Solvolysis of Sodium 4-Acetoxy-3-nitrobenzenesulfonate Catalyzed by Oligo(4(5)-vinylimidazole)

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ABSTRACT: The oligomers of 4(5)-vinylimidazole with molecular weights from a few hundred to 3600 were prepared and separated by gel permeation chromatography. In order to determine the structure of the oligomers, the equilimolar reaction of 4(5)-vinylimidazole with azobisisobutyronitrile (AIBN) was carried out. The products isolated were tetramethylsuccinodinitrile (**2**), monomeric imidazole compounds with two isobutyronitrile groups **4a**, **4b**, and **4c**, and a dimeric compound **5**. Based on the above products and the nmr spectra of the oligomers, it was found that the main component in the oligomers was oligomer **8** which was formed by a combination reaction between two 4(5)-vinylimidazole radicals. The catalytic activities of the oligo(4(5)-vinylimidazole) toward an anionic substrate, sodium 4-acetoxy-3-nitrobenzenesulfonate (NABS), were studied at various pH values in 28.5 vol % ethanol–water at 26°. Generally, the catalytic activity increased with increasing molecular weight of the oligomers. The oligomers with degree of polymerization (DP) more than eight showed higher reactivity than imidazole and a bell-shaped rate–α_1 (fraction of neutral imidazole group) profile. On the other hand, the oligomers with DP < 6 were less reactive than imidazole and demonstrated an upward rate–α_1 profile. These results indicate that electrostatic interaction between the cationically charged imidazole groups on the oligomer and the anionic substrate was important only for high molecular weight oligomers, and the interaction between two short-range neutral imidazole groups also enhanced the catalytic activity of the oligomer. The sterically hindered monomeric compounds **4b** and **4c** had no catalytic activity.

Systems which have a charged substrate and a polymer containing both charged groups and catalytically active groups have been described.[1] The reaction of poly(4(5)-vinylimidazole) with a negatively charged substrate, sodium 4-acetoxy-3-nitrobenzenesulfonate (NABS), has been investigated in 28.5 vol % ethanol–water at 26°.[2] In this catalysis, a rate–α_1 profile indicated a bell-shaped curve with a maximum at about 75% of the fraction of neutral imidazole. The catalytic rate constant for a poly(4(5)-vinylimidazole)-catalyzed reaction at this point was approximately fivefold greater than the value obtained for imidazole. The shape of the plots for the polymer revealed that this reaction is principally dependent upon two factors,[3] *viz.*, a proper concentration of charged groups in the polyion to facilitate an electrostatic interaction with the substrate and a proper concentration of neutral imidazole groups acting as catalytically active nucleophiles. The combination of these factors gives a rate maximum when three-quarters of the imidazole groups are in the neutral form. Similar results have been found in the system of poly(4-vinylpyridine).[4]

The existence of bifunctional neutral–neutral imidazole interactions has been demonstrated for the solvolysis of a neutral substrate, *p*-nitrophenyl acetate by poly(4(5)-vinylimidazole).[5,6] Recently, Overberger and Shen[7] have studied the hydrolysis of *p*-nitrophenyl acetate catalyzed by oligo-(4(5)-vinlyimidazole) with molecular weight ranges from a few hundred to 2500 in order to determine the relative position and steric requirements between two neutral imidazole groups on the polymer chain. It was found that the catalytic activity increased with an increase in the molecular weight of the oligomers, but relatively short-range interactions provided the major portion of activity.

In this paper, we describe the reactivity of oligomeric poly-(4(5)-vinlyimidazoles) with a charged substrate over a wide pH range.

Experimental Section[8]

4(5)-Vinylimidazole. This was prepared as previously described.[9]

Sodium 4-Acetoxy-3-nitrobenzenesulfonate. According to a modified procedure of Gnehm and Knecht,[10] sodium 4-hydroxy-3-nitrobenzenesulfonate was prepared by the reaction of *o*-nitrophenol (28 g) with a mixture of 20% fuming sulfuric acid (30 ml) and concentrated sulfuric acid (30 ml) at room temperature. The yield of the sulfonate was 80% as the sodium salt. The sulfonate (10 g) obtained was then converted to the acetyl derivative by refluxing for 2 hr in a solution of acetic acid (60 ml) and acetic anhydride (60 ml).[4] The yield of the substrate was 80%.

Anal. Calcd for $C_8H_6NNaO_7S$: C, 33.93; H, 2.14; N, 4.95; S, 11.32. Found: C, 33.77; H, 2.24; N, 4.98; S, 11.37.

