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Polypeptoid Brushes by Surface-Initiated Polymerization of N-Substituted Glycine *N*-Carboxyanhydrides

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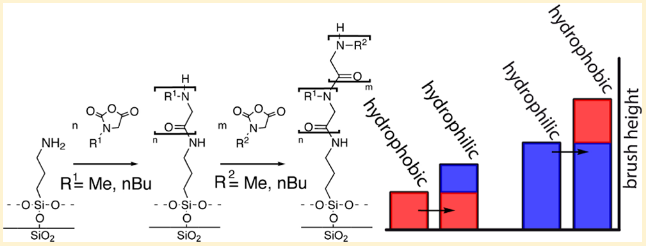
ABSTRACT: Polypeptoid brushes were synthesized by surface-initiated polymerization of N-substituted glycine N-carboxyanhydrides on self-assembled amine monolayers. Using the presented grafting-from approach, polypeptoid brush thicknesses of approximately 40 nm could be obtained as compared to previously reported brush thicknesses of 4 nm. Moreover, hydrophilic, hydrophobic and amphiphilic polymer brushes were realized which are expected to have valuable applications as nonfouling surfaces and as model or references systems for surface grafted polypeptides.



INTRODUCTION

In various fields, like biotechnology,[1] food processing,[2] and biomedical/biomaterials science,[3−5] much attention is paid to protein adsorption and denaturation at solid surfaces. This property is critically influencing biocompatibility, nonfouling coatings, and selective attachment of specific proteins.[4−7] A promising attempt features peptide-based self-assembled monolayers to prevent the attachment of proteins.[8] The versatile peptide chemistry enables the creation of a manifold of coatings with desired and switchable functions and excellent biocompatibility.[9,10] However, peptides are prone to degradation and tend to undergo secondary structure formation via intra- and intermolecular hydrogen bonds, which influences biocompatibility.

Polypeptoids are a class of biomimetic polymers that resemble polypeptides to some extent.[11] They feature a poly(glycine) backbone, but in contrast to polypeptides, they are substituted at the amide nitrogen. Polypeptoids are either synthesized by nucleophilic living ring-opening polymerization (NuLROP) of N-substituted glycine *N*-carboxyanhydrides (NNCA) or by iterative submonomer solid-phase synthesis (SSPS).[11] The simplest polypeptoid is poly(*N*-methylglycine), also known as polysarcosine (PSar). Due to this substitution, secondary structure formation due to H bonding is impossible. In combination with the excellent hydrophilicity and the electroneutrality, PSar meets all the requirements for the development of a protein repellent coating.[4] Messersmith and co-workers[12−17] prepared substrates with surface tethered hydrophilic polypeptoids, including PSar, and demonstrated the excellent nonfouling properties of the polypeptoids. They synthesized the polymer via SSPS and tethered the polymer onto the surfaces via a peptide anchor. Layer thickness was typically about 4 nm.[13]

For PSar, NuLROP was established already in 1949,[18,19] while other N-substituted NCAs (NNCAs) have only been investigated recently.[20−28] In stark contrast to the ring-opening polymerization (ROP) of NCAs, NuLROP of NNCAs is much less plagued by side reactions.[29] Surface grafted polypeptides have been of interest for researchers for a variety of applications.[30−39] Chang and Frank described the surface initiated ring-opening polymerization (SI-ROP) of amino acid NCAs in solution and by means of chemical vapor deposition.[30,32] On the other hand, Higashi and co-workers utilized prearranged surface-tethered helices to influence the growth of new polymer from the surface.[40] However, the preparation of polypeptide brushes from surfaces is apparently hampered by a number of factors, as is the polymerization of *N*-carboxyanhydrides in solution. Since polypeptoids are intriguing alternatives to polypeptides and NNCA polymerization has shown to be much more robust as compared to NCA polymerization,[11] SI-ROP of NNCAs should be feasible. Comparison of the SI-ROP of NCAs and NNCAs may eventually be helpful to better understand the mechanism and limitations of the method, as was successfully demonstrated for the polymerization in solution.[29] Thus, we investigated the SI-ROP of NNCAs on defined amino-functionalized surfaces [i.e., a self-assembled monolayer (SAM) of aminopropylsilane (APS) on silicon dioxide surfaces (Scheme 1)]. From our present work, it is apparent that there are similarities and differences between the SI-ROP of NCAs and NNCAs. While there appears to be a similar limitation in brush height, we were able to demonstrate the successful preparation of amphiphilic block copolypeptoids using SI-ROP, which has, to the best of

