from each culture were also saved. Extracts prepared from these cells were assayed for DAHP synthase activity as described above.

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Registry No. DAHP synthase, 9026-94-2; D-glucose, 50-99-7; transketolase, 9014-48-6.

Synthesis and Polymerization of *N*-Z-L-Serine-β-lactone and Serine Hydroxybenzotriazole Active Esters

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Abstract: The reaction of Z-L-serine **1a** with 1-hydroxybenzotriazole (HOBt) in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) yielded oligomeric poly(*N*-Z-serine ester) **4a** and not Z-L-serine-β-lactone (**2**, R = Z), as described in a widely cited report by König and Geiger. After modifying the reaction conditions, the elusive HOBt active ester of Z-L-serine (**3**, R = Z) was obtained in 90% yield. Bulk polymerization of **3** gave poly(Z-L-serine ester) **4a** with a weight average molecular weight (M_w) of about 22 000 da. Reaction of N-protected serine derivatives **1b–d** with HOBt and DCC afforded poly(serine esters) **4b–d** directly, typically with M_w in excess of 20 000 da. In contrast, *N*-Z-threonine **5** failed to yield poly(*N*-Z-threonine ester). The optical purity of L-serine was preserved during the synthesis of the HOBt active ester and the subsequent polymerization. The approach described here represents the first, convenient multigram synthesis of serine derived polyesters, new polymers with potential biomedical applications.

Introduction

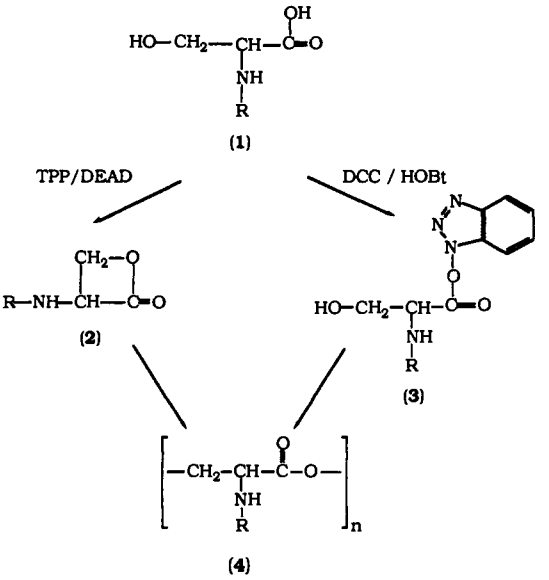
Serine-β-lactones **2** (Scheme I) are important intermediates in amino acid synthesis and polymer chemistry: Among other transformations, Vederas et al.[1,2] recently reported the synthesis of N-protected β-substituted alanines via **2**, while Zhou and Kohn[3] as well as Spassky et al.[4] described the ring-opening polymerization of **2** leading to poly(N-protected serine esters) **4**. Polyesters **4** belong to a new group of polymers defined as "pseudo" poly(amino acids)[5] which are currently being investigated as biodegradable implant materials in a variety of medical applications.[6]

Lactones **2**, however, are not readily available. Several methods giving **2** have been reported but are laborious, give low yields, or are limited to specific protecting groups. For example, Sheehan et al.[7] described the cyclization of *N*-trityl-L-serine (**1**, R = trityl) using *N,N'*-diisopropylcarbodiimide. The corresponding lactone was obtained with 15% yield. This method was later modified by employing (dimethylamino)pyridine as a catalyst and *N,N'*-diisopropylcarbodiimide[8] or *N,N'*-dicyclohexylcarbodiimide[4] as the carboxyl activation agents. The reported yields, however, were not significantly higher than the yields obtained by Sheehan's approach. An alternate method via Hofmann rearrangement of *N*-(benzenesulfonyl)asparagine[9,10] gave higher yields (45%) but appears to be restricted to the use of the benzenesulfonyl protecting group.