Reaction of 4(5)-Vinylimidazole with Azobisisobutyronitrile. Equimolar amounts of 4(5)-vinylimidazole (3.0 g) and AIBN (5.3 g) were dissolved in tetrahydrofuran (250 ml) in a glass ampoule. The ampoule was sealed under vacuum and heated for 2.25 hr at 100°. After evaporation of the solvent, the reaction mixture was separated by column chromatography on Florisil (2.2 × 70 cm) with ethyl acetate and acetone as solvents. Characterization of the compound isolated is given in Table I. The compounds, other than those in this table, were oligomers with higher molecular weight than the dimeric compound **5**.[11]

Oligomerization of 4(5)-Vinylimidazole. Monomeric 4(5)-vinylimidazole (4.3 g, 46 mmol) and AIBN (1.08 g, 6.6 mmol) were dissolved in tetrahydrofuran (100 ml) in a glass ampoule. After being sealed under vacuum, the ampoule was heated for 2 hr at 100°. The reaction mixture was poured into diethyl ether (1 l.), and the

(1) C. G. Overberger and J. C. Salamone, *Accounts Chem. Res.*, **2**, 217 (1969), and references cited therein.

(2) C. G. Overberger, J. C. Salamone, and S. Yaroslavsky, *J. Amer. Chem. Soc.*, **89**, 6231 (1967).

(3) H. Morawetz, "High Polymers," Vol. XXI, Interscience, New York, N. Y., 1965, p 420.

(4) R. L. Letsinger and T. J. Savereide, *J. Amer. Chem. Soc.*, **84**, 3122 (1962); H. Ladenheim, E. M. Loebl, and H. Morawetz, *ibid.*, **81**, 20 (1959).

(5) C. G. Overberger, T. St. Pierre, N. Vorchheimer, J. Lee, and S. Yaroslavsky, *ibid.*, **87**, 296 (1965).

(6) C. G. Overberger, T. St. Pierre, C. Yaroslavsky, and S. Yaroslavsky, *ibid.*, **88**, 1184 (1966).

(7) C. G. Overberger and C.-M. Shen, *Bioorg. Chem.*, **1**, 1 (1971).

(8) The infrared spectra were measured with a Perkin-Elmer Model 257 spectrophotometer in Nujol. The nmr spectra were taken with a Varian T60 spectrometer at room temperature. The electronic spectra were measured on a Beckman DU-2 spectrophotometer. The microanalyses were performed by Spang Microanalytical Lab., Ann Arbor, Mich.

(9) C. G. Overberger and N. Vorchheimer, *J. Amer. Chem. Soc.*, **85**, 951 (1963).

(10) R. Gnehm and O. Knecht, *J. Prakt. Chem.*, [2] **73**, 519 (1906).

(11) G. S. Hammond, J. N. Sen, and C. E. Boozer, *J. Amer. Chem Soc.*, **77**, 3244 (1955).

TABLE I
PRODUCTS OF THE EQUIMOLAR REACTION OF 4(5)-VINYLIMIDAZOLE WITH AIBN

Compound[a]	Yield[b]	Mp, °C		Elementary analysis, % C	H	N	Mol wt	Ir (C≡N), cm^{-1}	Nmr δ, ppm[c]
2	27	167–169[e]	$C_8H_{12}N_2$	70.55	8.88	20.57	136	2360	1.53 (s, CH_3)
			Found	70.43	8.94	20.51			
4a	19	157–158	$C_{13}H_{18}N_4$	67.79	7.88	24.33	230	2255	1.17, 1.28, 1.36 (s, 6 H, 3 H, 3 H, CH_3), 1.8, 3.1 (m, 3 H, CH_2 and CH), 6.97, 7.57 (s, 1 H, 1 H, –CH=)
			Found	67.84	7.94	24.21	235		
4b	19	83–84	$C_{13}H_{18}N_4$	67.79	7.88	24.33	230	2255	1.36, 1.80 (s, 6 H, 6 H, CH_3), 1.9–3.2 (m, 4 H, CH_2), 7.43 (s, 1 H, –CH=)
			Found	67.66	7.94	24.15	230	1260	
4c	3	148–149	$C_{13}H_{18}N_4$	67.79	7.88	24.33	230	2250	1.40, 1.75 (s, 6 H, 6 H, CH_3), 1.9~3.0 (m, 4 H, CH_2), 6.70 (s, 1 H, –CH=)
			Found	67.86	7.86	24.29		2262	
5	5	298~301 dec	$C_{18}H_{24}N_6$	66.14	7.46	25.91	324	2250	1.05, 1.15 (s, 6 H, 6 H, CH_3) 1.2–3.0 (m, 6 H, CH_2 and CH) 6.97, 7.66 (s, 2 H, 2 H, –CH=)[d]
			Found	66.58	7.51	25.71	330		

[a] See Scheme I. [b] Mol % based on AIBN. [c] In chloroform-*d* (Me_4Si). Compounds **4a**, **4b**, and **4c** showed the broad peaks due to the NH group at around 9.5 ppm. [d] In methanol-d_4 (Me_4Si). [e] Lit.[11] 167–168°.

precipitated oligomers were recovered by filtration. Reprecipitation of the oligomers from methanol–diethyl ether gave 1.57 g of insoluble product. The combined filtrates were evaporated under reduced pressure, followed by heating for 2 hr at 120° *in vacuo* to give 2.3 g of viscous compounds.

Separation of Oligomers. The oligomers (both fractions) obtained were separated by means of gel permeation chromatography (Sephadex LH-20, 3.5 × 120 cm), which was described in detail in the previous paper.[7] Methanol was used as a solvent.

