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Synthesis and Hydrolysis of Polymers Having Anesthetic or Amantadine Residues in Sidechains

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ABSTRACT

The polymerizable derivatives of chemotherapeutic agents such as benzocaine, procaine, and amantadine were prepared and free-radical copolymerized with styrene or methyl methacrylate in order to obtain polymers with pharmacological activity and increased duration of action of the drugs. The monomeric and polymeric derivatives were subjected to hydrolysis in vitro in order to measure the release of the active ingredient.

INTRODUCTION

As the retention of drugs in the body can be increased by use of macromolecular controls, much interest has been manifested recently in the synthesis of pharmacologically active macromolecular compounds which are able to release the free drug component by enzymatic degradation or hydrolysis [1, 2]. A hydrolyzable bond between drug and macromolecules is required if the drug is active only in its free form. The macromolecule-drug complex then acts as a reservoir and can be considered a macromolecular prodrug. In such polymers the chemotherapeutic agents are fixed either directly or by means of

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spacer groups to carrier macromolecules such as starch [3-6], protein [7, 8], and vinyl [9-15] or other [16-19] synthetic polymers. In the present work, benzocaine and procaine, well-known local anesthetics, and amantadine, a known antiviral agent, were modified or provide polymerizable derivatives for making the macromolecular prodrug with possibly prolonged activity.

EXPERIMENTAL

Materials

Benzocaine hydrochloride (ethyl 4-aminobenzoate) and procaine hydrochloride (2-(diethylamine)ethyl 4-aminobenzoate) were commercial products of the highest purity available (Aldrich, Merck). Methacrylyl chloride was prepared from methacrylic acid and benzoyl chloride [20].

Preparation of Monomeric Derivatives Without Spacer Group, 1. 100 mmol of drug was dissolved in 300 mL freshly distilled chloroform and 120 mmol triethylamine. Then 5 mg 1,4-benzoquinone was added with stirring and cooling at 0°C, and 120 mmol methacrylyl chloride was dropped into the solution. After stirring 1.5 h at 0°C, ~200 mL water was added to the reaction mixture. The chloroform layer was washed with water and evaporated to dryness. The sticky residue obtained was left to crystallize for a week at 0°C and recrystallized from ethanól-ether.

1a: mp 106-108°C, yield 88.4%. NMR ($CDCl_3$), δ (ppm): 1.3 (t, 3H,$CH_2\underline{CH_3}$), 2.0 (s,3H,$\underline{CH_3}$), 4.4 (q,2H,$\underline{CH_2}CH_3$), 5.4 (m,1H,$\underline{H}$–CH=), 6.7 (m,1H,$\underline{H}$–CH=), 7.5-8.2 (q,4H,aromatic), 8.4 (br,1H,CONH). $C_{13}H_{15}NO_3$ = 233.267. Calculated: C:H:N = 66.96:6.48:6.00%. Found: C:H:N = 66.24:6.54:5.86%.

1b: mp 78-80°C, yield 57.2%. NMR ($CDCl_3$), δ (ppm): 1.4 (t, 6H,$CH_2\underline{CH_3}$), 2.0 (s,3H,CH_3), 2.7 (q,4H,$\underline{CH_2}CH_3$), 2.8 (t,2H,$CH_2\underline{CH_2}N$), 4.4 (t,2H,$\underline{CH_2}CH_2N$), 5.5 (m,1H,$\underline{H}$–CH=), 6.8 (m,1H,$\underline{H}$–CH=), 7.8 (q, 4H, aromatic), 8.3 (br,1H,CONH). $C_{17}H_{24}N_2O_3$ = 304.389. Calculated: C:H:N = 67.08:7.97:9.20%. Found: C:H:N = 67.56:7.75:9.16%.

1c: 104-105°C, yield 53.2%. NMR ($CDCl_3$), δ (ppm): 1.7 (s, 3H,$\underline{CH_3}$), 1.5-2.3 (m,15H, adamantyl), 5.3 (m,1H,H–CH=), 6.5 (m, 1H,H–CH=). $C_{14}H_{21}NO$ = 219.330. Calculated: C:H:N = 76.67:9.65: 6.39% Found: C:H:N = 76.55:9.45:6.42%.

Preparation of Imine, 3. 50 mmol vanillin and drug in 300 mL dry benzene was heated under reflux for 10 h, during which time

an equimolar quantity of water was collected in a Dean-Stark trap. After removal of the solvent, the pure imine was obtained in above 90% yield by recrystallization from ethanol.

