Peptoid Polymers: A Highly Designable Bioinspired Material

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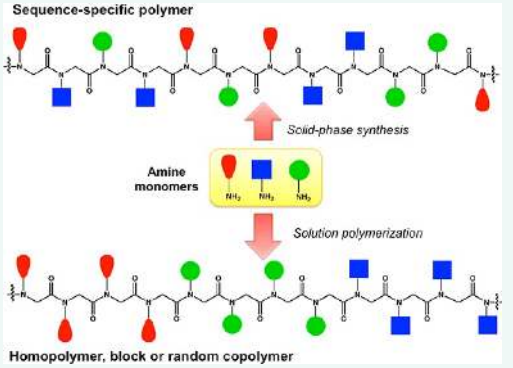
ABSTRACT Bioinspired polymeric materials are attracting increasing attention due to significant advantages over their natural counterparts: the ability to precisely tune their structures over a broad range of chemical and physical properties, increased stability, and improved processability. Polypeptoids, a promising class of bioinspired polymer based on a N-substituted glycine backbone, have a number of unique properties that bridge the material gap between proteins and bulk polymers. Peptoids combine the sequence specificity of biopolymers with the simpler intra/intermolecular interactions and robustness of traditional synthetic polymers. They are highly designable because hundreds of chemically diverse side chains can be introduced from simple building blocks. Peptoid polymers can be prepared by two distinct synthetic techniques offering access to two material subclasses: (1) automated solid-phase synthesis which enables precision sequence control and near absolute monodispersity up to chain lengths of ~50 monomers, and (2) a classical polymerization approach which allows access to higher molecular weights and larger-scale yields, but with less control over length and sequence. This combination of facile synthetic approaches makes polypeptoids a highly tunable, rapid polymer prototyping platform to investigate new materials that are intermediate between proteins and bulk polymers, in both their structure and their properties. In this paper, we review the methods to synthesize peptoid polymers and their applications in biomedicine and nanoscience, as both sequence-specific materials and as bulk polymers.



KEYWORDS: polypeptoids · solid-phase synthesis · sequence-specific polymers · protein-mimetic materials

Polypeptoids, or N-substituted glycines, are peptidomimetic polymers that offer many advantageous properties for studies in nanoscience.[1−10] The polypeptoid backbone is identical to that of a polypeptide, but the side chain is appended to the nitrogen rather than the α-carbon. This difference removes inter- and intrachain hydrogen bonding in the backbone[11] and also eliminates the main-chain chirality.[12] These differences result in a polymer family whose properties are dominated by the side-chain identity and monomer sequence. Furthermore, their reduced structural complexity makes them easier to synthesize and simplifies their engineering and design. It also results in substantial flexibility of the main chain,[12,13] good solubility in many common solvents, and accessible thermal processability.[11] Similar to polypeptides, peptoid polymers exhibit excellent biocompatibility and potent biological activities.[14−16] For example, they can fold into protein-mimetic secondary and tertiary structures,[17−19] serve as an effective siRNA transfection reagent,[20,21] diagnostic agents,[22−24] lung surfactant mimetics,[25,26] antimicrobial agents,[27] and other therapeutics[4] and can be incorporated site-specifically into polypeptide sequences[28] and exhibit stability to proteolysis.[29,30]

From a synthetic point of view, polypeptoids are a class of highly designable polymers. Depending on the desired degree of control over structure and scalability, two fundamentally different synthetic approaches are possible: solid-phase synthesis and solution polymerization. With the solid-phase submonomer synthesis method,[31] sequence specificity and near absolute monodispersity are readily obtained for chains of shorter lengths.[32−35] The precise control over the exact placement and choice of monomers offered by this method enables an exceptionally fine degree of control over the functional properties (*e.g.*, thermal, mechanical, optical, conformational, *etc.*) of the peptoid polymer chain.[11,12,36] The chemical diversity of polypeptoids is vast because the side-chain moiety is introduced from a primary amine synthon (of which there are literally

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hundreds readily available) *via* an S_N2 displacement reaction. This approach allows for chains up to 50 monomers long to be synthesized in reasonable yield in one shot because the yield for each monomer addition cycle is typically in excess of 99%.[7,37] Alternatively, solution polymerization techniques offer an effective way to achieve high molecular weights and larger-scale syntheses, however, with heterogeneous products (due to the inherent polydispersity) and limited atomic level synthetic control over the polymer chemical structure.[38] However, the combination of solid-phase submonomer synthesis with polymerization techniques offers unique opportunities to tailor polypeptoid design to solve a wide variety of problems in molecular biomimicry and nanomaterials science. In this review, we will discuss recent developments relevant to synthesis, functional properties, and nanoscience applications of peptoid polymers.

