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Polymers and Copolymers of Imidazole-Containing Isocyanides. Esterolytic Activity and Enantioselectivity[1]

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ABSTRACT: Rate constants have been measured for the hydrolysis of nitrophenyl and dinitrophenyl esters catalyzed by imidazolyl-containing polymers and copolymers of isocyanides, $[\mathrm{R{-}N{=}C{<}}]_n$. The isocyanides $\mathrm{R{-}N{=}C}$ were derived from L- (and D-) alanyl-L-histidine, L-alanyl-L- (and D-) serine, L- (and D-) alanyl-L-histidyl-L-serine, and L-alanyl-L-histidyl-D-serine. Active species are the neutral imidazolyl groups. Generally, the polymers show markedly higher activities than corresponding low molecular weight compounds. This enhancement in activity is ascribed to cooperative effects involving interactions of imidazolyl with neighboring imidazolyl and carboxylate groups. The activities are appreciably higher in the presence of positively charged surfactants. This effect is ascribed to the formation of a hydrophobic pseudophase by arrangement of surfactant molecules around a negatively charged polymer molecule. Enantioselectivities have been determined in the hydrolysis of two chiral amino acid esters. In the presence of surfactant, k_L/k_D values up to 2.94 have been obtained.

Introduction

The development of new catalysts after the example of enzymes in nature is currently a topic of main interest.[2] Many studies are dealing with catalytic systems that mimic proteases. The reason for this choice is that the principles of protease action have been studied extensively and are now starting to be understood.[3] For the construction of an artificial proteolytic catalyst the following features are thought to be required:[3d] (i) a nucleophile and a proton transfer system; organized to complement the structures of the amide or ester substrate; (ii) a water-soluble chiral frame to anchor the catalytic functions and to provide a binding site; and (iii) a hydrophobic microenvironment to mimic the hydrophobic interior of a protein.

The realization of all these features is difficult to achieve. Substantial progress, however, has been made in both low

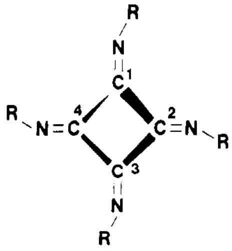


Figure 1. Schematic picture of a polymer of an isocyanide. Repeating unit C^5 is behind C^1, C^6 behind C^2, etc.

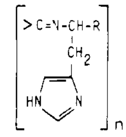
molecular[2a-d] and polymeric[2e-g] model systems.

In our laboratory we use polymers of isocyanides, also called poly(iminomethylenes), $[R-N=C<]_n$, as frames for the construction of proteolytic catalysts.[4] Poly(iminomethylenes) are easily prepared from isocyanides by the catalytic action of nickel(II) salts.[5]

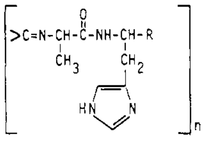
$$nR-N=C \xrightarrow{Ni^{II}} [R-N=C<]_n$$

The isocyanides are accessible in great variety from the corresponding amines, including amino acids.[6] Poly(iminomethylenes) have a stable helical structure (Figure 1). Their side chains are arranged in stacks that enclose four grooves running parallel to the polymer axis. These grooves provide, at least in principle, a chiral surface suitable for chiral recognition.

Our first studies dealt with poly(carbylhistamine) (1) and poly(carbylhistidine) (2).[4a,b] The anchored imidazolyl functions of the latter polymer showed an appreciable activity in the hydrolysis of activated esters. No enantioselectivity could be measured as 1 and 2 were racemic.



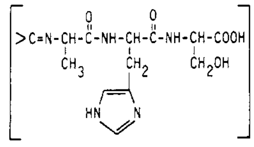
1 R = H
2 R = COOH



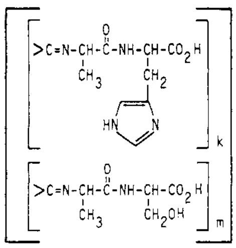
3 R = COOH; L-Ala, L-His
4 R = COOH; D-Ala, L-His
5 R = H; L-Ala, Histamine

As an extension of this work, we recently synthesized optically active poly(iminomethylenes) containing imidazolyl, carboxyl, and hydroxymethyl functions in their side chains.[4g,h] These functions are also present in the active center of the protease chymotrypsin.[3b] The polymers were prepared in two ways: by homopolymerization of isocyanides derived from alanylhistidylserine tripeptides and by copolymerization of isocyanides derived from the dipeptides alanylserine and alanylhistidine. The polymers are soluble in water and have an excess of one screw sense (feature ii). The present paper reports on their catalytic activity and enantioselectivity in the hydrolysis of activated achiral and chiral esters. Our goals are the realization of a cooperative action between catalytic functions (feature i) and the creation of a hydrophobic microenvironment for catalysis (feature iii). In order to achieve the latter goal, we added surfactants to our polymeric catalysts. Polymer–surfactant complexes are widely known and have been studied by using various techniques.[7] Surprisingly, no studies have appeared on the catalytic activity of these complexes.[8] Herein we report a first example of a positive effect on catalysis by complexation of a surfactant to a polymeric catalyst.

Results



6 L-Ala, L-His, L-Ser
7 D-Ala, L-His, L-Ser
8 L-Ala, L-His, D-Ser

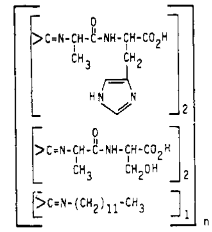


9 L-Ala, L-His; L-Ala, L-Ser
k = 1 and m = 2

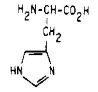
10 L-Ala, L-His; L-Ala, L-Ser
k = 1 and m = 1

11 L-Ala, L-His; L-Ala, L-Ser
k = 2 and m = 1

12 L-Ala, L-His; L-Ala, D-Ser
k = 1 and m = 1



13 L-Ala, L-His; L-Ala, L-Ser; dodecyl



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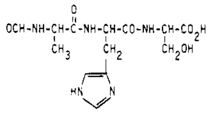

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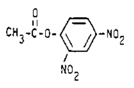

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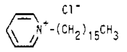

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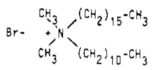

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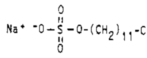

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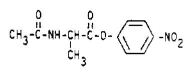

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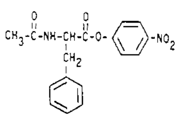

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The activity of polymers and copolymers 3–7 and 9–12 as well as of the monomeric compounds L-histidine (14) and tripeptide 15 in the hydrolysis of 2,4-dinitrophenyl acetate (DNPA) (16) was determined under essentially the same conditions as reported previously,[4b-d] viz., excess of imidazolyl groups at 25.00 °C in buffered 30 vol % aqueous ethanol, [cat] ≫ [substrate]. Aqueous ethanol was chosen for reasons of solubility and in order to facilitate comparison with literature data.[2e]

Rates were determined by following the increase in absorption of the dinitrophenolate ion that is released in the reaction. All experiments obeyed first-order kinetics. The difference between the first-order rate constant k_{measd} (with catalyst) and k_{blank} (without catalyst), $k_{obsd} = k_{measd} - k_{blank}$, is proportional to the molar concentration of imidazolyl groups, $k_{obsd} = k_a$ [cat]. The second-order catalytic rate constants, k_a, at various pH values are listed in Table I.

