Polypeptoids: A Perfect Match for Molecular Definition and Macromolecular Engineering?

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Polypeptoids: A Perfect Match for Molecular Definition and Macromolecular Engineering?

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ABSTRACT: Precision synthesis of polymers has been a hot topic in recent years. While this is notoriously difficult to address for polymers with a C—C backbone, Merrifield has discovered a way many decades ago for polypeptides. Using a similar approach, N-substituted polypeptides, so-called polypeptoids have been synthesized and studied for about 20 years. In contrast, the living ring-opening polymerization (ROP) of N-substituted N-carboxyanhydrides was among the first living polymerizations to be discovered. More recently, a surge in new synthetic approaches led to the efficient synthesis of cyclic or linear multiblock copolypeptoids. Thus, polypeptoids can be synthesized either by solid phase synthesis to yield complex and exactly defined oligo- and small polymers or by ROP of appropriately N-substituted N-carboxyanhydrides (NNCA) to give linear, cyclic, or star-like polymers. Together with an excellent biocompatibility, this polymer family may have a bright future ahead as biomaterials. © 2013 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2013**, *00*, 000–000

KEYWORDS: biomaterials; biomimetic; cyclic polymers; living polymerization; multiblock copolymers; nonfouling; precision polymers; solid phase synthesis; surface initiated polymerization

INTRODUCTION Precise control of polymer structure or the structure of polymer assemblies has been crucial since prebiotic times. From today's perspective, dawn of life on earth would have been impossible without sequence-controlled polymers such as polypeptides (proteins, enzymes) or polynucleotides (DNA, RNA). Nevertheless, also in modern science, control over polymer and assembly structure and architecture remains a heavily investigated field,[1–6] and we have learned much on the effects of structural variation of synthetic polymers and theirs assemblies on their interaction with biological entities.[7–11]

Polypeptoids resemble polypeptides in some ways but are strikingly different in others. Here, we will discuss polypeptoids and closely related polymers (Fig. 1). Despite their interesting properties, truly extraordinary synthetic control and flexibility, comparably few researchers have studied this class of polymers. As a result, a vast field of possibilities remains unexplored. In this highlight, we shall attempt to summarize what has been done, what is being done and what is left to do with polypeptoids.

Sigmund and Wessely were probably the first to study polypeptoids, in particular polysarcosine, in 1926.[12] In this early work, it was reported that sarcosine (Sar) N-carboxyanhydride (NCA) does undergo polymerization upon treatment with pyridine despite the substitution at the nitrogen of the monomer. Several years later in 1949, Waley and Watson demonstrated that SarNCA, similar to ethylene oxide, is able to form polymers via the "third type of polymerization,"[13] the first and second being polyaddition and polycondensation, respectively. Today, more than 60 years later, we know much more than three types of polymerization and polymers dominate modern life and culture; to date, however, polysarcosine and the polypeptoids do not play a significant part in this and even most polymer and materials scientists have lost attention to this interesting class of polymer.

In fact, for decades, polysarcosine was mainly of interest to better understand the mechanism of polypeptide synthesis.[14] This is even more remarkable, as it has been shown repeatedly, that the polymerization is of living character and the products molar mass distributions are in excellent agreement with a Poisson distribution (Fig. 2).[15]

Despite the notorious difficulties with its controlled synthesis, poly-L-proline became interesting for polypeptide researchers in the 1950s and especially 1960s.[16–19] In contrast to

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Corinna Fetsch studied chemistry at the TU Dresden and received her MSc in 2010. After her master thesis under the supervision of Robert Luxenhofer she started as a PhD student in the group of Prof. Rainer Jordan. In 2012 she moved to the Würzburg University, where she is currently working on the synthesis and characterization of well-defined polypeptoids in the group of Prof. Robert Luxenhofer.

Arlett Grossmann was born in Döbeln in 1983. After professional training to be a pharmaceutical technician, she studied chemistry at the TU Dresden. In 2011, she received her MSc for a work on the synthesis of new amphiphilic block copolypeptoids at the chair of macromolecular chemistry. She is currently working on her PhD thesis studying poly(*β*-peptoid)s.

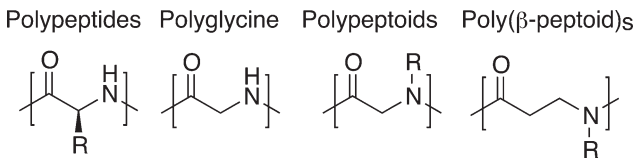

FIGURE 1 Schematic representation of polypeptoids and related materials discussed in this highlight.

polysarcosine, which assumes random coil in solution, poly-L-proline is able to form a fairly stable secondary structure in solution.[18,20] Later, this was found to be true also for other polypeptoids[21–23] and other pseudo-polypeptides.[24]

Maurer et al. studied the immunogenicity of polysarcosine in rabbit and found it to be very low, if detectable.[25] Despite these very encouraging and interesting properties, polypeptoids did not become very popular in the polymer sciences. In fact, during the 1990s and the early 2000s, polysarcosine and related materials, prepared by polymerization, appear to have been investigated almost exclusively by a few groups in Japan, which concentrated on biomedical applications[26–32] and Kricheldorf and coworkers in Germany, which studied the polymerization mechanism in more detail.[33–39]

However, around the same time, the first reports on polypeptoids obtained by a step-wise solid phase synthesis approach can be found in the literature.[22,40–43] In contrast to the well-defined, yet dispers polypeptoids obtained by ring-opening polymerization (ROP), these materials can be prepared in a sequence specific manner and can be obtained as monodispers products (typically after some purification).

POLYPEPTOID SYNTHESIS IN SOLUTION

Polypeptoids

Synthesis of polypeptoids as well as polypeptides by ROP of NNCAs or NCAs, respectively, has been reported in solution or bulk. In 1950, Wessely et al. suggested that these compounds are exceedingly sensitive to hydrolysis,[44] which may be one reason why NNCAs, except for SarNCA, have been widely ignored over the last 6 decades, despite the fact that it has been demonstrated early that the polymerization has a living character.[13,15]

In recent years, a number of NCA with substituents other than methyl have been prepared and polymerized (Fig. 3). It is apparent that only saturated and unsaturated aliphatic side chains have been realized to date. Their polymerization has been demonstrated after initiation by nucleophiles, in particular primary amines, or N-heterocyclic carbenes (NHC).

Nucleophiles as Initiators

As noted before, the living character of the nucleophilic living ring opening polymerization (NuLROP) of SarNCA has been essentially demonstrated very early.[13,15] Besides simple monovalent primary amines, Aoi et al. demonstrated that complex multiamines [Fig. 4(a)] such as dendrimers are very suitable, too,[30] while Kricheldorf used diamines to prepare

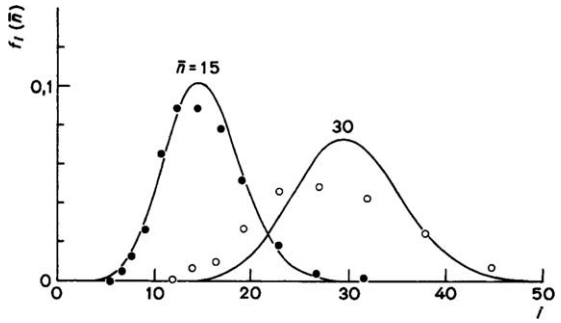

FIGURE 2 Comparison of theoretical distribution (Poisson distribution) and experimentally obtained distribution of polysarcosine of degrees of polymerization = 15 and 30. (Reproduced from Ref. 15).

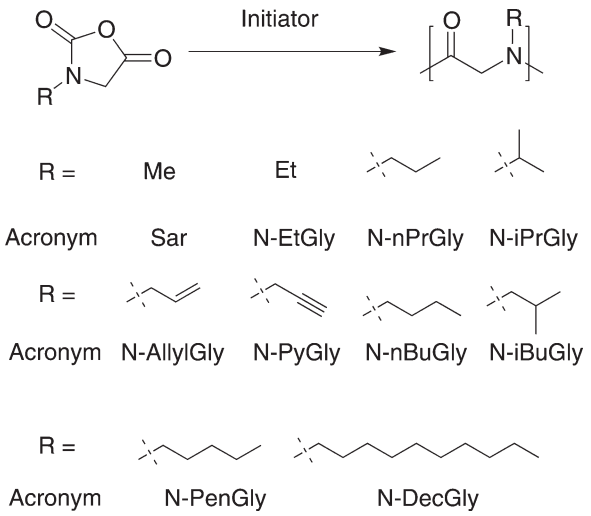

FIGURE 3 N-Substituted N-carboxyanhydrides that have been polymerized by ring opening polymerization to give the corresponding polypeptoids. As initiators, primary amines and NHC have been used.

homobisfunctional telechelic polysarcosine (PSar).[36] In the latter report, the determined degrees of polymerization by ^{1}H-NMR spectroscopy were in good agreement with the feed ratios ($[M]_0/[I]_0$) and Maldi-ToF mass spectrometry revealed a narrow distribution with the absence of side reactions and cyclic polypeptoids.

The first proof of principle regarding the synthesis of block copolypeptoids gave Guo and Zhang.[46] This work concentrated on the synthesis of cyclic polypeptoids (*vide infra*), but to characterize and compare their products they also synthesized linear polypeptoids. However, here the characterization of the linear products was limited to ^{1}H-NMR spectroscopy and measurements of the viscosity.[46] Thus, assessment of the quality of the block copolymer synthesis is difficult.

Recently, the same group prepared linear copolypeptoids consisting of N-ethylglycine and N-butylglycine units. Determination of the reactivity rates by the Fineman-Ross method revealed similar values, therefore, random copolymers should be obtained by the ROP.[47]

More extensive studies on the synthesis and characterization of homo and block copolypeptoids bearing short aliphatic side chains (C1–C4) were reported by Luxenhofer et al.[45,48,49] Kinetic investigations under different conditions (monomer, solvent, addition of acid, CO_2 partial pressure) were performed. All polymerizations revealed a linear pseudo first order plot to high monomer conversion and a linear correlation of the monomer consumption and the molar mass of the polymers (Fig. 5). Furthermore, resulting polypeptoids gave characteristic narrow molar mass distributions. Polymerization rates for the homopolymerization were heavily dependent on the substituents at the nitrogen (Me >> Et > Pr > nBu > iBu) and on the used solvent (polymerization rates benzonitrile > N-methyl-2-pyrrolidone > THF).[48] Interesting to note, Schlaad succeeded recently to polymerize N-isopropylglycine NCA.[50] An early report by Ballard and Bamford suggested that this monomer cannot be polymerized.[51] Indeed, Schlaad reported that this is not possible in solution, but by adding initiator to the monomer melt, polymers with low dispersity could be obtained.

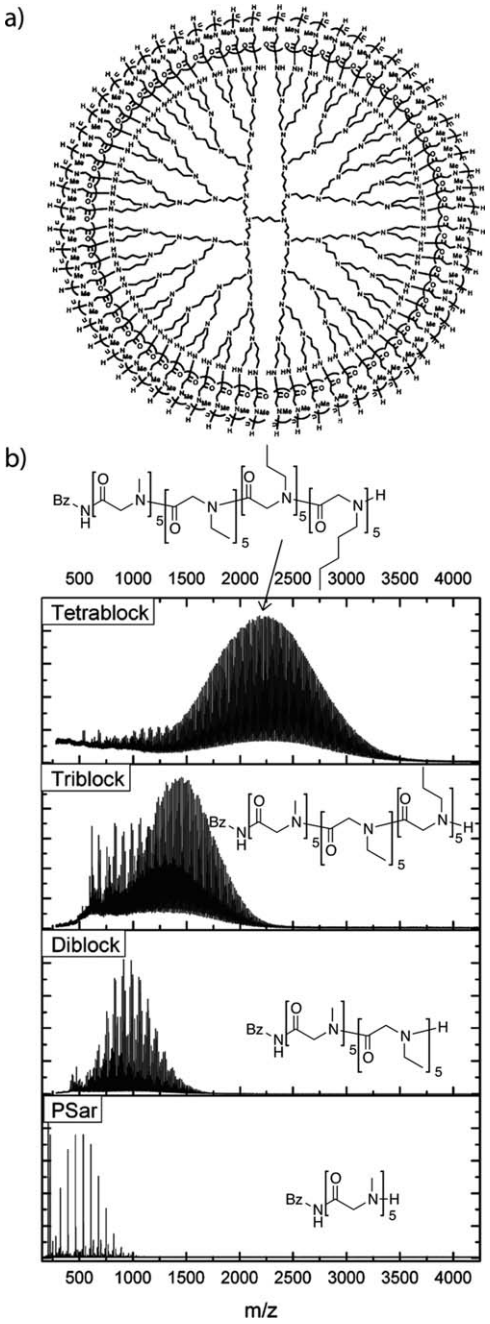

FIGURE 4 Complex polypeptoids, such as (a) star-like and (b) multiblock copolypeptoids are accessible via NuLROP of NNCAs. (Reproduced from Refs. 30 and 45, with permission from Wiley-VCH).