3a: mp 148-149°C. NMR ($CDCl_3$), δ (ppm): 1.4 (t,3H, $CH_2\underline{CH}_3$), 3.9 (s,3H,$OC\underline{H}_3$), 4.2-4.6 (q,2H,$C\underline{H}_2CH_3$), 7.1-8.3 (m,7H,aromatic), 8.4 (s,1H,$C\underline{H}$=N). $C_{17}H_{17}NO_4$ = 299.326. Calculated: C:H:N = 68.22:5.72:4.68%. Found: C:H:N = 67.83:5.53:4.73%.

3b: mp 86-88°C. NMR ($CDCl_3$), δ (ppm): 1.1 (t,6H,$CH_2C\underline{H}_3$), 2.6 (q,4H,$C\underline{H}_2CH_3$), 2.9 (t,2H,$CH_2C\underline{H}_2N$), 3.9 (s,3H,$OC\underline{H}_3$), 4.4 (t,2H,$C\underline{H}_2CH_2N$), 7.4 (q,4H,aromatic), 6.8-8.1 (m,3H,aromatic), 8.3 (s,1H,$C\underline{H}$=N). $C_{21}H_{26}N_2O_4$ = 362.477. Calculated: C:H:N = 69.59:7.23:7.73%. Found: C:H:N = 69.30:7.00:7.95%.

3c: mp 147-148°C. NMR ($CDCl_3$), δ (ppm): 1.3-2.3 (m,15H, adamantyl), 3.5 (s,3H,$OC\underline{H}_3$), 6.4-7.4 (m,3H,aromatic), 7.8 (s,1H, $C\underline{H}$=N). $C_{18}H_{23}NO_2$ = 285.391. Calculated: C:H:N = 75.76:8.12:4.91%. Found: C:H:N = 75.55:7.85:4.90%.

Preparation of Monomeric Derivatives with Spacer Group, 2. 30 mmol of 3 was dissolved in 200 mL dry chloroform and 36 mmol triethylamine. Then 5 mg 1,4-benzoquinone was added while stirring and cooling at 0°C, and 36 mmol methacrylyl chloride was slowly added to the solution. After stirring for 1.5 h at 0°C, 200 mL water was added to the reaction mixture. The chloroform layer was washed with water and evaporated to dryness. The product obtained was recrystallized from ethanol and ether.

2a: mp 93-94°C, yield 33.4%. NMR ($CDCl_3$), δ (ppm): 1.3 (t,3H, $CH_2C\underline{H}_3$), 2.1 (s,3H,$C\underline{H}_3$), 3.8 (s,3H,$OC\underline{H}_3$), 4.4 (q,2H,$C\underline{H}_2CH_3$), 5.6 (m,1H,$\underline{H}$–CH=), 6.4 (m,1H,$\underline{H}$–CH=), 7.0-8.2 (m,7H,aromatic), 8.4 (s, 1H,$C\underline{H}$=N). $C_{21}H_{21}NO_5$ = 367.401. Calculated: C:H:N = 68.65:5.76:3.81%. Found: C:H:N = 68.55:5.90:3.80%.

2b: mp 86-88°C, yield 30.4%. NMR ($CDCl_3$), δ (ppm): 1.3 (t,6H, $CH_2C\underline{H}_3$), 2.2 (s,3H,$C\underline{H}_3$), 2.7 (q,4H,$C\underline{H}_2CH_3$), 3.0 (t,2H,$CH_2C\underline{H}_2N$), 3.9 (s,3H,$OC\underline{H}_3$), 4.5 (t,2H,$C\underline{H}_2CH_2N$), 5.7 (m,1H,$\underline{H}$–CH=), 6.3 (m, 1H,$\underline{H}$–CH=), 7.5 (q,4H,aromatic), 7.1-8.2 (m,3H,aromatic), 8.4 (s, 1H,$C\underline{H}$=N). $C_{25}H_{30}N_2O_5$ = 438.524. Calculated: C:H:N = 68.47:6.90:6.39%. Found: C:H:N = 68.01:6.80:6.50%.