Combinatorial Synthesis and Applications of Sequence-Specific Polypeptoids. *Solid-Phase Synthesis.* Zuckermann *et al.* initially approached the synthesis of short peptoid oligomers in analogy to the well-established Merrifield method of solid-phase peptide synthesis (SPPS) using N-protected N-substituted glycine monomers.[1,2] They subsequently developed a much cheaper and higher yielding submonomer synthesis method that uses no main-chain protecting groups and simpler building blocks, or "submonomers". The two-step monomer addition cycle involves an acylation step with a haloacetic acid submonomer, followed by a displacement reaction with a primary amine submonomer, in which the functional side chain is incorporated (Figure 1).[31,39,40] In the first step, bromoacetic acid is preferred generally; however, when the side chains include unprotected heteroatoms, chloroacetic acid can be used to minimize side reactions.[41] The beauty of the displacement step is that the only functional group needed to incorporate a side-chain unit into the main chain is a reactive primary amine. There are many hundreds of commercial primary amines available in gram quantities, enabling a tremendous range of chemical and sequence diversity in peptoid polymer chains. As the displacement is an S_N2 reaction with an electrophilic haloacetamide, amines with competing pendant nucleophilic centers need to be side-chain-protected. Extensions of the standard submonomer synthesis method allow one to introduce a number of chemoselective functional groups to enable facile conjugation strategies.[42]

As one equivalent of HBr is the only byproduct generated in the displacement step, the amine in the reaction mixture, typically in substantial molar excess, can be recycled by pumping it back into the original reagent reservoir and reused in subsequent displacement steps.[43] As in SPPS, acid-removable side-chain protecting groups are typically used, so that the side-chain deprotection and resin cleavage can be affected simultaneously using a trifluoroacetic acid cocktail. The displacement reaction is not air- or moisture-sensitive, and no heating is typically required. It has been reported that microwave-assisted solid-phase synthesis of polypeptoids can reduce the reaction time dramatically (from ~1 hour to just a few minutes per monomer addition) with purity and yields of products as good as or even better than those achieved using standard methods.[44−48] Additionally, the two-step submonomer cycle involves only the simple pipetting of stable reagent solutions at room temperature. Therefore, the entire procedure can be accomplished either manually or automatically and can be readily adapted to most any commercial peptide synthesizer.[3,33,49]

Zuckermann *et al.* have developed custom robotic synthesizers that have been optimized over several generations to perform the fully automated synthesis of polypeptoids.[1,34] Individual compounds can be prepared in parallel, or combinatorial libraries of high complexity can be prepared. "Mix & split" combinatorial synthesis allows a very large number of different sequences to be synthesized simultaneously in equimolar amounts and in such a fashion that each resin bead in the combinatorial library contains a single compound.[50−52] This means that tens of thousands of unique peptoid sequences can be generated in a single run. Mass spectrometry-based sequencing methods have been developed,[53,54] where the peptoid on an individual library bead can be

VOCABULARY: bioinspired polymers - A broad class of polymeric materials that can have folded secondary and tertiary structures resulting from a complex monomer sequence involving chemically distinct monomers; **nanosheet** - a high aspect ratio two-dimensional material that has a nanoscale thickness and lateral dimensions in the micrometer range; **oligomer** - a short polymer chain with a degree of polymerization less than 10−20 residues; **protein-mimetic material** - a polymer chain comprising at least two dissimilar monomers that can fold into a specific conformation in water, as dictated by its monomer sequence; **secondary structure** - local structural order along a stretch of a polymer chain, typically characterized by a regular pattern of repeating conformations; helices and sheets are common examples; **sequence-specific polymer** - a polymer with a precise order of monomer units, typically found in biology; **solid-phase synthesis** - a stepwise polymerization method where the growing polymer chain is anchored to a solid support, and coupling reagents are iteratively passed over the matrix, adding one monomer at a time to afford a polymer with an exact monomer sequence and near absolute monodispersity; **submonomer** - simple chemical building blocks that can be used to assemble a monomer in the course of stepwise polymer formation; **tertiary structure** - three-dimensional fold of a polymer chain into a specific conformation that often gives rise to functions like molecular recognition and catalysis, typically based on a combination of multiple secondary structural elements along the chain;