So far, only two procedures have been reported that provide N-protected serine-β-lactones with yields in excess of 50%. Most noteworthy is the synthesis published in 1970 by König and Geiger,[11] furnishing **2** (R = Z) in 91% yield in a simple, one-step reaction of **1a** with *N,N'*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt). Unfortunately, König and Geiger provided only melting point and elemental analysis as the sole identifying properties for their reaction product. This synthesis was disclosed in their pioneering paper on the use of HOBt in peptide synthesis. Today this paper is frequently cited and has been included in major textbooks on peptide synthesis.[12,13]

More recently, Vederas et al.[1,2] reported the successful synthesis of **2** (R = Z, Boc) by means of a modified Mitsunobu[14] reaction in yields of up to 81%. Vederas et al. published a detailed structural analysis of their products. Furthermore, in a footnote

Scheme I



1, 4	R
a	benzyloxycarbonyl (Z)
b	p-methoxybenzylcarbonyl (Moz)
c	p-nitrobenzyloxycarbonyl
d	tert-butoxycarbonyl (Boc)

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Table I. Comparison of König and Geiger's Reaction Product with Authentic Z-Serine-β-lactone and Authentic Poly(Z-serine ester)

property	authentic lactone[1] 2 (R = Z)	König's product[11]	authentic polyester 4a[3]
elemental anal. (found: C,H,N)	59.60, 5.10, 6.21	59.71, 5.01, 6.33	59.44, 5.16, 6.21
melting point (°C)	133–134 (EtOAc/hexane)	177–179 (isopropanol)	>250, dec
IR spectra data			
(THF cast/cm^{-1})	1845 (lactone C=O)	1751 (ester C=O)	1751 (ester C=O)
(KBr pellet/cm^{-1})	n/a	1724 (ester C=O)	1724 (ester C=O)
^{1}H NMR spectral data (ppm)	5.57 (NH) 5.04 (C*H*-CH$_2$) 4.42 (CH-C*H*$_2$)	7.82 (NH) 4.55–4.15 (C*H*-C*H*$_2$)	7.84 (NH) 4.46–4.15 C*H*-C*H*$_2$)
wt av molecular wt GPC (Da)	<400	3000	29000

they indicated that in their hands the procedure of König and Geiger did not furnish lactones without further elaborating on the nature of König and Geiger's product.[1]

In view of this discrepancy we reviewed the studies of König and Geiger.[11] Our investigation was not only prompted by the need to clarify the literature[12,13] but also by the consideration that König and Geiger's procedure[11] would represent a much more convenient synthesis of **2** than the reaction described by Vederas et al.[1,2]

Results and Discussion

We started our investigation[15] by repeating the reaction of Z-L-serine **1a** with DCC in the presence of HOBt, as described by König and Geiger.[11] We also reacted **1a** with a preformed adduct of triphenylphosphine (TPP) and diethyl diazodicarboxylate (DEAD), as described by Vederas et al.[1,2] Although reportedly both pathways lead to **2** (R = Z), it became immediately evident that the two products were not identical. The product obtained from the reaction of **1a** with TPP/DEAD (Vederas' procedure) could be readily identified as authentic β-lactone based on its IR and ^{1}H NMR spectra, whereas the product obtained by König and Geiger's procedure had a virtually identical elemental composition but distinctively different spectral and physical properties (Table I).

Our reinvestigation of the König and Geiger reaction[11] yielded a product with a melting point of 175–178 °C which is close to that reported by König and Geiger (177–179 °C). We hence concluded that we indeed obtained the same material these authors had erroneously regarded as β-lactone **2**. While lactones commonly exhibit a strong ester carbonyl vibration around 1845 cm^{-1}, the product we obtained via König and Geiger's procedure showed a strong absorption at 1751 cm^{-1} (THF cast) which we assigned to the carbonyl vibration of an unstrained, linear ester linkage (Table I). Next, we analyzed a sample of the König and Geiger product by gel-permeation chromatography (GPC). The chromatogram showed a peak corresponding to a weight average molecular weight of about 3000 Da (relative to polystyrene standards). This finding together with the spectral properties of the product indicated that König and Geiger had inadvertently prepared a low molecular weight oligomer of structure **4a**. Apparently, König and Geiger had overlooked the fact that lactone **2** (R = Z) and polymer **4a** have the same elemental composition (see Table I). Thus, in the absence of further structural verification (e.g., by IR spectroscopy), elemental analysis is not sufficient to distinguish between the structures of **2** and **4**.