The activity of the polymeric catalysts was markedly affected by the presence of the cationic surfactants *N*-cetylpyridinium chloride (17) and cetylundecyldimethylammonium bromide (18), whereas the anionic surfactant sodium dodecyl sulfate (19) did not show any effect. Generally, addition of small amounts of 17 and 18 caused precipitation. In the presence of larger amounts (molar ratio of surfactant to polymer repeating unit >3) precip-

Table I
Catalytic Rate Constants[a] of Poly(iminomethylenes) and Model Compounds in the Hydrolysis of DNPA

	$k_a/(M^{-1} \cdot s^{-1})$ at pH						
compd	5.35	6.17	6.79	7.34	8.10	8.57	8.93
3	0.07	0.15	0.28	0.42	0.69	0.78	0.69
4	0.19	0.36	0.74	1.14	1.71	1.62	3.80
5	0.08	0.10	0.12	0.10	0.60	1.14	1.64
6	0.09	0.17	0.32	0.54			
7	0.06	0.21	0.45	0.97	1.21	1.78	2.32
9	0.03	0.09	0.00	0.14	1.12	1.06	4.06
10	0.00	0.13	0.11	0.00	0.94	0.64	0.85
11	0.04	0.02	0.13	0.19	0.81	1.45	1.11
12	0.08	0.14	0.28	0.42	0.80	0.58	0.54
13	0.10	0.12	0.44	0.73	1.26	1.02	1.02
14	0.08	0.18	0.29	0.42	0.72	0.93	1.41
15	0.07	0.22	0.34	0.37	0.40	0.44	0.45

[a] The concentration of compounds **3–15** is 1 × 10^{-4} M repeating units; the initial concentration of DNPA is 6.5 × 10^{-5} M.

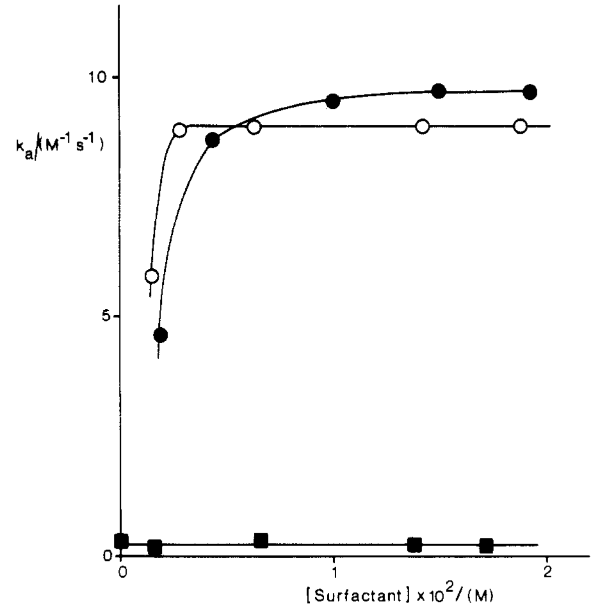


Figure 2. Catalytic rate constants of polymer **3** in the hydrolysis of DNPA as a function of the concentration of surfactants **17** (○), **18** (●), and **19** (■). Concentration polymer repeating units 3.4 × 10^{-4} M; pH 9.00.

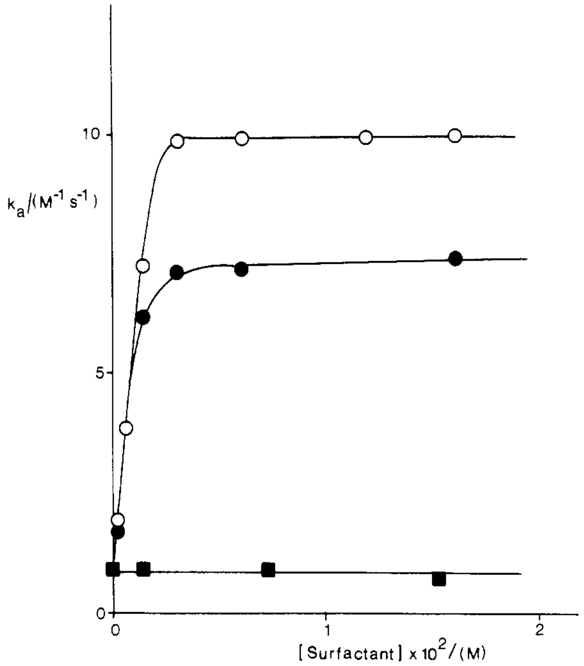


Figure 3. Catalytic rate constants of polymer **6** in the hydrolysis of DNPA as a function of the concentration of surfactants **17** (○), **18** (●), and **19** (■). Concentration polymer repeating units 2.7 × 10^{-4} M; pH 9.00.