Molecular Weights. The molecular weights were determined with a Hitachi Perkin-Elmer Model 115 vapor pressure osmometer using methanol as a solvent. A calibration curve was obtained with benzil as a standard. Since the observed molecular weight of the oligomer was dependent upon the concentration of the sample, especially when the molecular weight of the oligomer was high, the observed molecular weights were measured at several different concentrations. The final molecular weight was determined by extrapolation to zero concentration.

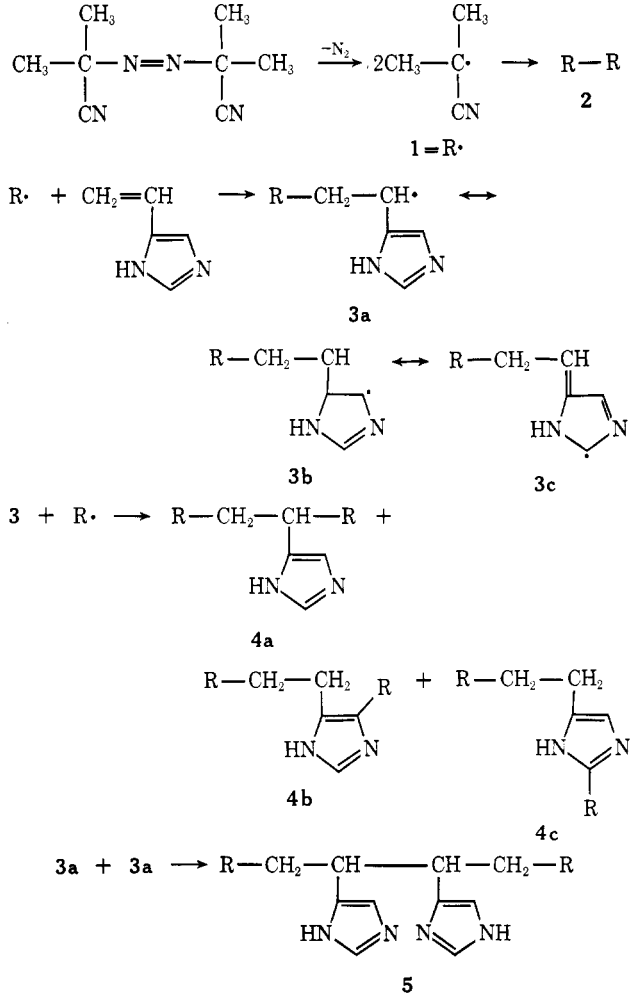
Potentiometric Titrations. Each solution (28.5 vol % ethanol–water, ionic strength 0.02, 15 ml) containing the oligomers (5–9 mg) and 1.0 *N* hydrochloric acid (100 μl) was titrated with 1.0 *N* sodium hydroxide with stirring at 26° by using a Manostat Digi-Pet micropipet and a Radiometer pH meter, type TT1c. A blank solution without the oligomer was also titrated under the same conditions. Differential titration curves were derived graphically according to the method of Park and Davis.[12]

Kinetic Measurements. Stock solutions, *ca.* 2.5 × 10^{-3} *M* (in imidazole units), were prepared by dissolving the oligomers (10–30 mg) in 50 ml of 30.5 vol % ethanol–water. Aliquots of the above solutions (2 ml) were then diluted to 10 ml with 28.0 vol % ethanol–water buffer solution with ionic strength 0.0267 to give 28.5 vol % ethanol–water solutions with ionic strength 0.0213. At a pH value of 10, the solution was buffered with 0.0213 *M* 3-(diethylamino)-propanol and hydrochloric acid; between pH 7 and 9, the solutions were buffered with 0.0213 *M* tris(hydroxymethyl)aminomethane and hydrochloric acid. Solutions with pH < 7 were buffered with 0.0213 *M* sodium acetate–acetic acid. The substrate was dissolved in 28.5 vol % ethanol–water. The catalyst solution (3.0 ml) and the substrate solution (200 μl) were mixed in a quartz cell to give a solution containing *ca.* 5 × 10^{-4} *M* catalyst, and the rate was followed with a spectrophotometer thermostated at 26°.

Results and Discussion

Equimolar Reaction of 4(5)-Vinylimidazole with AIBN. In order to clarify the structure of the oligo(4(5)-vinylimidazole) and also to get monomeric and dimeric imidazole compounds, the equimolar reaction of 4(5)-vinylimidazole with AIBN was carried out. The compounds isolated (Table I) may be explained through Scheme I. The formation of compounds **4b** and **4c** suggests that the radical **3a** can be stabilized through the resonance forms **3b** and **3c**. Since the compounds which were expected by a disproportionation reaction of two of the **3a** radicals could not be isolated, the main termination reaction in the radical polymerization of 4(5)-vinylimidazole may be combination reactions between polymer radicals, as found

SCHEME I



(12) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954).