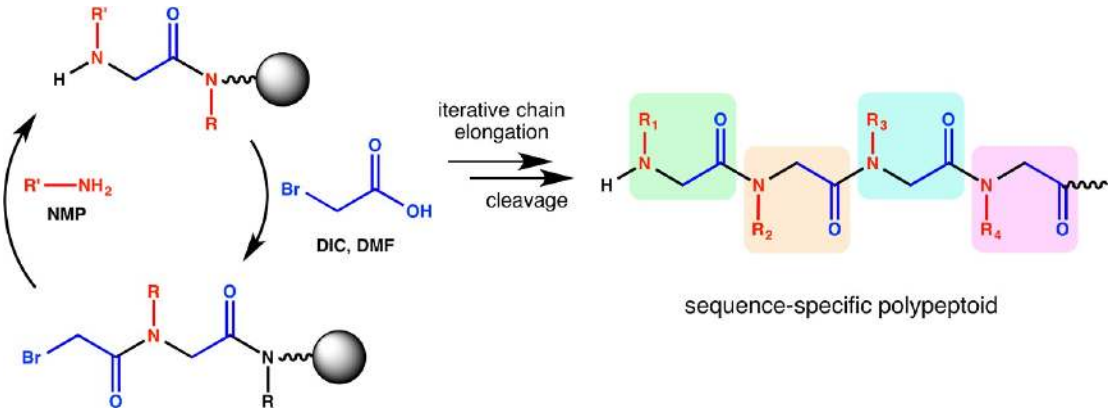

Figure 1. Solid-phase submonomer method allows the rapid synthesis of sequence-specific peptoids from cheap and readily available starting materials (amines and haloacetic acid submonomers), using a repeating two-step monomer addition cycle of acylation followed by nucleophilic S_N2 displacement. Each two-step cycle is performed at or near room temperature and takes <1 h and can be performed manually or by automated synthesizers. DIC = *N*,*N*′-diisopropylcarbodiimide, NMP = *N*-methylpyrrolidinone.

sequenced, which greatly facilitates the identification of a hit sequence after library screening.

Combinatorial Libraries for Peptoid Ligand Screening. Combinatorial library synthesis provides an efficient way to achieve great molecular diversity for the discovery of biomolecular ligands. A variety of library formats have been utilized with peptoids including the following: SPOT peptoid arrays,[55] equimolar mixture screening,[50,56] OBOC (one-bead-one-compound) screening,[57,58] spotted microarrays,[24] and positional scanning libraries.[59,60] Zuckermann and coworkers at Chiron Corp. synthesized large libraries of chemically diverse short peptoid oligomers and screened them for biological activities. By 1994, they discovered several potent peptoid trimer ligands for G-protein-coupled receptors[50] and the urokinase receptor.[61] This was one of the first demonstrations that a diverse combinatorial library of synthetic compounds could provide high-affinity ligands for pharmaceutically relevant receptors.[62] Subsequently, many groups in both biopharmaceutical industry and academic laboratories became inspired to work on the discovery of potential therapeutics from peptoid libraries.[4,57,63−65] Many specific biologically active peptoid oligomers have been described.[66−70] For example, a library of cationic and hydrophobic peptoids yielded novel compounds with antimicrobial activity. These peptoids are a promising class of antimicrobial therapeutics, as they exhibit broad-spectrum antibacterial activity and low mammalian cytotoxicity.[27] The proteolytic stability of peptoids make them particularly well-suited for diagnostic applications where the sample may contain degradative enzymes. For example, peptoids were identified by Novartis Corp. that specifically detect amyloidogenic misfolded proteins in blood.[22,23] Using combinatorial peptoid microarrays, the Kodadek lab developed a general method to identify diagnostically useful antibodies without the need for antigen identification. They demonstrated the discovery of potentially useful diagnostic biomarkers in humans *via* identification of candidate IgG biomarkers for Alzheimer's disease.[24] In addition to linear protein ligands, several cyclic peptoid ligands have also been explored that we will address later. Peptoid−fluorophore conjugates have also been prepared as reporters for intracellular delivery[71] or the folding into secondary structures.[72,73] These examples demonstrate that peptoid libraries are a powerful, inexpensive, and convenient source of diverse ligands for a variety of biomedical applications.