The above findings were in accord with the earlier observation by Vederas et al.[1] that König and Geiger's procedure[11] is unsuitable for the synthesis of serine β-lactones. Like Vederas, we were unable to detect the formation of lactones upon carefully monitoring the reaction by IR or TLC. However, the sporadic occurrence of an IR absorption at 1827 cm^{-1} (THF cast) in the crude reaction product pointed to the formation of the HOBt active ester of L-serine as the reactive intermediate in König and Geiger's procedure. Thus we speculated that König and Geiger's original procedure could potentially be modified to yield two important products: the elusive HOBt active esters **3** (which had so far not been prepared in pure form) and high molecular weight polyesters **4**.

Since a recent paper[16] hinted at the possible self-condensation of active ester **3** in boiling THF, we speculated that the oligomerization of **3** may have occurred in the final purification step in which König and Geiger recrystallized their crude material from boiling isopropanol. We therefore avoided elevated temperatures in the work up of the crude reaction mixture by evaporating the reaction mixture in vacuo at a bath temperature of less than 25 °C. The crude material was purified by repeated washings with cold isopropyl alcohol, and the recrystallization from boiling isopropyl alcohol was omitted.

The FT-IR spectrum of the product obtained in this way showed a strong band at 1827 cm^{-1} (THF cast). This absorption was in agreement with the carbonyl vibration generally observed for HOBt active esters.[11,17,18] Moreover, in the ^{1}H NMR spectrum (acetone-d_6), a multiplet between 7.2 and 8.1 ppm (9 H) clearly indicated the presence of the HOBt moiety in the reaction product. Since free HOBt displayed a multiplet at 7.4–7.9 ppm and could be easily distinguished from covalently bound HOBt, the material obtained by our modified procedure must be the active ester **3** (R = Z).

The purity of **3** (R = Z) was determined by reaction with a known excess of benzylamine, followed by back-titration of unreacted benzylamine with a dioxane solution of $HClO_4$. Calculation of the amount of consumed benzylamine showed that the products furnished by our procedure had an active ester content of about 85–91%.

The thermogram of **3** obtained by differential scanning calorimetry (DSC) showed three peaks: The first peak was identified as an initial melting point (onset: 99 °C), followed by a second, sharp exotherm with a maximum at 109 °C. This peak indicated the occurrence of an exothermic reaction subsequent to melting,

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(14) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(15) Gelbin, M.; Kohn, J. *Polym. Preprints* **1991**, *32(2)*, 241–242.
(16) A recent report described the self-condensation of active ester **3** in boiling THF without providing any details on **3** or the self-condensation products obtained: Iwagami, H.; Yasuda, N. *Heterocycles* **1990**, *31*, 529–536.
(17) McCarthy, D. G.; Hegarty, A. F.; Hathaway, B. J. *J. Chem. Soc. Perkin II* **1977**, 224–231.
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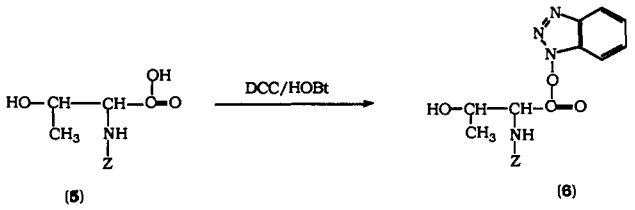
Scheme II



releasing a heat flow of about 0.3 W/g. Finally, we observed the decomposition exotherm at above 250 °C.

One possible explanation for the exothermic reaction observed at about 109 °C was that **3** would undergo a thermally initiated polymerization to give polyester **4a**. To test this, carefully dried **3** was sealed in nitrogen-flushed ampules under reduced pressure. The ampules were then heated to temperatures ranging from 95–155 °C for various intervals. Thereafter the molecular weight of the reaction products was determined. These experiments showed the optimum polymerization conditions to be heating to 105 °C for 5 h. This temperature was close to the peak of the reaction exotherm observed at around 109 °C by DSC.

