Synthesis of highly branched block copolymers of enantiomerically pure amino acids

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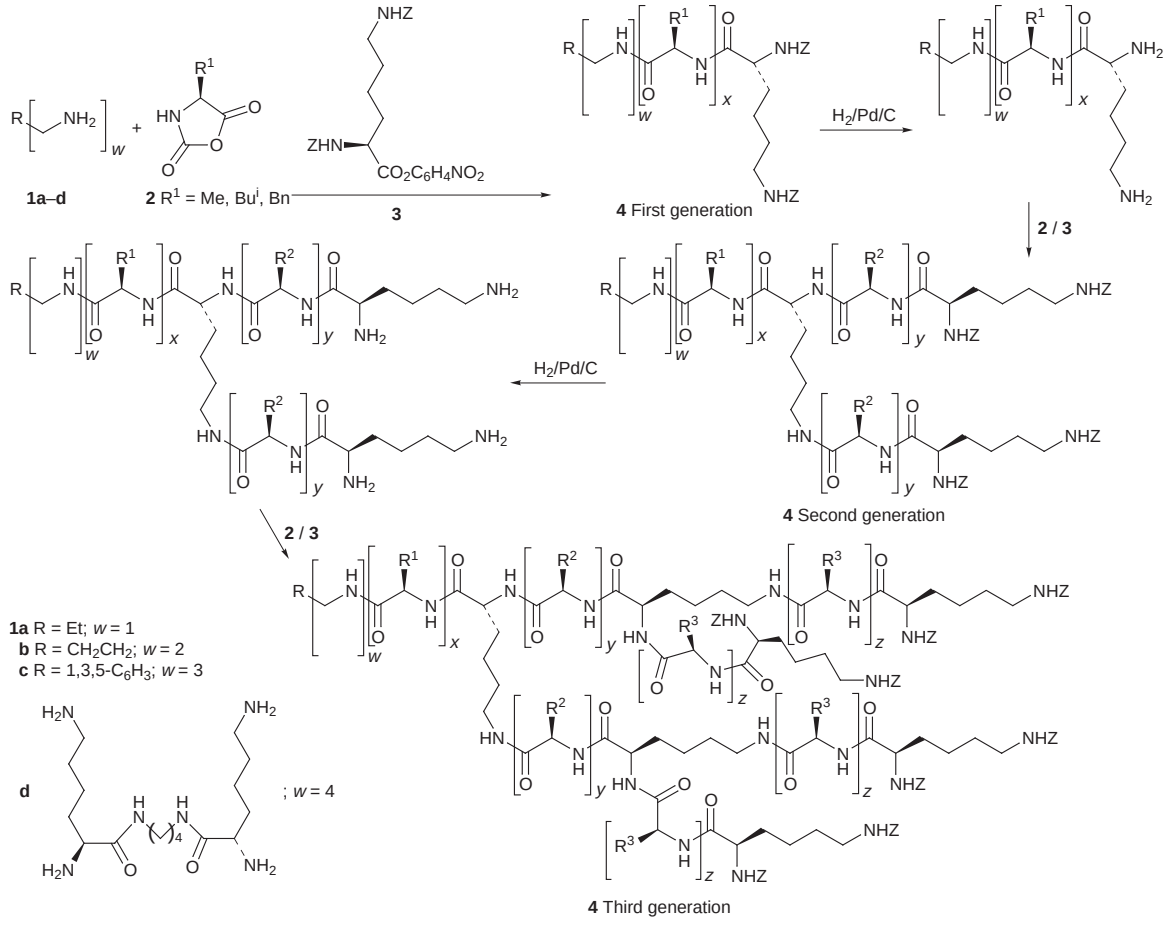
The combination of multifunctional initiators and the use of lysine residues to introduce branch points into poly(amino acids) allow the synthesis of highly branched poly(amino acids).

In recent years, there has been considerable interest in the synthesis of synthetic polymers with non-linear molecular architectures.[1] Much work in this area has concentrated on the synthesis and investigation of dendrimers,[2] polymers which have precisely controlled molecular weights and geometry. However, for many applications, the variety of molecular weights found in conventional synthetic polymers leads to desirable physical properties. Thus there is a need for methodology which will allow the synthesis of polydisperse, highly branched polymers. We have an ongoing interest in the preparation of synthetic polymers derived from biomonomers,[3] and here the synthesis of highly branched, polydisperse poly(amino acid)s is reported.

