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Synthesis and Secondary-Ion Mass Spectrometry of Linear Single Oligomers of Nylon-6

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ABSTRACT: Linear single oligomers of nylon-6, up to 12 repeat units, have been prepared by stepwise synthesis using protection, deprotection, and coupling reactions. The dimer was synthesized starting with 6-aminohexanoic acid; the tetramer, hexamer, octamer, and dodecamer were synthesized by coupling oligomers of lower molecular weight. The synthesized oligomers were characterized by ^{1}H NMR and TOF-SIMS to confirm their structures and molecular weights. In addition to silver cationized oligomer peaks, which are usually observed in TOF-SIMS spectra, oligomer peaks cationized by sodium and hydrogen were observed. No fragmentation other than loss of H_2 was observed even for the highest oligomer prepared in this study.

Introduction

Mass spectrometry is a powerful method for the structural characterization of organic molecules due to its high sensitivity, broad dynamic range, specificity, and selectivity and has been used extensively to study polymers since the 1970s. Mass spectrometric techniques can provide information about oligomer distributions, average molecular weights, fingerprint patterns for polymer identification, monomeric unit sequences, branching, cross-linking or other side-chain substitution, copolymer structures, and additives or impurities.

The development of time-of-flight secondary-ion mass spectrometry (TOF-SIMS) has made it possible to investigate polymer structure in the high mass range. TOF-SIMS has been used to determine oligomer distributions and to identify end groups and the mass of repeat units. Fragmentation mechanisms of various polymers have been studied by TOF-SIMS. Effects of molecular weight, terminal group, functional group, and tacticity on polymer fragmentation have been observed.[1] However, understanding polymer fragmentation in TOF-SIMS is frequently limited by the inability to distinguish between primary and secondary fragmentation processes. A large original oligomer can fragment to yield a smaller oligomer during the primary fragmentation process which subsequently can fragment further to yield other smaller oligomer ions during secondary fragmentation. Thus, many times it is impossible to determine whether the ions observed in a TOF-SIMS spectrum are the products of primary or secondary fragmentation. This will always be a problem if fragmentation studies are performed on polymers having typical oligomer distributions; i.e., the original polymer itself will have oligomer molecules with a range of molecular weights starting from low to high. Even for a small polymer ($M_n = 5000$) having a narrow MW distribution ($M_w/M_n = 1.05$) the mass range of oligomers is typically from 3500 to 6500 Da. This means that there are approximately 30 different molecules containing from 35−65 repeat units, making it difficult to interpret a given fragmentation route with certainty. In addition, impurities present in polymer samples cause problems in assessing the role of cyclic formation in fragmentation, and the presence of end groups often complicates interpretation. These problems can be overcome by studying simpler “single oligomer” systems. A single oligomer is a model polymer having a uniquely defined number of repeat units (i.e., molecular weight). Time-of-flight mass spectrometry of these single oligomers will provide the information uniquely about fragmentation patterns.

The accuracy of oligomer distributions measured by TOF-SIMS is directly related to the secondary ion yields of oligomers with different molecular weights. The synthesis of single oligomers makes it possible to study the variation of secondary ion yields with oligomer size, potentially for a wide variety of polymers.

Very little work has been reported on the mass spectrometry of nylons. A recent publication has studied nylon-6 terminated by different end groups using MALDI mass spectrometry. It was possible to distinguish end groups in four samples and to detect simultaneously cyclic and linear oligomers.[1j] The present paper reports the synthesis of linear single oligomers of nylon-6 and their time-of-flight secondary-ion mass spectra. This is the first systematic study of the synthesis of single molecular weight oligomers of 6-aminohexanoic acid and their SIMS spectra. After this work was completed, we became aware that single nylon oligomers had been synthesized by another route.[1k]

Results and Discussion

The overall strategy for the synthesis involves selective protection of amine[2] and carboxyl[3] functional groups, coupling,[4] selective deprotection,[4] and then once again coupling to give larger oligomers. Synthesis of the dimer is shown in Scheme 1. Compound **1** was prepared by protecting the amine functionality of 6-aminohexanoic acid with the *tert*-butyloxycarbonyl (BOC) group. Compound **3** was prepared by protecting the carboxylic acid functional group of **1** with a carboxamidomethyl (CAM) ester and its salt. Compound **4** was prepared by dissolving **3** in trifluoroacetic acid and then precipitating with excess ether.[5] The amine functional group of **4** was coupled with the carboxyl functional group of **1** using benzotriazolyloxytris(dimethylamino)phosphonium hex-

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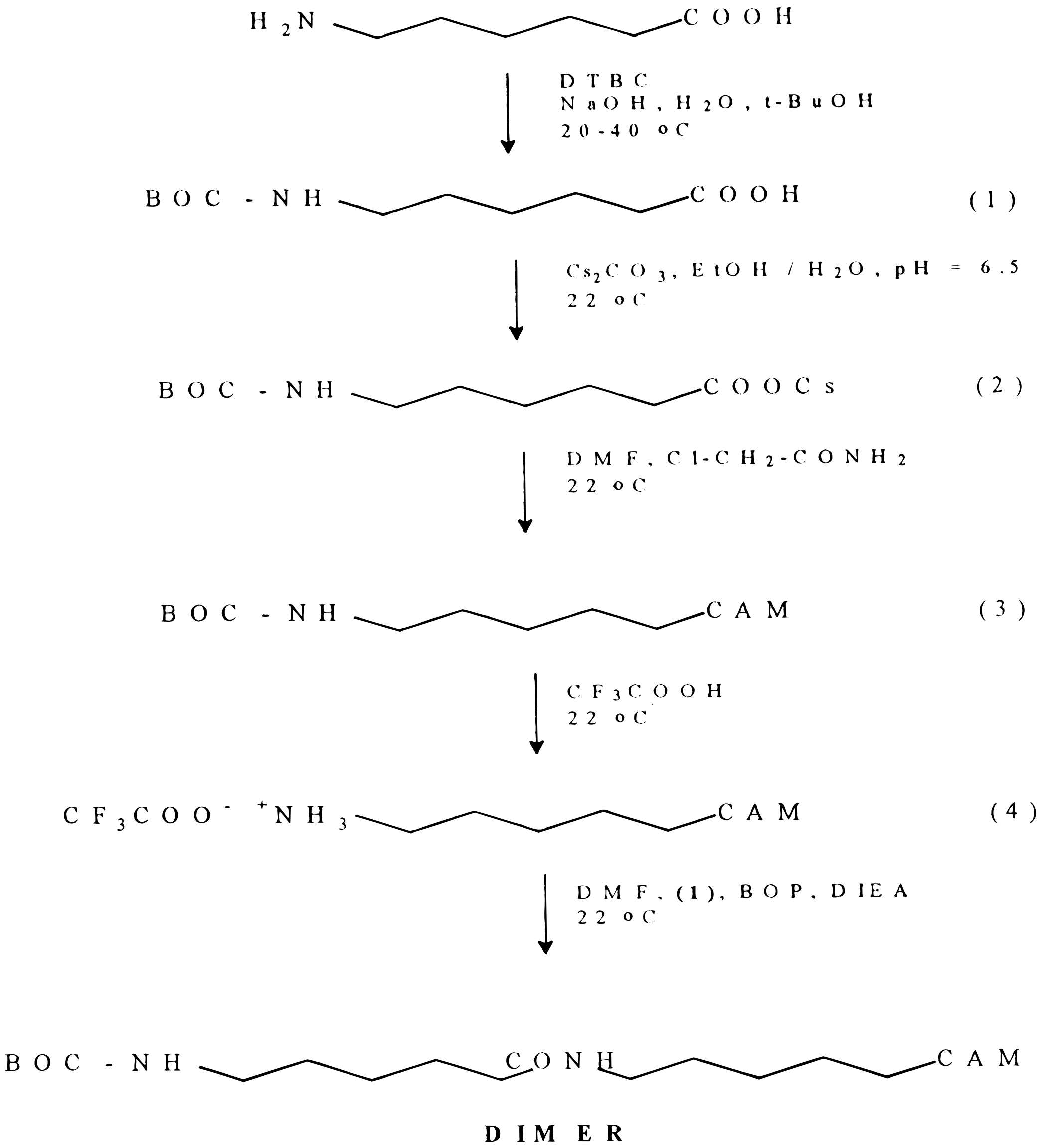
Scheme 1. Synthesis of Dimer