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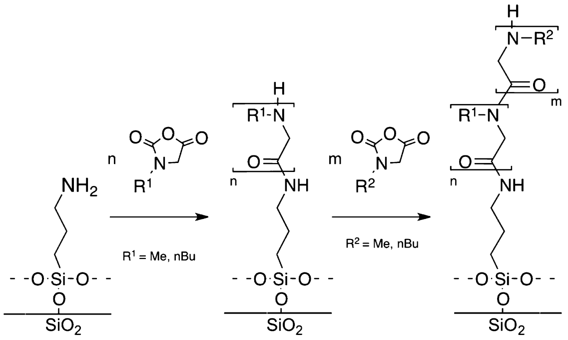
Scheme 1. Reaction Scheme of the Surface-Initiated Polymerization of N-Substituted Glycine *N*-Carboxyanhydrides on Amino-Functionalized SAMs to Yield Hydrophilic or Hydrophobic Polypeptoid Brushes[a]



[a]A consecutive surface-initiated polymerization with different monomers can yield amphiphilic polypeptoid brushes.

our knowledge, not been demonstrated for SI-ROP of NCAs. However, further work will be necessary to elucidate the underlying mechanistic differences.

EXPERIMENTAL METHODS

Materials. All chemicals were purchased from Sigma-Aldrich (Steinheim, Germany) or Acros (Geel, Belgium) and used as received, unless otherwise stated. Acetonitrile (ACN) (extra dry, Acroseal) was transferred and stored in a glovebox. Benzonitrile (BN) and triethylamine (TEA) were refluxed over P_4O_{10} (BN) and CaH_2 (TEA), and distilled under argon prior to use. Dichlormethane (DCM) was stored over $CaCl_2$. All organic solvents were tested regarding their water content using a C20 compact coulometer (Mettler-Toledo, Giessen, Germany) and showed a typical water content <30 ppm. The monomers Sar-NCA and nBuGly-NCA were prepared according to a published procedure.[23] Only bidistilled water was used to treat the samples.

Pretreatment of Substrates. Silicon wafer pieces (approximately 10 × 5 mm) with a 300 nm oxide layer were obtained as a generous gift from Wacker AG, Burghausen, Germany. Substrates were cleaned with piranha solution (H_2O_2:H_2SO_4, 1:3 v/v, 90°C, 30 min; WARNING: Piranha solution reacts violently with organic matter!), washed extensively with bidistilled water, and dried with a stream of dry argon.

Preparation of Self-Assembled Monolayers (SAMs). Freshly cleaned substrates were immersed in a 5% (v/v) aminopropyltrimethoxysilane (APTMS) solution in dry acetone and subjected to treatment with ultrasound for 30 min. After SAM formation, the samples were extensively rinsed with dry acetone and dried under argon atmosphere. Curing of the substrates took part overnight at room temperature. The quality of this SAM preparation method was confirmed by X-ray photoelectron spectroscopy (XPS) ($d = 0.72$ nm) and water contact angle ($\Theta = 55 \pm 3°$) measurements as published earlier.[24] All substrates were transferred to a glovebox and rinsed with dry acetonitrile prior to use.

Polymerization Procedures. The monomer solution was prepared in dried Schlenk tubes in the glovebox by dissolving 1 mmol monomer (115 mg of Sar-NCA, 157 mg of nBuGly-NCA) in 1 mL BN. After complete dissolution of the monomer, the substrates were immersed and 0.1 mL TEA was added to deprotonate any surface ammonium groups. The reaction solution was stirred under an inert and dry atmosphere at r.t. in an open reaction vial (evolution of CO_2!). The same procedure was performed for consecutive polymerization experiments. In this case, substrates were removed from the reaction mixture and rinsed thoroughly. Subsequently, the substrates were reimmersed in fresh monomer solution.

Characterization of Substrates. The optical thickness of polymer layers was determined on a Sentech SE 800 spectral ellipsometer, assuming a refractive index of 1.45 and applying the Cauchy model for fitting. The used parameters were in good agreement with the parameters used for protein layers[41] and were identified by the group of Messersmith.[15,16]

Static water contact angles were measured on a Krüss DSA10. The given contact angle presents the average of at least 5 measurements on different sample spots selected randomly.