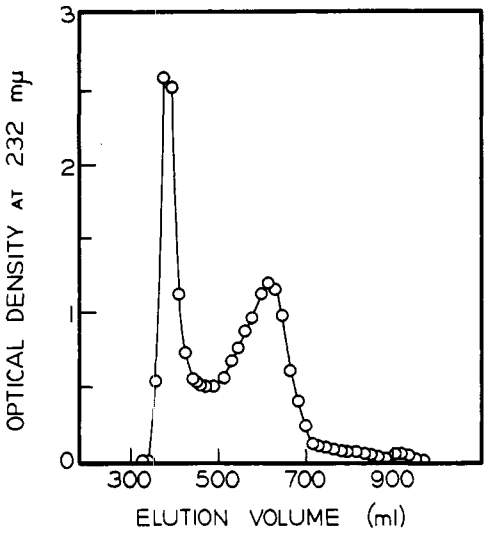


Figure 1. Separation of oligo (4(5)-vinylimidazole) by gel permeation chromatography.

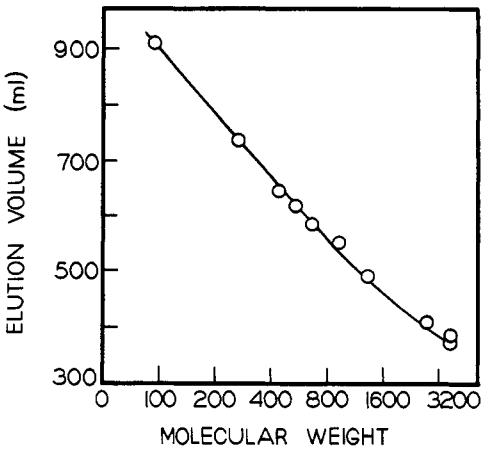


Figure 2. Relationship between molecular weight of oligo(4(5)-vinylimidazole) and elution volume in gel permeation chromatography.

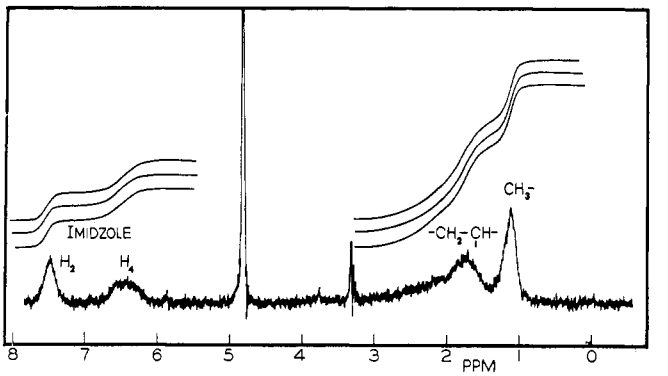
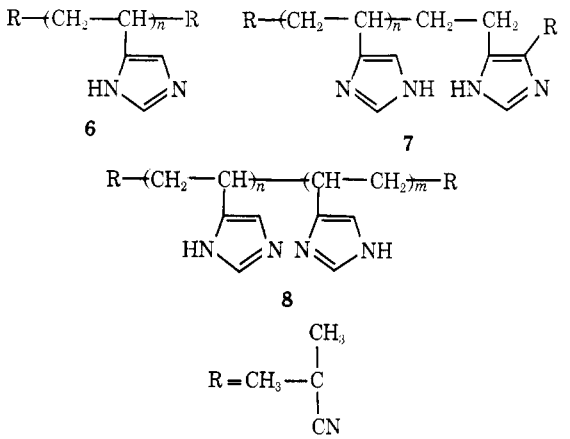


Figure 3. Nmr spectrum of oligo(4(5)-vinylimidazole) (DP = 5.5) in methanol-d_4–deuterium oxide (1:1).

in the polymerization of styrene.[13] This was supported by the isolation of the product **5**. There was no evidence for combination reactions among the radicals **3a**, **3b**, and **3c**.

Fractionation of Oligomers. The diethyl ether soluble and insoluble oligomers were separated by gel permeation chromatography. A typical separation of the ether-insoluble oligomer is shown in Figure 1. The fractionation was followed spectrophotometrically at 232 mμ. A small peak at the elution volume 910 ml was due to 4(5)-vinylimidazole; the peaks between 450 and 700 ml were attributed to the oligomers with molecular weight from 300 to *ca.* 2500. The molecular weights of the oligomers in the fractions eluted in less than 450 ml were more than 2500. The elution volume was plotted against the molecular weight of the oligomer on a logarithmic scale (Figure 2). The diagram showed that good fractionation was obtained in a molecular weight range up to 2500. The ether-soluble fraction was mainly composed of unreacted monomer and low molecular weight oligomers (300–500).