Polyester **4a** was conveniently purified from HOBt and unreacted starting material by reprecipitation from DMF/methanol. Typically, purified polymer had a weight average molecular weight (M_w) of about 22 000 da, and a number average molecular weight (M_n) of about 17 500 da, corresponding to an approximate degree of polymerization (DP) of 73. The chemical structure was verified by FT-IR and ^{1}H NMR. These spectra were consistent in all aspects with the spectra of authentic **4a** prepared via ring-opening polymerization of **2** (R = Z).[3]

In order to determine to which extent the optical purity of L-serine was preserved during the formation of ester **3** (R = Z) and, especially, the bulk polymerization, appropriate samples of **4a** were hydrolyzed at 110 °C for 18 h in 6 N HCl. Subsequently, the hydrolysate was reacted with pentafluoropropionic anhydride and analyzed on a chiral GC column following the method of Frank et al.[19] This method had a detection limit of 0.5%. Since only a trace amount of D-serine (0.55%) was found, active ester formation, bulk polymerization, and polymer hydrolysis proceeded with extremely high retention of optical purity.

During the anionic ring-opening polymerization of **2** a chain-transfer reaction was observed that gave rise to the formation of dehydroalanine derivatives.[3] Chain transfer is a frequently observed side reaction during the ring-opening polymerization of β-propiolactones carrying hydrogen atoms in the α-position.[20] The presence of dehydroalanine in **4a** obtained via **2** could be readily confirmed by ^{1}H NMR due to the characteristic alkene resonances. Polymer **4a**, prepared via **3** (R = Z), was free of dehydroalanine as judged by the absence of the alkene absorptions in the ^{1}H NMR spectrum. In this respect, the bulk polymerization reaction gave polymers of higher chemical purity than the more laborious lactone approach.

We then extended our studies to other N-protected serine derivatives. Since urethane-type protecting groups linked to the N-terminus of amino acids can be removed under a variety of conditions,[12,13] we identified *N*-Moz-L-serine **1b**, *N*-(((*p*-nitrobenzyl)oxy)carbonyl)-L-serine **1c**, and *N*-Boc-L-serine **1d** as suitable starting materials. When **1b–d** were reacted with HOBt in the presence of DCC, no active esters **3** could be isolated. Instead, even after extremely careful workup of the reaction mixtures, the corresponding poly(serine esters) **4b–d** were obtained. Subsequent screening by GPC revealed M_w of 23 000 and 21 000 for **1b** and **c**, respectively. For poly(*N*-Boc-L-serine ester) **4d**, no accurate molecular weight data could be obtained since this polymer was insoluble in almost all organic solvents. Even in DMF or DMSO, only partial dissolution was observed.[21] Poly(serine esters) **4b–d** were obtained free of detectable amounts of dehydroalanine.

Next, we included the closely related amino acid threonine in our investigations. The reaction of Z-L-threonine **5** with HOBt and DCC proceeded readily and yielded the corresponding HOBt active ester **6** (Scheme II).[22] In our hands, **6** could be isolated with extremely high purity: the titrimetric procedure described above typically indicated active ester contents of about 99%.

Samples of **6** were then prepared for bulk polymerization, as in the case of **3** (R = Z). We expected **6**, which differs from **3** by one methyl group only, to undergo the same polymerization reaction as **3**. However, under a variety of reaction conditions (e.g., heating up to 5 h at 105–155 °C) we obtained either unreacted starting material **6** or dark brown products, indicative of decomposition.

The difference in reactivity between the HOBt esters of serine **3** and threonine **6** may be explained by steric considerations: Polymerization of the active esters proceeds via the intermolecular nucleophilic attack of the hydroxyl group in the side chain at the ester carbonyl group. Since the ester group itself bears a bulky HOBt substituent, the presence of an extra methyl group in the side chain of **6** may significantly reduce the reaction rate of the threonine hydroxyl group as compared to the serine hydroxyl group.

Conclusions

Our results confirmed that the reaction of Z-L-serine **1a** with DCC in the presence of HOBt does not furnish *N*-Z-serine-β-lactone, in contrast to a widely cited report by König and Geiger. Rather, our results establish that König and Geiger obtained low molecular weight **4a**, formed upon spontaneous polymerization of the HOBt active ester during the recrystallization step from boiling isopropyl alcohol. By suitably modifying König and Geiger's procedure, two valuable products could be obtained: For benzyloxycarbonyl protected derivatives (R = Z), the active ester **3** could be isolated. This represents the first convenient preparation of the highly reactive HOBt ester of Z-L-serine. In a subsequent bulk polymerization step, **3** (R = Z) could be readily polymerized to **4a** with M_w of about 22 000 Da. The reaction of other N-protected derivatives of serine **1b–d** with HOBt and DCC yielded the corresponding poly(serine esters) **4b–d** directly. In these cases, the intermediate active esters could not be isolated. The formation of the active esters and the subsequent bulk polymerization proceeded without significant racemization, and the obtained polymers were free of dehydroalanine, a contamination found in polymers obtained via the ring-opening polymerization of lactones **2**.