AFM scans were recorded with a Ntegra Aura (NT-MDT) atomic force microscope with a SMENA head in the semicontact mode. The used probes have a typical curvature radius of 6 nm, a resonant frequency of 47−150 kHz, and a force constant of 0.35−6.10 N/m.

The surface roughness (arithmetic average of absolute values, Ra) was determined with the free data analysis software "Gwyddion" (http://gwyddion.net/) at several characteristic areas of the sample in the dimension of 5 × 5 μm. IR spectra were recorded with a Nicolet 5700 (Thermo) IR spectrometer. The polymer powder was ground with potassium bromide, pressed into a clear disc, and mounted in the optical path. The spectrum was recorded in the transmission mode using a DTGS detector. The spectrum of the polymer brushes was recorded with a VariGATR (Harrick) grazing angle ATR accessory with Ge ATR crystal and a liquid nitrogen cooled MCT detector.

XPS was performed on several freshly prepared APS monolayers to verify reproducibility of the SAM preparation. The spectra were recorded with an Omicron Multiprobe spectrometer using monochromatic aluminum K alpha radiation. The spectra were calibrated by setting the Si 2p signal to 102.0 eV. Spectra were fitted by symmetric Voigt functions with a Shirley background correction.

RESULTS AND DISCUSSION

Primary amino functions are the initiator of choice for the ROP of NCAs and NNCAs.[23,28,29] It is expected that the grafting-from approach in combination with living polymerizations ensures a high grafting density of linear chains. Thus, a better surface screening in combination with thicker layers for a given polymerization degree as compared to the grafting-onto approach should result. Moreover, the use of SAMs as thin two-dimensional initiator systems offers the possibility of direct patterning at any length scale.[42] APS-SAM-modified silicon wafer pieces bearing a 300 nm silicon dioxide layer were immersed in a 1 M solution of NNCA in benzonitrile. In this solvent, high polymerization rates at room temperature have been observed.[23] The successful preparation of a homogeneous APS-SAM was confirmed by contact angle measurement (data not shown) and X-ray photoelectron spectroscopy (XPS). First, we investigated the increase of the layer thickness with the SI-ROP reaction time using Sar-NCA as the monomer (Figure 1). The initial growth rate was found to be 0.55 nm/h, but eventually a plateau at a brush thickness of about 40 nm is reached. In comparison, PSar brushes prepared by grafting-onto only gave approximately 4 nm thick layers.[15,16] This increased brush thickness, accessible through our approach, could be particularly important for effective surface screening and long-term use of PSar brushes. The layer growth rate we observed was about 1 order of magnitude smaller as compared to the rates observed by Frank et al.,[34,39] presumably due to our solution-phase approach.

Moreover, Frank et al. and Schouten and co-workers found a similar limitation of the brush layer thickness for the SI-ROP of various unsubstituted NCAs.[35,43−45] They attributed the layer thickness limitation to the formation of chemically or physically "dead" chain ends, which is commonly regarded as major limitation on controlling NCA polymerization, also in solution.[29] However, the mechanisms responsible for chemical inactivation of NCAs should not apply for NNCAs, as these

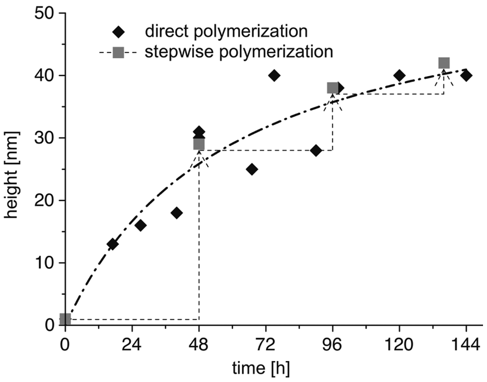


Figure 1. Layer thickness vs time as determined by ellipsometry (individual experiments) for surface-initiated polymerization of sarcosine *N*-carboxyanhydride. The arrows connect data points obtained by consecutive polymerization of one sample using fresh monomer solution. The dotted−dashed line indicates the fit of all data points, using a Langmuir isotherm model.

cannot deprotonate at the nitrogen atom; the attack at the 2-position of the ring leading to hydantoic acids termini is blocked,[46] and the *β*-sheet or *α*-helix formation within the brush[34] can be ruled out due to the lack of inter- or intramolecular hydrogen bonding.[11] Thus, our results hint that other factors or mechanism may be responsible, potentially also in the case of SI-ROP of NCAs.