Structure of the Oligomer. Based on the products in the equimolar reaction (Table I), compounds **6**, **7**, and **8** can be expected as the components in the oligomers. Since the yield of the product **4c** was low, the structure of the oligomer expected from product **4c** was neglected. In the previous



paper,[7] it was found that each oligomer had two isobutyronitrile groups from elementary analysis. Figure 3 shows a typical nmr spectrum of the oligimer (DP = 5.5) in methanol-d_4–deuterium oxide (1:1). The ratio of the protons of the main chain (-CH_2—CH-) to imidazole (-CH=) is 1.5 for components **6** and **8** regardless of the degree of polymerization, but the ratio for component **7** is larger than 1.5 depending on the degree of polymerization. The ratios observed for the oligomers (DP = 2–6) were 1.6–1.8 depending on DP.[14] Judging from the nmr spectrum of compound **4b**, the peaks due to isobutyronitrile groups attached to the imidazole ring probably overlapped those due to the main chain. If we assume that the oligomers contain only these three components and the yields of the components **6** and **7** are the same as those found in the equimolar reaction, we can determine the degree of polymerization and the ratio of these components in the oligomer from the intensity ratio of the nmr spectrum by using

$$\frac{3n + 7x}{2n - x} = \frac{\text{-CH}_2\text{-CH-}}{\text{imidazole}} \quad \text{(I)}$$

$$\frac{12 - 6x}{2n - x} = \frac{\text{CH}_3^-}{\text{imidazole}} \quad \text{(II)}$$

where n is the degree of polymerization (DP) and x is the content of the component **7**. These values, n and x ,are collected in Table II together with the DP's obtained by vapor pressure

(13) C. H. Bamford, "The Kinetics of Vinyl Polymerization by Radical Mechanism," Butterworths, London, 1957, p 67.

(14) The nmr spectrum of the oligomer (DP = *ca.* 3.4) was measured under various mechanical conditions of the instrument (Varian T60). Statistical treatment of seven different spectra indicated that the ratio was 1.68 ± 0.04, suggesting a rather high reliability for nmr.

TABLE II
DEGREE OF POLYMERIZATION (DP) DETERMINED BY NMR AND VAPOR PRESSURE OSMOMETRY (VPO)

Oligomer	DP from nmr	x	DP from VPO[a]
9	1.8	0.12	1.9
10	3.3	0.19	3.2
11	4.2	0.13	4.3
12	5.3	0.10	5.5
13	8.5	~0	8.2

[a] Obtained by assuming that each oligomer has two isobutyronitrile groups.

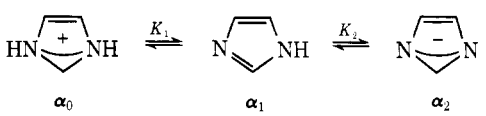
TABLE III
ELEMENTARY ANALYSES OF OLIGOMERS

Oligomer	Calcd,[a] %			Found (cor),[b] %		
	C	H	N	C	H	N
9	66.62	7.72	25.66	66.70	7.68	25.62
10	65.90	7.19	26.96	65.81	7.11	27.07
11	65.51	7.05	27.44	65.58	7.15	27.27
12	65.22	6.94	27.84	65.03	6.90	28.07
13	64.82	6.79	28.39	64.85	6.93	28.22
14	64.51	6.66	28.83	64.69	6.79	28.52
15	64.15	6.55	29.30	64.16	6.65	29.19
16	64.06	6.52	29.42	64.14	6.67	29.17

[a] Calculated by assuming that each oligomer has two isobutyronitrile groups. [b] Corrected for ash. Found (cor) = 100(found/total found).

osmometry. Good agreement was observed for the DP's determined by the two different methods. The main component in the oligomers must be **8** except in the dimeric oligomer **9** (Table II), in which the main component was probably **6** because the nmr spectrum was very similar to that of compound **4a** and quite different from that of dimeric compound **5**. The elementary analyses of the oligomers are shown in Table III.

Potentiometric Titrations. Since the catalytically active imidazole group is known to be in the neutral form in the solvolysis of an ester, it is important to know the fraction of the neutral imidazole groups in order to understand the kinetic reaction. The dissociation of the imidazole groups has been



defined as where K is the dissociation constant and α is the fraction of each imidazole form. For a polyelectrolyte, the well-known Henderson-Hasselbalch equation is no longer valid.[15] A modified equation (III) should be used. Here,

$$\mathrm{pH} = \mathrm{p}K_1 + n \log \frac{\alpha_1}{1 - \alpha_1} \qquad \text{(III)}$$

n is not always equal to unity. The plots of pH *vs.* log $\alpha_1/(1 - \alpha_1)$ afforded straight lines in the range of $0.1 < \alpha_1 < 0.9$ except for the dimeric compounds **5** and **9**. The pK_1 values obtained are summarized in Table IV. The data indicate that the pK_1 value at ionic strength 0.02 slightly decreased with an increase in the molecular weight. In 30% 1-propanol–water at 26°, the dissociation constants at ionic strength 0.003 decreased from 5.7 for the lowest molecular weight oligomer (molecular weight = 390) to 5.0 for the polymer, and those at ionic strenth 0.05 were 5.6 regardless of the molecular weight.[7] These results indicate that the dissociation constants were dependent on the ionic strength and were independent of the molecular weight at high ionic strength.

(15) A. Katchalski and P. Spitnik, *J. Polym. Sci.*, 2, 432 (1947).