Peptoid Modulation of Crystal Growth. Peptoid oligomers have recently been used to passivate the surface of inorganic nanoparticles[74,75] and to modulate the nucleation and growth of inorganic crystals.[76,77] Peptoids offer a unique opportunity to selectively bind to or influence the growth of particular crystal faces, mimicking key aspects of biomineralization proteins. For example, carboxylic-acid-rich amphiphilic peptoids were used to mineralize CO_2 in the presence of calcium ion to form calcite (Figure 2).[77] It was demonstrated that specific peptoid sequences, containing a balance of charge and hydrophobicity, offer both a high degree control over calcite growth morphology and an unprecedented acceleration of crystal growth rates. These peptoids were active at nanomolar concentrations and depended strongly on the monomer sequence. Peptoids have also been demonstrated to influence the morphology and growth rate of ice crystals.[76] Given the substantial structural diversity of peptoids and their ready preparation as combinatorial libraries, it is reasonable to expect more effective peptoid−inorganic crystal interactions to be discovered in the near future.

Covalent Architectures of Sequence-Specific Polypeptoids. In addition to linear polypeptoids, various other polypeptoid architectures have also been explored. Kirshenbaum *et al.*[78] have prepared head-to-tail macrocyclic peptoids by the solution cyclization of the secondary amine N-terminus to the free carboxyl group on the C-terminus. Cyclic 5−20mers have been reported with >90% yields within 5 min, and high cyclization efficiencies are observed across diverse sequences and chain lengths. Peptoid macrocycles

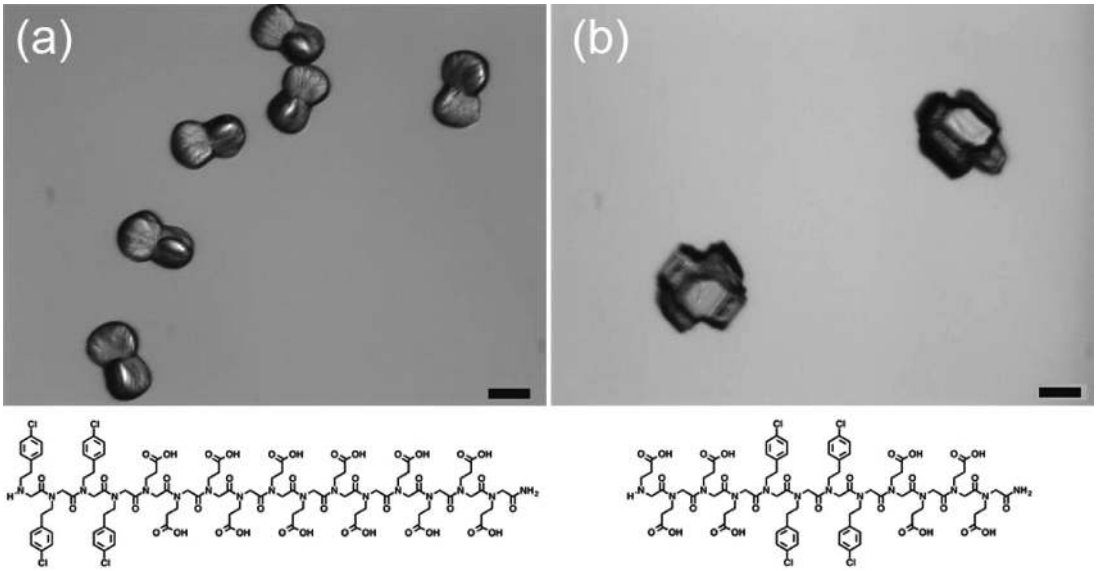

Figure 2. Anionic and aromatic amphiphilic peptoid oligomers exhibit significant control over the morphology of $CaCO_3$ crystals grown aqueous solutions, depending on subtleties in the monomer sequence.[77] (a) Diblock 16mer and (b) triblock 12mer made from the same two monomers have very different effects. Scale bars = 100 μm.