Another possibility for the limitation of brush height is the gelation of the monomer solution and therefore, reduced access of fresh monomer to the surface. Hence, we performed consecutive polymerization experiments by repeated addition of fresh SarNCA solution to surfaces (after removal of previous reaction medium). In solution, the living ring-opening polymerization of Sar-NCA allowed consecutive monomer addition for at least ten times.[27] Also for SI-ROP of Sar-NCA, we were able to restart the polymerization for several times and the resulting brush thickness after a given total polymerization time fits excellently to the brush heights obtained by a series of individual experiments and show the living character of the SI-ROP (Figure 1, arrows).[27] However, a similar limitation of the maximum layer thickness at approximately 40 nm was observed. Thus, gelation or increase in solution viscosity can be ruled out to be a significant factor regarding the limitation of the layer thickness. Interestingly, Shouten and co-workers found that in a first step, polymerization of *γ*-benzyl-L-glutamate-NCA yielded 20 nm thinkness after 24 h, while in a second polymerization of the same monomer only an 8 nm increase in layer thickness was observed.[44] In that work, the limitation was attributed to a formation of nongrafted, physisorbed material on top of the chemisorbed ones. However, why after washing a reduced growth rate is observed remained and remains unclear.

In our case, a layer thickness of 40 nm would correlate to a contour length of PSar with a degree of polymerization (DP) of 111. However, it should be noted that it is not assumed that the PSar is fully extended, so a larger DP is expected. The polymerization of Sar-NCA has been used for decades to elucidate the polymerization mechanisms of NCAs. It has been well-established that the common limitations of NCA polymerizations can be ruled out for NNCAs, yet on surfaces, a limitation of the brush height is clearly evident. Possible reasons for this are currently under investigation in our laboratories. One hypothesis is that the attack at the 2-position of the monomer is severely limited but cannot be ruled out entirely. However, since this appears to be no significant limitation in solution polymerization, we find it unlikely to be of major importance. It more likely appears to be a mechanism which is specific to the surface initiated polymerization (and the resulting high local chain density) that has yet to be discovered. The surface coverage was found to be very homogeneous, and the surface appeared to be very smooth with a mean surface roughness of <1 nm (Ra) (Figure 2). This stands in contrast to the observations for surfaces which were coated with different polypeptides [e.g., poly(*γ*-benzyl-L-glutamate, poly(*β*-benzyl-L-aspartate) and others], which were thinner and exhibited a higher surface roughness.[34] Although hypothetical, this may be attributed to the formation of secondary structures in the case of polypeptides and their absence in the case of polypeptoids, respectively.

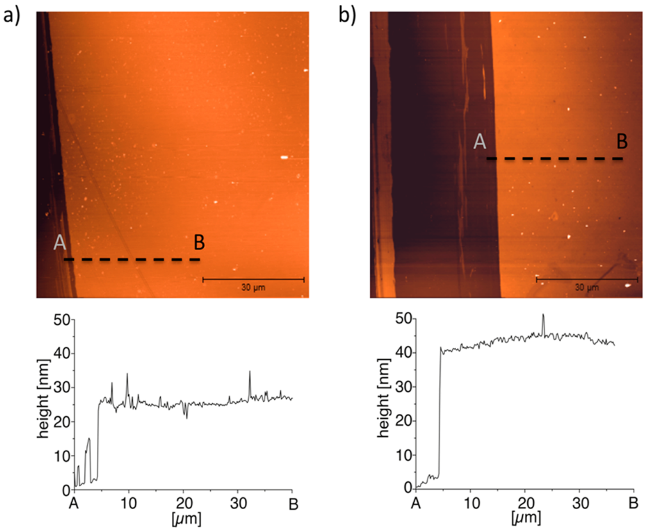


Figure 2. The AFM scans of (a) PSar brushes after 48 h of polymerization and (b) PSar homoblock brushes after the third consecutive polymerization and a total polymerization time of 138 h. The roughness analysis of representative areas showed for both samples a typical arithmetic average roughness of less than 1 nm.

In Figure 3, transmission Fourier-transform infrared spectra of bulk PSar prepared by solution polymerization and attenuated total reflectance Fourier-transform infrared spectra of a PSar layer prepared by SI-ROP on APS-SAMs are compared. In both spectra, the typical absorption bands are present, confirming the successful preparation of surface-tethered PSar by SI-ROP.