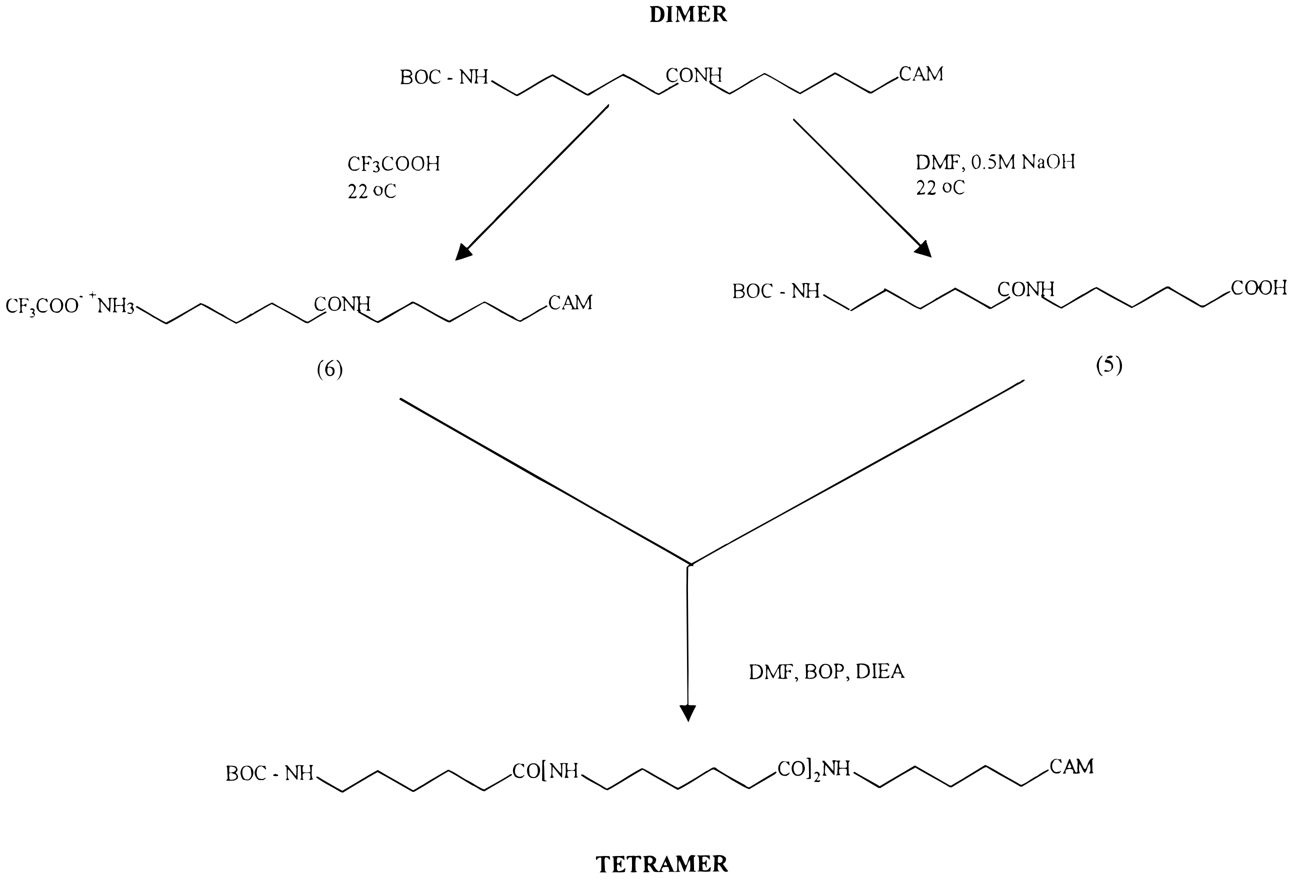
fluorophosphate (BOP) to produce the dimer with a BOC protected amine function at one end and CAM ester protected carboxyl functional group at the other.

Selective deprotection of the CAM ester end of the dimer gave compound **5** as shown in Scheme 2. In a separate step, a salt of the dimer **6** was prepared by dissolving the dimer in trifluoroacetic acid and precipitating with excess ether.[6] Similar to the dimer synthesis, the tetramer was prepared by coupling **5** with **6.** Similar to the dimer, the end product of the tetramer had both amine and carboxyl functional groups protected with BOC and CAM ester groups, respectively. The same process was repeated with the tetramer to produce the octamer. Coupling the salt of the tetramer **7** with the dimer **5** produced the hexamer. In the same manner, coupling the salt of the octamer **9** and the tetramer **7** produced the dodecamer. All oligomers synthesized possess amine and carboxylic functional groups protected with BOC and CAM ester groups, respectively.