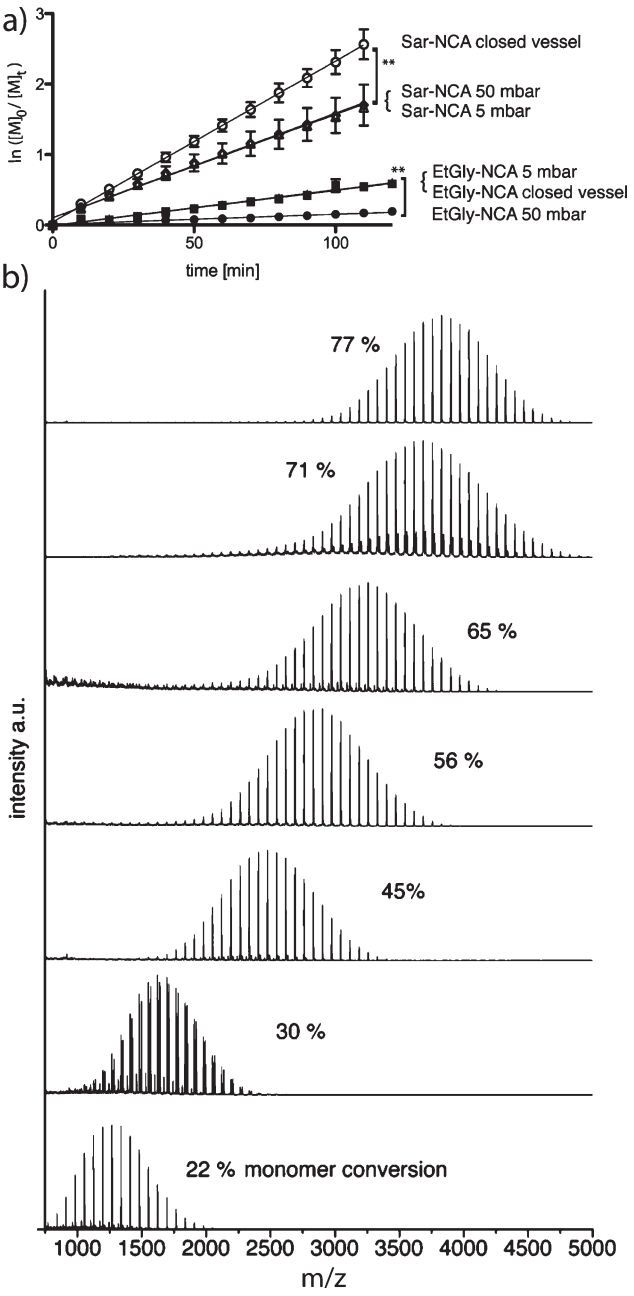

FIGURE 5 Demonstration of the living character of the nucleophilic living ROP by kinetic investigations. (a) Pseudo-first order kinetic plots are typically linear to quantitative monomer conversion (>95 %) and (b) the molar mass of the polypeptoids increases linear with the monomer conversion. (Reproduced from Ref. 48, with permission from Wiley-VCH).

The living character of the ROP of NNCAs allows for the preparation of multiblock copolymers [Fig. 4(b)].[45] To demonstrate this, but allow for Maldi-ToF mass spectrometry of the products, multiple chain extensions of polysarcosine by multiple consecutive monomer addition steps was performed. Furthermore, the synthesis of a defined pentablock quinquiespolymer, that is, a block copolymer comprising five different monomers, could be realized.[45] Moreover, the NuLROP was shown to be highly reproducible (Fig. 6).

Monomer synthesis of NCAs bearing functional substituents at the nitrogen is a significant challenge. However, such side chains are essential to create complex and smart biomimetic biomaterials. An alternative to monomer synthesis is post-polymerization modification, for example, via click chemistry, after the polymerization of the monomers. This was first demonstrated by Zhang and coworkers.[52] After copolymerization of N-propargylglycine, copper catalyzed azide-alkyne 1,3-dipolar cycloaddition of azides to alkynes was used to PEGylate a polypeptoid backbone. After polymerization, ^{1}H-NMR and ESI mass spectra of the products revealed the formation of 1,4-di(prop-2-ynyl)piperazine-2,5-dione in small quantities. In previous studies on NHC-mediated polymerization of aliphatic side chains, no similar products were observed.

More recently, Schlaad et al. synthesized N-allylglycine NCA and polymerized the monomer with benzylamine in different solvents.[50] As demonstrated before with aliphatic side chains[48] the characterization of the obtained poly(N-allylglycine)s showed that benzonitrile is the most suitable solvent for the polymerization. Thiol-ene chemistry was performed subsequently and ^{1}H-NMR spectroscopy as well as Maldi-ToF

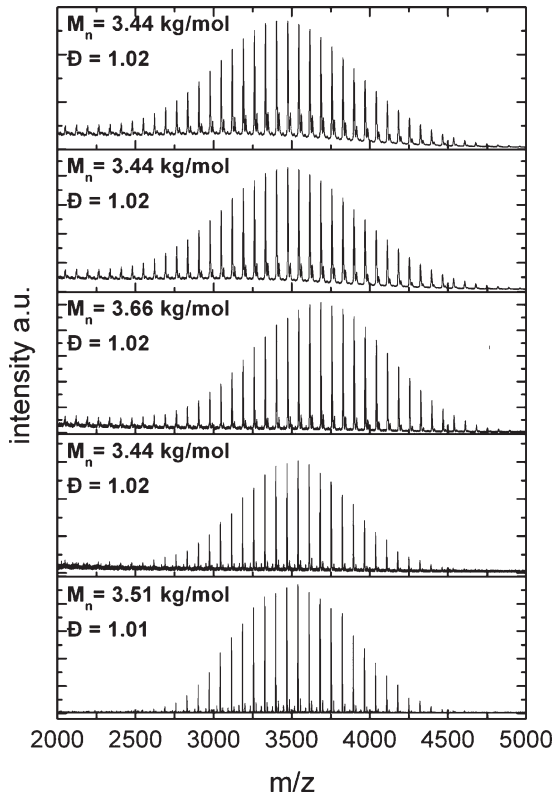

FIGURE 6 The NuLROP of NNCAs allows for a highly reproducible polymer synthesis as depicted for 5 different batches of PSar (DP = 50). (Reproduced from Ref. 45, with permission from Wiley-VCH).

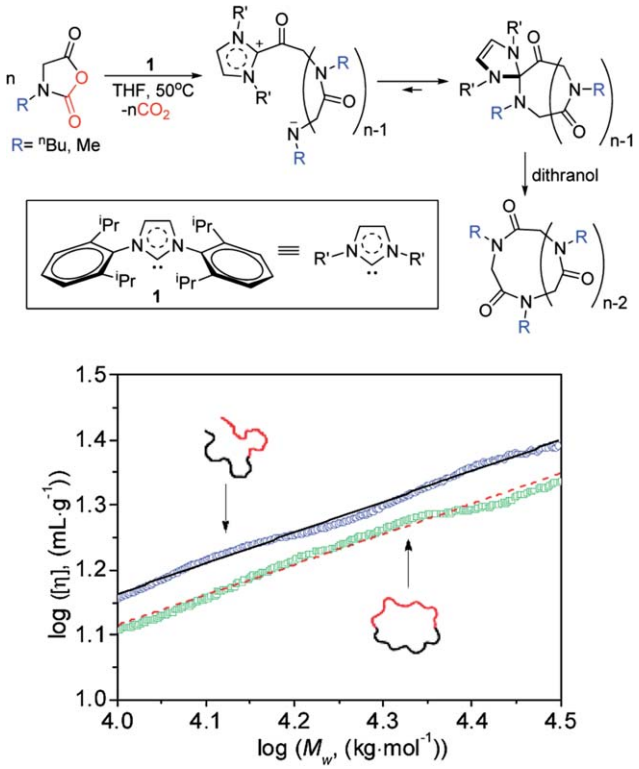

FIGURE 7 Schematic representation of the preparation of cyclic polypeptoids using NHC as catalysts. (Reproduced from Ref. 46, with permission from American Chemical Society).

mass spectrometry revealed quantitative degrees of side arm modifications, within the analytical limitations.[50]

NHC as Initiators

NHC are an interesting class of catalysts for a large variety of reactions.[53,54] Also for the ROP of cyclic dilactides, these catalysts have been used before.[55,56] Interestingly, the primary product are cyclic polymers. Along these lines, Zhang and coworkers studied the ROP of NNCAs (Fig. 7).[46,47,52,57–60] In contrast to NuLROP and analog to NHC mediated ROP of dilactides, mechanistic studies revealed a zwitterionic ROP with a living character. Steric and electronic properties of the used NHC, solvent, N-substitution at the NCA as well as reaction temperature affects the control of the polymerization and the polymerization rate in varying degrees. However, different NHCs provide a comparable control over the polymer molecular weight and the dispersity; however, polymerization in solvents of high electric constants, for example, DMSO or DMF, the control is substantially diminished. The polymerization rates of investigated monomers in toluene were in the following order ethylglycine-NCA > propylglycine-NCA = butylglycine-NCA > allylglycine-NCA.[60]

Early studies about the syntheses of cyclic poly(N-butylglycine)s as well as cyclic poly(N-methylglycine)-b-(N-butylglycine) by sequential monomer addition revealed products with controlled molecular weights and narrow dispersities in high purity. In contrast to the linear analogues, cyclic polypeptoids exhibited lower intrinsic viscosities, but nearly identical Mark-Houwink exponents.[46] As mentioned before, Zhang et al. studied the polymerization of N-propargylglycine-NCA and its copolymerization with nBuGly. Homopolymers and copolymers were subjected to post-polymerization modification. Grafting densities were noticeably higher when a copolymer with nBuGly was employed. AFM measurements of the cyclic brush-like polymers displayed donut-shape-nanostructures (Fig. 8). Important to note, using the zwitterionic ROP of NNCAs, there may be a tendency for the formation of high molar mass products, as evidences repeatedly by GPC measurements for a variety of different monomers.[46,47,52,57] Whether this is an artefact produced by the analytical technique or can be attributed to a particular feature of the zwitterionic ROP of NNCAs remains to be elucidated.

