of SZ11-3-3 is three times larger than that of SZ11-3-1. This may indi-

Table III. Hydrolyses of PNPA, PNPPR, and NABA in the Presence of SZ811 or SZ11-3 Series Catalysts at 30°, pH 8.0

Catalyst	Ester	K_m, mM	k_3, min^{-1}
SZ811 (butyl 0.75; *n*-cetyl 0.028; His 0.05)	PNPA[a]	4.6	0.26
SZ811	PNPPR[b]	0.74	0.015
SZ811	NABA[a]	2.3	0.25
SZ11-3-1 (butyl 0.62; *n*-cetyl 0.08; His 0.15)	PNPA[c]	3.8	0.047
SZ11-3-3 (butyl 0.62; *n*-cetyl 0.08; $-C_2H_4OH$ 0.08; His 0.07)	PNPA[c]	7.1	0.14
SZ11-3-7 (butyl 0.62; *n*-cetyl 0.08; $-C_2H_4COOH$ 0.08; His 0.07)	PNPA[c]	6.1	0.11

[a] In H_2O, 0.1 M KCl. [b] In 50% EtOH–H_2O, 0.1 M KCl. [c] In 10% EtOH–H_2O, 0.025 M KCl.

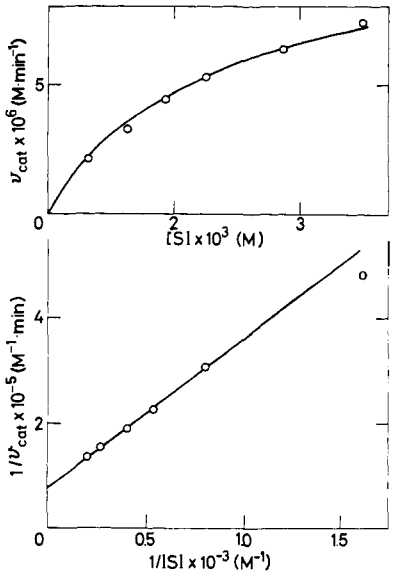


Figure 3. Hydrolysis of PNPA with SZ11-3-1 at 30°. [SZ11-3-1] = 1.6 × 10^{-3} equiv l.$^{-1}$, [His] = 2.82 × 10^{-4} M, pH 8.0, 0.025 M KCl, in 10% EtOH-H_2O.

cate a cooperative effect between imidazolyl and hydroxyl groups, as first proposed by Overberger et al.[25] A cooperativity between imidazolyl and carboxylic acid groups also seems to exist since k_3 is much larger for SZ11-3-7 than for SZ11-3-1.

Both the nucleophilicity of imidazole and the conformation of the polymer chain are expected to be very sensitive to ionic strength, because the present polyelectrolytes are strongly basic. In Figure 4, the initial rates of the hydrolyses of PNPA with SZ11-3-1 at various concentrations of added KCl are shown. The hydrolysis rate decreased monotonically with KCl concentration, probably because of shrinkage of the polymer coil as often observed for linear polyelectrolytes, which would "bury" the imidazolyl groups into the inner part of the polymer domain.

On the other hand, in the absence of catalyst, the hydrolysis rate increased with increasing KCl concentration. This is due to a lowering of the activities of the reactants and the activated complex by the salt in alkaline hydrolysis reaction between dipole ester and ionic (OH^-) species.[26]

C_{16}BzPVP in Figure 4 stands for a copolymer of 4-vinyl-*N*-benzylpyridinium chloride (95%) and 4-vinyl-*N*-cetylpyridinium bromide (5%), which is a strong basic and hydrophobic polymer containing no nucleophilic groups. In the absence of KCl, C_{16}BzPVP accelerated the hydrolysis rate of PNPA several times as is seen from the figure. This is due to a cooperative acceleration by electrostatic interactions between the polycations and OH^- and hydrophobic

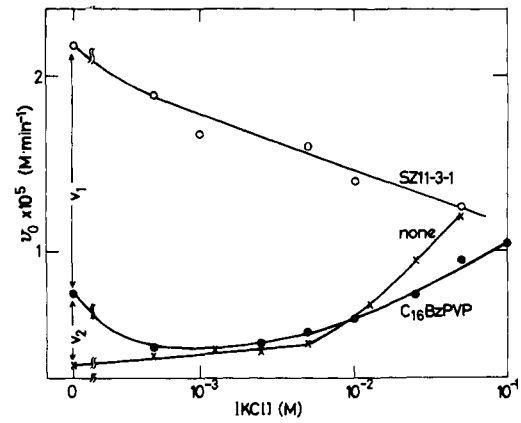


Figure 4. Hydrolysis of PNPA with SZ11-3-1 and C_{16}BzPVP at 30°. [SZ11-3-1] = 1.6 × 10^{-3} equiv l.$^{-1}$, [PNPA] = 2.5 × 10^{-3} M, [C_{16}BzPVP] = 2.5 × 10^{-3} equiv l.$^{-1}$, pH 8.0, in 10% EtOH–H_2O.