The reduced solubility of higher molecular weight oligomers poses a problem in the purification of these compounds, actually limiting synthesis of higher oligomers. Analytically pure samples were obtained through dissolving in a solvent and precipitating with ether and then washing with selective solvents to remove impurities. The different oligomers are soluble in different solvents which is helpful in purification. Yields for each of the coupling steps are moderate to good.[7]

All spectrometric studies were consistent with the proposed molecular structures.[8] The ^{1}H NMR chemical shifts were the same for all oligomers irrespective of the number of repeat units. Unlike their higher analogue high molecular weight polymers, the peaks of the oligomers are very sharp. The ^{1}H NMR spectra of the dimer, tetramer, hexamer, octamer, and dodecamer show a triplet at 6.75 ppm corresponding to a single proton attached to the amine terminal (BOC−NH−) nitrogen and another triplet at 7.75 ppm which corresponds to a single proton attached nitrogen at the coupling point (CO−NH−). The peak at 7.75 ppm is a sharp triplet for lower oligomers, but it broadened (difficult to differentiate as a triplet) as the oligomer number increased. The oligomer number can be calculated using the 7.75 ppm to 6.75 ppm peak ratios. The ratio is slightly higher than expected, even though the oligomers were found to be pure by TOF-SIMS.[9]

Scheme 2. Synthesis of Tetramer[a]



[a] Abbreviations: BOC = *tert*-butyloxycarbonyl (t-but-OCO); CAM = carboxamidomethyl ester ($-COOCH_2CONH_2$); BOP = benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate; DTBC = di-*tert*-butyl dicarbonate; DIEA = ethyl-*N*,*N*-diissopropylamine.

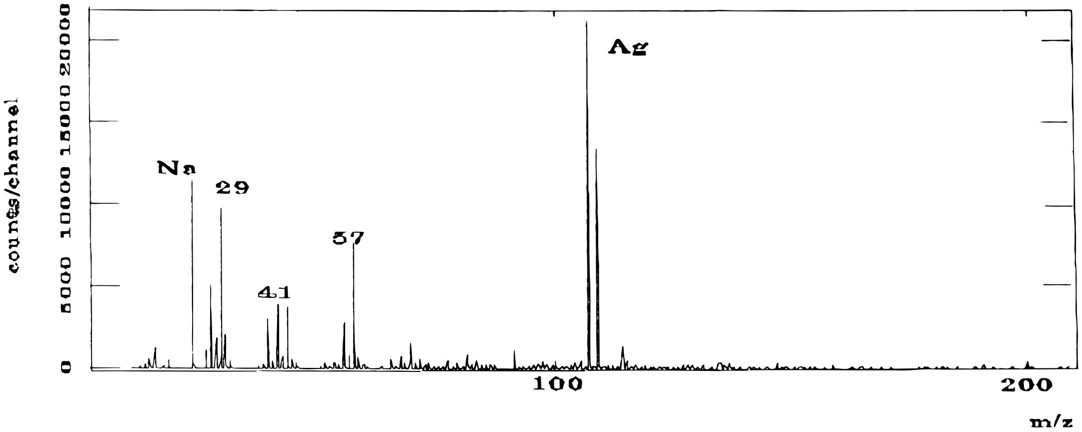


Figure 1. Low mass range TOF-SIMS spectrum of the tetramer.

Samples for TOF-SIMS were dissolved in trifluoroacetic acid (TFA) at a concentration of 1 mg/mL, and 1 μL of solution was deposited on a silver substrate for SIMS analysis. (See Experimental Section for details.) Because of the rough nature of the etched Ag substrate, polymers are deposited at less that monolayer coverage.[10] The low mass range spectrum (10−300 Da) of the tetramer is shown in Figure 1. The spectra of all oligomers are quite similar; the major peaks are those of small fragments coming from the aliphatic chain. Table 1 presents a listing of the major peaks in the low mass range TOF-SIMS spectrum. Peaks for silver, sodium, and potassium were also observed in this mass range. It is interesting to note that the monomer ($M + H)^+$ peak at 132 Da is not observed, although the protonated repeat unit is seen at 114 Da as has been reported by others.[11]

Table 1. Identification of Small Oligomer Fragments in the Low Mass Range

metal ion	*m*/*z*	fragment ion	*m*/*z*
Na^+	23	$(CH_3)^+$	15
K^+	39	$(C_2H_3)^+$	27
Ag^+	107, 109	$(C_2H_5)^+$	29
		$(C_3H_5)^+$	41
		$(C_4H_9)^+$	57

Figure 2 shows the quasi-molecular ions of the oligomers observed by TOF-SIMS. When the oligomers are

