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Enantioselective solvolyses of amino acid p-nitrophenyl esters by optically active imidazole-containing copolymeric surfactants

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SUMMARY

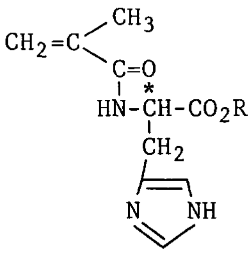
The imidazole-containing copolymeric surfactant, poly(N-methacryloyl-L-histidine methyl ester(1a)-co-N,N-dimethyl-N-hexadecyl-N-(11-methacryloyloxyundecanyl)ammonium bromide(I)) was prepared and subjected to catalyze the hydrolyses of N-carbobenzoxy-D- and L-phenylalanine p-nitrophenyl esters (D-NBP and L-NBP). The copolymers exhibited enantioselective catalysis, viz., $k_{cat}(L)/k_{cat}(D)=10.3$ for poly(1a-co-I) containing 3.7 mole % of 1a. The solvolytic systems employed were confirmed to form large ordered aggregate structure by electron microscopic observation.

INTRODUCTION

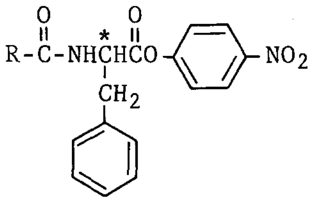
Recently hydrophobic interactions or non-polar interactions have received considerable attention in the studies of enantioselective solvolyses of optically active ester substrates by imidazole-containing polymers or peptides(1). Most of reported investigations are, however, enantioselective solvolytic studies in micellar or bilayer systems of histidyl peptides of low molecular weight(2-5), and stereochemical studies in hydrolytic systems catalyzed by polymeric imidazoles are limitted to only a few instances(6-11).

We have previously reported enantioselective hydrolyses of optically active activated esters by polymeric catalysts containing L-histidyl pendant groups(7,9). In previous investigations we prepared polymers from imidazole-containing monomers with different funtions, N-methacryloyl-L-histidine methyl ester (1a) and N-methacryloyl-L-histidine (1b), and copolymers of 1a and 1b with dodecyl methacrylate(DMA), and investigated the catalytic activity exhibited by those polymers toward the solvolyses of optically active activated esters, N-carbomethoxy-D- and L-phenylalanine p-nitrophenyl esters (D-NCP and L-NCP) and D-NBP and L-NBP. The homopolymers, poly(1a) and poly(1b), did not show any significant difference in the solvolytic rates of D- and L- substrates. However, the copolymers with monomers of hydrophobic character did exhibit a certain degree of enantioselectivity, especially toward the more hydrophobic esters, D-NBP and L-NBP, and it was enunciated that hydrophobic interactions play a certain role in enantioselective catalysis by the optically active imidazole-containing polymers.

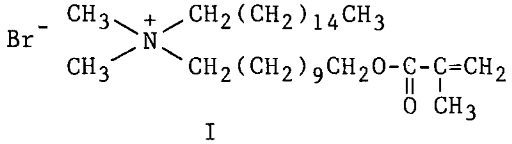
In the course of our investigation of polymeric catalysts, to further explore the role of hydrophobic interation in the solvolyses of optically active activated esters by optically active imidazole-containing polymers, we have constructed the surfactant systems containing imidazole moiety in such a way that the systems were expected to form ordered structures when subjected to the solvolytic reactions. For the optically active imidazole-



1a: R= CH_3
1b: R= H



D(L)-NBP: R= $C_6H_5CH_2O$
D(L)-NCP: R= CH_3O



I

catalyst moiety, N-methacryloyl-L-histidine methyl ester (1a) was prepared. And as a polymerizable surfactant comonomer we synthesized the quarternary ammonium salt, N,N-dimethyl-N-hexadecyl-N-(11-methacryloyloxy-undecanyl) ammonium bromide(I), according to the scheme of Regen(12). The copolymers were prepared from 1a with I and the catalytic activities exhibited by those copolymers toward the solvolyses of optically active activated esters, D-NBP and L-NBP, were examined in the sonicated buffer solution. Those copolymers of increased hydrophobicity and chirality were expected to show enhanced catalytic activity and possibly a higher enantioselective catalysis toward the solvolyses of optically active substrates. And to look into the aggregate morphology of imidazole-containing copolymeric surfactants in the sonicated solvolytic solution, the turbidity and electron micrographs were observed.

EXPERIMENTAL

Syntheses of Substrates and Monomers

D-NBP, L-NBP, and 1a were prepared according to the procedure described previously(7,9). I was prepared according to the scheme of Regen(12).