By circumventing both the synthesis and laborious column purification of serine-β-lactones, the polymerization of HOBt esters of serine is the first practical method for the multigram synthesis of serine-derived polyesters of reasonably high molecular weight. This makes it now possible to investigate in detail the physicomechanical properties of a variety of poly(serine esters) and their potential application as degradable biomaterials.

The pronounced tendency of the HOBt esters of serine to polymerize spontaneously explains why HOBt esters of serine are unsuitable reagents for peptide synthesis. On the other hand, the HOBt ester of *N*-Z-threonine **6** failed to polymerize under conditions suitable for the bulk polymerization of the HOBt ester of serine. Thus, **6** is an unsuitable intermediate in the preparation of threonine derived polyesters but appears to be a promising reagent for peptide synthesis.

Experimental Section

Materials. *N*-Z-L-Serine was purchased from Chemical Dynamics, South Plainfield. *N*-Boc-L-serine (98%) was obtained from Aldrich Chemical Company. *N*-Moz-L-serine was prepared following the method

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(21) When **4d** was dissolved in either hot THF, DMF, 0.1% (w/v) LiBr/DMF, or DMSO, a highly viscous (waxy) portion of the material would not go into solution. For analytical purposes (IR, NMR, GPC), the supernatant was used.

(22) Z-L-Threonine **5** was reacted with HOBt and DCC following the procedure of König and Geiger[11] (Scheme II). Based on its major spectral data and mp, the obtained product was identical to the HOBt active ester of Z-L-threonine **6** described by König and Geiger.[11]

of Weygand and Hunger.[23] *N*-(((*p*-Nitrobenzyl)oxy)carbonyl)-L-serine was prepared using a modification of the method of Weygand and Hunger.[24] 1-Hydroxybenzotriazole hydrate (Aldrich) was dried prior to use over P_2O_5 at 5×10^{-2} mmHg, 50 °C for 24 h. Thermogravimetric analysis was used to confirm that all water of crystallization had been removed during drying. Tetrahydrofuran (THF) was obtained from Fisher, Springfield, NJ. THF was dried by distillation under Ar from metallic sodium and benzophenone. All other solvents were of HPLC grade and were used as received.

All glassware was oven dried overnight at 145–155 °C. Typically, it was then transferred to a glovebox where it was cooled and charged with the material, as indicated, under a N_2 atmosphere.

Analysis. NMR spectra were recorded on a VXR 200 MHz spectrometer (Varian). IR spectra were obtained on a Mattson Cygnus 100 FT-IR spectrophotometer. For differential scanning calorimetry a 910 calorimeter (DuPont) was used. Thermogravimetric analysis was performed on a 951 analyzer (DuPont). Gel permeation chromatography (GPC) was performed using a chromatographic system consisting of a Perkin-Elmer Series 410 LC pump, a Waters Model 410 RI detector, and a Perkin-Elmer DEC 3000 data station. Chromatograms were obtained in DMF containing 0.1% (w/v) of LiBr, at a flow rate of 1 mL/min on two PL-gel columns (300 mm × 7.7 mm id, 5 μm particle size, 1000 and 100 Å pore size, respectively) connected in series.

***N*-Z-L-Serine 1-Hydroxybenzotriazole Ester, 3.** Z-L-Serine (2.4 g, 10 mmol) and HOBt (1.5 g, 11 mmol) were dissolved in THF (20 mL). The mixture was cooled to −10 °C when a solution of *N,N'*-dicyclohexylcarbodiimide (2.2 g, 11 mmol) in THF (10 mL) was added. Stirring was continued at 0 °C for 1 h and then at room temperature for another hour. The urea precipitate was removed by filtration, and the filtrate evaporated to dryness in vacuo. Throughout the concentration step the bath temperature was not allowed to exceed 25 °C. After washing twice with cold isopropyl alcohol, 3.3 g (92% yield) of ester **3** was collected as a colorless material by filtration: mp 97–100 °C, remelts at 115–117 °C, dec >250 °C; IR (THF cast) 3500–3250, 2950, 1827, 1715, 1537, 1430, 1260, 1029 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.08–7.31 (m, 9 H, 1 × C_6H_5 + 1 × $C_6H_4N_3$), 5.18 (s, 2 H, $CH_2C_6H_5$), 4.92 (m, 1 H, $CHCH_2$), 4.35–4.10 (m, 2 H, $CHCH_2$).