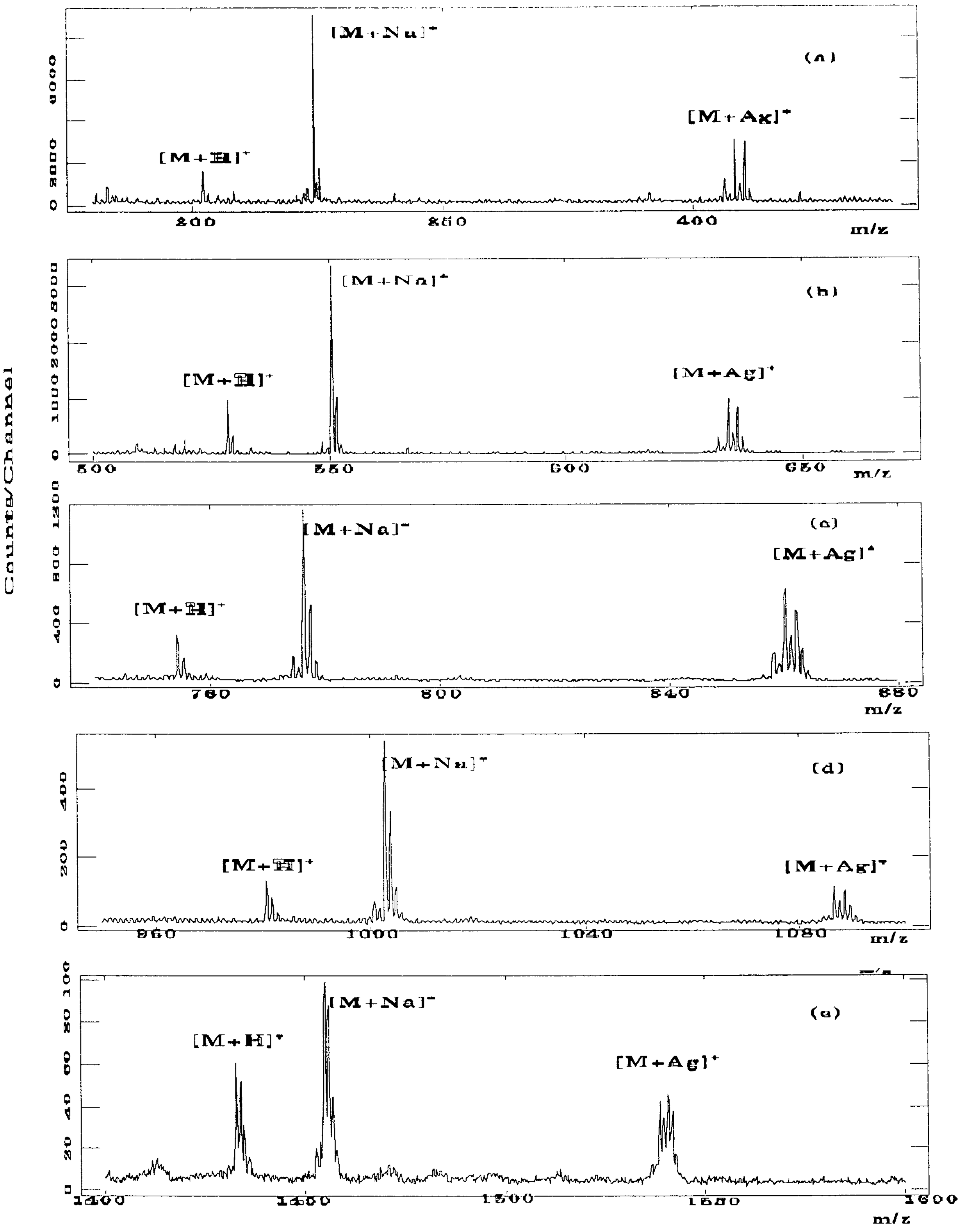


Figure 2. Quasi-molecular ion peaks of oligomers: (a) dimer, (b) tetramer, (c) hexamer, (d) octamer, and (e) dodecamer.

dissolved in trifluoroacetic acid, deprotection occurs at the amine terminal to give pure oligomers with a reactive amine functional group at one end and a CAM ester protected carboxyl functional group at the other end. As shown in Figure 2, oligomers were cationized by Ag^+, Na^+, and H^+. No strong metal cationized fragment ion peaks were observed in the TOF-SIMS spectra. Clearly, the highest oligomer that we have synthesized is small enough that significant fragmentation does not occur. The primary action area for sputtering polymers is an area roughly 50 Å in diameter.[12] Although the length of stretched-out octamer polyamide is longer than 50 Å, it probably has a coiled structure on the substrate rather than a linear structure. As a result, the oligomer can be desorbed intact. Figure 2 also shows that the absolute ion yield decreases for nylon oligomers with increasing mass. This same effect has been observed for polystyrene and other polymers.[13]

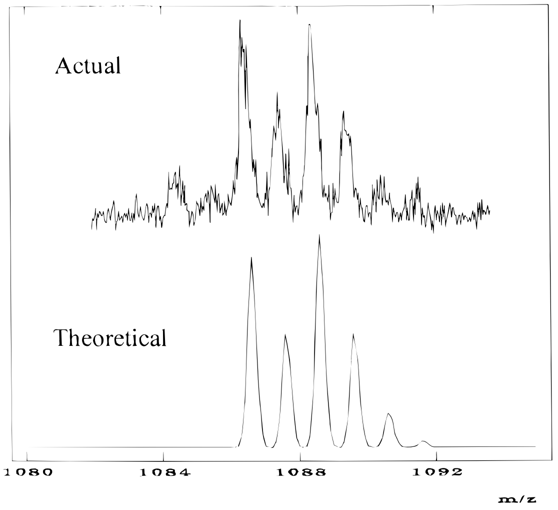


Figure 3. Comparison of theoretical and actual isotopic distribution of $[M + Ag]^+$ of the octamer.

This effect is due to a combination of increasing size of the polymer molecules and the greater binding energy of large oliogmers to the substrate (Ag) surface.

Figure 3 shows a comparison between the theoretical and actual isotopic distributions of $[M + Ag]^+$ for the octamer. The agreement is quite good. There is a small peak at $[M-2 + Ag]^+$ in addition to the $[M + Ag]^+$. Peaks of $[M-2 + Ag]^+$ are also observed in the spectra of the dimer and the tetramer, indicating that the oligomer forms a fragment by loss of hydrogen. It is possible for the oligoamide to lose hydrogen to form an unsaturated fragment because of the $(-CH_2CH_2CH_2CH_2CH_2-)$ unit in the oligomer structure. Unsaturated fragments cationized by Na are also observed in all mass spectra. Although the unsaturated fragment apparently is cationized by both silver and sodium, no peaks corresponding to $[M-2 + H]^+$ were observed in any spectra.

In summary, a general strategy for the stepwise synthesis of linear single oligomers of nylon-6 has been demonstrated; the oligomers were characterized by ^1H NMR and TOF-SIMS. Higher molecular weight single oligomers, synthesis of which is currently in progress, should be useful as model compounds to study TOF-SIMS fragmentation patterns. These compounds also should be useful as standards for calibrating GPC in the low mass range. The systematic study of these model compounds by mass spectrometry is also in progress, to provide information about analysis of different molar proportions (absolute oligomer distribution) of the oligomers in a polymer mixture. The variation of cationization efficiency with molecular size will also be studied.

Experimental Section

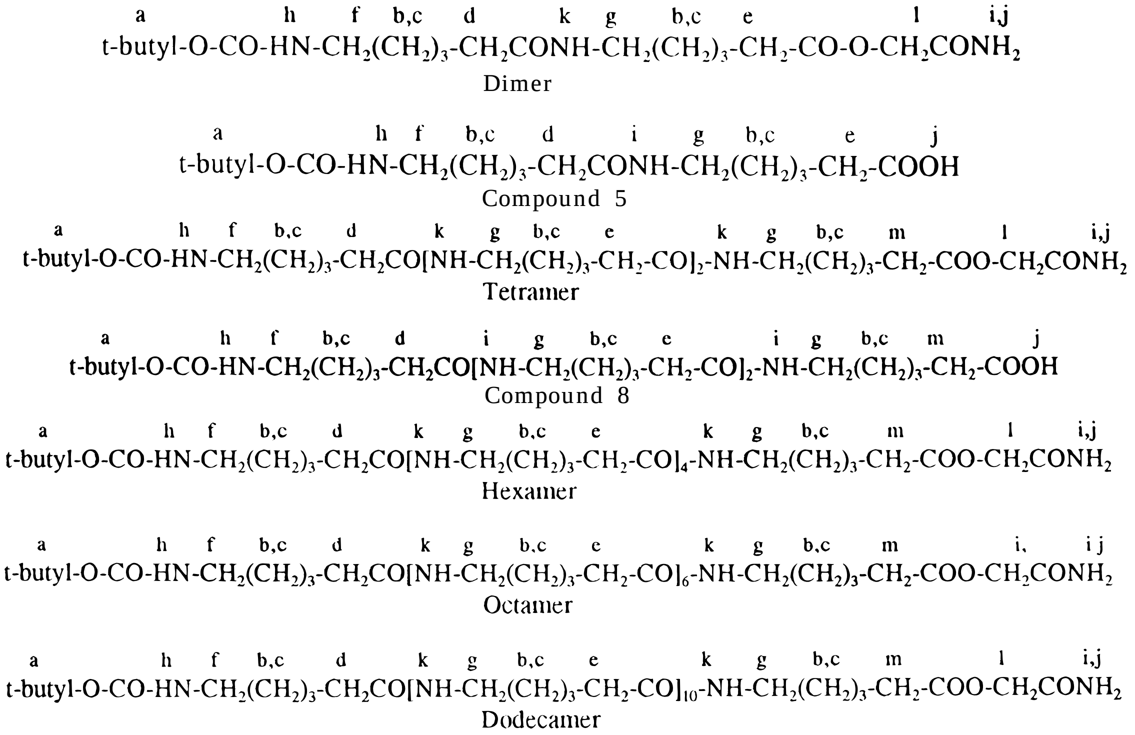
Synthesis. Except for common solvents and reagents, all special reagents were purchased from Aldrich and used without further purification. Abbreviations used are those recommended by the IUPAC. Other abbreviations used are the following: BOC, *tert*-butyloxycarbonyl; CAM, carboxamidomethyl ester; BOP, benzotriazolyloxytris(dimethylamino)-phosphonium hexafluorophosphate; TFA, trifluoroacetic acid; EtOAc, ethyl acetate; EtOH, ethanol; DMF, dimethylformamide; DMSO-D6, dimethyl sulfoxide-deuterated; and DIEA, ethyl-*N*,*N*-diisopropylamine. Proton NMR spectra were taken on a Brucker 300 MHz instrument with Me_4Si as the internal standard. Thin-layer chromatograms were run on commercial silica gel plates in the solvent system AcOEt−hexane for compound **1**. TLC spots were detected by iodine vapor.