Poly(*β*-peptoid)s

By a formal addition of a methylene group to the backbone of polypeptoids, poly(*β*-peptoid)s are obtained. This family of polymers, which could be also formalized as N-substituted polyamide 3 has been much less investigated as compared with the polypeptoids. This is despite the fact that compared with polypeptoid synthesis, more synthetic routes toward

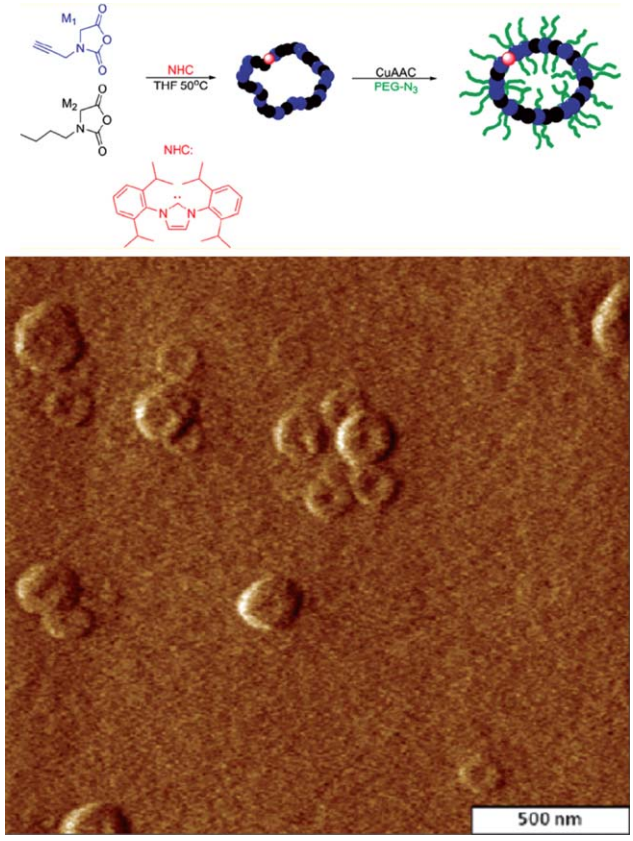

FIGURE 8 Schematic representation of the preparation of cyclic PEGylated polypeptoids brushes and atomic force amplitude scan of the brushes on mica. (Reproduced from Ref. 52, with permission from American Chemical Society).

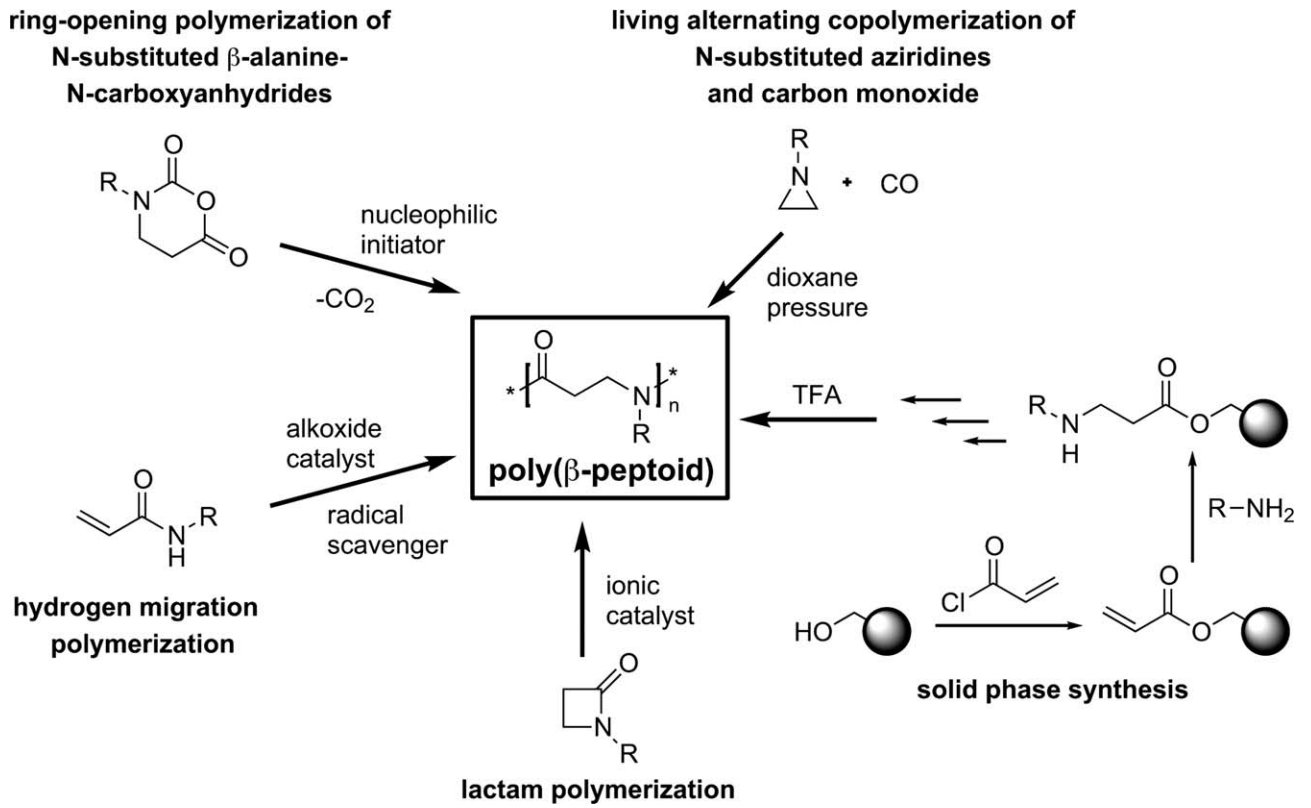

FIGURE 9 Synthetic approaches towards poly(β-peptoids) that have been described in the literature.

poly(β-peptoid)s have been discovered. Overall, five different approaches can be found in the literature (Fig. 9).

As will be outlined, there are mainly two reasons that limit access to poly(β-peptoid)s, in our opinion. First, monomer and polymer synthesis is more challenging as compared with their smaller homologues. Second, polymer solubility is typically very poor in most solvents.

Poly(β-peptoid)s from β-NNCAs

Only a few different N-substituted β-alanine-NCAs (β-NNCAs) have been reported to date (Fig. 10). The first β-NNCA was reported by Birkofer and Kachel in 1954.[61] N-*p*-Tolyl-β-alanine-NCA was synthesized by treatment of N-*p*-tolyl-β-alanine with phosgene in dioxane. As intermediate, the crystalline N-*p*-tolyl-N-chloroformyl-β-alanine was obtained, which forms the 6-membered N-*p*-tolyl-β-alanine-NCA after addition of triethylamine in etheric solution. The polymerization was observed by heating the β-NNCA above its melting point.

Three years later the same group described the synthesis of N-phenyl-β-alanine-NCA.[62] Monomer synthesis was again performed by addition of phosgene to the N-substituted β-alanine in dioxane via the N-chloroformyl intermediate. The monomer was obtained in 71% yield. Interestingly, the formed triethylamine hydrochloride could be removed by extraction with ice water, a method Poché and Daily reported much later for NCAs.[63] Birkhofer et al. report a relatively higher stability of N-phenyl-β-NNCA and the N-*p*-tolyl-β-NNCA against hydrolysis, in comparison to N-substituted α-amino acid-NCA. Nevertheless, carbon dioxide formation started immediately, when the mentioned β-NNCAs were heated in water.[62]

Subsequently, the polymerization of N-phenyl-β-NNCA was studied. After a few hours, ongoing precipitation of polymer was observed after addition of one drop of water to a β-NNCA solution in dioxane. The obtained polymer exhibited a melting point of 226–228 °C and was found to be only soluble in glacial acetic acid and dimethyl formamide. The observed degree of polymerization was about 18–20 and could not be increased by an extended reaction time. The molar mass ($M_n = 2.8$ kg/mol) was determined by end-group titration. In contrast, by heating the monomer to 145 °C at

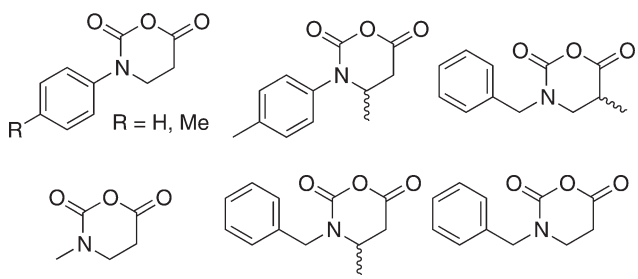

FIGURE 10 N-Substituted N-carboxyanhydrides of β-amino acids reported to date.

50 mbar (0.04 torr), poly(N-phenyl-β-alanine) with a degree of polymerization of 111 and M_n of 16.3 kg/mol was obtained.

In 1964, Zilkha et al. reported on the synthesis of poly(N-benzyl-β-alanine).[64] The polymerization of N-benzyl-β-NNCA was studied in detail by variation of the types of initiator in various solvents and investigated the effect of variation of the monomer/initiator ($[M]_0/[I]_0$) ratios on the molecular weight of the polymer. A high reactivity and ready polymerization of N-benzyl-β-NNCAs was noted. In dioxane with *n*-hexylamine as initiator, they obtained poly(N-benzyl-β-alanine) with the highest degree of polymerization of about 109 and a molar mass of 17.5 kg/mol. In general, *n*-hexylamine was found to be the best initiator and dimethylsulfoxide, benzene or dioxane were the most suitable solvents for the N-benzyl-β-NNCA polymerization. For those systems the DP vs. $[M]_0/[I]_0$-plot shows linear behavior in the range of 10–100 units. The obtained poly(N-benzyl-β-alanine)s were insoluble in most organic solvents. Only dichloroacetic acid and *m*-cresol were good, glacial acetic acid a mediocre solvent. Interestingly, all polymers, even shorter samples, show high decomposition temperatures, in the range of 220–240 °C.

Only very recently, first kinetic studies of the polymerization of N-benzyl-β-NNCA were reported.[65] Also, for the first time, the polymerization of N-methyl-β-NNCA and the preparation of an amphiphilic block copoly(β-peptoid) was shown. Important to note, monomer synthesis was realized via a phosgene-free route. The ring closure was forced by treatment of the N-protected N-substituted amino acid with phosphorus trichloride. Pure product was obtained in poor overall yields (N-methyl-β-NNCA in $<$5% yield, N-benzyl-β-NNCA in 16% yield) by recrystallization. Monomer conversion during polymerization of N-benzyl-β-NNCA was followed via IR. The $\ln([M]_0/[M]_t)$ vs. time plot shows linear behavior to high monomer conversion (80%), which indicates a living character of the polymerization. Maldi-ToF MS indicates that products follow a Poisson-like distribution. The polymerization of N-methyl-β-NNCA was investigated in different solvents. In DMSO, poly(N-methyl-β-alanine) precipitated after a few minutes. Nevertheless, Maldi-ToF analysis of the obtained polymer yielded a degree of polymerization of 24 ($[M]_0/[I]_0 = 25$) and a low dispersity ($Đ = 1.04$). However, when higher degrees of polymerization were attempted, the obtained polymers remained much smaller then expected while generally low dispersities were observed. These results suggest that solubility problems may be responsible for the lower DPs. Generally the obtained poly(N-methyl-β-alanine)s are only soluble in a mixture of chloroform and methanol or ethanol as well as water.

Despite the limitations that remain at present in the control over the NuLROP of β-NNCAs, an amphiphilic block copoly(β-peptoid) was prepared successfully. N-Methyl-β-NNCA was used for preparation of the hydrophilic block, N-benzyl-β-NNCA as monomer for a hydrophobic block. Maldi-ToF measurements confirmed the successful formation of an amphiphilic block copoly-(β-peptoid), which was well-soluble in water and exhibited a marked surface activity.

Poly(β-peptoid)s via alternating polymerization of CO and N-substituted aziridines

Jia et al. developed an alternative route for the preparation of poly(β-peptoid)s. The copolymerization of N-substituted aziridines and carbon monoxide using cobalt catalysts exhibits characteristics of a living polymerization.[66] The method was used to prepare poly(N-methyl-β-alanine) and poly(N-ethyl-β-alanine) in dioxane at 60 °C and 69 bar (1000 psi) CO. Interestingly, the copolymerization of poly(N-methyl-β-alanine) stopped after $\sim$20 catalyst turnovers. It was assumed that the termination of the reaction is due to precipitation of the polymer, which interrupts the access to the catalyst. This is in line with our more recent observation of poor solubility of poly(N-methyl-β-alanine) in organic media. In the case of poly(N-ethyl-β-alanine), higher degrees of polymerization could be realized and a linear correlation of the molar masses vs. monomer to catalyst ratio-plot was observed. These data and the obtained low dispersities are a hint for the living character of the copolymerization.