The synthesis of the desired polymers is outlined in Scheme 1. An initiator **1a**–**d** containing one to four primary amino groups was used to polymerize the *N*-carboxy anhydride **2** of an amino acid.‡ This is a well known process for the preparation of poly(amino acid)s,[4] however it was anticipated that, provided termination reactions could be avoided, the addition of *N*,*N*′-di(benzyloxycarbonyl)lysine *p*-nitrophenyl ester **3** to the polymerization mixture would produce capped polymers **4**. Subsequent hydrogenation of polymers **4** would reveal two primary amino groups on each chain of the initial polymer which could be used to initiate the polymerization of a second *N*-carboxy anhydride of an amino acid. Capping of this polymerization by lysine derivative **3** would give the next generation of the polymer, and the process could be repeated indefinitely to give highly branched poly(amino acids).

In practice, unfunctionalized amino acid *N*-carboxy anhydrides **2** were employed in order to avoid the undesired termination reactions which are known to occur with functionalized amino acids such as γ-esters of glutamic acid.[5] It was also found to be advantageous to keep each polymer chain relatively short (5–10 amino acids) in order to avoid solubility problems, although even polymers prepared in this way were soluble only



Scheme 1

Table 1 Structures and molecular weight data for polymers **4**

Entry	Initiator	AA1[a]	AA2[a]	AA3[a]	M_n[b]	M_w[b]	PDI	M_n[c] (calc.)	Yield (%)
1	**1a**	Leu (8)	—	—	1100	1230	1.1	1359	58
2	**1a**	Leu (8)	Ala (7)	—	3220	3720	1.2	2877	70
3	**1a**	Leu (8)	Ala (7)	Phe (4)	5240	7820	1.5	6277	56
4	**1a**	Phe (10)	—	—	1800	2000	1.1	1925	71
5	**1a**	Phe (10)	Leu (8)	—	1700	2000	1.2	4257	61
6	**1a**	Phe (10)	Leu (8)	Ala (4)	2200	2200	1.0	6441	94
7	**1b**	Ala (5)	—	—	2400	2900	1.2	1590	96
8	**1b**	Ala (5)	Leu (5)	—	2200	2700	1.2	4898	57
9	**1b**	Ala (5)	Leu (5)	Phe (4)	4300	7900	1.8	11798	66
10	**1b**	Leu (4)	—	—	2300	2640	1.1	1784	71
11	**1b**	Leu (4)	Phe (4)	—	3870	5300	1.4	5184	64
12	**1b**	Leu (4)	Phe (4)	Ala (4)	3570	5340	1.5	9552	57
13	**1b**	Phe (4)	—	—	2200	2680	1.2	2056	65
14	**1b**	Phe (4)	Leu (4)	—	3810	4890	1.3	4912	86
15	**1b**	Phe (4)	Leu (4)	Ala (4)	2430	4420	1.8	9280	74
16	**1c**	Phe (5)	—	—	2910	3740	1.3	3558	78
17	**1c**	Phe (5)	Leu (4)	—	2800	3600	1.3	7842	54
18	**1c**	Leu (5)	—	—	3500	4000	1.1	3048	63
19	**1c**	Leu (5)	Phe (4)	—	4500	5100	1.1	8148	81
20	**1d**	Phe (4)	—	—	4530	5440	1.2	4280	80
21	**1d**	Phe (4)	Leu (3)	—	4590	5920	1.3	9088	65
22	**1d**	Leu (4)	—	—	3070	4100	1.3	3736	60
23	**1d**	Leu (4)	Phe (3)	—	8270	33600	4.1	9360	77

[a] The numbers in brackets correspond to the average number of amino acids incorporated into each branch of the polymer as determined by ^{1}H NMR spectroscopy. [b] M_n and M_w values were obtained from GPC data calibrated with polystyrene standards. [c] Calculated from the integration trace of the ^{1}H NMR spectrum.