Poly(*N*-Z-L-serine ester) 4a. Freshly prepared active ester **3** (200 mg) was thoroughly dried in vacuo and then transferred to a 10-mL Wheaton ampule. The ampule was repeatedly flushed with dry nitrogen and then sealed under a pressure of 5×10^{-3} mmHg. It was immersed into an oil bath for 5 h at 105 °C. The reaction product was first washed with THF, then dissolved in DMF, and reprecipitated with methanol to give 81 mg (41% recovery) of polyester **4a**: IR (THF cast) 3337, 3068, 2950, 1751, 1715, 1529, 1431, 1392, 1315, 1264, 1245, 1062 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.82 (d, 1 H, NH), 7.28 (s, 5 H, C_6H_5), 4.99 (s, 2 H, $CH_2C_6H_5$), 4.55–4.15 (m, 3 H, $CHCH_2$); ^{13}C NMR (DMSO-d_6) δ 168.7, 156.0, 136.5, 128.3, 127.7, 65.8, 63.8, 52.8; molecular weight M_w = 22 200 da; M_n = 17 500 da; DP = 72–73. Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.49; H, 5.13; N, 6.23.

Preparation of Poly(serine esters) 4b–d (General Procedure). A 100-mL, three-necked, round-bottomed flask was charged with 10 mmol of N-protected-L-serine **1b–d** and 11 mmol of HOBt. Under a nitrogen atmosphere THF was added with stirring until a clear solution formed. The mixture was then cooled to −10 °C followed by dropwise addition of a solution of 11 mmol of DCC in THF (10 mL); the temperature was not allowed to exceed −10 °C. Stirring was continued at 0 °C for 1 h and then 1 h at room temperature. The precipitate of DCU was collected by filtration. The filtrate was evaporated to dryness in vacuo, yielding a foamlike residue (crude product).

Poly(*N*-Moz-L-serine ester), 4b. The crude product was stored in a freezer under isopropyl alcohol giving **4b** as a white solid. Reprecipitation from DMF/methanol gave an analytically pure sample (42% recovery): mp 149.5–152; IR (THF cast) 3329, 2961, 2942, 2359, 2341, 1757, 1718, 1627, 1514, 1246, 1048, 1032 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.75 (d, 1 H, NH), 7.24–6.83 (dd, 4 H, $CH_2C_6H_4OCH_3$), 4.91 (s, 2 H, $CH_2C_6H_4OCH_3$), 4.43–4.28 (br m, 3 H, $CHCH_2$), 3.68 (s, 3 H, $CH_2C_6H_4OCH_3$); ^{13}C NMR (DMSO-d_6) δ 168.7, 159.0, 156.0, 129.9, 129.7, 128.3, 113.6, 65.67, 63.8, 54.9, 52.8; molecular weight M_w = 23 000 da; M_n = 20 500 da; DP = 81–82. Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.21; N, 5.58. Found: C, 57.12; H, 5.24; N, 5.77.

Poly(*N*-(((*p*-nitrobenzyl)oxy)carbonyl)-L-serine ester), 4c. The crude product was stored in a freezer under isopropyl alcohol giving **4c** as a sand-colored solid. After reprecipitation from DMF/methanol, the analytically pure polymer was collected by centrifugation (41% recovery): mp 151–153 °C; IR (THF cast) 3339, 2957, 2876, 2360, 2290, 1752, 1727, 1607, 1518, 1380, 1190, 1030; ^1H NMR (DMSO-d_6) δ 8.12 (br s, 2 H, $CH_2C_6H_4NO_2$), 7.98 (d, 1 H, NH), 7.51 (br s, 2 H, $CH_2C_6H_4NO_2$), 5.14 (s, 2 H, $CH_2C_6H_4NO_2$), 4.49–4.35 (br m, 3 H, $CHCH_2$); ^{13}C NMR (DMSO-d_6) δ 168.7, 155.7, 146.8, 144.4, 127.9, 123.4, 64.5, 63.7, 52.8; molecular weight M_w = 21 200 da; M_n = 16 400 da; DP = 61–62. Anal. Calcd for $C_{11}H_{10}N_2O_6$: C, 49.63; H, 3.79; N, 10.25. Found: C, 49.65; H, 3.89; N, 10.46.