Table II
Catalytic Rate Constants[a] of Poly(iminomethylenes) and Model Compounds in the Presence of Surfactant 17 in the Hydrolysis of DNPA

	$k_a/(M^{-1} \cdot s^{-1})$ at pH						
compd	5.35	6.17	6.79	7.34	8.10	8.57	8.93
3	0.41	1.18	2.29	4.60	3.85	4.82	10.83
4	0.33	1.40	4.67	7.88	15.86	23.84	29.74
5	0.20	0.47	1.03	0.61	1.10	1.64	2.05
6	0.38	0.63	1.42	1.09	3.76	4.53	8.28
7	0.29	0.74	2.01	1.61	1.92	2.77	6.35
9	1.35	2.27	4.48	7.36	3.63	8.80	21.60
10	1.19	2.54	4.37	4.16	3.18	7.08	8.76
11	1.32	2.27	3.15	4.32	2.19	4.18	9.30
12	0.92	1.90	2.90	4.37	4.10	4.31	7.72
13	1.28	2.90	5.27	9.04	3.24	6.55	8.76
14	0.19	0.40	0.52	0.60	0.85	1.09	1.58
15	0.10	0.30	0.41	0.46	0.50	0.51	0.53

[a] The concentration of the polymeric catalysts and of the model compounds **14** and **15** is 1 × 10^{-4} M repeating units; the concentration of **17** is 15.8 × 10^{-4} M; the initial concentration of DNPA is 6.5 × 10^{-5} M.

itation did not occur. The activity of polymers **3** and **6** was determined as a function of the surfactant concentrations. The data are in Figures 2 and 3. The activity highly increases as a function of surfactant concentration up to a ceiling range, which is reached at a molar ratio of surfactant to polymer repeating unit, R—N=C<, of approximately 10. We have determined the catalytic activity of all compounds **3–7** and **9–13** at one surfactant concentration in the ceiling range at various pH values. The results are in Table II.

In order to check whether added surfactant indeed coordinates to the polymer, the esterolytic activity of one of the polymers, viz. **3**, was determined in the presence of an increasing concentration of 1,4-dioxane. In the absence of surfactant the activity increased slightly, whereas in the presence of surfactant a dramatic decrease in activity occurred. Apparently, a polymer–surfactant complex exists that is broken by dioxane.

The pK_a values of our polymers have been given in ref 4g,h. As surfactants can affect pK_a values, we also determined them in the presence of surfactant **17**. The results are in Table III; for comparison the corresponding pK_a values without surfactant are listed too. We checked separately that surfactant **16** does not change the blank pH titration profile. As can be seen from Table III, addition of surfactant lowers the pK_a values of the imidazolyl groups of polymers but not of model compounds. In a previous paper[4h] we showed that polymers **9–11** and probably also **12** and **13** contain two different imidazolyl groups: type A with pK_a (ImH^+) ≃ 7 and type B with pK_a (ImH^+) = 8.5–9.5. The pK_a values of group A are in the normal range. Those of B are high and suggest a strong interaction with neighboring carboxylate functions. The surfactant-induced pK_a shifts of A and B occur at different surfactant concentrations: B at a surfactant to polymer repeating unit ratio <3 and A not appreciably before a ratio >3. Apparently, imidazolyl groups B are more accessible to surfactant molecules than A. The isoelectric points of **3–13** in the absence as well as presence of surfactant were calculated from the titration data. Their values are given in Table IV.

In a similar series of experients we determined the catalytic activity of the polymers with respect to the en-

Table III
pK_a Values of Poly(iminomethylenes) and of Model Compounds Determined in the Absence and Presence of Surfactant 17[a]

	COOH				ImH$^+$ A				ImH$^+$ B			
	without		with		without		with		without		with	
compd	pK_a	*n*	pK_a	*n*	pK_a	*n*	pK_a	*n*	pK_a	*n*	pK_a	*n*
3	3.1	1.4	3.4	1.2					9.1	2.1	7.4	1.0
4	2.9	1.7	4.2	1.3					8.1	2.1	6.7	1.0
5					5.2	1.9	5.3	2.1				
6	3.8	1.8	3.7	1.9	7.1	2.0	6.8	2.1				
7	5.8	2.0	4.2	1.7					8.7	1.6	7.4	1.9
9	4.6	1.8	4.0	1.4	7.2	1.0	6.3	0.6	9.6	0.6	7.7	0.6
10	3.8	2.3	4.0	1.0	7.2	1.0	6.4	0.6	9.7	0.5	7.8	0.6
11	4.7	1.3	4.1	1.2	7.1	0.6	6.5	0.7	9.6	0.6	7.7	0.5
12	5.4	1.8	4.5	1.3					8.4	1.3	7.3	1.1
13	5.3	1.7	4.4	1.1					8.4	1.2	7.1	1.0
14	2.0	1.0	2.1	1.0	6.0	1.0	6.1	1.1				
15	2.1	1.0	2.0	1.0	6.3	1.1	6.4	1.0				

[a] In 30% v/v EtOH–H_2O at 25 °C; ionic strength 0.2 M; the data are calculated from the modified Henderson–Hasselbach equation (see Experimental Section) estimated error in pK_a is ±0.1, estimated error in *n* value is ±0.05–0.1.

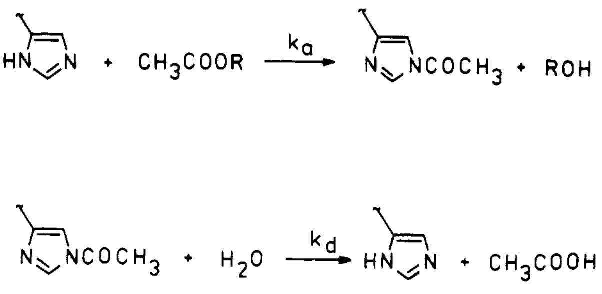
Table IV
Isoelectric Points of Poly(iminomethylenes) in the Absence and in the Presence of Surfactant 17

		isoelectric point	
compd	$10^{-3}\bar{M}_v$[a]	without 17	with 17
3	115	5.4	5.4
4		5.6	5.6
6	24	5.2	5.2
7	35	7.4	6.0
9	220	5.2	5.1
10	250	3.8	4.5
11	220	5.2	5.2
12	73	5.6	5.6
13	115	5.6	5.6

[a] See ref 4c,g,h.

antiomers of the chiral esters 4-nitrophenyl *N*-acetyl-2-aminopropionate (L-**20** and D-**20**) and 4-nitrophenyl *N*-acetyl-2-amino-3-phenylpropionate (L-**21** and D-**21**). The catalytic rate constants at three different pH values are given in Table V. The measurements were repeated in the presence of *N*-cetylpyridinium chloride (**17**). The concentration of surfactant was in the ceiling range (Table VI).