Later, the same group investigated the polymerization in more detail (kinetic investigation, mechanistic studies) employing N-butylaziridine and carbon monoxide with two different cobalt catalysts of the general structure $CH_3C(O)$-$Co(CO)_3L$ ($L = PPh_3$ or P(o-tolyl)$_3$).[67] Formation of a lactam was observed during the copolymerization when using the catalyst with the PPh_3 ligand. The lactam formation could be completely prevented by using the P(*o*-tolyl)$_3$ – ligand. This observation was explained by the steric demand of the P(*o*-tolyl)$_3$ ligand, which reduces the nucleophilicity of the cobalt center in the complex. Using the latter ligand, side reaction were eliminated. Accordingly, first-order kinetic plots during copolymerization of N-butylaziridine and CO were observed. The authors predicted the possibility for the preparation of block copolymers by addition of an alternative aziridine to the reaction mixture. In 2010, the same group could confirm this prediction by successful synthesis of a block copoly(β-peptoid) consisting of β-alanine and N-butyl-β-alanine.[68]

Alternative approaches towards poly(β-peptoid)s

Several decades ago, two other synthetic approaches for the preparation of poly(β-peptoid)s were reported. On the one hand Kagiya et al. described the polymerization of N-methyl-β-propiolactam with ionic catalysts and discussed different possible mechanisms for the polymerization.[69] Poly(N-methyl-β-alanine) was successfully polymerized in the presence of organic compounds with a carboxylic group such as benzoic acid, N-methyl-β-alanine, or β-alanine at 140 °C. The obtained polymer had a melting range of 198–225 °C and was only soluble in hot water, glacial acetic acid, and partially in methanol. While the latter corroborates findings of others and us, the notion that the polymer was only soluble in hot water contradicts our experience.

Yokota et al. reported the hydrogen migration polymerization of N-substituted acrylamides. The group used different

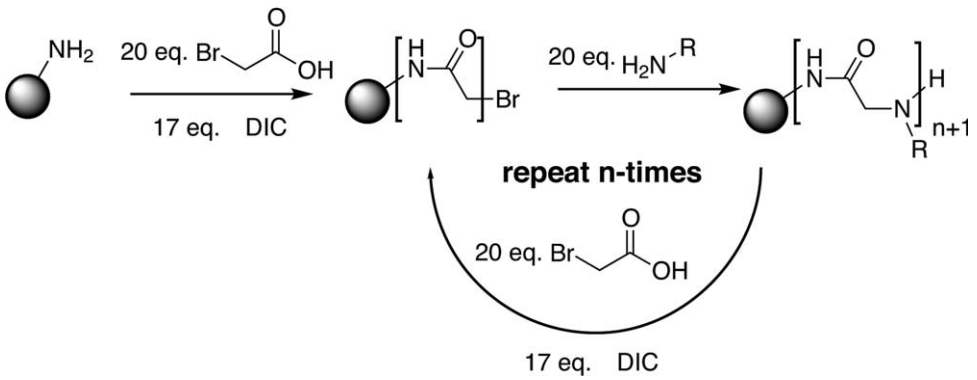

FIGURE 11 Schematic representation of the solid phase submonomer preparation of oligopeptoids and polypeptoids.

acrylamides, for example with cyclohexyl-, benzyl-, phenyl-, and *p*-nitrophenyl as N-substituents. The polymers were investigated by IR spectroscopy. Interestingly, for N-cyclohexyl- and N-*p*-nitrophenyl acrylamides only the vinyl polymer was obtained, while the other monomers gave the hydrogen migrated poly(β-peptoid)s. This effect could be explained by the electron donating effect of the cyclohexyl substituent, which decreases the tendency for the hydrogen to migrate. The *p*-nitrophenyl group has a strong electron withdrawing effect, which gives the amine an acidic character. Nevertheless, also in this case only the vinyl polymer was obtained due to the polar solvent dimethylsulfoxide, which was necessary to use to ensure a homogeneous reaction mixture during the whole polymerization.[70]

Kennedy and Otsu published an extensive review about the hydrogen migration polymerization of acrylamindes and N-substituted N-acrylamides.[71] Among others, the polymerization of N-methylacrylamide was reported by Sebille et al. in 1969. Important to note, only polymers with low molecular weights were obtained.[71]

In summary, the vast majority of the reported work on poly(β-peptoid)s find that the solubility of these polymers is the major limiting factor. This results in a limitation of the degree of polymerization due to the precipitation of the growing polymer chains. It is unclear whether it will be possible to find suitable solvents for the preparation of long-chain poly(β-peptoid)s.

POLYPEPTOID SYNTHESIS ON SURFACES AND SOLID SUPPORT

The synthesis of oligomers and polymers on solid support has been pioneered by Merrifield.[72] This has revolutionized medicinal chemistry and remains to date a synthetic method of outstanding importance. On the other hand, polymer brushes on surfaces exhibit outstanding properties that make them interesting for a variety of applications and technologies.[73–80]

Stepwise Synthesis from Solid Support

The step-wise synthesis from solid support to obtain well-defined oligomers and polymers has long been investigated beyond the original approach towards polypeptides.[81–84] In essence, the advantages and disadvantages have remained the same over the last decades. The control over the polymer sequence is paid by a highly inefficient synthesis, as large excesses of reagents are used, though these may be reused. In addition, polymers comprising >50 monomer units are typically extraordinarily challenging to realize in sufficient purity.

Polypeptoid

Polypeptoids are accessible via the so-called solid phase submonomer synthesis (SPSS). This method, which resembles the Merrifield solid phase peptide synthesis (SPPS) approach towards oligo- and polypeptides has been pioneered by Bartlett and coworkers and later modified and refined in the groups of Zuckermann, Kirshenbaum, Barron, and Messersmith.[21–23,40–43,85–114]

Several important differences to SPPS can be identified. The polypeptide synthesis uses protected amino acids, which are first coupled and deprotected in a second step. Polypeptoids, in contrast, are prepared by attachment of bromoacetic acid to the resin in a first step and nucleophilic substitution with primary amines in a second step (Fig. 11). Both bromoacetic acid and many primary amines are typically inexpensive in contrast to protected amino acids. In combination with the large variety of primary amines that is available, the molecular tool kit for the preparation of polypeptoids is probably bigger but certainly more easily accessed as compared with the one available for polypeptides.

The limitation with respect to the chain length appears to be currently around 50. However, efficient chain extension has been shown to be possible by "click-chemistry."[109] Similar to SPPS, the SPSS approach has been used to prepare polypeptoids which where subsequently cyclized.[115]

Poly(β-peptoid)s

Also β-peptoids are in principle accessible via SPSS. The first oligomers, prepared by this method were reported by Hamper et al. in 1998.[116] They described a two step approach, using a Wang resin as solid phase. First step was the reaction of acryloyl chloride with the resin, followed by adding the appropriate

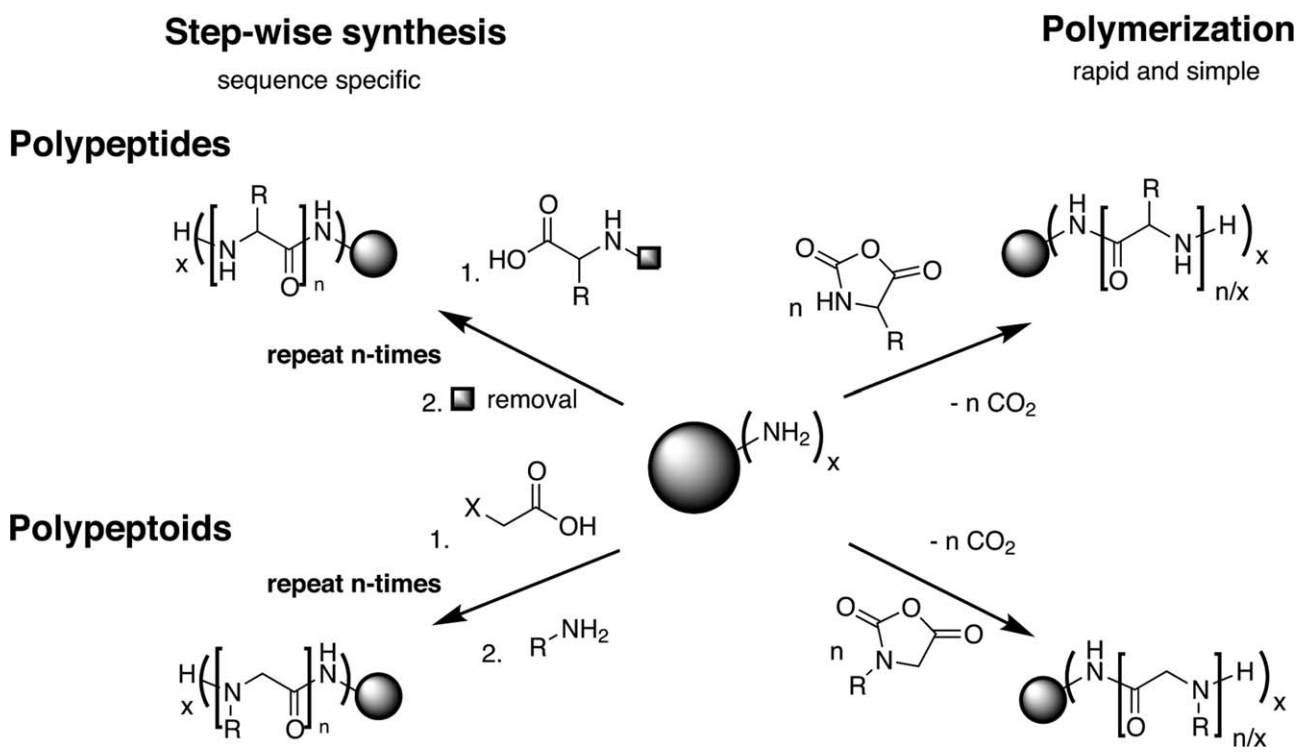

FIGURE 12 Illustration of polypeptide and polypeptoid synthesis using solid supports. While the stepwise synthesis of oligopeptoids and polypeptides has been pioneered by Merrifield, the solid phase submonomer synthesis has been developed over the last 20 years. In contrast, the ring-opening of NCAs and NNCAs using solid supports has been developed on recently. Chemists have now the tools to create very complex, yet highly defined polypeptides and polypeptoids and hybrids thereof, which opens exciting avenues in the biomaterials and nanomedicine synthesis.

amine in excess. Hamper et al. synthesized a broad range of different β-peptoids. However, all obtained oligomers comprised only two to three repeating units. Shuey et al. also investigated this method of solid phase synthesis. They observed precipitation of the β-peptoids after they reached approximately five repeating units. Therefore, they presented another approach for the synthesis of longer oligomers. Shuey et al. synthesized β-peptoid oligomers of three to four monomer units in solution and coupled them by a solid phase approach to obtain oligo(β-peptoid)s with 9 to 18 repeat units.[117] Norgren et al. and Olsen et al. reported nearly at the same time the solid phase synthesis of chiral β-peptoid oligomers with phenylethylamine substituents, with $\sim$11 monomer units.[118,119] Again, the solubility of the β-peptoids in suitable reaction media remains the limiting factor.

ROP from Solid Support

The advantages of the solid phase synthesis appear promising also for polymer analog modifications. To drive polymer modification to high yield, the use of a large excess of reactant, with which the polymer should be modified, is highly beneficial. For the preparation of bioconjugates, the possibility to use a gel, which is preloaded, for example, with a peptide sequence is intriguing.

Accordingly, some researchers have studied the combination of SPPS and solid phase initiated polymerization.[79,120–126] Very recently, Luxenhofer and coworkers have reported on the solid phase peptoid polymerization (SP3) using Rink-type resins for initiators and N-substituted NCA as monomers (Fig. 12).[127]

It was found that several parameters are important to obtain well-defined polymers. While the monomer concentration should be high, the amine density on the resin should be rather low. In addition, to slow down the polymerization rate with respect to monomer diffusion into the gel, addition of acids for partial protonation of the propagating species has proven to be beneficial for the product dispersity. After such optimization of experimental parameters, the polymerization was shown to be living to essentially quantitative monomer conversion. This was then used to prepare a multiblock copolymer, similarly as has been shown before in solution based synthetic approaches.[45] The pentablock copolymer was well-defined as was shown by GPC. This new approach allows for straightforward combination of SPPS, SPSS, and SP3, which is very intriguing for the preparation of complex macromolecular structures (Fig. 12).