$BOC-NH-(CH_2)_5-COOH$ **(1)**. A 500 mL, three-necked, round-bottom flask, equipped with a Teflon magnetic stirrer, reflux condenser, thermometer, and a septum, is charged with a solution of 2.68 g (67.08 mmol) NaOH in 67 mL of water. Stirring is initiated, and 8 g (61 mmol) of 6-aminohexanoic acid is added at ambient temperature and then diluted with 45 mL of *tert*-butyl alcohol. At this stage the reaction mixture has a pH of 12−12.5. To the well-stirred, clear solution is added dropwise within 1 h 13.31 g (61 mmol) of di-*tert*-butyl dicarbonate (Note: di-*tert*-butyl dicarbonate melts at 22−24 °C; this compound is liquified by immersing the reagent bottle in a water bath with a maximum temperature of 35 °C.) After a short induction period the temperature rose to about 30−35 °C. The reaction is brought to completion by further stirring overnight at room temperature. At this time, the clear solution reached a pH of 7.5−8.5. The reaction mixture is extracted two times with 40 mL of pentane, and the organic phase is extracted three times with 20 mL of saturated sodium bicarbonate solution. The combined aqueous layers are acidified to pH 1−1.5 by careful addition of a solution of 13.6 g of potassium hydrogen sulfate in 91 mL of water at 0 °C. The acidification is accompanied by copious evolution of carbon dioxide. The reaction mixture is then extracted with four 40 mL portions of ethyl ether. The combined organic layers are washed two times with 40 mL of water, dried over anhydrous sodium sulfate, and filtered. The solvent is removed under reduced pressure using a rotary evaporator at a bath temperature not exceeding 30 °C and then under vacuum to remove *tert*-butyl alcohol completely. The yellowish oil that remains is treated with about 1 L of hexane while stirring for about 1 day and then refrigerated to get the yellowish crude product. This yellowish solid is purified by column chromatography using a hexanes−EtOAc (50:50) solvent mixture. Yield 12.15 g (86 mol %); ^1H NMR (DMSO-D6) 1.24 (p, 2H, $-CH_2-\boldsymbol{CH_2}-CH_2-$), 1.36 (s, 9H, tert-***butyl***-OCO−NH−), 1.47 (m, 4H, $-CH_2-\boldsymbol{CH_2}-CH_2-\boldsymbol{CH_2}-CH_2-$), 2.18 (t, 2H, $-CH_2-\boldsymbol{CH_2}-COOH$), 2.88 (q, 2H, $-NH-\boldsymbol{CH_2}-CH_2-$), 6.78 (t, 1H, $-CO-\boldsymbol{NH}-CH_2-$), and 12.0 (s, 1H, $-COO\boldsymbol{H}$).

$BOC-NH-(CH_2)_5-CAM$ **(3)**. To a cooled solution of compound **1** (5 g, 21.6 mmol) in a mixture of EtOH−water (100 mL) (7:3) was added a solution of cesium carbonate in water until pH = 6.5. The solution was then evaporated to dryness in vacuo. Water was almost completely eliminated by addition of EtOH and benzene and azeotropically distilled. The residue was then dried in vacuo for 2 days to remove the water. The residue was dissolved in DMF (150 mL) in the presence of α-chloroacetamide 3.031 g (32.42 mmol), and the mixture was stirred for 24 h. The solvent was removed in vacuo and the residue dissolved in EtOAc (200 mL), washed with cold aqueous sodium bicarbonate (1 × 50 mL), water (2 × 50 mL), 10% citric acid solution (1 × 50 mL), and water (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was triturated with an ether−hexane solution to give crystals, yield 5 g (80 mol %); ^1H NMR (DMSO-D6) 1.24 (p, 2H, $-CH_2-\boldsymbol{CH_2}-CH_2-$), 1.4 (s, 9H, *tert*-***butyl***-OCO−NH−), 1.55 (m, 4H, $-CH_2-\boldsymbol{CH_2}-CH_2-\boldsymbol{CH_2}-CH_2-$), 2.38 (t, 2H, $-CH_2-\boldsymbol{CH_2}-COOH$), 2.88 (q, 2H, $-NH-\boldsymbol{CH_2}-CH_2-$), 4.4 (s, 2H, $-O-\boldsymbol{CH_2}-CO-NH_2$), 6.78 (t, 1H, $-CO-\boldsymbol{NH}-CH_2-$), 7.22 (s, 1H, $CH_2-CO-\boldsymbol{NH_2}$), and 7.42 (s, 1H, $CH_2-CO-\boldsymbol{NH_2}$).