2c: mp 117-119°C, yield 46.2%. NMR ($CDCl_3$) δ (ppm): 1.5 (t, 3H,$C\underline{H}_3$), 1.6-2.3 (m,15H,adamantyl), 3.7 (s,3H,$OC\underline{H}_3$), 5.5 (m,1H, $\underline{H}$–CH=), 6.3 (m,1H,$\underline{H}$–CH=), 6.9-7.5 (m,3H,aromatic), 8.1 (s,1H,

CH=N). $C_{22}H_{27}NO_3$ = 353.467. Calculated: C:H:N = 74.76:7.70:3.96%. Found: C:H:N = 74.55:7.81:3.75%.

Polymerization Procedure

15 mL dimethylsulfoxide solution containing the required amounts of monomeric drug derivative, comonomer, and 0.01 g azobisisobutyronitrile (AIBN) in a glass tube was degassed by the freeze-thaw technique using a Dry-Ice/methanol bath and sealed in vacuo. The sealed tube was shaken at 60°C. After polymerization for 3.5-6 h, the content of the tube was poured into a large amount of methanol (or petroleum ether) to precipitate the polymer. The intrinsic viscosities $[\eta]$ of the polymer were determined in dimethylformamide (DMF) at 30°C with an Ubbelohde viscometer after recrystallization from DMF-methanol. The composition ratios of the copolymers were calculated from the nitrogen content as obtained by elemental analyses.

Hydrolysis Procedure

A known amount of sample was sealed in a small packet made of filter paper (Toyo No. 5C). The packet was then placed in a 100-mL Erlenmeyer flask containing 30 mL of an aqueous solution with a specific pH. The flask was shaken in a thermostat maintained at 37°C. After hydrolysis for a given time, the aqueous layer was made basic and extracted with chloroform. The degree of hydrolysis was followed by the determination of the amount of drug in the chloroform, using calibration curves obtained independently against an internal standard, with a Shimadzu LC 5A HPLC (Column Zorbax sil 4.6 mm × 25 cm P.N.). The calibrations were as follows:

$y = 0.1859x + 0.0113$ for benzocaine (internal standard: thianthrene)

$y = 0.000952x - 0.01779$ for procaine (internal standard: thianthrene)

$y = 0.0102x - 0.0025$ for amantadine (internal standard: p-aminoethylbenzoate)

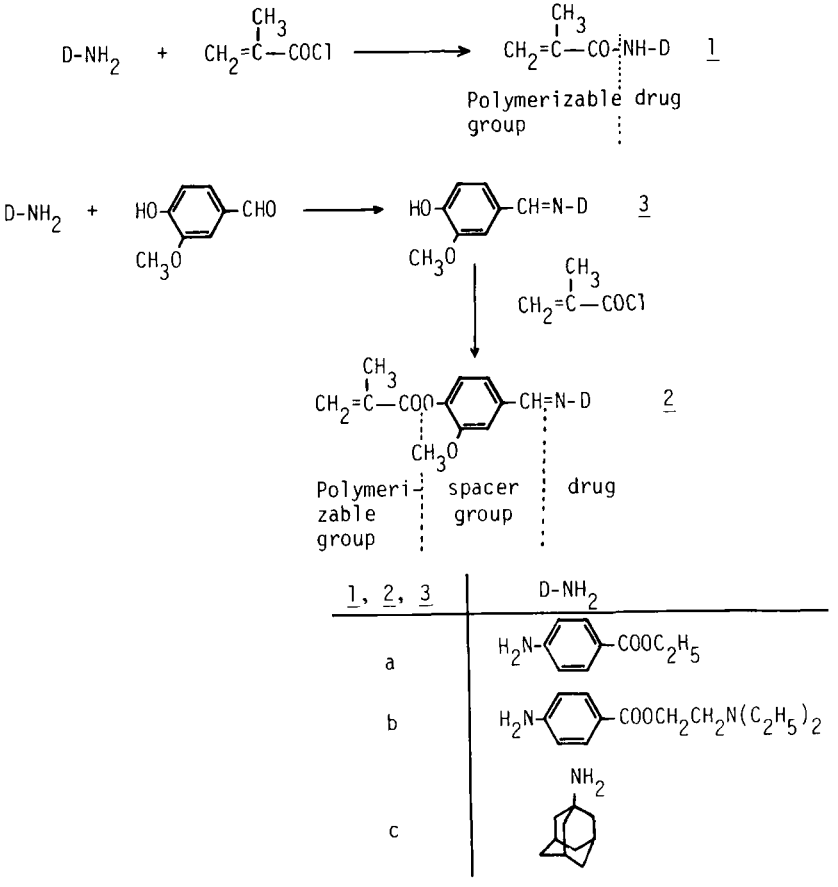
where x and y are the molar ratio in the feed (drug/standard) and the ratio of the area obtained from HPLC, respectively.