ROP of NNCAs from Surfaces (SI-ROP)

Surface initiated polymerizations are essential to create polymer brushes with high density; as such, dense brushes are not accessible by grafting-onto. Preparation of polypeptide brushes by grafting-from has been studied for some time. Initially, this was realized by surface initiated ROP (SI-ROP) of NCAs by immersing the amino-functionalized surfaces in

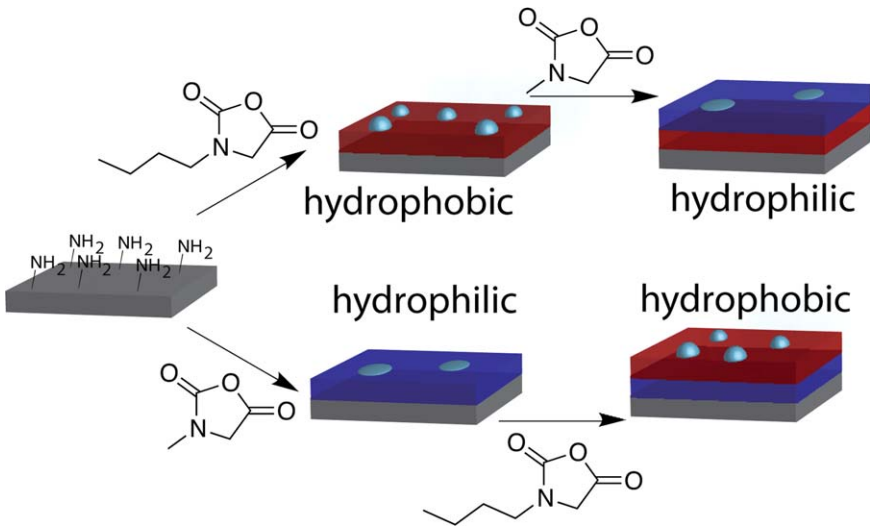

FIGURE 13 Schematic representation of the preparation of amphiphilic block copolypeptoid brushes from amine-functionalized surfaces by living surface initiated ROP via consecutive monomer addition. N-Butylglycine-NCA yields hydrophobic brushes (yellow) while Sar-NCA yields hydrophilic ones (blue). Consecutive addition of both monomers results in surface tethered block copolymers.

monomer solutions.[78,128] However, brush thicknesses were typically well below 20 nm. In a more recent work, Klok and coworkers used N^{ε}-oligo(ethylene glycol)succinate-L-lysine NCA as a monomer and brush heights of <5 nm were obtained.[129] Accordingly, reduction of protein adsorption was rather limited. Frank and coworkers have studied later the chemical vapor polymerization of NCAs to obtain polypeptide brushes using amine-functionalized surfaces.[130–132] This approach, termed also surface initiated vapor deposition polymerization (SI-VDP) allows preparation of comparably thick brushes of polypeptides, as has been shown, among others for poly(γ-benzyl-L-glutamate), poly(γ-methyl-L-glutamate), poly(γ-benzyl-L-aspartate), poly(O-benzyl-L-serine), poly(S-benzyl-L-cysteine), and poly(L-tryptophan).[130]

Jordan, Luxenhofer, and coworkers have recently investigated the SI-ROP using NNCAs from solutions.[133] Interestingly, the brush height that could be obtained resembles the result by Frank et al. obtained for SI-VDP.[130,132] From a given amine-functionalized surface, either hydrophilic or hydrophobic polypeptoid brushes can be obtained in a straightforward manner (Fig. 13). More importantly, however, it was demonstrated that the preparation of block copolymer brushes is feasible. By simple immersion of the polypeptoid surface into fresh monomer solution, the polymerization resumes and either chain extension or preparation of block copolymers could be realized.

The authors did not observe the expected restructuring of the polymer brushes when a hydrophilic brush was topped with a hydrophobic one and water contact angles on such block copolypeptoid brushes were measured. This may be viewed as an additional indicator for the very dense nature of the obtained brushes.

One open question remains. Why is the brush thickness limited to about 40 nm? Formation of secondary structure, as is commonly reported for polypeptide brushes should be strongly reduced in the case of polypeptoids. Moreover, permanent deactivation of the propagating species, which regularly plagues the NCA polymerization[14] is also very unlikely in the case of NNCAs.

In summary, the recently reported polypeptoid brushes may be valuable for the preparation of nonfouling surfaces. However, from an academic point of view, they may be even more interesting as reference systems form polypeptide brushes and may help to elucidate brush growth mechanism in more detail.

Ribosomal Synthesis of Peptoids

Suga and coworkers have pioneered biological synthesis of peptide-peptoid hybrids. The methodology relies on the combination of two systems, a reconstituted *E. coli* cell-free translation system (wPURE) and an artificial tRNA acylation ribozyme, called flexizyme. The expression levels depended strongly on the side chain of the N-substituted glycines with both bulky and charged side chains severely limiting the expression.[134] Although this approach is very promising for the creating of peptide-peptoid hybrids, this approach is currently not suited for the preparation of pure peptoids.

Although using a different synthetic approach, Lee and Zuckermann demonstrated potential applications of peptide- or protein-peptoid hybrids.[135] The incorporation of peptoid moieties into peptides and proteins may be generally used as a tool in protein engineering and for the modification of degradation profile and catalytic profile and activity.

PROPERTIES OF POLYPEPTOIDS

Polypeptoids other than PSar have only been very recently discovered as potential (bio)materials. Therefore, even some of the most basic materials properties like solubility, stability,

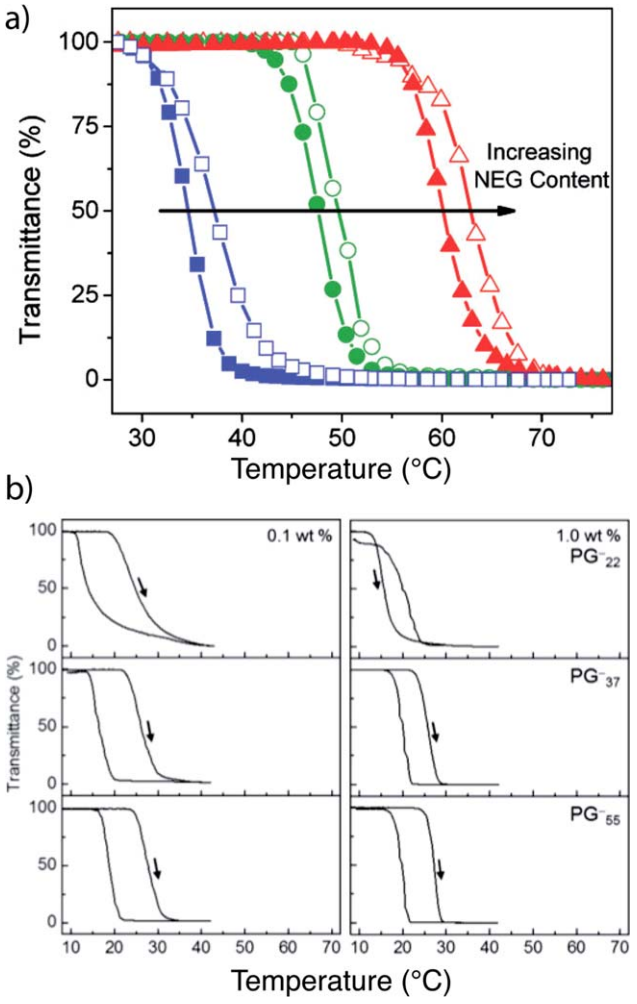

FIGURE 14 Reversible transition of aqueous solubility of polypeptoids depending on (a) the copolymer composition of copolymers of N-ethylglycine and N-*n*-butylglycine or (b) the degree of polymerization of poly(N-*n*-propylglycine) (Reproduced with from Refs. 47 and 149, permission from American Chemical Society).

melting point, and glass transition have not been investigated until very recently or remain unknown to date.

Polypeptoids in Solution

Solubility of Polypeptoids and Poly(β-peptoid)s

The solubility of polypeptoids is determined by substituent of the nitrogen. Only few cases with an additional substituent at the C-α have been reported. The solubility of poly(β-peptoid)s differ significantly from those of polypeptoids. With respect to solubility, the arguably most drastic difference between polypeptides and polypeptoids may be found between polyglycine and poly(N-methylglycine), i.e. polysarcosine. While polyglycine is virtually insoluble in any media due to formation of β-sheets, polysarcosine is excellently soluble in water and many organic solvents.[48] Viscosity measurements suggest that the polymer forms random coils in water.[13] In contrast, poly(N-methyl-β-alanine) appears to be less soluble in most organic solvents but is excellently soluble in water.[65,66,136] As has been mentioned earlier, poly(β-peptoids) appear to be generally much less soluble as compared to their smaller homologs. The polypeptoid with the most diverse solubility profile in aqueous and organic media is poly(N-ethylglycine). In this, the polypeptoids resemble again their structural isomers the poly(2-oxazoline)s, of which poly(2-ethyl-2-oxazoline) exhibits also a broader solubility profile as compared to either poly(2-methyl-2-oxazoline) or poly(2-propyl-2-oxazoline).[24,137–139] With an increase side chain length or bulkiness, the aqueous solubility of polypeptoids diminishes rapidly.[48]

Substitution of the nitrogen atom also strongly influences the solubility of oligo- and polypeptides.[140–142] Interestingly, however, the water sorption in polyamides can be decreased by incorporation of N-methylated polyamide.[143]

Lower Critical Solution Temperature (LCST)

Many water-soluble polymers, including different pseudo-polypeptides[24,138,144–148] exhibit a reversible transition in their water solubility upon a change in temperature, the LCST. Recently, Zhang and coworkers as well as Schlaad and coworkers studied the thermoresponsive behavior of polypeptoids (Fig. 14).[47,149]

As expected,[148] the polymer architecture (cyclic vs. linear) has an influence on the cloud point of the polymer solutions. Whether there is an effect of the architecture on the LCST remains to be elucidated. Similar to other polymers, the cloud points are sensitive to cosolutes and could be altered by salting-in or salting-out.[150] First, LCST was discovered for copolymers of N-ethylglycine and N-butylglycine of different composition. In this case, the relative monomer content did influence the thermoresponsiveness, while the degree of polymerization did not. In contrast, in the case of homopolypeptoids (N-propyl, N-allyl, and N-isopropyl), the degree of polymerization appeared to have some erratic effect on the cloud points and LCST. In the case of poly(N-allylglycine), the cloud points, reflecting the hydrophilicity, decreased with increasing chain length. In contrast, the cloud points increased with the chain length in the case of poly(N-propylglycine). Finally, in the case of poly(N-isopropylglycine) the correlation between chain length and cloud point appears to depend on the polymer concentration. Both groups report on a relatively pronounced hysteresis between heating and cooling curves [with the exception of poly(N-allylglycine)]. In addition, the transition appears to be rather broad as compared with POx. Similar to thermoresponsive POx,[151] Schlaad found that if thermoresponsive polypeptoids are heated above the transition temperature for prolonged time, the transition becomes irreversible.