TABLE IV
POTENTIOMETRIC TITRATION[a]

Compound	Mol wt	pK_1	n[b]
Imidazole	68	6.9	1.0
2-Ethylimidazole	96	7.7	1.0
4a	230	5.6	1.0
4b	230	4.8	1.0
4c	230	4.5	1.0
5	324	4.9, 6.6	1.2–1.3
Oligomer **9**	310	4.5, 6.7	1.7–1.9
Oligomer **10**	440	5.8	
Oligomer **11**	540	5.8	
Oligomer **12**	650	5.7	
Oligomer **13**	910	5.8	2.2–2.3
Oligomer **14**	1490	5.8	
Oligomer **15**	2700	5.6	
Oligomer **16**	3600	5.6	
Polymer	*c*	5.5	

[a] 28.5 vol % ethanol–water, ionic strength 0.02, 26°. [b] See eq III. [c] Intrinsic viscosity was 0.87 dl/g in methanol at 26°.

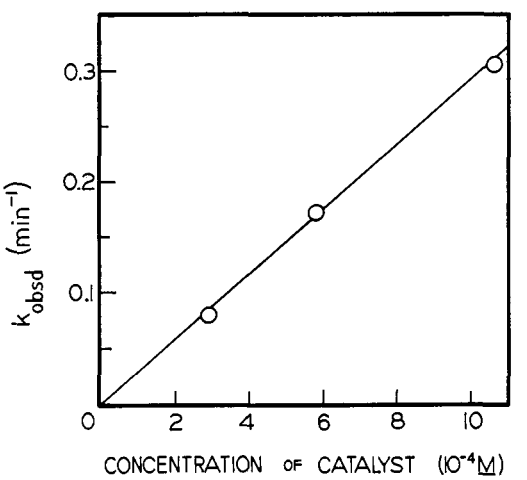


Figure 4. Observed rate of disappearance of NABS as a function of the concentration of oligo(4(5)-vinylimidazole) (molecular weight = 3600).

Catalytic Activity of Oligomer. The plot of k_{obsd} *vs.* concentration of the catalyst (oligomer **16**) at pH 7.1 revealed first-order reaction in catalyst, which was used in 6–22 times excess against the substrate (Figure 4). Second-order catalytic rate constants were determined with about tenfold excess of the catalyst against the substrate (Table V) and were plotted against α_1 (Figures 5 and 6). The oligomers with DP > 8 were more reactive than imidazole and showed bell-shaped α_1–rate profiles which had maximums at α_1 = *ca.* 0.8, whereas the oligomers with DP < 6 were less reactive than imidazole and showed upward curves, except for the monomeric compound **4a** and imidazole, which demonstrated linear dependencies on α_1. These results suggest that an electrostatic effect between the partially charged oligomers and the oppositely charged substrate may be important only for rather high molecular weight oligomers, and for low molecular weight oligomers bifunctional catalysis involving the interaction of two neutral imidazole groups[5,6] plays a more important role than the electrostatic effect. It is probable that when the sulfonate group in NABS is attracted by an electro-

TABLE V
CATALYTIC RATE CONSTANTS FOR SOLVOLYSIS OF NABS[a]

Compound	pH 4.22 α_1	pH 4.22 k_{cat}	pH 5.52 α_1	pH 5.52 k_{cat}	pH 6.11 α_1	pH 6.11 k_{cat}	pH 7.10 α_1	pH 7.10 k_{cat}	pH 8.0 α_1	pH 8.0 k_{cat}	pH 9.09[b] k_{cat}
Imidazole			0.02	4.6	0.13	14.7	0.65	46.7	0.91	68.9	76.8
4a			0.48	4.4	0.84	7.6	0.97	8.3	~1.0	8.0	9.5
9					0.59	7.3	0.84	14.0			26.1
5	0.07	0.80	0.46	5.9	0.59	10.5	0.88	19.8	0.97	24.5	27.4
10			0.44	11.3			0.78	33.7	0.92	50.3	53.6
11	0.14	3.8	0.44	17.0	0.57	27.2	0.78	43.4	0.92	56.4	62.0
12			0.45	26.5			0.80	54.3	0.93	64.2	70.9
13	0.15	13.3	0.45	52.0	0.58	69.1	0.80	81.1	0.93	80.9	77.7
14	0.15	26.3	0.45	114	0.58	156	0.80	163	0.93	118	101
15	0.17	36.9	0.47	180	0.61	235	0.82	259	0.94	175	114
16			0.48	200			0.83	293	0.94	200	115
Polymer[c]	0.19	43.5	0.50	218	0.64	272	0.84	348	0.95	257	148
k_{blank} (10^{-4} min)	0.67		0.70		1.1		3.2		15.0		73.2

[a] 28.5 vol % ethanol–water, ionic strength 0.02, 26°, $k_{cat} = M^{-1}$ min^{-1}. [b] $\alpha_1 = \sim 1.0$. [c] $[\eta] = 0.87$ dl/g in methanol at 26°.