RESULTS AND DISCUSSION

Preparation and Hydrolysis of Monomeric Derivatives

Polymerizable derivatives of the drugs, 1, were prepared by direct acylation of the amino groups of the drugs with methacrylyl chloride. Unsaturated derivatives containing the drug covalently fixed through vanillin as a spacer group, 2, were also synthesized in order to study the effect on the rate of release of the drug (Scheme 1).

In order to obtain basic information for the macromolecular prodrug, hydrolysis of monomeric derivatives 1 and 2 was first carried



SCHEME 1.

out heterogeneously in the pH range 1-7.5 at 37°C. These compounds are expected to be the active ingredient releasing the drug and, therefore, solutions of pH 1 and about 7 were employed to simulate the pH of gastric juice and saliva, respectively. The hydrolysis of polymerizable anesthetic monomers was first carried out at 37°C, varying the pH. Both derivatives with spacer groups (2a and 2b) hydrolyzed to give the anesthetic in large yield at pH 1, as can be seen in Figs. 1 and 2. On the other hand, the rate of hydrolysis of the directly fixed drugs (1a and 1b) was low and hardly affected by the pH of the reaction media. Accordingly, these monomeric drugs with spacer groups will be appreciably hydrolyzed in gastric juice, but will not be hydrolyzed by saliva. The rate of drug release from each monomer and reaction time are shown in Fig. 3. The rate of hydrolysis of monomeric derivatives with spacer groups 2 was found to be very fast, while that of hydrolysis of derivatives without spacer group 1 was found to be slow. Consequently, the susceptibility of polymerizable derivatives to hydrolysis is greater when spacer groups are present. The rate of drug release of 1 is too slow for practical purposes.

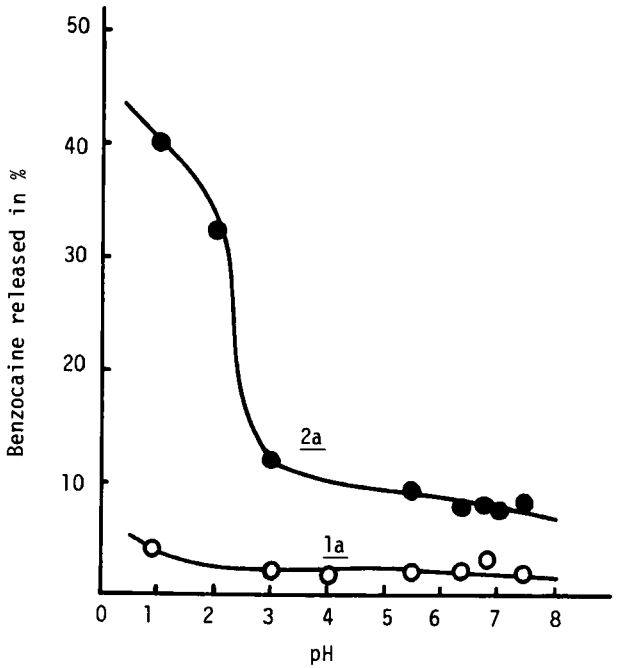


FIG. 1. Effect of pH on the hydrolysis of monomeric benzocaine derivatives without spacer 1a (○) and with spacer 2a (●) at 37°C for 6 h. Sample: 50 mg.