Scheme I



Discussion

Activity in the Absence of Surfactant. In a previous study we showed that the catalytic hydrolysis of activated esters by poly(carbylhistidine) (**2**) comprises an acylation and a deacylation step, as shown in Scheme I.[4b] The first step is rate determining when the catalyst, i.e., the imidazolyl group, is in excess, a condition we have in the present study. The imidazolyl groups participate in the equilibria

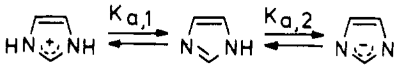


Table V
Catalytic Rate Constants k_L and k_D ($M^{-1}\bullet s^{-1}$) of Poly(iminomethylenes) in the Hydrolysis of Chiral Amino Acid Nitrophenyl Esters[a]

			pH 5.63		pH 6.23		pH 7.01	
polymer	screw sense	substrate	k_L	k_D	k_L	k_D	k_L	k_D
3	*M*	**20** L (D)[b]	*c*	*c*	0.03	0.03	0.12	0.11
		21 L (D)	0.05	0.05	0.07	0.07	*c*	*c*
6	*P*	**20** L (D)	0.03	0.04	0.12	0.11	0.03	0.04
		21 L (D)	0.03	0.03	0.03	0.02	0.40	0.41
7	*P*/*M*	**20** L (D)	0.03	0.03	0.08	0.09	0.15	0.16
		21 L (D)	0.04	0.03	0.15	0.14	0.16	0.18
8	*P*	**20** L (D)	0.04	0.04	0.13	0.12	*c*	0.02
		21 L (D)	0.02	0.01	0.05	0.04	0.01	*c*
9	*M*	**20** L (D)	0.07	0.08	0.26	0.28	0.09	0.10
		21 L (D)	0.23	0.23	0.02	*c*	0.08	0.10
10	*M*	**20** L (D)	0.04	0.04	0.04	0.04	*c*	0.01
		21 L (D)	0.09	0.11	*c*	*c*	0.34	0.32
11	*M*	**20** L (D)	0.03	0.04	0.02	0.03	0.07	0.09
		21 L (D)	0.05	0.05	0.02	0.03	0.12	0.14
12	*M*	**20** L (D)	*d*	*d*	0.12	0.11	0.06	0.06
		21 L (D)	*d*	*d*	0.08	0.10	0.03	0.02
13	*M*	**20** L (D)	*d*	*d*	0.07	0.05	0.04	0.03
		21 L (D)	*d*	*d*	0.04	0.06	*c*	0.02

[a] In water at 23.00 °C; 0.2 M acetate and phosphate buffers; [polymer repeating units] 1×10^{-4} M; all experiments were performed in triplicate. [b] The initial concentration of the esters is 5×10^{-5} M. [c] Calculated k_L and k_D values are slightly negative but not significantly different from 0. [d] No k_L or k_D data could be obtained as polymer precipitates (isoelectric point = 5.6).

Table VI
Catalytic Rate Constants k_L and k_D ($M^{-1}\bullet s^{-1}$) of Poly(iminomethylenes) in the Presence of the Cationic Surfactant *N*-Cetylpyridinium Chloride (17) in the Hydrolysis of Chiral Amino Acid 4-Nitrophenyl Esters[a]

			pH 5.63			pH 6.23			pH 7.01		
polymer	screw sense	substrate	k_L	k_D	k_L/k_D	k_L	k_D	k_L/k_D	k_L	k_D	k_L/k_D
3	*M*	**20** L (D)	0.32	0.11	2.94	0.70	0.59	1.19	1.83	1.82	1.00
		21 L (D)	1.84	1.59	1.16	4.12	3.92	1.05	13.18	9.28	1.42
6	*P*	**20** L (D)	0.28	0.23	1.18	0.81	0.68	1.18	1.22	1.37	0.87
		21 L (D)	1.83	2.09	0.88	5.64	6.08	0.93	10.88	8.70	1.25
7	*P*/*M*	**20** L (D)	0.29	0.30	1.03	0.95	0.92	1.04	1.84	1.84	1.00
		21 L (D)	3.52	2.53	1.50	6.52	6.59	1.01	12.61	12.31	1.02
8	*P*	**20** L (D)	0.37	0.15	2.40	0.75	0.71	1.06	1.41	1.45	0.96
		21 L (D)	1.85	1.86	1.00	5.70	5.27	1.10	9.26	10.08	0.92
9	*M*	**20** L (D)	1.52	1.72	0.89	2.81	3.36	0.84	9.04	7.29	1.24
		21 L (D)	4.33	3.67	1.18	18.70	19.33	0.97	34.60	40.22	0.72
10	*M*	**20** L (D)	0.50	0.57	0.88	1.03	0.74	1.37	3.26	2.43	1.34
		21 L (D)	1.36	2.58	0.53	5.04	5.74	0.88	19.05	22.29	0.86
11	*M*	**20** L (D)	0.39	0.46	0.83	1.17	0.98	1.21	2.96	2.70	1.10
		21 L (D)	2.58	3.01	0.86	6.44	5.64	1.15	12.57	11.88	1.07
12	*M*	**20** L (D)	*b*	*b*	*b*	1.51	1.47	1.03	2.66	3.07	0.87
		21 L (D)	*b*	*b*	*b*	9.11	8.47	1.08	18.26	15.85	1.15
13	*M*	**20** L (D)	*b*	*b*	*b*	2.27	2.40	0.95	3.87	4.69	0.83
		21 L (D)	*b*	*b*	*b*	5.57	5.88	0.95	17.45	15.95	1.09

[a] In water at 23.00 °C; 0.2 M acetate and phosphate buffers; [polymer repeating unit] 1.0×10^{-4} M; [CePyCl] 15.8×10^{-4} M. All experiments were performed in triplicate. [b] No data could be obtained as polymers precipitate.

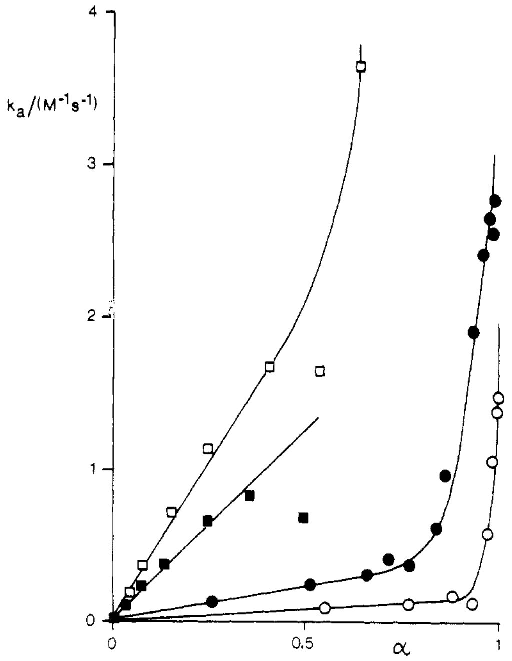


Figure 4. Catalytic rate constants of polymers **1** (●), **3** (■), **4** (□), and **5** (○) in the hydrolysis of DNPA as a function of α_{Im}.