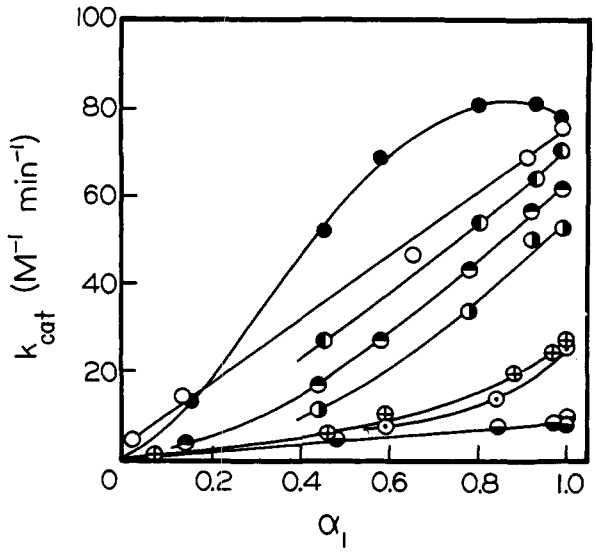


Figure 5. Solvolyses of NABS: (◒) **4a** (DP = 1), (⊙) **9** (DP = 1.9), (⊕) **5** (DP = 2.0), (◑) **10** (DP = 3.2), (◓) **11** (DP = 4.3), (◐) **12** (DP = 5.5), (○) imidazole, (●) **13** (DP = 8.2).

static force to the oligomer, the remaining neutral imidazole groups on the oligomers with high molecular weights will have a greater probability to react with the ester groups than the oligomers with lower molecular weight. If the DP is less than 4, the cooperative reaction between cationically charged and neutral imidazole groups seems difficult based on the molecular model, owing to steric factors, because of the catalyst end groups. Cooperative effects due to adjacent neutral imidazole groups may be one reason for the enhancement of the catalytic activity of the polymer, because the dimeric compounds **5** and **9** (Table II) show upward curves.[16] Furthermore, the rather higher reactivity of oligomer **10** (Table II) (DP = 3.2), about double in comparison with those of the dimeric compounds, may be due to the participation of 1,3 neutral imidazole–imidazole interactions.[7]

The relationship between k_{cat} and the degree of polymerization is shown in Figure 7. The differences in k_{cat} were smallest

(16) Drey and Fruton reported that 4,4′(5,5)-diimidazolylmethane was slightly less reactive for the hydrolysis of *p*-nitrophenyl acetate than imidazole, and there was no rate enhancement due to a cooperative effect of two imidazole groups: C. N. C. Drey and J. S. Fruton, *Biochemistry*, **4**, 1 (1965).

TABLE VI
CATALYTIC ACTIVITY OF DERIVATIVES OF IMIDAZOLE TOWARD NABS AT pH 7.10

Compound	α_1	k_{cat}, M^{-1} min^{-1}	k_{cat}/α_1, M^{-1} min^{-1}
Imidazole	0.65	46.7	72.0
2-Ethylimidazole	0.18	2.5	13.9
4a	0.96	8.3	8.7
4b	1.0	~0	~0
4c	1.0	~0	~0

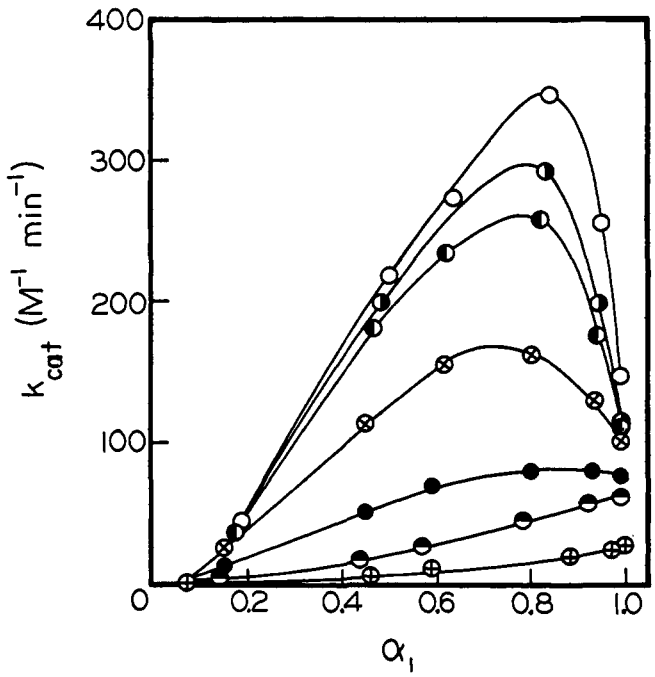


Figure 6. Solvolyses of NABS: (⊕) **5** (DP = 2), (◓) **11** (DP = 4.3), (●) **13** (DP = 8.2), (⊗) **14** (DP = 14), (◐) **15** (DP = 27), (◑) **16** (DP = 37), (○) polymer.

at pH 9, where the oligomers possessed no charge, and became greater when the oligomers possessed charge. These results also indicate that the electrostatic interaction is more important for higher molecular weight oligomers.