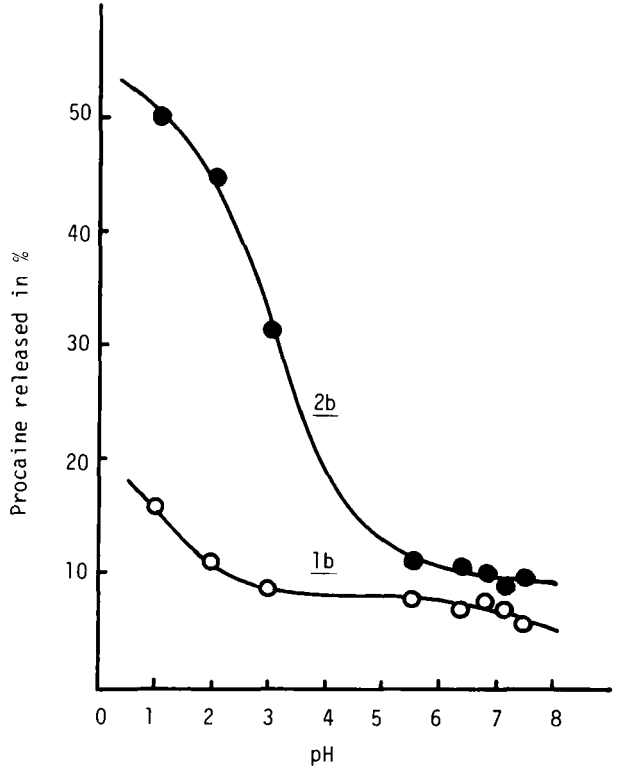


FIG. 2. Effect of pH on the hydrolysis of monomeric procaine derivatives without spacer 1b (○) and with spacer 2b (●) at 37°C for 6 h. Sample: 50 mg.

Preparation and Hydrolysis of Polymeric Derivatives

The monomeric derivatives were free-radical copolymerized with styrene (ST) and methyl methacrylate (MMA) to obtain the polymeric drugs. All of these macromolecular prodrugs were soluble in polar aprotic solvents, such as dimethylformamide, dimethylsulfoxide, and hexamethylphosphoramide, but insoluble in benzene, ethanol, and diethyl ether. Characterization data are shown in Table 1.

The polymeric derivatives were also hydrolyzed heterogeneously at 37°C for 24 and 48 h in order to study their potential use as the macromolecular prodrugs for the controlled slow release of active ingredients (Table 1). It was found that the copolymers with MMA

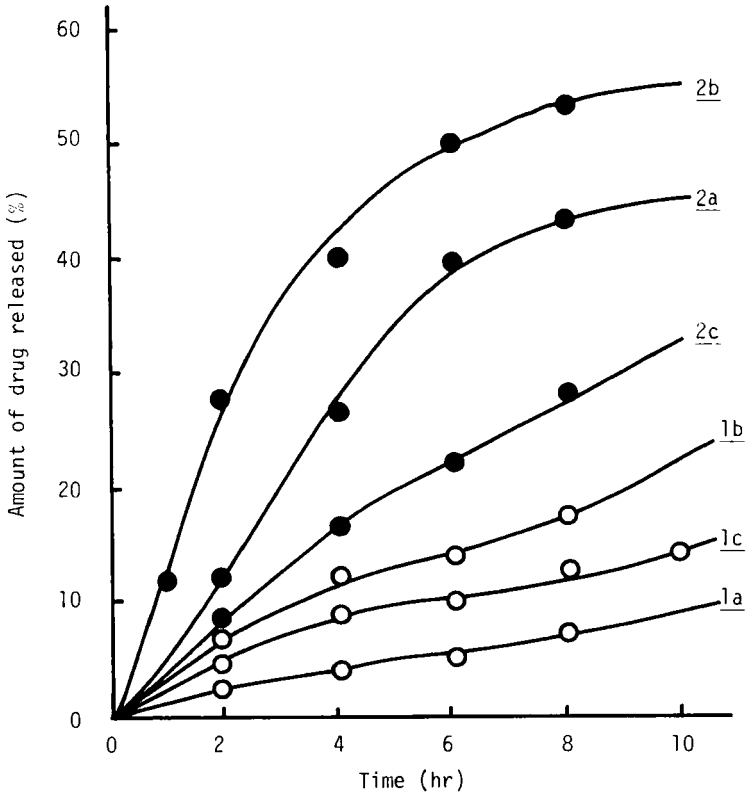


FIG. 3. Hydrolysis of monomeric drug derivatives without spacer 1 (○) and with spacer 2 (●) at 37°C, pH 1. Sample: 50 mg.

tend to be hydrolyzed more easily than those with ST. This might be because poly(methyl methacrylate) is more permeable to water than is poly(styrene) [21]. It was also found that the hydrolysis of copolymer with 2 occurred more easily than that of copolymer with 1. As for the monomers, the spacer group works effectively in all of the copolymers. These macromolecular prodrugs are then hydrolyzed acid-catalytically by gastric juice to remove local anesthetic or amantadine, nontoxic vanillin, and polymeric carrier residue.

The conclusions to be drawn from results are as follows: 1) vanillin as a spacer group plays an important role in hydrolysis, 2) these prodrugs can be hydrolyzed by gastric juice to give the free drug, 3) they are expected to increase the duration of drug action by controlled slow release of drug even though the prodrugs were not examined in vivo.