The cationic species is not sufficiently nucleophilic to be catalytically active. The concentration of the anionic species will be negligible because the pK_a of the second step is approximately 14.5,[9] which is far removed from our highest pH value of 8.93. Therefore, unprotonated imidazolyl groups will be the catalytically active species. The fraction of imidazolyl that is unprotonated at a certain pH value, α_{Im}, can be calculated from the pK_a and n data by applying the modified Henderson–Hasselbach equation

$$\mathrm{pH} = \mathrm{p}K_a - n \log \left[(1 - \alpha_{Im})/\alpha_{Im}\right]$$

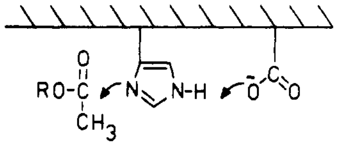
The pK_a and n values are given in Table III.

In Figure 4 the catalytic rate constants of polymers **3**–**5** are plotted as a function of α_{Im}. For comparison the figure includes the activity of the polymer of 2-(4-imidazolyl)ethyl isocyanide (**1**) previously studied by us.[4b] The initial parts of the curves are linear. The slopes of the linear parts are given in Table VII. These slopes are appreciably higher for **3** and **4** than for **1** and **5**. This increase in activity can be ascribed to carboxylate anions that are present in **3** and **4** but not in **1** and **5**. We suggest that the carboxylate increase the nucleophilicity of their neighboring imidazolyl groups.

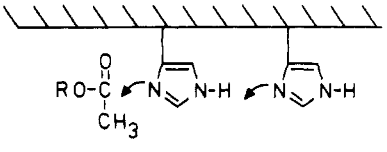
Table VII
Slopes of the k_a Values α_{Im} Relationships of Poly(iminomethylenes) and Model Compounds

	without 17		in the presence of 17	
compd	initial slope	slope at α_{Im} > ≃0.8	initial slope	slope at α_{Im} > ≃0.8
1	0.44[a]	30[a]		
3	2.6	*b*	8.0	100
4	4.0	*b*	8.0	100
5	0.2	30	0.3	35
6	1.2	*b*	2.5	*b*
7	1.2	*b*	2.5	*b*
9	0.4	*b*	8.0	100
10	0.4	*b*	8.0	100
11	0.4	*b*	8.0	100
12	2.3	*b*	8.0	100
13	3.6	*b*	15.0	100
14	0.44		0.50	
15	0.50	*c*	0.50	*c*

[a] Reference 4b. [b] No data available because α_{Im} = 1 is not reached. [c] Linear up to α_{Im} = 1.



The plots of **1** and **5**, strongly curve upward at α_{Im} = 0.8. This sharp increase in activity can be ascribed to mutual assistance of neighboring imidazolyl groups. At higher α_{Im} values the number of neighboring neutral imidazolyls increases rapidly. One imidazolyl enhances the nucleophilicity of another. Since imidazolyl is more basic than COO^-, the slopes of the plots for **1** and **5** at α_{Im} > 0.8 are higher than the initial slopes for **3** and **4** where COO^- is the assisting species.



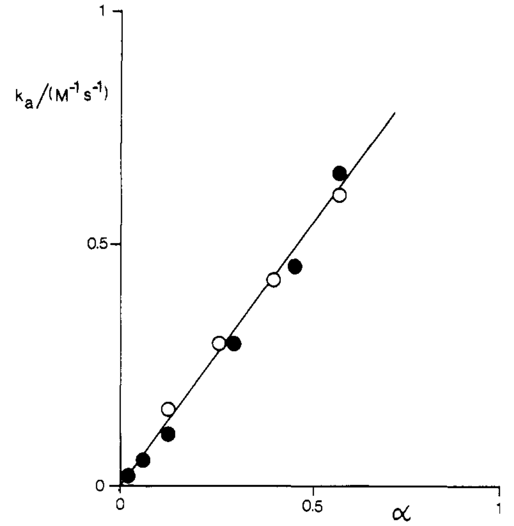


Figure 5. Catalytic rate constants of polymers **6** (○) and **7** (●) in the hydrolysis of DNPA as a function of α_{Im}.

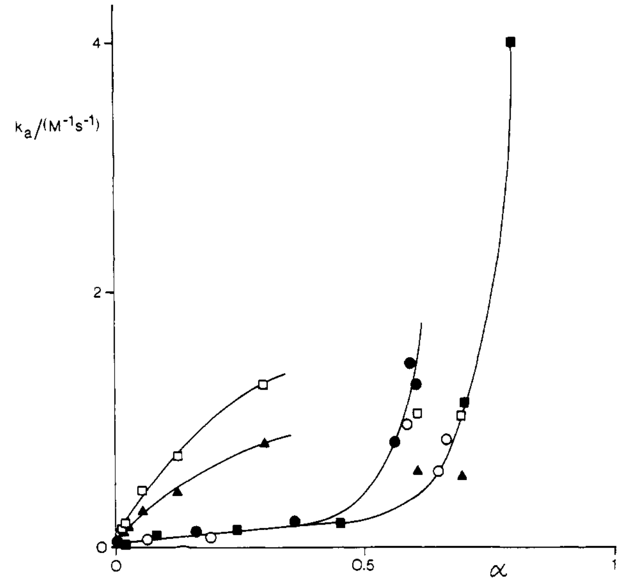


Figure 6. Catalytic rate constant of copolymers **9** (■), **10** (●), **11** (○), **12** (▲), and **13** (□) in the hydrolysis of DNPA as a function of α_{Im}.

The catalytic rate constants of the "tripeptide" polymers **6** and **7** are plotted in Figure 5, and the corresponding slopes are given in Table VII. Both curves are linear with equal slope. This slope is rather high compared to the slopes of **1** and **5**, which do not have COO^- groups. The explanation is the same as for the "dipeptide" polymers **3** and **4**: COO^- increases the nucleophilicity of neighboring imidazolyl. However, when the activities are compared with those of **3** and **4**, it can be concluded that the hydroxymethyl groups in the "tripeptide" polymers do not exercise an accelerating effect.