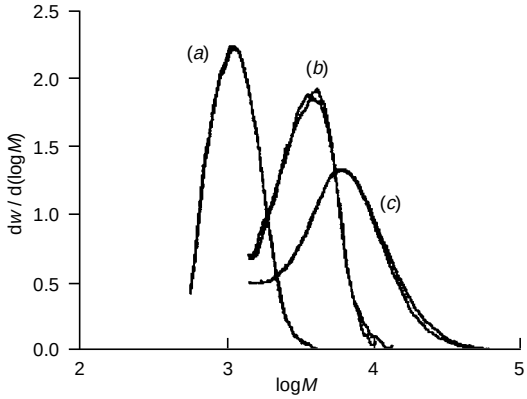


Fig. 1 The GPC chromatograms for the polymers corresponding to entries (*a*) 1, (*b*) 2 and (*c*) 3 in Table 1. Each chromatogram was run in duplicate.

in polar aprotic solvents, which restricted the methods which could be used for their characterization. Initial studies were carried out using propylamine **1a** as a monofunctional initiator, and the polymerizations were repeated to the third generation. The structures and molecular weights of the polymers are given in Table 1. In each case, the polymers were characterized by solution state ^{1}H NMR spectroscopy, solution or solid state ^{13}C NMR spectroscopy and GPC. Typical GPC chromatograms are shown in Fig. 1. It is apparent from Fig. 1 that the molecular weight of the polymer increases as each amino acid is added to the polymer, and that the peak corresponding to the precursor polymer disappears at each stage. In some cases (*e.g.* entries 4–6 in Table 1), however, the low molecular weights of alanine and leucine combined with the small number of residues being introduced meant that GPC was unable to detect the change in the size of the polymer.

Having shown that branched polymers could be prepared by this methodology, the use of initiators **1b**–**d**[6]§ bearing two to four primary amino groups was investigated. As Table 1 shows, in each case it was possible to obtain the desired branched poly(amino acid)s exactly as in the case of initiator **1a**. However, an increasing discrepancy between the calculated and experimental M_n values is apparent in these polymers (*e.g.* entries 7–9 in Table 1). This is probably due to the fact that GPC separation is based on molecular size rather than molecular weight, and for branched polymers, the relationshp between molecular size and molecular weight is non-linear.

In conclusion, we have shown that it is possible to prepare highly branched polymers derived from amino acids. The polymers are expected to have a number of applications including asymmetric catalysts, biomimetic polymers, biodegradable polymers and biocompatible polymers. Our work in this area is continuing.

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Notes and References

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‡ All amino acids used in this work have the *S*-configuration.

§ Initiator **1d** was prepared by the reaction of lysine derivative **3** with 1,4-diaminobutane, followed by hydrogenolysis of the benzyloxycarbonyl protecting groups.

1 For recent examples see: A. Mueller, T. Kowalewski and K. L. Wooley, *Macromolecules*, 1998, **31**, 776; W. Radke, G. Litvinenko and A. H. E. Muller, *Macromolecules*, 1998, **31**, 239; L. J. Hobson, A. M. Kenwright and W. J. Feast, *Chem. Commun.*, 1997, 1877.

2 D. A. Tomalia, A. M. Naylor and W. A. Goddard III, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 138; J. Issberner, R. Moors and F. Vogtle, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2413.

3 S. M. Bush and M. North, *Polymer*, 1998, **39**, 933; S. C. G. Biagini, M. P. Coles, V. C. Gibson, M. R. Giles, E. L. Marshall and M. North, *Polymer*, 1998, **39**, 1007 and references cited in these two papers.

4 H. R. Kricheldorf, *α-Amino Acid N-Carboxy Anhydrides and Related Materials*, Springer, New York, 1987.

5 D. Coleman, *J. Chem. Soc.*, 1951, 2294; W. E. Hanby, S. G. Waley and J. Watson, *J. Chem. Soc.*, 1950, 3239.

6 Y. Tor, J. Libman, A. Shanzer, C. E. Felder and S. Lifson, *J. Am. Chem. Soc.*, 1992, **114**, 6653.

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