The smooth and homogeneous surface coverage is important for the use of tethered polypeptoids for nonfouling coatings as polymer brushes exhibit superior properties due to their effective substrate surface screening as well as the polymer brush repelling effect on strongly adhering proteins.[24,47,48] As in both cases the tethering was performed by living SI-ROP from a defined SAM, it can be concluded that this method results in the formation of dense polymer brushes. Additionally, the chemical composition of the initiator layer (APS-SAM) and the PSar brush was verified by XPS (Figure 4). All expected signals of the monolayer and the SiO_2 signals of the substrate were observed. After polymerization, the Si signals are barely visible because of the screening by the thick polymer layer (h = 30 nm). A detailed scan of the PSar surface (Figure 4c) shows two

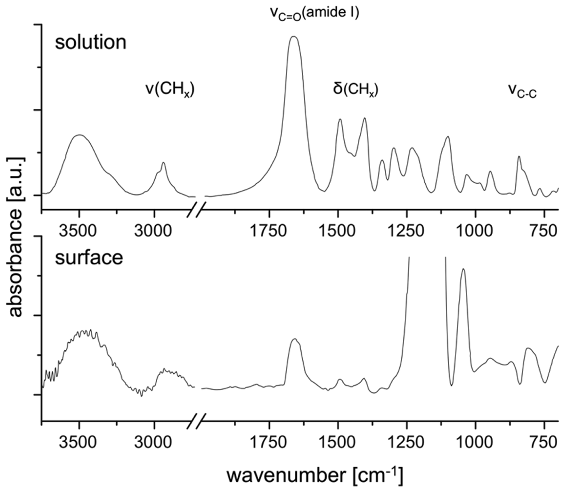


Figure 3. Comparison of the infrared spectra of polysarcosine obtained by solution polymerization and as a polymer brush.

different carbon peaks in a 2:1 ratio. These peaks can be assigned to the different carbon species (CH_2/CH_3 and C═O) of the polymer. The binding energy of the oxygen atom is consistent with a carbonyl group, as expected.

As depicted in Scheme 1, consecutive polymerization was also performed using two different monomers. Sar-NCA yields hydrophilic brushes, while nBuGly-NCA is expected to result in hydrophobic brushes.[23] By consecutive polymerization of the two monomers, amphiphilic polypeptoid brushes should be accessible, the orientation of the brush depending on the order of the monomers employed. Schouten and co-workers have previously prepared block copolypeptides using the same approach, but to the best of our knowledge, no brushes based on amphiphilic polymers were reported, using this methodology.[43]

First, hydrophobic P(nBuGly) brushes were prepared by SI-ROP for 90 h with nBuGly-NCA. It is known that nBuGly-NCA has a much smaller polymerization rate compared to that of Sar-NCA,[23] which is reflected here by smaller brush heights after the same polymerization time. Nevertheless, with a static water contact angle of Θ = 89°, the resulting brushes of 12 nm height exhibits a hydrophobic character (Figure 5). The same substrate was then reacted for 48 h with Sar-NCA to result in an amphiphilic brush [P(nBuGly-b-Sar)] of a total height of 21 nm and Θ < 20°. Apparently, the thin 9 nm PSar brush was sufficient to mask the underlying hydrophobic brush.

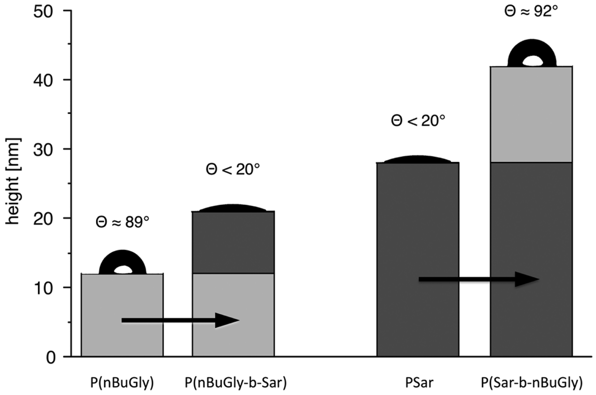


Figure 5. Amphiphilic polypeptoid brushes by consecutive SI-ROP of Sar-NCA and nBuGly-NCA. Brush layer height as determined by atomic force microscopy. Contact angles refer to the static water contact angle (depicted are the actual photos of the sessile water drop).