The catalytic data of copolymers **9**–**13** are plotted in Figure 6. In the region up to $\alpha_{Im} = 0.5$ the curves for copolymers **9**–**11** coincide and have a slope of 0.4 $M^{-1} \cdot s^{-1}$ (Table VII). Copolymers **12** and **13** are more active in this region. Particularly noteworthy is the ninefold increase by the dodecyl component which becomes apparent when **13** is compared with **10**. This increase is probably due to the dodecyl hydrophobicity (cf. the hydrophobicity effect of the surfactants; see below). Around $\alpha_{Im} = 0.5$ the plots for copolymers **9**, **10**, and **11** bend upward, whereas those for **12** and **13** are more or less horizontal in this region. The curving upward may not only be due to the usual cooperative effect of unprotonated imidazolyl groups but also to a relatively high activity of the imidazolyl groups type B.

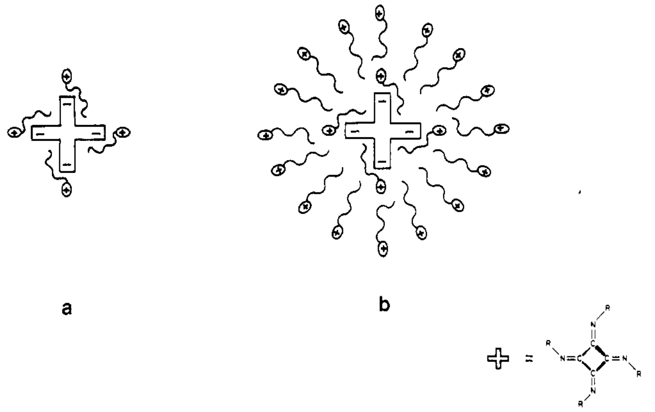


Figure 7. Possible structure of the polymer–surfactant complex at low (a) and high (b) concentration of surfactant.

Table VII includes the slopes of the k_a vs. α_{Im} curves for the low molecular weight compounds L-histidine (**14**) and the formylated tripeptide L-alanyl-L-histidyl-L-serine (**15**). The activities of these nonpolymeric compounds, expressed by their initial slopes, are relatively low. Apparently, assistance by neighboring COO^- is absent in these nonpolymeric compounds.

Activity in the Presence of Surfactant. The addition of cationic surfactants markedly enhances the activity of the polymeric catalysts (cf. Table I and II). This enhancement can be explained in the following way. The pH is almost always above the isoelectric points of the polymers. Consequently, the polymers have a net negative charge. At a surfactant to polymer repeating unit ratio <3, a precipitate is formed. We ascribe this behavior to the formation of a complex as sketched in Figure 7a. The complex has a hydrophobic mantle and, therefore, tends to precipitate in the aqueous hydrophilic environment. At higher surfactant concentrations the polymer remains in solution because species with a charged outer sphere, as drawn in Figure 7b, are formed. The structure and physical properties of these species are currently under investigation.[11]

Added surfactant could affect the reaction in the following ways: (i) pK_a change of the catalytically active functions and, (ii) preferred dissolution of the substrate in the hydrophobic pseudophase and, thus, concentration of the substrate in the vicinity of the imidazolyl groups. The addition of surfactant appreciably lowers the imidazolyl pK_a values (Table III). Therefore, at a certain pH the number of unprotonated imidazolyls increases and consequently the rate constant. However, the data in Table VII reveal that the activity also increases per unprotonated imidazolyl group. Therefore, effect i cannot be the only factor; effect ii will also contribute. For example, substrate **21** is more hydrophobic than **20** and has greater catalytic rate constants in the presence of surfactant.

Polymer **5** does not have carboxylate groups. Consequently its interaction with surfactant will not be large. Indeed, the effect of surfactant on its $pK_a(ImH^+)$ (Table III) and its activity (Tables I and II) is relatively low.

Just as in the experiments without surfactant, the lower activity of **5** compared to that of **3** and **4** is ascribed to the lack of carboxylate groups and thus of carboxylate–imidazolyl interaction (Figure 8). The bending upward of all curves in Figure 8 is due to interaction between neutral imidazolyl groups, as was discussed for the plot of data of

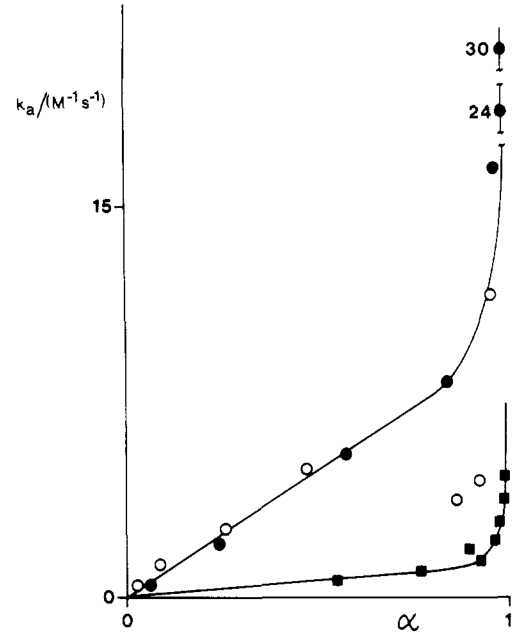


Figure 8. Catalytic rate constants of polymers **3** (○), **4** (●), and **5** (■) in the presence of surfactant **17** as a function of α_{Im}.

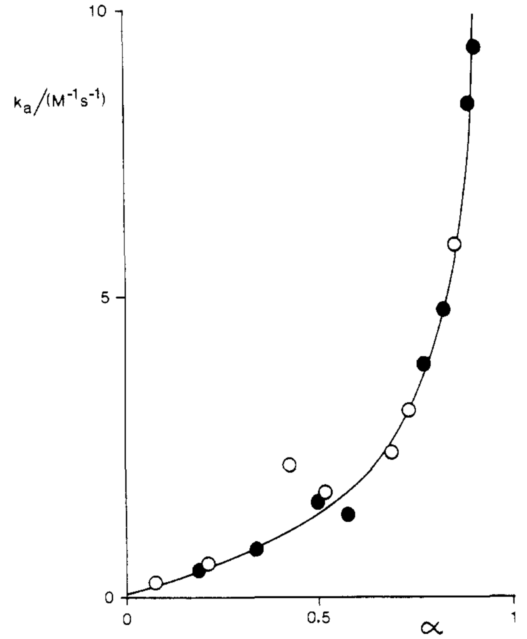


Figure 9. Catalytic rate constants of polymers **6** (●) and **7** (○) in the presence of surfactant **17** as a function of α_{Im}.