Polymerization

A representative copolymerization procedure was as follows: 1a(2 mmol), I(2 mmol), and AIBN (1mol%) in dried ethanol were introduced into a polymerization tube. The solution was then degassed under vacuum and tube was sealed. After 48hr at 65°C, the tube was opened and the content was added to a large volume of ethanol and stirred for 30min. The polymer was isolated on sintered glass funnel and dried in vacuum oven. Examination of the ^1H NMR spectrum revealed the complete disappearance of the vinyl and allyl protons. Yield; 56 %, η_{inh}=0.29 dl/g (1N HCl, 30°C).

Determination of copolymer composition: From the UV absorption values of the homopolymer and the copolymer at 219 nm, stoichiometric compositions of the copolymers were determined as described previously(7). The compositions of copolymers thus obtained are given in Table 1.

Table 1. Compositions of Imidazole-Containing Copolymers

Polymer[a]	Concentration (in MeOH)	A (219nm)	ε	Mole % of imidazole--containing monomer	η_{inh}[b]
Poly(1a)	1.58×10^{-4}M/L	0.731	4627	100	0.33
Copoly(1a-I)					
1	0.211 g/L	1.420		36.5	0.29
5	1.052 g/L	1.134		21.3	0.25
10	2.712 g/L	0.976		9.7	0.31
20	4.147 g/L	1.138		3.7	0.23

a The mumbers below polymer mean the monomer feed ratio ([I]/[1a]).

b Concentration of 0.5 g/dl in 1 N HCl at 30°C

Kinetic Measurement of Solvolytic Reactions

Solvolytic rates were measured in aqueous solution buffered with 0.02 M tris(hydroxymethyl)aminomethane and hydrochloric acid with sufficient potassium chloride to adjust the ionic strength to 0.02. In all cases, the solvolytic solutions were sonicated with Branson B-52 sonicator at 50°C for 2 hr, and a 10-fold molar excess of catalyst over substrate was used. The reactions were followed by monitoring the released p-nitrophenolate ion at 400 nm with a Shimadzu UV-200 spectrophotometer. Kinetic data were treated as pseudo first-order by least square method ($r > 0.99$). The slope(k_{meas}) was corrected by subtracting the blank rate to obtain the observed rate constant k_{obsd}. The second-order rate constant k_{cat} was then calculated by dividing k_{obsd} by the catalyst concentration. Thus obtained k_{cat} values are to be called apparent catalytic constants. $k_{cat} = k_{obsd}$ / [catalyst].

Electron Microscopy

The negatively stained samples were prepared as follows: To the solvolytic solutions (10 ml) of copoly(1a-I) was added a 2% (w/w) aqueous solution(1 ml) of uranyl acetate. The aqueous sample was applied on a copper grid and the excess was blotted off. After being dried in a vacuum desiccator, the sample was introduced to a JEOL JEM-100CX electron microscope.

RESULTS AND DISCUSSION

The solvolyses of optically active D-NBP and L-NBP by copolymers, poly(1a-co-I), were performed. Representative results are shown in Table 2.

The kinetic data in Table 2 show that all the copolymeric surfactants, poly(1a-co-I), did exhibit much more enhanced catalytic activity than poly(1a-co-DMA). It can be understood that the increased reaction rate is due to the higer local concentration of hydroxide ion promoted by the presence of cationic surfactant of I in poly(1a-co-I)(13). However it was notable that the enantioselectivity as well as the catalytic activity was increased as the mole % of surfactant monomer I in the copolymer increased, indicating that hydrophobic interaction is operative in the rate determining complex-formation step in the mechanism below(14) (E is the catalyst, S the

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (ES) \xrightarrow{k_2} (ES)' + P$$

Table 2. Apparent Catalytic Rate Constants of Solvolyses of Optically Active D-NBP and L-NBP by Copoly(1a-I) in 0.02 mol/l Tris (0.02 mol/l KCl) Buffer at 30°C (pH 7.2). (k_{cat} , l/mol·sec)

Substrate[a,c] / Catalyst[b]	D-NBP	L-NBP	k_{cat} (L-NBP) / k_{cat} (D-NBP)
poly(1a-co-DMA)[d]	2.0	3.4	1.71
1	10.0	14.5	1.45
5	11.7	23.4	2.00
10	21.7	48.6	2.24
20	44.2	457.8	10.30

[a] The numbers bellow catalyst mean the monomer feed ratio ([I]/[1a]). Practical compositions are expressed in Table 1.
[b] The concentration of the substrates : 1.0x 10^{-5} mole/l.
[c] The concentration of the catalysts : 1.0x 10^{-4} mole/l. (with respect to imidazole-containing residues)
[d] In 20 vol.-% aqueous ethanol at 10°C (pH 7.07)(9).