$BOC-NH-(CH_2)_5-CONH-(CH_2)_5-CAM$ **(Dimer).** A sample of compound **3** (1 g, 3.47 mmol) was treated with trifluoroacetic acid (7 mL) for 30−45 min. Addition of ether (100 mL) under stirring yielded the TFA salt of compound **4**. This salt, which is sticky, is washed several times with ether and dried in vacuo for about 2 days. This salt was dissolved in DMF (10 mL) containing $BOC-NH-(CH_2)_5-COOH$ (0.8 g, 3.47 mmol) and BOP (1.5 g, 3.4 mmol), followed, after cooling to 0 °C, by addition of DIEA (1.22 mL, 6.94 mmol). After stirring all night at room temperature in the dark, the solvent was removed in vacuo, the residue was dissolved in EtOAc, and the solution washed with 1 N citric acid, water, cold 1 N $NaHCO_3$(aq), and dried over anhydrous sodium sulfate. The solvent was evapo-

Chart 1



$\overset{a}{\text{t-butyl}}\text{-O-CO-}\overset{h}{\text{HN}}\text{-}\overset{f}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{d}{\text{CH}_2}\text{CO}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{e}{\text{CH}_2}\text{-CO-O-}\overset{l}{\text{CH}_2}\text{CO}\overset{i,j}{\text{NH}_2}$

Dimer

$\overset{a}{\text{t-butyl}}\text{-O-CO-}\overset{h}{\text{HN}}\text{-}\overset{f}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{d}{\text{CH}_2}\text{CO}\overset{i}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{e}{\text{CH}_2}\text{-}\overset{j}{\text{COOH}}$

Compound 5

$\overset{a}{\text{t-butyl}}\text{-O-CO-}\overset{h}{\text{HN}}\text{-}\overset{f}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{d}{\text{CH}_2}\text{CO[}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{e}{\text{CH}_2}\text{-CO]}_2\text{-}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{m}{\text{CH}_2}\text{-COO-}\overset{l}{\text{CH}_2}\text{CO}\overset{i,j}{\text{NH}_2}$

Tetramer

$\overset{a}{\text{t-butyl}}\text{-O-CO-}\overset{h}{\text{HN}}\text{-}\overset{f}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{d}{\text{CH}_2}\text{CO[}\overset{i}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{e}{\text{CH}_2}\text{-CO]}_2\text{-}\overset{i}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{m}{\text{CH}_2}\text{-}\overset{j}{\text{COOH}}$

Compound 8

$\overset{a}{\text{t-butyl}}\text{-O-CO-}\overset{h}{\text{HN}}\text{-}\overset{f}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{d}{\text{CH}_2}\text{CO[}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{e}{\text{CH}_2}\text{-CO]}_4\text{-}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{m}{\text{CH}_2}\text{-COO-}\overset{l}{\text{CH}_2}\text{CO}\overset{i,j}{\text{NH}_2}$

Hexamer

$\overset{a}{\text{t-butyl}}\text{-O-CO-}\overset{h}{\text{HN}}\text{-}\overset{f}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{d}{\text{CH}_2}\text{CO[}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{e}{\text{CH}_2}\text{-CO]}_6\text{-}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{m}{\text{CH}_2}\text{-COO-}\overset{i,}{\text{CH}_2}\text{CO}\overset{i\,j}{\text{NH}_2}$

Octamer

$\overset{a}{\text{t-butyl}}\text{-O-CO-}\overset{h}{\text{HN}}\text{-}\overset{f}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{d}{\text{CH}_2}\text{CO[}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{e}{\text{CH}_2}\text{-CO]}_{10}\text{-}\overset{k}{\text{NH}}\text{-}\overset{g}{\text{CH}_2}\overset{b,c}{(\text{CH}_2)_3}\text{-}\overset{m}{\text{CH}_2}\text{-COO-}\overset{l}{\text{CH}_2}\text{CO}\overset{i,j}{\text{NH}_2}$

Dodecamer

rated in vacuo and the residue triturated with ether and dried. This crude product was recrystallized in EtOAc−hexane (95:5) solution. Yield 584 mg (42 mol %). (For structures see Chart 1.)

^{1}H NMR (DMSO-D6). 1.15 ppm (m, 4H, corresponds to protons on the center carbon of "b" and "c" group of carbons), 1.36 ppm (s, 9H, corresponds to protons on *tert*-butyl-), 1.50 (m, 8H, corresponding to protons on the carbons "b" and "c"), 2.0 ppm (t, 2H, corresponds to protons on carbon "d"), 2.35 ppm (t, 2H, corresponds to protons on carbon "e"), 2.86 ppm (q, 2H, corresponds to protons on carbon "f"), 2.98 ppm (q, 2H, corresponds to protons on carbon "g"), 4.4 ppm (s, 2H, corresponds to protons on carbon "l"), 6.75 ppm (t, 1H, corresponds to proton on nitrogen "h"), 7.22 and 7.42 ppm (2s, 2H, corresponds to protons on nitrogen "i, j"), and 7.72 ppm (s, 1H, corresponds to proton on nitrogen "k").

BOC−NH−$(CH_2)_5$−CONH−$(CH_2)_5$−COOH **(5)**. A sample of **dimer** (1.5 g, 3.74 mmol) was dissolved in DMF (15 mL). A solution of 0.5 N NaOH (10.5 mL, 5.24 mmol) and a small amount of water were added to obtain a clear solution. After 30 min stirring, hydrolysis was over. The mixture was then neutralized with 0.5 N citric acid until a pH of 7 was obtained. This solution was concentrated in vacuo. The oily residue was dissolved in saturated $NaHCO_3$ (40 mL) and washed with EtOAc (2 × 25 mL). After cooling of the aqueous layer in ice, solid citric acid was added (pH 2.5), and the separated precipitate was extracted with EtOAc (3 × 30 mL). The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, dried, and concentrated in vacuo to yield 1.1 g (86 mol %) of compound **5**.

^{1}H NMR (DMSO-D6). 1.20 ppm (m, 4H, corresponds to protons on the center carbon of "b" and "c" group of carbons), 1.35 ppm (s, 9H, corresponds to protons on tert-***butyl***-), 1.45 (m, 8H, corresponds to protons on the carbons "b" and "c"), 2.0 ppm (t, 2H, corresponds to protons on carbon "d"), 2.17 ppm (t, 2H, corresponds to protons on carbon "e"), 2.85 ppm (q, 2H, corresponds to protons on carbon "f"), 2.98 ppm (q, 2H, corresponds to protons on carbon "g"), 6.75 ppm (t, 1H, corresponds to proton on nitrogen "h"), 7.74 ppm (s, 1H, corresponds to proton on nitrogen "i"), and 12.0 ppm (broad, 1H, corresponds carboxylic acid proton "j").