Secondary Structure and cis-trans in Solution

Formation of secondary structures is one crucial feature of synthetic polypetides and natural proteins.[152–154] In polypeptides, the amide groups are almost exclusively present in the trans-conformation. Constituting secondary structures of proteins include helices, sheets, and specific turns. As will be elaborated, all these types of secondary structures have been realized using peptoids. The synthetic poly-L-proline has

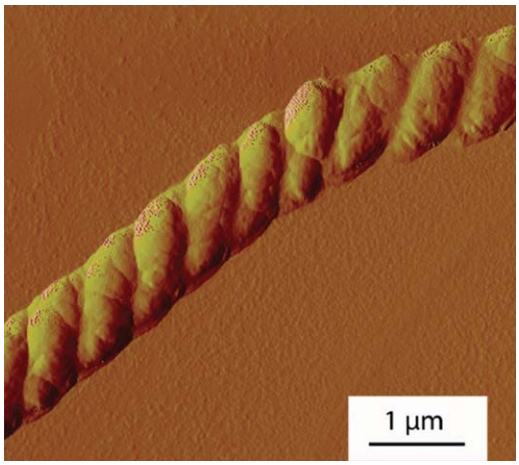

FIGURE 15 Atomic force microscopy scan of a helix formed from sequence specific peptoids with alternating hydrophobic and anionic moieties. (Reproduced from Ref. 98, with permission from American Chemical Society).

been well-known for the formation of two distinct types of helices, despite the absence of intramolecular H-bonding.[17,19] L-Proline or hydroxyproline units are also critically influencing the secondary structure formation in proteins.[17] The ring constraint found in proline is not responsible for the secondary structure formation as similar helices are found for acyclic polyiminoacids, such as poly(N-methyl-alanine)[155] or poly(ɣ-ethyl N-methyl-L-glutamate).[156] In the case of polypeptoids, Sisido et al. have found a marked flexibility in the backbone and that, in contrast to polypeptides, both cis and trans conformation of the backbone are significantly populated.[157] The extend of cis/trans ratio was strongly dependent on the solvent. While in DMSO, both conformations were equally populated, in trifluoroacetic acid the amide bound was mainly in trans-conformation. In this early NMR study, the rotational barrier between cis and trans amide conformation was determined to be approx. 80 kJ/mol (19 kcal/mol) in polysarcosine. Moreover, it was found that more bulky substituents on the nitrogen induce a shift towards smaller cis/trans ratios.

Much later, Sui et al. reinvestigated the issue of cis/trans isomerization in peptoids and confirmed the rotational energy barrier.[158] It was found that half-lives for the cis/trans exchange was in the order of several seconds.

The early observation of Sisido, that the nitrogen substituents can be used to influence the amide conformation has since been exploited intensively.[159,160] Similar to polyproline, polypeptoids bearing chiral side chains have been reported to form stable helical conformations[22,161] and multihelical assemblies.[162] These early reports were triggered by CD spectra of peptoid pentamers that closely resemble those of oligopeptide α-helices.[22] Molecular mechanics calculations supported formation of polyproline like helices for these acyclic, chiral polypeptoids.[161]

Kirshenbaum and coworkers have made substantial contributions to our understanding on the possibilities to introduce turns into peptoids.[99,104,115,163,164] In fact, recently de novo structure prediction of peptoids oligomers has been demonstrated.[107]

Secondary structures such as helices are not restricted to sequence specific peptoids but have also been described in polypeptoids obtained by NNCA polymerization.[57] Similar to the early reports on helical peptoids, this was achieved by introducing chiral side chains. Interestingly, linear polypeptoids yielded less intense circular dichroism as compared with cyclic ones, suggesting less stable helices.

Formation of secondary structures has also been reported for oligo(β-peptoid)s.[118,119,165–168] Again, the reported results suggest that the β-peptoid solubility remains a limiting factor. It may be hypothesized that the formation of secondary structures is a contributing factor to the poor solubility of poly(β-peptoid)s but this remains to be elucidated.

Despite the spectroscopical evidence for polypeptoid helices in solution, their stability and relevance may be somewhat overemphasized. Using small angle neutron scattering Rosales et al. recently found that the flexibility of helical poly-peptoids is nearly identical to that of random coils. The persistence length of the helices was found to range between 4 and 1 nm, depending on the chain length. Short helices exhibited much larger persistence lengths as compared to achiral polymers of similar structure. In contrast, for longer chains the differences are only minor.[169]

In the absence of chiral side chains, it is difficult to detect secondary structures if they formed. However, Kirshenbaum and coworkers have demonstrated that achiral peptoids can form chiral atropisomers. Introduction of bulky substituent increases the rotational energy barrier such that different species could be analyzed.[170]

Interesting to note, as structural isomers of peptoids, POx can undergo similar secondary structure formation if chiral moieties are introduced.[24,171]

Aggregation in Solution

It is well known that the polymer architecture of, for example, amphiphilic polymers, has a major influence on their aggregation. Moreover, the sequence control available with peptoids is also important for their self-assembly.[95,98]

Zuckermann, Segalman, and coworkers have prepared polypeptoids (36 mers), in which charged (A) and hydrophobic (B) monomer units alternate in different patterns (AB, ABB, and ABBB). Interestingly, only the polymers with AB pattern self-assembled into defined structures.

When anionic and hydrophobic monomer units were strictly alternating, the polymers formed upon nanosheets upon dissolution in water. After several days, however, superhelical structures appear, which are, once formed stable for months in solution (Fig. 15).[98] The helices are submicron (624 ± 69

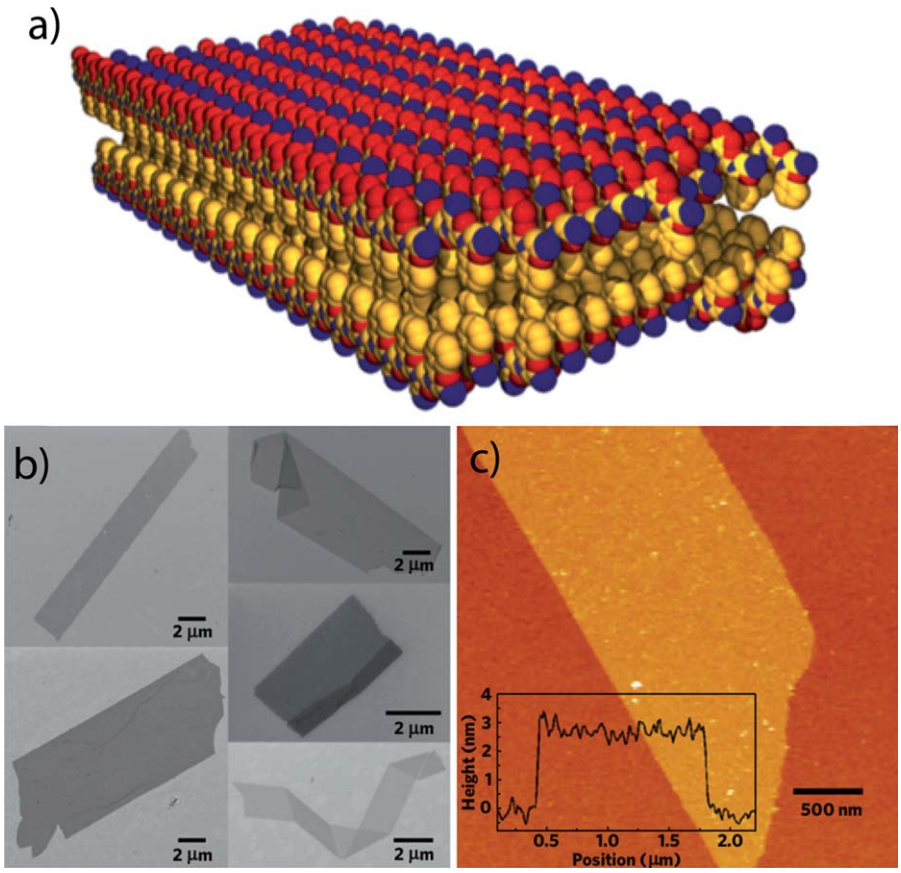

FIGURE 16 (a) Molecular model of 2D sheets formed by self-assembly of amphiphilic oligopeptoids. (b) Scanning electron microscopy images and (c) atomic force microscopy height scans of sheets on substrate. (Reproduced from Ref. 95, with permission from Macmillan Publishes Limited).

nm) in diameter and were found to be up to 40 μm long. Most interestingly, the observed helices were homochiral, despite the fact that the building blocks are achiral.

In a similar approach, two such polypeptoids of same architecture but opposite charge were mixed. Initially, and in contrast to the anionic/hydrophobic homoaggregates, globular aggregates form. However, within several hours, large but ultra-thin sheets of 2.7 nm thickness formed in high yields (Fig. 16).[95] The peptoid chains are highly extended as evidences by aberration-corrected transmission electron microscopy. Extraordinary large aspect ratios and the exceedingly simple preparation of these sheets, by simple mixing of appropriate peptoids are highlights of this approach.

Interesting peptoid self-assembly phenomena are not restricted to sequence specific materials obtained by solid-phase synthesis. Zhang and coworkers studied the self-assembly of nonionic amphiphilic copolypeptoids of N-methylglycine and N-decylglycine.[59] In this case, differences in self assembly between linear and cyclic polypeptoids was investigated. The differences were minor with respect of the final product. Initially, spherical micelles form in methanolic or aqueous solutions/suspensions. However, within a few days, both materials eventually form cylindrical (worm-like) micelles. These micelles are only a few nanometers in diameter but several micron in length.

Zuckermann recently investigated the coil-to-globule transition using polypeptoids of different microstructure (Fig. 17).[109] As theoretical predictions by Khokhlov and Khalatur suggested,[172] a segmented distribution of the comonomers lead to an increase in transition temperature as well as in a sharpening of the transition.

Antifreeze Effect of Polypeptoids

Ward and coworkers recently discovered that some peptoids have an anti-freeze-effect in aqueous solution that exceeds simple colligative effects.[106] Moreover, it has been shown that the structure of formed ice crystals depend on the peptoid structure (Fig. 18). Effects that may be similar in nature to what is observed with anti-freeze proteins were reported. In contrast to the case with proteins, the facile structural variation of peptoids, in particular when obtained by SPSS, should allow a comparably simple elucidation of structure-property relationships in the future.

Polypeptoids as Solid Materials

Depending on the side chain length of the polypeptoids, the materials are amorphous or semi-crystalline. The glass

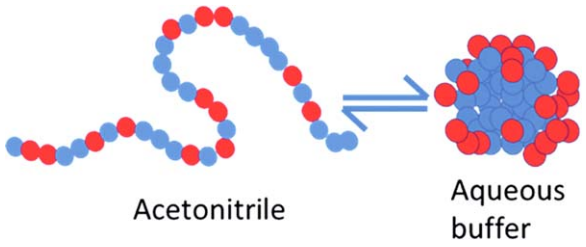

FIGURE 17 Schematic representation of the globule to coil transition of a monodisperse polypeptoid. When the monomers are present in a segmented manner, the transition is sharper and occurs at higher temperature. (Reproduced from Ref. 109, with permission from American Chemical Society).

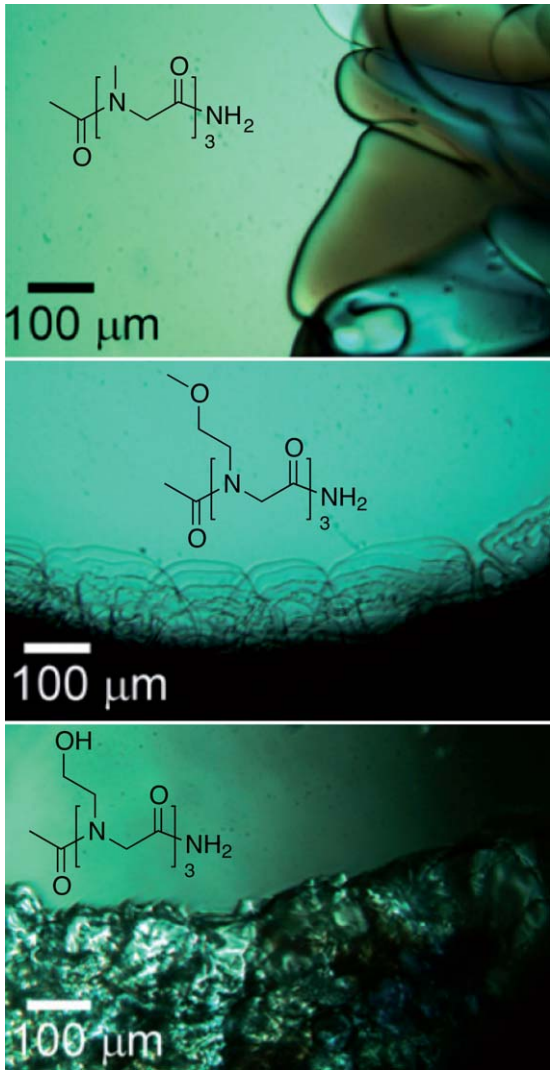

FIGURE 18 Microscopy images of crystal growth in ice water ($T = -1$ °C). Different morphologies are observed in dependence of the peptoid structure (10 g L^{-1}). (Reproduced with modifications from Ref. 106, with permission from National Academy of Science U.S.A.).

transition temperature depends, as expected, on the degree of polymerization as well as on the side chain length. Polypeptoids with longer side chains may exhibit two melting points. One, typically at lower temperature (< 80°C) that can be attributed to the side chains and a second, typically between 150 and 200 °C, that can be attributed to crystalline domains of the polymer chains. Polysarcosine and poly(N-ethylglycine) are amorphous solids, while the higher homologues are semi-crystalline polymers. A selection of thermal properties of polypeptoids is given in Table 1.

