SYNTHESIS OF A SARCOSINE DECABLOCK POLYMER

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Introduction

Historically, a large number of researchers have been dealing with the ring-opening polymerization (ROP) of *N*-carboxyanhydrides (NCAs)[1,2,3]. In particular, methods to obtain defined polypeptides are investigated after the initial success of Deming and co-workers[4,5,6,7].

By ROP a wide variety of polypeptides and polypeptoides (N-substituted polyglycines) can be generated. It is well known, that sarcosine-NCA polymerizes in a living manner, however, whether other N-substituted *N*-carboxyanhydrides (NNCAs) undergo controlled ROP remained unclear. In a recent publication we demonstrated that several other NNCAs can be polymerized in a very defined manner, yielding polymers with Poisson-distributions. This enabled us to synthesize amphiphilic block copolypeptides[8]. Being non-ionic, amphiphilic block copolymers with a degradable main chain, these polymers may be interesting for next generation (bio)materials.

To analyze in detail the "livingness" of the polymerization without having to cope with difficulties of the analysis of heteromultiblocks, here, we report on the synthesis of a decablock polymer, in which the same monomer sarcosine-NCA was polymerized in multiple consecutive steps. After each step, an aliquot of the reaction was taken and molar mass including dispersity of the product was determined by gel permeation chromatography.

Experimental

Materials. All substances for the preparation of monomer and polymer were purchased from Aldrich and Acros and were used as received unless otherwise stated. *N*-methyl-2-pyrrolidinone (NMP) was dried by refluxing over P_2O_5, benzylamine over BaO and petrolether over CaH_2 under dry argon atmosphere und subsequent distillation prior to use. Water levels were determined using a C20 compact coulometer (Mettler-Toledo, Giessen, Germany). In general, solvents were used at water levels of <30 ppm. The monomer sarcosine-NCA was handled preferably in a glovebox (UNIlab, MBraun, Garching, Germany).

Instrumentation. Gel permeation chromatography (GPC) was performed on a PL-GPC-120 (Polymer Laboratories) running under WinGPC software (PSS, Mainz, Germany) with two consecutive Gram columns (100 and 1000 Å) with *N*,*N*-dimethylacetaminde (DMAc) (5 g/L LiBr, 70 °C, 1 mL/min) as eluent and calibrated against PMMA standards (PSS, Mainz, Germany).

Synthesis of Sarcosine-*N*-Carboxyanhydride. Sarcosine-*N*-carboxyanhydride was synthesized in tetrahydrofuran (THF) in the presence of triphosgene as described previously[8].

Preparation of Decablock Sarcosine. In a glovebox 0.0951 g (0.83 mmol) of sarcosine-NCA were weighed into reaction vessel and 275 µl NMP were added. After complete dissolution, 9 µl benzylamine (83 µmol) were added ($[M]_0/[I]_0$ = 10). Outside of the glovebox the reaction mixture was stirred at room temperature under constant pressure (20 mbar). For the following blocks the corresponding amount of sarcosine-NCA was weighed into separate vessels and dissolved in NMP to obtain a 3 M monomer solution. This solution was added at each step to the polymerization mixture. For analytical investigations of each single block, 22.5 µl were removed from the reaction mixture and precipitated into diethyl ether, dried under reduced pressure, dissolved in water and subsequently freeze-dried. The time of polymerization was between one and 12 hours corresponding to the increasing of the polymer chain. The polymerization time was predetermined from our previous studies on the polymerization kinetics of Sar-NCA in NMP. All relevant data for the polymerization conditions are listed in **Table 1**.

Table 1. Polymerization Conditions for the ROP of Consecutive Block of Sarcosine-NCA.

block ID	$n_{monomer}$ [mmol]	$c_{monomer}$ [mol/l]	$[M]_0/[I]_0$	reaction time [h]
1	0.83	3	10	1
2	0.76	1.52	9.84	1
3	0.74	1	10	1.5
4	0.68	0.73	9.48	1.5
5	0.65	0.57	9.51	1.75
6	0.58	0.44	9.07	2
7	0.54	0.37	9.43	12
8	0.51	0.32	9.49	3.6
9	0.49	0.28	9.65	4
10	0.46	0.24	9.27	12

Results and Discussion

To obtain a decablock of polysarcosine the polymerization was performed in ten consecutive reaction steps, each step with a targeted degree of polymerization of 10. The corresponding reaction scheme is displayed in **Figure 1**. First the ROP of Sar-NCA was initiated with benzylamine. Initiator and reaction conditions are based on previous investigations[8]. After complete monomer consumption as estimated from our kinetic investigations, fresh monomer (Sar-NCA) solutions were added after different time intervals (**Table 1**).