are more conformationally constrained than their linear counterparts, and several structures have been elucidated by X-ray crystallography (Figure 3). Kodadek and co-workers also developed a "one bead two compound" approach to synthesize an encoded combinatorial library of cyclic peptoid microarrays.[71] Macrocyclic peptoids were also found that crystallized in a tube-like array, permitting reversible sequestration of cocrystallized water molecules through a single-crystal-to-single-crystal transformation (Figure 3b).[79] Cyclic peptoids can also form stable complexes with metal ions in the solid state to form interesting 1D metal organic framework structures (Figure 3c).[80] Macrocyclic peptoids adopt rigid and compact folded conformations, which can result in an enhancement of binding affinities and specificities.[16,81,82] For example, the Blackwell group reported a series of cyclic peptomers as mimics of the quorum sensing signaling molecules autoinducing peptides (AIPs) in bacteria and identified one peptomer that can inhibit the AIP receptor proteins.[83] Strategies to synthesize on-bead combinatorial libraries of cyclic peptoids have also been developed.[84] More recently, new types of triazole-linked bicyclic peptoids have been synthesized directly on the resin[85] *via* post-synthesis azide–alkyne chemistry.[86] Given the constrained structure and relatively larger size, these bicyclic peptoids hold great promise as modulators of protein–protein interactions and may serve as scaffolds for drug design.

"Hairy" architectures, peptoids with complex side chains also known as polymer brush-like structures, have been prepared by chemical functionalization of peptoid scaffolds.[87] Azide–alkyne cycloaddition reactions have been employed as an efficient approach to post-display bioactive ligands in a potential application for the modular synthesis of biosensors.[88] An *N*-alkylaminooxy strategy provides a convenient way to generate an extensive range of biologically functional glycopeptoids.[89]

A peptoid-based dendrimer with three generations has been obtained by microwave-assisted solid-phase methods.[90] The third generation compound displayed minimal cytotoxicity and was demonstrated to be an efficient mediator of DNA transfection. β-Peptoids differ from polypeptoids (also referred as α-polypeptoids) by addition of a methylene unit in the backbone.[91] This class of polypeptoids has a lower synthetic efficiency than α-polypeptoids, especially when incorporating sterically α-branched amines.[92,93] However, β-peptoids have been prepared by solid-phase synthesis from Fmoc-protected β-peptoid dimers and trimers or α-amino acid/β-peptoid hybrid dimers with high purity and efficiency.[94,95] These versatile peptoid architectures, particularly with various controllable functional groups, offer tremendous advantages for molecular recognition, scaffolds, and supramolecular assemblies.[71,82,96–101]

Control of Secondary Structure in Sequence-Specific Polypeptoids. In general, the peptoid backbone is inherently flexible due to the lack of main-chain chirality and hydrogen bond donor. Recent small-angle neutron scattering (SANS)[12] and NMR spectroscopy[102] data confirmed this. It was shown that the persistence lengths of (*R*)-*N*-(1-phenylethyl)glycine-containing polypeptoids ranged from 0.5 to 1 nm, which is quite low and similar to that of polystyrene (1 nm).[103] In comparison, the persistence length of a polyproline 20mer in a polyproline type-II helix is estimated to range from 9 to 13 nm.[104] The *cis*/*trans* isomerization of the tertiary backbone amides is a major contributor to the conformational heterogeneity of the peptoid backbone.[105]