Stability of Polypeptoids

In medicinal chemistry, N-substitution of amino acids in peptide sequences is a common tool to increase proteolytic stability of the peptide, similar to incorporation of D-amino acids.[142,173] Alternatively, N-substitution of amino acids has been used as a tool to alter peptide geometry and conformational space.[174,175]

Water-soluble polypeptoids are degraded rapidly under conditions regularly used for protein/peptide hydrolysis (6 N HCl, 100 °C).[18] However, enzymatic degradation is generally ruled out for polypeptoids.[41] This, however, may not be entirely the case. The only naturally occurring proteinogenic imino acid is L-proline. Its polymer, poly-L-proline, is not a naturally occurring polymer but collagen, an extremely important structural protein, is rich in diprolyl units. Accordingly, poly-L-proline has been studied as a collagen model and a control in the enzymatic digestion of collagen. It was reported that the polypeptoid poly-L-proline is enzymatically degradable. The responsible exopeptidase was named proline iminopeptidase.[176] In this study, as control, the authors used synthetic copolymers of L-proline, hydroxyproline, D-proline, glycine, and Sar, respectively, to validate the specificity of the newly identified protease for N-terminal L-prolyl units. The results are striking. While hydroxyproline and D-proline

TABLE 1 Glass Transition and Melting Temperature of Various Polypeptoids

Polypeptoid	T_g[a]	T_m^1 (°C)[b]	T_m^2 (°C)[c]
Polysarcosine	127 – 143	n.a.	n.a.
P(N-EtGly)	77 – 114	n.a.	n.a.
P(N-PrGly)	34 – 93	163 – 198	n.a.
P(N-iPrGly)	121	n.a.	n.a.
P(N-AllylGly)	50 – 64	150 – 170	n.a.
P(N-PyGly)	108	n.a.	n.a.
P(N-nBuGly)	4	153 – 225	63 – 70
P(N-nPenGly)	−3 to −5	145 – 207	49 – 67
P(N-HexGly)	n.d.	145–160	n.d.
P(N-OctGly)	n.d.	130 – 160	n.d.
P(N-DecGly)	n.d.	166 – 176	72 – 79

[a] Range of glass transition temperatures found for polypeptoids of different degrees of polymerization.
[b] Melting points of polypeptoids.
[c] If applicable, melting points of polypeptoid side chains.

appears to work quite well in preventing further enzymatic degradation when present at the N-terminus, Sar apparently does not. The amount of L-proline released from copolymers of L-proline and Sar is 4.4 times higher than expected. Taking into account that L-proline-NCA polymerizes faster than Sar-NCA, copolymers of L-proline and Sar are in fact gradient copolymers with Sar units significantly enriched toward the N-terminus of the polymer.[18] Therefore, if Sar units would indeed hinder the enzymatic degradation of poly-L-proline by proline iminopeptidase, the amount of L-proline would have to be diminished and not, as experimentally determined, significantly increased.[176]

In a later study, Kirschke and Hanson found a very low, but measurable hydrolysis after 1 h of poly-L-proline in rat liver and kidney homogenate.[177] However, in this study, release of L-proline from Pro-Gly and Pro-Gly-Gly peptides was compared with release of L-proline from poly-L-proline of unknown molar mass. Naturally, L-proline release from small dipeptide and tripeptide is much higher even if rate of bond cleavage in the peptide and the polymer would be comparable. Thus, it may be deduced that the polypeptoid poly-L-proline is biodegradable but it remains to be elucidated in what time frame. Since, very few studies investigated the biodegradability of polypeptoids.

Apart from enzymatic degradation, oxidative degradation of proteins is an important pathways in protein metabolism.[178,179] Sung and coworkers have recently investigated the oxidative degradation of PEG-based hydrogels that were cross-linked using oligo-L-proline sequences.[180] In this work, it is demonstrated that the oligo-L-proline linker is degraded oxidatively in the absence of enzymes within 4 days. We would like to note, however, that PEG is also well known to be very unstable with respect to oxidative degradation.[181] Specifically, under the conditions used by Sung et al., PEG has been demonstrated to be degraded within 2 days or less.[181]

Polypeptoid Modified Surfaces

Surface modification with soft matter, in particular polymer brushes is a very intriguing and heavily investigated topic in materials science.[75,85,86,182–184] In biomaterials research, surface modification is particularly important to reduce or prevent the adsorption of proteins, which has a strong influence on the adhesion of cells to such surfaces. Typically, it is desired to prevent nonspecific protein adsorption, which may be realized by coating with hydrophilic polymers,[185,186] micropatterning and nanopatterning or responsive polymer coatings.[187,188] Messersmith was the first to investigate the potential of peptoids for anti-biofouling surfaces.[86,87,89–91] On a short term, these surfaces were very effective in reducing protein adsorption and cell adhesion. However, these surfaces were modified using a grafting-to approach of polypeptoids derived by solid-phase organic synthesis. In comparison to NuLROP, this synthetic approach is tedious and expensive and the grafting method does typically not yield dense or thick brushes. Luxenhofer, Jordan and coworkers have recently reported on polymer brushes obtained by surface-initiated NuLROP of NNCAs.[133] Such surfaces are much thicker and can be expected to be much denser. However, it takes several days to achieve brushes of 40 nm heights. To overcome this limitation, the approach reported by Frank et al. may be interesting.[130–132] Frank prepared polypeptide brushes by surface-initiated vapor deposition polymerization. It remains to be seen whether such approach would help enhance the polymerization rate and/or increase the brush thickness in the case of polypeptoids.

Besides polypeptoids, poly(β-peptoid)s have demonstrated potential for surface modification. After conversion of the polymer termini into thiols and subsequent grafting onto gold surfaces, Jia and coworkers were able to demonstrate the non-fouling properties of hydrophilic poly(β-peptoid)s.[136] All poly(β-peptoid) modified gold surfaces were hydrophilic. Water contact angle measurements for poly(N-methyl-β-alanine) showed values in the range of 15° to 20°. In comparison, poly(N-ethyl-β-alanine) with its additional methylene group is somewhat less hydrophilic ($\Theta = 30°$). Nevertheless, all poly(β-peptoid) surfaces show very low protein absorption (Fig. 19).

Biocompatibility of Polypeptoids

Early work by Maurer et al. suggests that PSar is nonimmunogenic in rabbit.[25,189] Since, little information with respect to the biocompatibility of polypeptoids could be found in literature. Very recently, Kimura and coworkers investigated amphiphilic block copolymers bearing PSar as hydrophilic block for their feasibility as drug delivery vehicles.[190,191] Long circulation times, similar to PEGylated systems suggest low protein binding and opsonization and accordingly avoidance of RES *in vivo*. Corroborating these results, Zhang et al. found very low cytotoxicity *in vitro*.[47] These results, in combination with the non-fouling properties of surfaces modified with hydrophilic polypeptoids and poly(β-peptoid)s and the increased stability with respect to degradation are very promising for the preparation of biomaterials using the polypeptoid platform.

Pharmacologically Active Peptoids

Peptoids exhibit a number of characteristics that make them very interesting for medicinal chemistry. First, the possibility of solid phase synthesis makes combinatorial approaches feasible and high throughput standard techniques, well established in drug discovery, can be applied.[42,192] Compared with peptides, peptoids are much more stable against enzymatic degradation. Finally, peptoids are typically more cell-permeable as compared to peptides.[193]

Biologically Active Peptoid Surfactants

Surfactant proteins B and C play an important role in respiration. For treatment of the respiratory distress syndrome, development of non-natural biomimetic analogues is warranted. For this, peptoids are ideally suited. While peptides are prone to denaturation/misfolding, peptoids can adopt the critical secondary structure, but due to the lack of intramolecular H-bonding, denaturation is less of an issue.

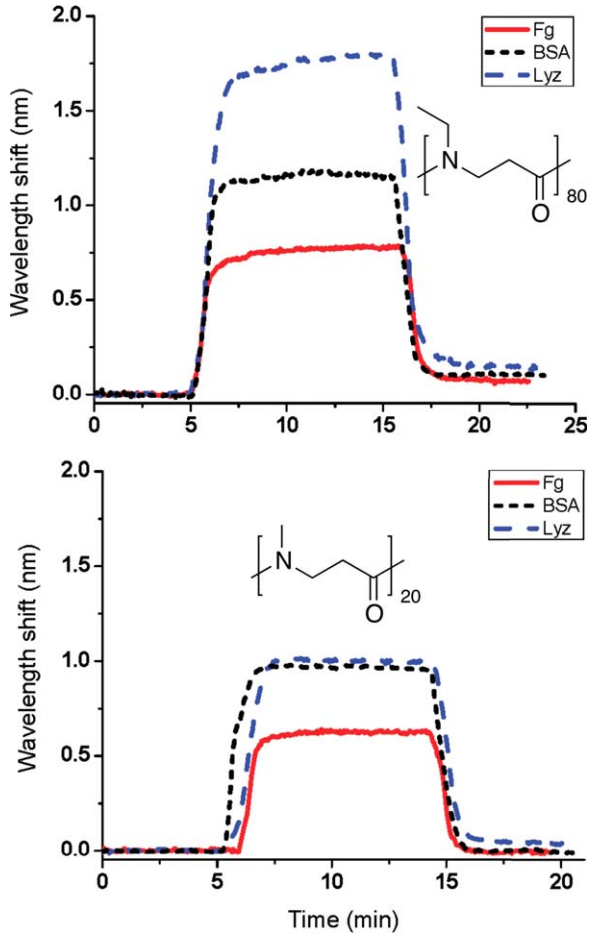

FIGURE 19 Surface plasmon resonance sensorgrams of poly(β-peptoid) coated gold surfaces that were flushed with solutions of human plasma fibrinogen (Fg) bovine serum albumin (BSA) and chicken white lysozyme (Lyz) and PBS, subsequently. Residual wavelength shifts after PBS wash after ~15 min corresponds to protein binding on surfaces. (Reproduced with modifications from Ref. 136, with permission from American Chemical Society).

Accordingly, Barron and coworkers have developed biomimetic surfactant peptoids that are able to imitate the properties of the biological samples while reducing some of its disadvantages.[113,194]

Antimicrobial Peptoids

Barron and coworkers also pioneered the field of antimicrobial peptoids. Taking clues from natural antimicrobial peptides, biomimetic analogues were studied (Fig. 20). Important to note, structural variation allowed to identify peptoids that exhibited very good antimicrobial activities against a variety of clinically relevant bacteria such as *mycobacterium tuberculosis*, *streptococcus pneumoniae,* and *enterococcus feacalis*, with comparably low toxicity against mammalian cells.[111,112,195] The importance of structural variation in such antimicrobial peptoids was recently demonstrated. *In vivo* biodistribution studies revealed that deletion of a singly hydrophobic residue from a 12-mer lead to a significant reduction in liver uptake and to an increased uptake in the kidney. Importantly, the antimicrobial activity remained essentially unchanged.[110]

More recently, Kirshenbaum compared the antimicrobial activity of linear and cyclic peptoids. It was demonstrated that the cyclic peptoids often exhibit superior activity, presumably to the structural constraints embedded by cyclization. This, however, strongly depended on the peptoid structure, highlighting the importance of structure property elucidation.[196]

Peptoids with Molecular Recognition

Vicent, Pérez-Payá and coworkers have identified a family of peptoids, that are able to inhibit the activity of the apoptosome, a large protein complex that regulates apoptosis.[197,198] By conjugation of the peptoid to a polypeptide, poly(L-glutamic acid), a first targeted peptoid based polymer therapeutic was created.[199]

Kodadek and coworkers have shown that peptoids bind to specific receptors such as the vascular endothelial growth factor receptor 2 and elicit signaling.[200,201] As expected, structural variation of the peptoids was demonstrated to affect affinity, cell permeability, and specificity.