BOC−NH−$(CH_2)_5$−CO[NH−$(CH_2)_5$−CO$]_2$NH−$(CH_2)_5$−CAM **(Tetramer).** A sample of compound **dimer** (1.22 g, 3.05 mmol) was treated with trifluoroacetic acid (6 mL) for 30−45 min. Addition of ether (100 mL) under stirring yielded the TFA salt of the dimer **(6)**. This sticky salt was washed several times with ether and dried in high vacuo for about 24 h. This salt was dissolved in DMF (10 mL) containing **5** (1.05 g, 3.05 mmol) and BOP (1.28 g, 2.9 mmol), followed, after cooling to 0 °C, by addition of DIEA (1.06 mL, 6.1 mmol). After stirring overnight at room temperature in the dark, some insoluble solid separated from the reaction mixture. The solvent was removed completely in vacuo. The residue was not soluble in EtOAc. The solid residue was washed with 1 N citric acid (the solid was stirred vigorously with citric acid in a round-bottomed flask, filtered), water (same treatment as done with citric acid), and cold 1 N $NaHCO_3$(aq) (same treatment as done with citric acid) and was washed with ether in excess. The resulting solid was dissolved in diethyl phosphate, filtered, and poured into ether while stirring to obtain a white precipitate. This white precipitate was washed with excess ether and dried. Yield 1 g (53 mol %).

^{1}H NMR (DMSO-D6). 1.18 ppm (m, 8H, corresponds to protons on center carbon of "b" and "c" group of carbons, 1.38 ppm (s, 9H, corresponds to *tert*-***butyl***), 1.46 (m, 16H, corresponds to protons on carbons "b" and "c"), 2.0 ppm (t, 6H, corresponds to protons on carbons "d" and "e"), 2.36 ppm (t, 2H, corresponds to protons on carbon "m"), 2.86 ppm (q, 2H, corresponds to protons on carbon "f"), 3.0 ppm (q, 6H, corresponds to protons on carbons "g"), 4.4 ppm (s, 2H, corresponds to protons on carbon "l"), 6.76 ppm (t, 1H, corresponds to proton on nitrogen "h"), 7.22 ppm, 7.42 ppm (2s, 2H, corresponds to protons nitrogen "i, j"), and 7.72 ppm (t, 3H, proton attached to nitrogen "k").

BOC−NH−$(CH_2)_5$−CO[NH−$(CH_2)_5$−CO$]_2$NH−$(CH_2)_5$−COOH **(8)**. A sample of **tetramer** (0.97 g, 1.54 mmol) was dissolved in DMF (12 mL). A solution of 0.5 N NaOH (4.5 mL, 2.16 mmol) and a small amount of water were added to obtain a clear solution. After 30 min of stirring, hydrolysis was over. The mixture was then neutralized with 0.5 N citric acid until a pH of 7 was obtained. This solution was concentrated in vacuo. The oily residue was dissolved in saturated $NaHCO_3$ (30 mL). After cooling of this solution in ice, solid citric acid was added (pH 2.5), and the separated precipitate filtered and washed several times with water and then with ether. This precipitate is dried overnight under vacuo and then redissolved in slightly warm methanol and precipitated by pouring into ether, filtered, washed with excess ether, and dried under vacuum to give an yield of 0.7 g (80 mol %) of compound **8**.

^{1}H NMR (DMSO-D6). 1.18 ppm (m, 8H, corresponds to protons on center carbon of "b" and "c" group of carbons), 1.35 ppm (s, 9H, corresponds to *tert-**butyl***), 1.42 (m, 16H, corresponds to protons on carbons "b" and "c"), 2.0 ppm (t, 6H, corresponds to protons on carbons "d" and "e"), 2.15 ppm (t, 2H, corresponds to protons on carbon "m"), 2.85 ppm (q, 2H, corresponds to protons on carbon "f"), 3.0 ppm (q, 6H, corresponds to protons on carbons "g"), 6.75 ppm (t, 1H, corresponds to proton on nitrogen "h"), 7.75 ppm (t, 3H, proton attached to nitrogen "i"), and 11.8 ppm (broad, 1H, corresponds to proton on carboxylic acid "j").

$BOC-NH-(CH_2)_5-CO[NH-(CH_2)_5-CO]_4NH-(CH_2)_5-CAM$ **(Hexamer).** A sample of **tetramer** (0.4 g, 0.64 mmol) was treated with trifluoroacetic acid (2.5 mL) for 60 min. Addition of ether (100 mL) under stirring yielded the TFA salt of the tetramer **(7).** This sticky salt was washed several times with ether and dried in high vacuo overnight to remove the traces of trifluoroacetic acid. This salt was dissolved in DMF (10 mL) containing compound **5** (0.26 g, 0.64 mmol) and BOP (0.27 g, 0.61 mmol), followed, after cooling to 0 °C by addition of DIEA (0.22 mL, 1.28 mmol). After stirring for 24 h at room temperature the reaction mixture is heated to 50 °C and stirred for another 48 h in the dark. Solvent was removed completely from the reaction mixture by applying vacuum overnight. The solid residue was washed with 1 N citric acid (the solid was stirred vigorously with citric acid in a round-bottomed flask and then filtered) for about 2 h, water (same treatment as done with citric acid), and cold 1 N $NaHCO_3$(aq) (same treatment as done with citric acid) and washed with acetone, methanol, and excess ether. Yield 0.44 g (80 mol %).

^{1}H NMR (DMSO-D6). 1.18 ppm (m, 12H, corresponds to protons on the center carbons of "b" and "c" group of protons, 1.38 ppm (s, 9H, corresponds to protons on *tert-**butyl***), 1.46 ppm (m, 24H, corresponds to protons on carbons "b" and "c"), 2.0 ppm (t, 10H, corresponds to protons on carbons "d" and "e"), 2.36 ppm (t, 2H, corresponds to protons on carbon "m"), 2.86 ppm (q, 2H, corresponds to protons on carbon "f"), 3.0 ppm (q, 10H, corresponds to protons on carbons "g"), 4.4 ppm (s, 2H, corresponds to protons on carbon "l"), 6.76 ppm (t, 1H, corresponds to proton on nitrogen "h"), 7.22 ppm, 7.42 ppm (2s, 2H, correspond to protons on nitrogen "i" and "j"), and 7.72 ppm (t, 5H, corresponds to proton on nitrogen "k").

$BOC-NH-(CH_2)_5-CO[NH-(CH_2)_5-CO]_6NH-(CH_2)_5-CAM$ **(Octamer).** A sample of **tetramer** (0.77 g, 1.23 mmol) was treated with trifluoroacetic acid (3 mL) for 90 min. Addition of ether (100 mL) under stirring yielded the TFA salt of the tetramer **(7).** This sticky salt was washed several times with ether and dried in high vacuo for about 2 days to remove the traces of trifluoroacetic acid. This salt was dissolved in DMF (10 mL) containing compound **8** (0.7 g, 1.23 mmol) and BOP (0.516 g, 1.167 mmol), followed, after cooling to 0 °C by addition of DIEA (0.43 mL, 2.46 mmol). After stirring for 48 h at 50 °C in the dark, solvent was removed completely in vacuo. The residue was not soluble in EtOAc. The solid residue was washed with 1 N citric acid (the solid was stirred vigorously with citric acid in a round-bottomed flask and then filtered), water (same treatment as done with citric acid), and cold 1 N $NaHCO_3$(aq) (same treatment as done with citric acid) and washed with ether in excess. The resulting solid was dissolved in hot methanol, filtered, and poured into ether while stirring to get a slightly yellow precipitate. This precipitate was washed with excess of ether and dried in vacuo. Yield 1 g (75 mol %).