TABLE 1. Results of the Copolymerization of Monomeric Derivatives with Comonomer and Hydrolysis of Polymeric Derivatives

Monomeric derivatives, mmol	Comonomer, mmol	Polymerization time, h	Yield, %	$[\eta]$, dL/g	N content of copolymer, %	Mole fraction of drug unit in copolymer	Drug released,[a] %	
							24 h	48 h
1a 4.29	MMA 28.2	3.5	19.2	0.39	1.79	0.15	3.20	3.30
1a 4.29	ST 26.0	5.0	8.8	0.20	1.64	0.14	2.23	5.00
1b 3.29	MMA 28.2	3.5	14.5	0.13	2.56	0.11	12.7	16.0
1b 3.29	ST 26.0	6.0	27.8	0.15	2.23	0.10	11.9	15.2
1c 4.56	MMA 28.2	6.0	32.1	0.61	1.82	0.15	13.0	-
1c 4.56	ST 26.0	6.0	28.2	0.24	1.81	0.16	6.4	-
2a 2.72	MMA 28.2	3.5	19.1	0.27	1.79	0.19	16.8	24.3
2a 2.72	ST 26.0	5.0	16.4	0.33	1.72	0.19	14.4	22.1
2b 2.28	MMA 28.2	3.5	23.0	0.23	2.11	0.10	31.6	49.7
2b 2.28	ST 26.0	6.0	11.0	0.30	2.37	0.12	11.9	15.2
2c 2.83	MMA 28.2	6.0	33.2	0.55	1.90	0.08	27.7	-
2c 2.83	ST 26.0	6.0	15.3	0.13	2.90	0.15	18.3	-

[a]Hydrolysis of copolymers was carried out in aqueous solution of pH 1 at 37°C. Sample sizes: 500 mg.

REFERENCES

[1] L. G. Donaruma and O. Vogl, Polymeric Drugs, Academic, New York, 1978.
[2] H. Ringsdorf, J. Polym. Sci., Polym. Symp. Ed., 51, 135 (1975).
[3] J. A. Campbell, J. Pharm. Sci., 52, 76 (1963).
[4] B. Z. Weiner, M. Tahan, and A. Zilkha, J. Med. Chem., 15, 410 (1972).
[5] F. Lapicque and E. Dellacheaie, Makromol. Chem., 184, 277 (1983).
[6] A. A. Harris, A. K. Redersen, P. Stenberg, U. Ulmusten, and L. Wingerup, J. Pharm. Sci., 69, 1271 (1980).
[7] M. Asano, M. Yoshida, and I. Kaetsu, Kobunshi Ronbunshu, 39, 327 (1982).
[8] M. Asano, M. Yoshida, I. Kaetsu, K. Nakai, H. Yamanaka, H. Yuasa, and K. Shida, Ibid., 40, 525 (1983).
[9] J. Bartulin, M. Przybylsky, H. Ringsdorf, and H. Ritter, Makromol. Chem., 175, 1007 (1974).
[10] H. Ritter, Makromol. Chem., Rapid Commun., 3, 431 (1982).
[11] H. Ringsdorf, H. Ritter, and H. Rolly, Makromol. Chem., 177, 741 (1976).
[12] K. Kondo, A. Takimoto, and K. Takemoto, Makromol. Chem., Rapid Commun., 4, 341 (1983).
[13] V. Hoffmann, H. Ringsdorf, A. Seganova, and W.-H. Wagner, Makromol. Chem., 180, 837 (1979).
[14] A. Lääne, M. Haga, and A. Aaviksaar, Ibid., 184, 1339 (1983).
[15] J.-C. Soutif, F. M.-Moussounda, and J.-C. Brosse, Makromol. Chem., Rapid Commun., 4, 61 (1983).
[16] M. D. Purgett, W. Deits, and O. Vogl, J. Polym. Sci., Polym. Chem. Ed., 20, 2477 (1982).
[17] L. G. Donaruma and J. Razzano, J. Polym. Sci., 14, 244 (1971).
[18] B.-Z. Weiner and A. Zilka, J. Med. Chem., 16, 573 (1973).
[19] H. R. Allcock, P. E. Austin, and T. X. Neeman, Macromolecules, 15, 689 (1982).
[20] G. H. Stempel Jr., R. P. Cross, and R. P. Mariella, J. Am. Chem. Soc., 72, 2299 (1950).
[21] D. W. Morgan, Ind. Eng. Chem., 45, 2296 (1953).

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