More recently, Levine et al. reported on peptoids that were modified to bind the androgen receptor.[102,103] Such constructs may be valuable for the treatment of prostate cancer.

Drug Delivery with (Poly)peptoids

Apart from being the pharmaceutically active ingredient, peptoids and polypeptoids have also been employed for the delivery of active compounds. Polysarcosine and other hydrophilic polypeptoids have been demonstrated to exhibit

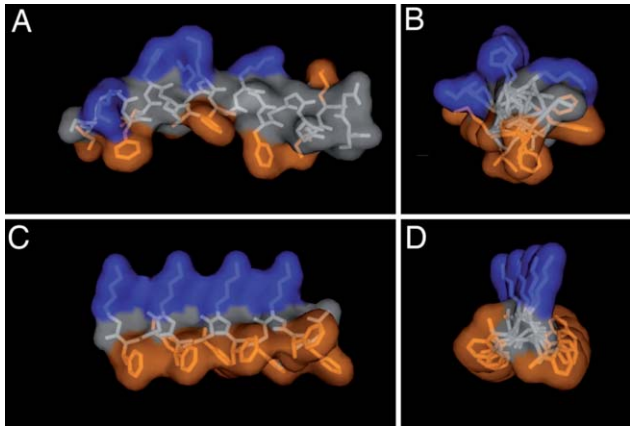

FIGURE 20 Comparison NMR-derived structures of the natural antimicrobial peptide magainin-2 in DPPC micelles (a and b) and a peptoid-based antimicrobial (c and d). Cationic residues are color coded in blue, hydrophobic ones in orange. (Reproduced with modifications from Ref. 195, with permission from National Academy of Sciences U.S.A).

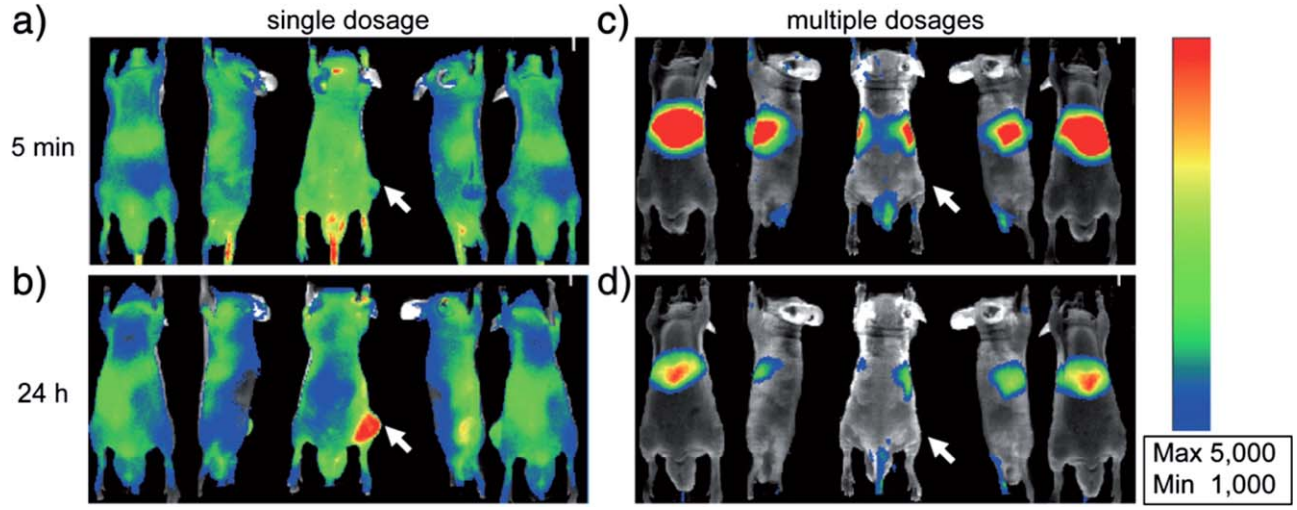

FIGURE 21 Comparison of the biodistribution of a polysarcosine based drug delivery platform. While after a single dose, no major organ accumulation and long blood circulation was observed (a and b), the biodistribution dramatically changes after a second injection (c and d), upon which the administered polymer is almost exclusively trapped in the liver. (Reproduced from Ref. 204, with permission from Elsevier).

very low nonspecific protein binding[87,90,91] In addition, polysarcosine was reported to be non-immunogenic.[25] This suggests that these polymers should be excellently suited as drug carriers. Indeed, in initial and more recent reports, Kimura and coworkers have reported very good biocompatibility and biodistribution after single injection with prolonged circulation of drug delivery systems (polymer micelles and polymersomes) comprising polysarcosine as the hydrophilic moiety.[190,191,202] Interestingly, the biodistribution of nanoparticles of block copolymers of polysarcosine and polylactide depended on the stereochemistry of the hydrophobic component, polylactide.[203] Blood circulation was longest for nanoparticles to which poly(D-lactic acid) was added. In contrast, addition of poly-(DL-lactic acid) led to reduced blood circulation times.

More recently, however, the same group reported on accelerated blood clearance of the polysarcosine based nanoparticles after repeated injection (Fig. 21).[204] Very similar effects are observed for PEGylated drug delivery platforms.[205] Kimura were able to identify B-lymphocytes as responsible for the immune response. Moreover, polysarcosine was identified as the responsible epitope. Therefore, the earlier mentioned assessment that polysarcosine is non-immunogenic must be relativized.

In a similar approach, Barron et al. suggested attachment of short N-methoxyethylglycine oligomers to therapeutic proteins.[114] Taking advantage of the facile synthesis of large libraries of structurally diverse peptoids, Zuckermann and coworkers have also studied the use of cationic peptoids as nonviral vectors for gene delivery.[192]

A PERSPECTIVE ON POLYPEPTOIDS

Although polypeptoids are among the first polymers that were prepared by living polymerization, this class of polymers has not received too much attention over the last decades as a material. Obviously, there is much potential left untapped. In particular, the recent advances on the living polymerization of NNCAs demonstrating access to cyclic and multi blockcopolymers in combination with the more established submonomer solid phase synthesis may give new impulses for advanced macromolecular engineering. It has become clear, that for numerous applications and properties sequence control and definition is essential. However, it has been also shown that lack thereof may be useful or even necessary in other cases.[206] This makes the potential combination of solid phase synthesis and living polymerization particularly intriguing.

Investigations on the (Co)polymerization Behavior of NNCAs

Kinetic investigations of all NNCAs [Fig. 5(a)] studied to date reveal a first-order dependence. Molar masses of polymers with degrees of polymerization < 50 fitted well with the theoretical values from the $[M]_0/[I]_0$ ratio, but at higher degrees of polymerization repeatedly a discrepancy from the theoretical values was observed.[33,45,48,50] We believe that this can be mainly attributed to problems accurately determining the $[M]_0/[I]_0$ ratio at higher ratios or the analytical tools used for the characterization of the products as opposed to an inherent limitation of the degree of polymerization of NuLROP. Indeed, we have prepared polypeptoids with degrees of polymerization exceeding 1000 (unpublished data) but predetermination of the degree of polymerization remains erratic at the moment. At such large degrees of polymerization, traces of water in the solvent are expected to have an increasing influence but end-group analysis is typically not reliable.

As the NuLROP of NNCAs other than SarNCA has not been studied until very recently, no copolymerization parameters

between the various monomers are known. Polymerization kinetics of NNCAs are typically studied via IR spectroscopy, probing the time-dependence of the C═O stretching modes of the NNCA. Unfortunately, this mode is not expected to be very suitable to study the copolymerization behavior of NNCA as a significant overlap is expected. We have investigated the use of gas chromatography for online polymerization kinetics, a method well established for the cationic polymerization of 2-oxazolines,[147,207] but although NNCA can be analyzed by gas chromatography, it appears a reliable and quantitative analysis is not feasible this way (unpublished results). In most cases, it will be more suitable to study the composition of polymers with other means, such as nuclear magnetic resonance spectroscopy, as has been demonstrated by Lahasky et al.[47] It will be particularly interesting, whether the copolymerization parameters during NuLROP and the NHC mediated zwitterionic ROP of the same monomers correlate.

Since only a simple nucleophile is necessary to initiate the polymerization of NNCAs, structural variation and introduction of functional termini appears easy. Star-like PSar has been realized some years ago,[30] polymer brushes will be an obvious next step and can be expected to be realized soon. Thiol initiators should be possible, but it can be expected that initiation may be slow compared with the propagation. Therefore, access to defined polymers may be limited using thiol initiators.

"Smart" Polypeptoids

Already, first reports can be found on polypeptoids that are responsive to external triggers, namely temperature (vide supra). Although not discussed as such, other peptoids previously reported can be considered pH sensitive materials.[95,98,109] Imanishi and coworkers have reported on the polypeptide-polypeptoid copolymers that were used as pH sensitive materials.[26,27,32] In this case, the responsive material were polypetides, but it is apparent that similar structure are also accessible by polypeptoids.

Considering that backbone degradable polymers hold a significant advantage over polymers with C—C backbone in particular when it comes to development of biomaterials for *in vivo* applications, we expect that smart polypeptoids that respond to other stimuli will be developed soon. Other than temperature and pH, interesting stimuli for the use in smart biomaterials are reduction-oxidation,[208,209] glucose concentration,[210,211] and light.[212–214] As we expect significant advances on the use of polypeptoids on surfaces, we also expect to see smart surfaces employing polypeptoids in the near future.

Drug Delivery

Polypeptoids offer an excellent level of synthetic control, either by solid phase synthesis or polymerization, can exhibit very low toxicity, and proteolytically stable but eventually biodegradable in the backbone. These facts make this platform uniquely suited for the development of synthetic drug delivery vehicles. The discrepancy between potential and level of investigation is quite striking, giving a multitude of opportunities to researchers to develop this field. However, it must be noted that the recent report on antibody formation against polysarcosine must be considered very seriously. It would be interesting to identify a more detailed structure-immunogenicity relationship.

Artificial Enzymes

Artificial enzymes or modification of natural enzymes has been another hot topic for many researchers. Protein engineering has come a long way and still offers exciting avenues. However, protein engineering is severely restricted in many ways. Use on non-natural amino acids is possible but often has detrimental effects on protein expression. Deviation from the polypeptide backbone may be impossible altogether. Polypeptoids have always been discussed or used as model compounds from synthetic polypeptides. More recently, polypeptoids have been discussed as biomimetic protein surrogates[162] and a first study related polypeptoid rod-coil transition to proteins folding.[109] At the same time, peptides and peptoids have investigated successfully as very efficient organic catalysts for a wide variety of chemical reactions.[215–218] Polypeptoids have been repeatedly tailored to exhibit secondary structures similar to those present in proteins and enzymes.

Therefore, we hypothesize that polypeptoids should represent an excellent platform for the development of synthetic biomimetic proteins-like structures and enzymes. Detailed and straightforward structure property relationship evaluation would become accessible in ways that would be difficult for natural or engineered proteins. In addition, peptoids and polypeptoids can be thermoplastic and exhibit tunable thermoresponsiveness. All these properties may be very interesting for the design of artifical enzymes.

CONCLUSIONS

Despite recent advances, much of the potential of polypeptoids as a materials platform remains untapped. The chemical and structural versatility in combination with the definition of the materials that can be obtained has probably no match in current polymer science. Polypeptoid synthesis may be considered by many researchers to be somewhat more challenging as compared to other methods, such as reversible deactivation radical polymerization, but in our opinion the accessible complexity and definition more than outweighs this slight disadvantage.

Considering the many limitations other biomaterials platforms suffer, it is high time to investigate the bountiful opportunities polypeptoids hold.

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