substrate, (ES) the catalyst-substrate complex, (ES)' the intermediate acylate catalyst, and P is the leaving nitrophenolate ion). It is conceivable that as hydrophobic interaction becomes more operative, the equilibrium concentration of (ES) will increase, exhibiting a higher solvolytic rate. The increase in equilibrium concentration of (ES) is due to the increased stability of (ES) resulting from the surrounding tighter hydrophobic environment, thus exhibiting more thermodynamic enantiomeric preference in the (ES) formation. Particular to point out was the case of poly(1a-co-I) of 3.7 mole % of imidazole-containing monomer, in which the copolymer did exhibit remarkably enhanced enantioselective catalysis, viz., $k_{cat}(L)/k_{cat}(D)$ = 10.3. This sudden increase in enantioselectivity as well as reaction rate should be attributed to that the poly(1a-co-I) containing 3.7 mole % of 1a and 96.3 mole % of I take different morphological structures from other copolymers, namely,"ordered aggregate structures"(13).

To investigate the aggregate morphology of imidazole-containing polymeric surfactant, poly(1a-co-I), in the sonicated solvolytic solution, the turbidity and electron micrographs were taken. The turbidities measured from absorbance at 400 nm of the solvolytic solutions at pH 7.2 are shown in Table 3.

The data in Table 3 show that the turbidities of sonicated solvolytic solutions of copoly(1a-I) were all larger than those of vesicle(vide infra)

Table 3. Turbidities of Solvolytic Solutions Measured from Absorbance at 400 nm

System[a] / Catalyst	1	5	10	20
copoly(1a-I)	0.288	0.342	0.610	1.187

[a] The numbers nearby system mean the monomer feed ratio ([I]/[1a]). Practical compositions are expressed in Table 1.

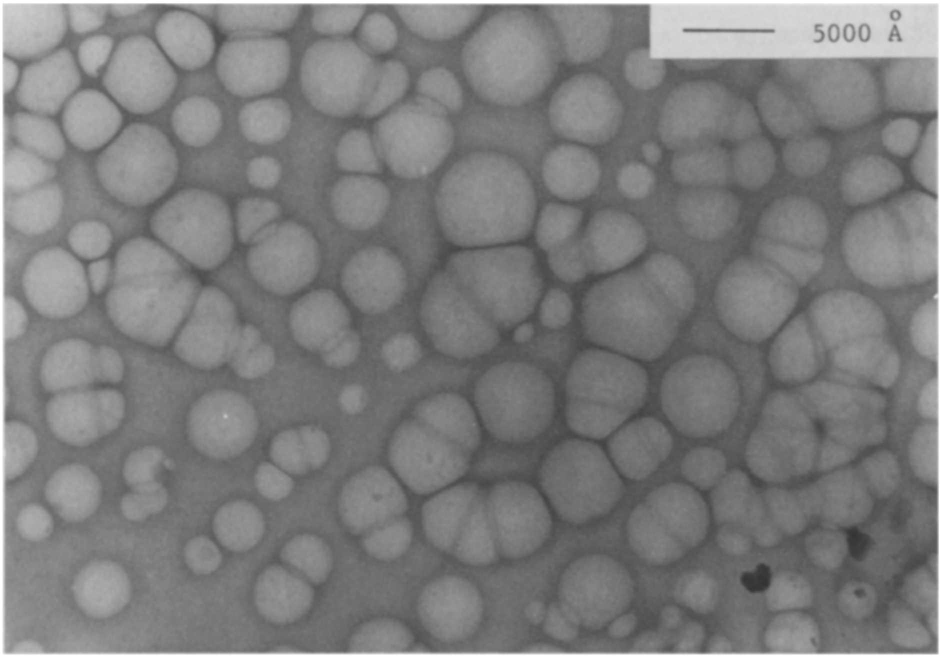


Figure 1. Electron micrograph of the aggregates of copoly(1a-I) in solvolytic solution ; negatively stained with 2.0 wt % uranyl acetate.

solution of poly(I) (12) and increased in proportion to the decrease of mole % of imidazole-containing monomer in the copolymer. The turbidity measured from absorbance at 400 nm of the solution of copoly(1a-I) containing 3.7 mole % 1b was 1.187. From the observation on the relation between turbidity and vesicular size in aqueous solution(15), it is supposed that all the solvolytic solutions employed have large extended aggregates of copolymers.

The electron micrograph of the aggregates of copoly(1a-I) of 3.7 mole % 1a in solvolytic solution is shown in Figure 1. The electron micrograph shows that the solvolytic system employed has large extended ordered aggregate with the diameter of 2000-6000 Å(16), which appears to be large multilayered vesicles. And it is consistent with the observation of the change in turbidity of the solvolytic solution. Although the certain ordered aggregate structures were seen in other copolymer solvolytic solutions in the electron micrographs, the formation of the above structures were not clear. This result seems to suggest that hydrophobic interaction in ordered aggregate structure plays an important role in the enantioselective catalysis of optically active imidazole-containing polymers.

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