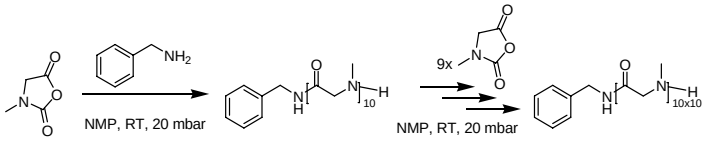

Figure 1. Schematic representation of synthesis of the decablock.

The growth of the polymer chains was followed by gel permeation chromatography (**Figure 2**). The elugrams of each step showed a clear shift to shorter elution times with increasing number of blocks corresponding to a molar mass increase after each polymerization step. Please note that the signal intensities were not normalized.

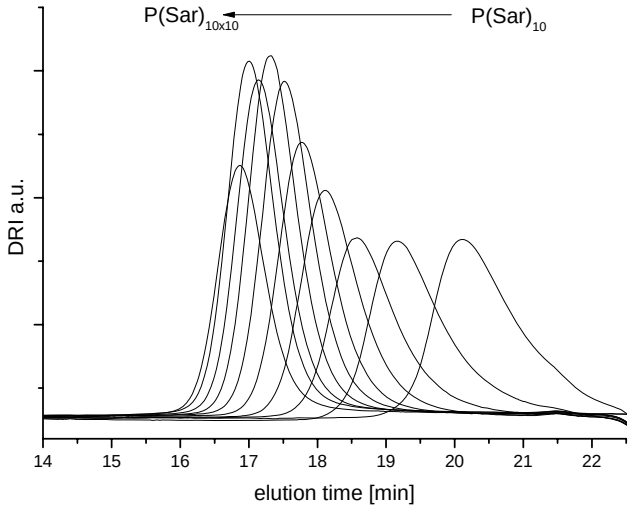

Figure 2. Gel permeation chromatography elugrams of the multiblock polysarcosine samples prepared in this study. Each elugram, starting from $P(Sar)_{10}$ represents the macroinitiator for the polymerization of the subsequent polymer. (block IDs 1 through 10, **Table 1**).

The analytical data of products of the different polymerization steps are listed in **Table 2** . The development of M_n vs. number of blocks shows a continuous increase of the molar mass. This demonstrates clearly, that the

polymer termini (secondary amine) remain active throughout the entire process. We were unable to find evidence for chain transfer, corroborating earlier results[8]. Moreover, no significant amount of remaining macroinitiator could be identified in any of the 10 steps as evidenced by lack of low-molar mass shoulders or peaks. The slight asymmetry in the signals of the first three polymers (block ID 1-3) is attributed to line broadening in the GPC experiment. The dispersities (Đ) of the polymers steadily decrease to values around 1.1.

Table 2. Analytical Data of the Decablock Including All Polymerization Steps from GPC

block ID	$M_{theo.}$[a] [kg/mol]	M_n [kg/mol]	M_w [kg/mol]	Đ
1	0.82	0.58	0.87	1.52
2	1.52	1.15	1.46	1.26
3	2.23	1.85	2.21	1.20
4	2.90	2.66	3.02	1.14
5	3.57	3.35	3.76	1.12
6	4.22	4.13	4.45	1.08
7	4.89	4.64	5.04	1.08
8	5.56	5.14	5.59	1.09
9	6.25	5.46	6.05	1.11
10	6.91	5.96	6.57	1.10

[a] As calculated from $[M]_0/[I]_0$

The experimentally obtained molar masses differ somewhat from the theoretical molar mass (calculated from $[M]_0/[I]_0$). However, apart from the first block, the experimental values range between 75 % and 95 % of the calculated ones. To some extend this may be attributed to the applied calibration standard PMMA, short polymerization times or weighing errors. On the other hand, we and others have observed repeatedly that molar masses of polypeptoides in general and polysarcosine in particular tend to be somewhat lower as targeted[8,9]. Moreover, monomer hydrolysis may also be responsible, because it is well-known that NNCAs are exceedingly sensitive to hydrolysis[10]. We have studied the polymerization of multiple blocks of the same monomer in order to ensure straightforward and artefact free analysis of the product. Our results corroborate earlier findings of us and others[1,8], that the amine terminus is virtually "immortal", i.e. does not undergo termination reactions. This finding should hold true when other NNCAs are polymerized. However, other issues such as monomer reactivity and different polymerization rates may interfere with the preparation of highly defined block copolymers of different NNCAs.

Conclusions

We have presented that sarcosine-*N*-carboxyanhydride can be polymerized via ROP in multiple consecutive steps. The molar masses increase steadily with the sequential monomer addition with no evidence of chain transfer events or termination of chains throughout the entire experiment. We obtain an acceptable agreement between calculated ($[M]_0/[I]_0$) and observed molar masses. Additional characterization, such as MALDI-ToF MS as well as extension of the presented approach is currently under way.

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