5 in Figure 5. In the latter figure this bending upward was not detectable for **3** and **4** because of their higher pK_a values in the absence of surfactant.

The activity of polymers **6** and **7** as a function of α_{Im} is plotted in Figure 9. The plots are almost identical. Apparently, in these "tripeptide" polymers, the reversal in configuration of the alanyl residue does not affect the catalytic activity at all. The upward curvature will again be due to increasing interaction between neutral imidazolyls. The catalytic behavior of the copolymers **9–13** in the presence of surfactant is represented by the curves in Figure 10. Copolymers **9–12** behave similarly. The activity of **13** is higher, which again will be due to the hydrophobicity of its dodecyl side chains. There is a remarkable discontinuity at $\alpha_{\mathrm{Im}} \simeq 0.8$. This discontinuity occurs at the change from phosphate to Tris buffer. Possibly, the Tris buffer reduces the accelerating effect of the surfactant; the tris(hydroxymethyl)methylammonium ions of this buffer could compete more favorably with the surfactant than sodium or potassium ions.

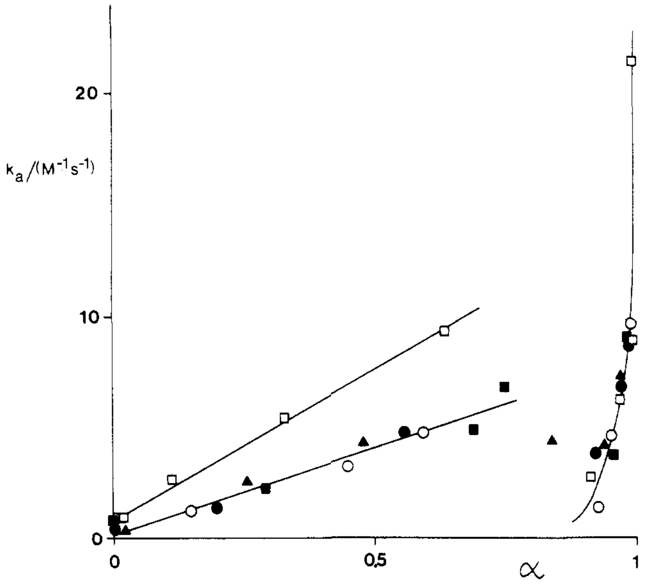


Figure 10. Catalytic rate constants of copolymers **9** (■), **10** (●), **11** (○), **12** (▲), and **13** (□) in the presence of surfactant **17** as a function of α_{Im}.

The effect of surfactant on the activity of the low molecular weight compounds **14** and **15** is negligible. This result supports our picture according to which a polymer–surfactant complex is responsible for the observed rate enhancements.

Enantioselectivity. The polymeric catalysts in this study are chiral, not only because of the chirality in the "peptide" side chains but also because of the helical configuration of the main chain. The main chain of each of our samples has a preferred screw sense, *P* or *M*, which has been determined by CD spectroscopy and which is given in Tables V and VI.

The catalytic rate constants, k_a, in the hydrolysis of substrates **20** and **21** by polymers **3–13** are very low (Table V). These low activities are related to the high pK_a values of the imidazolyl functions. Because of these high pK_a values, the fraction of unprotonated imidazolyl is extremely low under our pH conditions. More basic solutions could not be used because of too high blank rates. Significant differences in activity with respect to L- and D-esters could not be observed. However, in the presence of surfactant, activities are much higher and enantioselectivities falling outside the insignificant range ($k_L/k_D \simeq 0.9$–1.1) are clearly observed in a number of cases (Table VI). The latter observation is remarkable because the surfactant itself is achiral.

The enantioselectivity is pH and substrate dependent. In many cases k_L/k_D reverses when going from low to high pH. Because of this capricious behavior a detailed interpretation is impossible as yet.

Two factors could be responsible for the observed enantioselectivities: (i) difference in Gibbs function of the initial state or, in other terms, preferential solubility or steric incorporation of one enantiomer in the chiral phase of the polymer–surfactant complex; (ii) difference in Gibbs function of the diastereomeric transition states. The second factor should also play a role in the reactions without surfactant. Since in these reactions the enantioselectivity is negligible, we believe that the first factor predominates. An even larger selectivity can be expected with the right choice of chiral surfactant. Experiments in this direction will be performed.

In conclusion, our work shows the presence of cooperative effects in the polymeric system that are not present in corresponding low molecular weight compounds. These effects enhance the catalytic activity. Moreover, the activity and also the enantioselectivity are increased by creation of a hydrophobic pseudophase around the polymeric catalysts.

Experimental Section

Materials. 2,4-Dinitrophenyl acetate (mp 70–71 °C) was prepared according to a literature procedure.[12] L- and D-4-nitrophenyl *N*-acetyl-2-aminopropionate (L-**20** and D-**20**) and L- and D-4-nitrophenyl *N*-acetyl-2-amino-3-phenylpropionate (L-**21** and D-**21**) were obtained according to the procedure of Ingles and Knowles.[13] These esters had the following physical properties, which agree with values reported in literature (ester, mp, $[\alpha]^{20}_{\mathrm{D}}$ (c 1, $CHCl_3$)): L-**20**,[14] 104–105 °C, −68.0°; D-**20**,[14] 105–106 °C, +63.3°; L-**21**,[13] 139–140 °C, −18.5°; D-**21**,[13] 134–135 °C, +17.5°. *N*-Cetylpyridinium chloride and sodium dodecyl sulfate were commercial products; cetylundecyldimethylammonium bromide was prepared from cetyldimethylamine[15] and undecyl bromide. L-Histidine was a commercial product. *N*-Formyl-L-alanyl-L-histidyl-L-serine (**15**) was obtained from its methyl ester[4g] by hydrolysis under weakly acidic conditions. The compound was recrystallized from ethanol–ether: $[\alpha]^{20}_{\mathrm{D}}$ −8.8° (c 0.1, water); ^1H NMR (D_2O) δ 8.9 and 7.6 (2 × s, 2 H, imidazole), 8.2 (s, 1 H, CHO), 4.7–4.1 (m, 3 H, 3 × CH), 4.0 (d, 2 H, CH_2-Ser), 3.4 (d, 2 H, CH_2-His), and 1.4 ppm (d, 3 H, CH_3).