^{1}H NMR (DMSO-D6). 1.18 ppm (m, 16H, corresponds to protons on the center carbons of "b" and "c" group of protons, 1.38 ppm (s, 9H, corresponds to protons on *tert-**butyl***), 1.46 ppm (m, 32H, corresponds to protons on carbons "b" and "c"), 2.0 ppm (t, 14H, corresponds to protons on carbons "d" and "e"), 2.36 ppm (t, 2H, corresponds to protons on carbon "m"), 2.86 ppm (q, 2H, corresponds to protons on carbon 'f'), 3.0 ppm (q, 14H, corresponds to protons on carbons "g"), 4.4 ppm (s, 2H, corresponds to protons on carbon "l"), 6.76 ppm (t, 1H, corresponds to proton on nitrogen "h"), 7.22 ppm, 7.42 ppm (2s, 2H, correspond to protons on nitrogen "i" and "j"), and 7.72 ppm (t, 7H, corresponds to proton on nitrogen "k").

$BOC-NH-(CH_2)_5-CO[NH-(CH_2)_5-CO]_{10}NH-(CH_2)_5-CAM$ **(Dodecamer).** A sample of **octamer** (0.2 g, 0.19 mmol) was treated with trifluoroacetic acid (2.0 mL) for 60 min. Addition of ether (100 mL) under stirring yielded the TFA salt of the octamer **(9).** This sticky salt was washed several times with ether and dried in high vacuo overnight to remove the traces of trifluoroacetic acid. This salt was dissolved in DMF (8 mL) containing compound **8** (0.105 g, 0.185 mmol) and BOP (0.078 g, 0.176 mmol), followed, after cooling to 0 °C, by addition of DIEA (0.06 mL, 0.371 mmol). After stirring for 24 h at room temperature the reaction mixture was heated to 50 °C and stirred for another 48 h in the dark. Solvent was removed completely from the reaction mixture by applying vacuum overnight. The solid residue was washed with 1 N citric acid (the solid was stirred vigorously with citric acid in a round-bottomed flask and then filtered) for about 2 h, water (same treatment as done with citric acid), and cold 1 N $NaHCO_3$(aq) (same treatment as done with citric acid) and washed with methanol and ether in excess. Yield 0.22 g (77 mol %).

^{1}H NMR (DMSO-D6). 1.18 ppm (m, 24H, corresponds to protons on the center carbons of "b" and "c" group of protons, 1.38 ppm (s, 9H, corresponds to protons on *tert-**butyl***), 1.46 ppm (m, 48H, corresponds to protons on carbons "b" and "c"), 2.0 ppm (t, 22H, corresponds to protons on carbons "d" and "e"), 2.36 ppm (t, 2H, corresponds to protons on carbon "m"), 2.86 ppm (q, 2H, corresponds to protons on carbon "f"), 3.0 ppm (q, 22H, corresponds to protons on carbons "g"), 4.4 ppm (s, 2H, corresponds to protons on carbon "l"), 6.76 ppm (t, 1H, corresponds to proton on nitrogen "h"), 7.22 ppm, 7.42 ppm (2s, 2H, correspond to protons on nitrogen "i" and "j"), and 7.72 ppm (t, 11H, corresponds to proton on nitrogen "k").

TOF-SIMS Analysis. The spectra of oligoamides were obtained with a time-of-flight secondary-ion mass spectrometer, TOF-SIMS III, designed and manufactured by Ion-Tof GmbH, Münster, Germany. The TOF-SIMS has been described in detail elsewhere.[14] Targets were bombarded by a 10 keV Ar^+ pulsed primary ion beam with current varying from 0.3 to 0.5 pA. The primary ion has a variable spot diameter between 5 and 50 μm. Secondary ions generated by a primary ion pulse on the target surface were extracted and accelerated to an energy of 3 keV. An Enzel lens and reflectron optics were used for focusing the secondary ion beam and for energy compensation, respectively, in the 2 m flight tube. The ions were postaccelerated to 10 keV just ahead of the detector, which was a channel plate−scintillator−photomultiplier combination. A time-to-digital converter (TDC) was used for data collection. The total collection time for a spectrum was 300 s. The total primary ion dose during data acquisition was less than 10^{13} ions/cm^2, which corresponds to static SIMS. The base pressure of the main chamber of the instrument was typically 3×10^{-8} Pa, and the operating pressure was about 10^{-6} Pa with a pressure of 4×10^{-4} Pa in the primary ion source.

The silver substrate had been etched in nitric acid (20 vol %) and ultrasonicated in distilled water for about 3 min and then rinsed in distilled water and methanol. Oliogmers were dissolved in TFA at concentrations of 1 mg/mL. Sample solution volumes of 1 μL were deposited onto 20 mm^2 silver substrates. TOF-SIMS spectra for the dimer and tetramer were recorded by desolving the samples in methanol at a concentration of 1 mg/mL. Data analysis was completed using in-house-generated software, GOOGLY, written by Andrew Proctor.

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(5) This salt is sticky in nature; after repeated washings with an excess of ether a free-flowing solid can be obtained. This solid is dried overnight in vacuo to remove the traces of volatile trifluoroacetic acid impurities.

(6) The salt of the dimer is less sticky than the salt of the monomer. The treatment for compound **4** was employed to remove the trace impurities of volatile trifluoroacetic acid and to obtain a free-flowing solid. In the preparation of higher oligomers, salts of the tetramer and octamer were more free flowing than the dimer salt.

(7) The yields for each coupling step: dimer, 40 mol %; tetramer, 53 mol %; hexamer, 80 mol %; octamer, 75 mol %, 77 mol. The higher oligomer yields were increased by heating the reaction mixture at 50−60 °C for about 48 h. Dimer and tetramer yields also can be increased by employing the same process. Small-scale reactions produced higher yields than large-scale reactions.

(8) The ^{1}H NMR were recorded in DMSO-D6 using a Bruker 300 MHz instrument. The octamer and dodecamer were made soluble by heating the solution, whereas the dimer, tetramer, and hexamer were soluble at room temperature.

(9) The peak ratio of 7.75 ppm to 6.75 ppm peaks for dimer is 15%, tetramer 18%, hexamer 25%, octamer 31%, and for dodecamer 40% higher than the expected value. The increase in the error for these oligomers as the number of repeating units increased may be due to the fact that the peak at 6.75 ppm, which corresponds to the end group BOC−NH proton (which is just one proton), is difficult to see in the larger oligomer chain.

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