The catalytic activities of monomeric imidazole compounds were measured (Table VI). Ethylimidazole had the

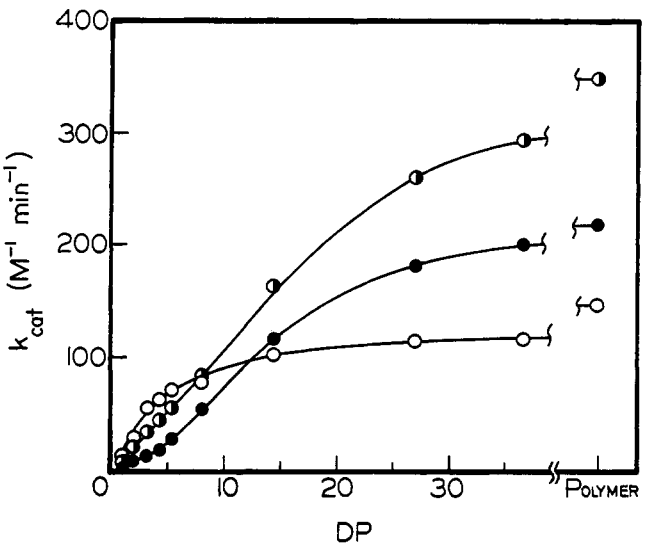


Figure 7. Plot of second-order rate constants *vs.* degree of polymerization of oligo(4(5)-vinylimidazole): (●) pH 5.5, (◑) pH 7.1, (○) pH 9.1.

highest pK_1 value, which is attributed to the inductive effect of the ethyl group. This compound may be expected to be the most active catalyst based on the Brönsted relationship.[17] However, the catalytic activity (k_{cat}/α_1) was much less than that of imidazole. The same phenomenon has been found in the catalyses of 2-methylimidazole and imidazole.[18] The reason for this may be that 2-ethylimidazole and 2-methylimidazole are sterically hindered in the hydrolysis of the ester, but not in the addition of a proton. The most sterically hindered compounds, **4b** and **4c**, had the smallest pK_1 values and no catalytic activity, indicating that these bulky groups exhibit a steric effect even for a proton.

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(17) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 170.
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Synthesis and Resolution of *cis*- and *trans*-5-Methylproline

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ABSTRACT: The synthesis and resolution of *cis*- and *trans*-5-methylproline are described. *cis*-5-Methylproline was synthesized by catalytic hydrogenation of Δ^1-2-methylpyrroline-5-carboxylic acid. The structural assignment was made by conversion of *cis*-5-methylproline to *cis*-2,5-dimethylpyrrolidine. A mixture of *cis*- and *trans*-5-methylproline was obtained by sodium borohydride reduction of Δ^1-2-methylpyrroline-5-carboxylic acid. The methylproline isomers can be separated by reaction with *p*-toluenesulfonyl chloride because the trans isomer only reacts slowly. The *cis*- and *trans*-5-methylproline enantiomeric pairs were resolved with tartaric acid. The absolute configurations of the diastereomers were determined by optical rotatory dispersion.

The biochemical and metabolic roles played by metabolites, analogs, homologs, and novel derivatives of proline have recently been the focus of many investigations. As a result, the synthetic routes to a wide variety of these compounds have been developed.[1]

Among the compounds described are the simple monomethyl derivatives of proline. Up to the time this work was undertaken, only the *cis*- and *trans*-3- and -4-methylprolines had been separated, resolved, and unequivocally characterized.[1] We wished to investigate the effect of a methyl group in the 5 position of proline on the conformational behavior of the polypeptides derived from this amino acid.[2]

5-Methylproline has been synthesized by ammonolysis of methyl 2,5-dibromocaproate,[3] by decarboxylation of diethyl Δ^1-2-methylpyrroline-5,5-dicarboxylate,[4] and by catalytic hydrogenation of Δ^1-2-methylpyrroline-5-carboxylic acid[5] or its ethyl ester.[4] The isomer of 5-methylproline obtained by catalytic hydrogenation is reported to have mp 188°,[4,5] while for the isomer synthesized by the two other methods, mp 207°[3,4] has been reported. The cis configuration has been assigned to the former and the trans configuration to the latter 5-methylproline by comparing the pK_a' values of the derived 1,5-dimethyl-2-pyrrolidine methanols.[6] In this paper this assignment is considered in more detail. Furthermore, we report a new synthesis, the separation of *cis*- and *trans*-5-methylproline, and the resolution of both isomers to give the optically active amino acids.

Synthesis and Separation of *cis*- and *trans*-5-Methylproline (Figure 1). The hydrochloride of Δ^1-2-methylpyrroline-5-carboxylic acid (II) was prepared by cyclization of ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate (I) with hydrochloric acid. A variation of the method described in the literature[5] resulted in higher yields and a purer product. Catalytic hydrogenation gave predominantly one isomer of 5-methylproline hydrochloride (IIIa) as shown by the nmr spectrum and vapor-phase chromatography (vpc). The small amount of the other isomer present could be removed by recrystallization. The free amino acid (IVa) had mp 185–189° dec, which

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