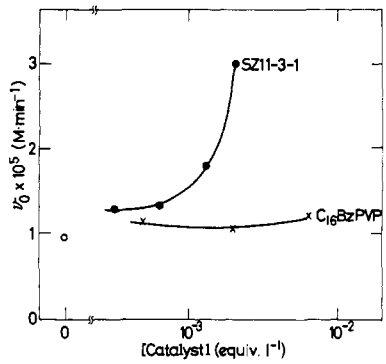


Figure 5. Hydrolysis of PNPA with SZ11-3-1 and C_{16}BzPVP at 30°. [PNPA] = 2.5 × 10^{-3} M, pH 8.0, 0.025 M KCl, in 10% EtOH–H_2O.

interactions between the hydrophobic groups of the polymer and the ester molecules. An initial increase in KCl concentration shields the electrostatic interactions, and further increase causes a shrinking of the polymer coil, resulting in a higher local charge density and hence a stronger interaction with OH^-. Such a catalysis has been discussed in detail elsewhere.[27,28]

It should be noted here that SZ11-3-3 and C_{16}BzPVP are quite similar in their molecular structure, except for the imidazolyl groups in the former polymer. Thus, as seen from Figure 4, the observed rate enhancement with SZ11-3-1 in the absence of KCl is due both to the imidazole catalysis (v_1) and the electrostatic catalysis for the alkaline hydrolysis (v_2) above mentioned.

On the other hand, at the higher concentration regions of KCl than 5 × 10^{-4} M in Figure 4, the hydrolysis rates in the presence of C_{16}BzPVP and in its absence are similar; i.e., the catalytic effect of C_{16}BzPVP is negligible.[29] Under such conditions, the rate enhancement effect of SZ11-3-1 should be ascribed exclusively to the imidazole catalysis. As seen from the figure, C_{16}BzPVP had even a retarding effect in the presence of a large quantity of KCl (>10^{-2} M), though the reason for this is not clear. Under these circumstances, the observed rate acceleration by SZ11-3-1 is of course also ascribed to the imidazole catalysis.

In Figure 5, the changes of the hydrolysis rates of PNPA in the presence of 0.025 M KCl with SZ11-3-1 or C_{16}BzPVP, are compared. SZ11-3-1 accelerated the hydrolysis, whereas C_{16}BzPVP was not effective. This suggests that the imidazolyl groups of SZ11-3-1 play an important role in the observed catalysis as above mentioned. It is clear from the above discussion that the catalysis for the alkaline hydrolysis must be subtracted from rate enhancement demonstrated by any cationic polymer catalyst.

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References and Notes

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(29) In the presence of KCl, C_{16}BzPVP was found to be a weak catalyst for the alkaline hydrolysis of PNPA, though striking acceleration effect was observed for more hydrophobic esters, *p*-nitrophenyl laurate, for example.[27]

Solvolyses of 2-*endo*- and 2-*exo*-Chloro-7-thiabicyclo[2.2.1]heptanes[1]

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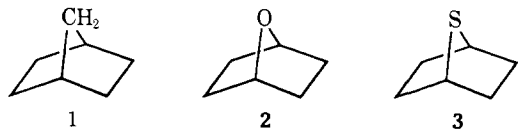
Abstract: 2-*endo*-Chloro-7-thiabicyclo[2.2.1]heptane (**5**) was prepared from the corresponding alcohols (2-exo and 2-endo alcohols) exclusively by common chlorination procedures. However, 2-*exo*-chloro-7-thiabicyclo[2.2.1]heptane (**7**) was only available by the selective reduction of 2-*exo*-chloro-7-thiabicyclo[2.2.1]heptane 7,7-dioxide with $LiAlH_4$. The kinetics of solvolyses of these two epimeric chlorides have been measured. Acetolysis of the endo chloride was observed to follow the second-order kinetics, $v = k$[R–Cl][AcONa]. The mechanism involving rate-determining attack of nucleophile (AcO^-) to the sulfonium intermediate (**11**) was first observed in the acetolyses of **5**, which related to the stereospecific product formation (100% endo) and the profound acceleration by a factor of at least 4.7×10^9 compared with the exo chloro counterpart (**7**). Hydrolysis of **7**, which followed the first-order kinetics, gave skeletally rearranged 3-*exo*-hydroxy-2-thiabicyclo[2.2.1]heptane.

A large amount of kinetic and mechanistic investigations has been performed on the solvolyses of various norbornyl derivatives (**1**).[3a-c] The rate-retarding effects of an oxygen bridge substituted in the place of the methylene bridge of norbornane were observed by Martin and Bartlett[3d] (**2**), indicating that the inductive effect of oxygen atom overcame the participation by 2p lone pair electrons on oxygen[4] and the incipient carbonium ion was rather destabilized. The neighboring sulfur atom has long been known as a very effective participating group, more effective than oxygen in β or remote participation.[5] In order to gain further insights into the sulfur participation in solvolysis, 2-exo- and 2-endo chlorides of 7-thiabicyclo[2.2.1]heptane (**3**) of known geometry[6] were prepared and solvolyses of them were performed to investigate the electronic and steric effects on the neighboring sulfur participation.



1 2 3

Results

2-*endo*-Chloro-7-thianorbornane (**5**) was prepared from 2,5-bis-*endo*-dichloro-7-thianorbornane[7] via the series of reactions as shown in Scheme I, involving the interesting stereospecific and practically quantitative endo chlorination of the corresponding endo alcohol (**4**) (overall yield of **4** from the dichloride was 73%). Partial reduction of 2,5-bis-*endo*-dichloro-7-thianorbornane with $NaBH_4$ also gave endo chloride **5** together with the recovered dichloride and thianorborane, which was identical with the chloride synthesized via Scheme I in every respect (GLC, ir, NMR).

2-*exo*-Chloro-7-thianorbornane (**7**) was, on the other hand, prepared from 7-thianorbornane dioxide via cationic chlorination with SO_2Cl_2[8,9] and the successful partial reduction with lithium aluminum hydride (see Scheme I). Endo alcohol **4** was successfully oxidized to 7-thianorborna-