Poly(*N*-Boc-L-serine ester), 4d. The crude product was extensively triturated with hexane, giving **4d** as an off-white, slightly waxy solid (85%). This material was virtually insoluble in a variety of organic solvents; it was somewhat soluble in DMF or DMSO.[21] Hence the crude was analyzed without further purification: mp 170–174 (dec); IR (THF cast) 3363, 2772, 2929, 1740, 1710, 1522, 1344, 1157, 1052; ^1H NMR (DMSO-d_6) δ 7.97 (d, 1 H, NH), 4.32–4.19 (m, 3 H, $CHCH_2$), 1.38 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (DMSO-d_6) δ 168.9, 155.2, 78.6, 63.7, 52.4, 27.9; molecular weight of the soluble fraction M_w = 8800 da; M_n = 5900 da; DP = 31–32.

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(23) Weygand, F.; Hunger, K. *Chem. Ber.* **1962**, *95*, 1–6. *N*-(((*p*-Methoxybenzyl)oxy)carbonyl)-L-serine **1b**: mp 96–98 °C; IR (KBr) 3368, 2945, 2360, 1690, 1623, 1515, 1246, 1182, 1075, 1032 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.30 (s, 1 H, OH), 7.30–6.87 (dd, 4 H, $CH_2C_6H_4OCH_3$), 7.18 (d, 1 H, NH), 4.93 (s, 2 H, $CH_2C_6H_4OCH_3$), 4.04–3.98 (m, 1 H, $CHCH_2$), 3.72 (s, 3 H, OCH_3), 3.63 (d, $CHCH_2$); ^{13}C NMR (DMSO-d_6) δ 168.7, 158.9, 156.0, 129.9, 129.7, 128.3, 113.6, 65.7, 63.7, 54.9, 52.7. Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.58; H, 5.62; N, 5.20. Found: C, 53.47; H, 5.48; N, 5.16.

(24) *N*-(((*p*-Nitrobenzyl)oxy)carbonyl)-L-serine **1c**: L-Serine (2.1 g, 20 mmol) and MgO (2.4 g, 60 mmol) were suspended in H_2O (40 mL). With vigorous stirring, a solution of (*p*-nitrobenzyl)chloroformate (4.7 g, 22 mmol) in dioxane (50 mL) was added dropwise within 50 min (temperature control: 5 °C). Subsequently, the reaction mixture was kept with further stirring at room temperature for 72 h. After removing MgO by filtration, the filtrate was extracted with ether. Then ethyl acetate (75 mL) was added, followed by ion-exchange resin Amberlite IR-120 (plus) (40 g). This mixture was kept with stirring for 2 h. The ion-exchange resin was removed followed by separating the organic from the aqueous phase. After washing the latter with ethyl acetate (1 × 50, 1 × 30 mL), the combined ethyl acetate fractions were first dried and then evaporated to dryness in vacuo. A yellow oil resulted which was triturated with hexane to give crude **1c** as white crystals (4.7 g, 83%). Crude **1d** gave analytically pure material after recrystallization from ethyl acetate/hexane (70/30%, v/v): mp 102–104 °C; IR (KBr) 3366, 2985, 2362, 2342, 1701, 1521, 1347, 1230, 1067 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.60 (s, 1 H, OH), 8.23–7.58 (dd, 4 H, $CH_2C_6H_4NO_2$), 7.50 (d, 1 H, NH), 5.17 (s, 2 H, $CH_2C_6H_4NO_2$), 4.06–4.02 (m, 1 H, $CHCH_2$), 3.67 (d, 2 H, $CHCH_2$); ^{13}C NMR (DMSO-d_6) δ 172.0, 155.7, 146.8, 144.9, 128.0, 127.7, 123.4, 64.2, 61.2, 56.6. Anal. Calcd for $C_{11}H_{12}N_2O_7$: C, 46.48; H, 4.26; N, 9.85. Found: C, 46.08; H, 4.22; N, 9.65.