Polymers **3**, **4**, and **6–13** were synthesized as described previously.[4c,g,h] Their molecular weights are given in Table IV. Polymer **5** was synthesized as follows. *N*-Formyl-L-alanine 4-nitrophenyl ester[4g] and histamine dihydrochloride (commercial product) were coupled by a procedure essentially the same as described previously.[4g] After protection of the imidazolyl function by a 4-toluenesulfonyl (tosyl) group,[4g] the product was purified by column chromatography (silica, eluent chloroform–methanol, 10:1 v/v): 58% yield of *N*-formyl-L-alanyl-N^{Im})-tosylhistamine; mp 132–135 °C; $[\alpha]^{20}_{\mathrm{D}}$ −13.3° (c 0.5, chloroform); IR (KBr) 3310 (NH), 1640 (NHCO), 1600, 1370, and 1180 cm^{-1} (tosyl). The preceding formamide was converted into the isocyanide by the phosphorus oxychloride–triethylamine procedure.[4g] Yield 42% of a slightly yellow syrup; $[\alpha]^{20}_{\mathrm{D}}$ +2.1° (c 0.5, chloroform); IR (neat): 3320 (NH), 2140 (NC), 1640 (NHCO), 1600, 1370, and 1180 cm^{-1} (tosyl). Polymerization of the isocyanide was performed with nickel(II) chloride in 4:1 v/v chloroform–methanol as described previously.[4g] After removal of the $N^{(Im)}$ tosyl group with acetic anhydride and pyridine,[4h] ultrafiltration of the acidified solution (Diaflo Ultrafilter UM-2), and freeze-drying, polymer **5** was obtained as a yellow-brown solid: 50% yield; $[\alpha]^{20}_{\mathrm{D}}$ +5.4° (c 0.1, water); IR (KBR) 3700–2800 (ImH^+), 1700–1600 cm^{-1} (NHCO, N=C).

Kinetics DNPA. Compounds **3–15** were dissolved in 30.0 vol % $EtOH-H_2O$ to a concentration of 10^{-4} M. The solutions were buffered with 0.2 M tris and HCl (pH 8.10, 8.57, 8.93), KH_2PO_4 and Na_2HPO_4 (ionic strength 0.2 M; pH 6.79, 7.34), or 0.2 M sodium acetate and HCl (pH 6.17, 5.35). DNPA was dissolved in 30 vol % $EtOH-H_2O$ to a concentration of 10^{-3} M. For each measurement the catalyst solution (2.8 mL) and the substrate solution (0.2 mL) were mixed in a quartz cell, which was subsequently placed in a Perkin-Elmer 254 spectrophotometer, thermostated at 25.00 °C. Absorbances (A_t) of 2,4-dinitrophenolate at 360 nm were followed as a function of time. After at least 10 half-lives the absorbance for complete reaction (A_∞) was measured in the same way. In the experiments with surfactant the reaction mixtures were sonicated for 1–5 min by using a Sonicar SC-50-22 bath, sonic power 55 W. All experiments were performed in triplicate. The estimated error is 5%.

Chiral Esters 20 and 21. Stock solutions of polymers **3** and **6–13** were prepared in 10^{-3} M aqueous NaOH. Samples of these stock solutions were mixed with 0.22 M acetate buffer (pH 5.63, 6.23) or phosphate buffer (pH 7.01). Blanks were prepared from 10^{-3} M aqueous NaOH. The final concentration of the polymer solutions was 10^{-4} M. In the experiments with *N*-cetylpyridinium chloride (final concentration 1.58×10^{-3} M) the mixture was sonicated for 5 min at 10 °C. Ester substrates **20** and **21** were dissolved in dioxane to a concentration of 10^{-3} M. For each measurement 2.9 mL of catalyst solution was mixed with 0.1 mL of substrate solution. After equilibration at 23.00 °C the absorbance of 4-nitrophenolate at 400 nm was followed as a function of time. Experiments were performed in triplicate. The estimated error is 5%.

Determination of pK_a. Potentiometric titrations were performed on a Mettler automatic titrator device, types DV10, DK12, DK14, and DK25. Compounds **3–15** were dissolved in 30 vol % $EtOH-H_2O$ to a concentration of 10 mg/20 mL. To these solutions 185 mg of *N*-cetylpyridinium chloride was added. The solutions were brought to pH 12 by adding 1 M aqueous NaOH. An amount of KCl was added such that at the end point of titration the ionic strength was 0.2 M. The solutions were titrated with 0.10 M HCl in 30 vol % $EtOH-H_2O$ while stirring. Blank titration curves were obtained by titrating 20-mL aliquots of 30 vol % $EtOH-H_2O$ adjusted to the same pH and ionic strength. Differential titration curves were derived graphically. Evaluation of the titration curves afforded the degrees of dissociation (α) as the function of pH. Values for pK_a and n in the modified Henderson–Hasselbach equation,[10] $\mathrm{pH} = \mathrm{p}K_a - n \log [(1 - \alpha)/\alpha]$, were calculated from plots of $\log [(1 - \alpha)/\alpha]$ vs. pH.

Registry No. **3** (SRU), 79995-91-8; **3** (homopolymer), 88033-01-6; **4** (homopolymer), 88033-03-8; **4** (SRU), 80040-39-7; **5** (SRU), 98064-53-0; **5** (homopolymer), 98064-55-2; **6** (homopolymer), 88033-10-7; **6** (SRU), 98167-26-1; **7** (homopolymer), 88082-22-8; **7** (SRU), 98064-52-9; **8** (homopolymer), 88082-24-0; **8** (SRU), 98167-25-0; **9** (copolymer), 88033-05-0; **12** (copolymer), 88033-07-2; **13** (terpolymer), 88033-08-3; **14**, 71-00-1; **15**, 98064-51-8; **17**, 123-03-5; **18**, 88122-96-7; L-**20**, 5013-08-1; D-**20**, 37721-02-1; L-**21**, 14009-94-0; D-**21**, 4232-27-3.

References and Notes

(1) Part of the PhD work of H. G. J. Visser, (Thesis, Utrecht, 1983). Preliminary publications have appeared in ref 4e,f. Part 22 in the series Poly(iminomethylenes); for part 21 see ref 4h.

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