Accordingly, a hydrophilic PSar brush (h = 28 nm, Θ < 20°) could be converted to P(Sar-b-nBuGly) (h = 42 nm, Θ = 92°), showing remarkably hydrophobic properties and the same water contact angle as a P(nBuGly) homopolymer brush. This not only demonstrates the livingness of the SI-ROP of NNCAs that gives direct access to block copolymer brushes but also demonstrates the formation of dense and homogeneous

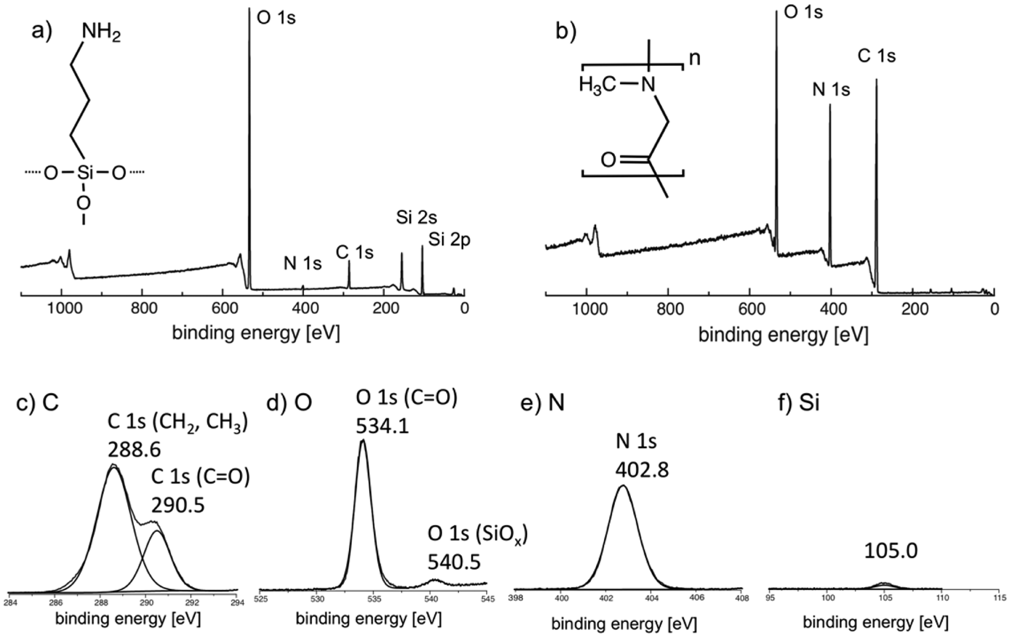


Figure 4. X-ray photoelectron spectra for (a) APS SAM on Si/SiO_2, (b) same substrate after SI-ROP of Sar, and detailed scans of the PSar brush for (c) carbon, (d) oxygen, (e) nitrogen, and (f) silicon.

brushes since in the last case, the underlying hydrophilic PSar block layer does not reduce the static water contact angle. At this stage, we did not perform a systematic long-term study to investigate potential long-term restructuring, but the large contact angles remained unaffected by storage at ambient air humidity over several days.

A more systematic study on the long-term brush restructuring, in dependence of the brush height and solvent challenges, will be necessary and is currently under way in our laboratories. Moreover, we are currently investigating the reasons for the limitation in brush height in SI-ROP of NNCAs.

■ CONCLUSION

In summary, we report on the synthesis of polypeptoid brushes by means of surface-initiated polymerization of different NNCAs on self-assembled monolayers. Exemplarily, the SI-ROP of sarcosine-NCA and *n*-butylgycine-NCA was shown. Dense and homogeneous brush layers were readily obtained with brush layer thicknesses being 10-fold higher than reported by a grafting-onto approach. Hydrophilic (PSar), hydrophobic [P(nBuGly)], as well as amphiphilic polypeptoid brushes are accessible by consecutive SI-ROP. This also demonstrates the living character of the nucleophilic ring-opening polymerization since consecutive homo- and block-copolymerization with a systematic layer thickness increase was observed. The chemical composition was verified by FTIR spectroscopy and XPS. As for NCAs, the SI-ROP of NNCAs was found to be limited in the maximal obtainable brush thickness. This straightforward method is suitable to prepare biomimetic nonfouling coatings that are expected to have improved and prolonged nonfouling properties.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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