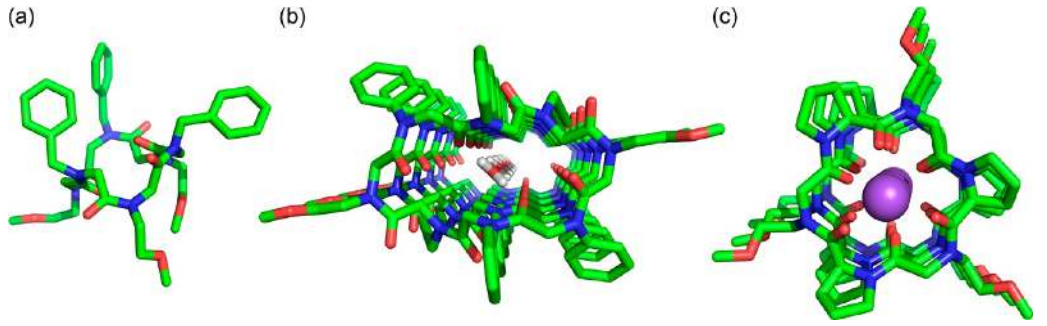

Figure 3. Peptoid macrocycles adopt well-defined conformations, and several have been crystallized and their structures determined by X-ray crystallography: (a) cyclic hexapeptoid,[80] (b) cyclic octapeptoid that forms nanotubes with a bound water molecule in the cavity in the solid state,[79] and (c) 1D metal−organic framework structure derived from a proline-containing cyclic hexapeptoid and sodium atoms (purple).[80] Atom designations: green = carbon, blue = nitrogen, red = oxygen.

However, stable secondary structure can be induced by the proper choice of side chains (Figure 4). Several side chains have been discovered which effectively control the *cis versus trans* geometry of the backbone amide bonds.[106−110] Early research on polypeptoid secondary structure mainly focused on the use of bulky α-chiral side chains which induce a helical fold in the chain. Both theoretical[111,112] and experimental[105] studies have shown that the preferred conformation of an oligo-(*S*)-*N*-(1-phenylyethyl)glycine (Nspe) helix is entirely composed of *cis*-amide bonds with a periodicity of three residues per turn and a pitch of approximately 6 Å, similar to a polyproline type-I-like helix (Figure 4a). The handedness of the helix is determined by the handedness of the α-chiral side chains. Barron and co-workers systematically investigated the relationship of peptoid sequence to helix stability.[113−115] It was demonstrated that the minimum chain length to observe a stable helix is five residues, with stability increasing with chain length up to about 15 residues. A minimum of 50% α-chiral side chains are necessary to form a stable helix as evidenced by CD. In addition to this chiral aromatic side chain, a pentamer with an α-chiral aliphatic side chain [(*R*)-*N*-(1-cyclohexylethyl)-glycine] can also form a left-handed helix with all *cis*-amide bonds.[115] However, all these systems are conformationally heterogeneous, as evidenced by low overall amide $K_{cis/trans}$ value (not more than 3.2).[113] It is worth noting that, despite the flexibility, these helical secondary structural folds are extremely stable to chemical denaturants such as urea or temperature, as measured by CD, which is thought to be a consequence of the steric interactions and not hydrogen bonding.[116] Thus, these peptoid helices exhibit a very different stability profile than polypeptide α-helices, due to their different mechanism of stabilization.

Strategies have been developed to enforce either *cis*- or *trans*- amides within the peptoid backbone. Blackwell and co-workers demonstrated that an n→π* interaction between the lone pair on the carbonyl oxygen of the backbone and the π* orbital of an adjacent aromatic side chain could be exploited to stabilize a *cis* backbone conformation.[107] Recently, helices consisting of chiral and even more bulky (*S*)-*N*-1-naphthylethyl side chains were found to be highly stabilized after only five monomer units (Figure 4d), partly due to the strong propensity of this monomer to stabilize the backbone *cis*-amide conformation ($K_{cis/trans}$ of 9.7).[106] Kirshenbaum and co-workers demonstrated the stabilization of the *trans*-amide conformation with more than 90% *trans*-amide conformer in the peptoid backbone by the incorporation of *N*-aryl side chains.[109] In their work, computational studies predicted that this type of peptoid could form polyproline type-II helices. Synthetic routes have also been developed to make functionalized peptoid helices.[120] A variety of polar and reactive functional groups have been introduced into chiral, aromatic amine submonomers, which were used to create covalent helix dimers and to gain increased water solubility.

In addition to helices, peptoid loops[121] and turns[78,122] have been discovered by investigators seeking to establish new structural scaffolds.[108,118,120] Huang *et al.* first reported an unusual "threaded loop" structure by a peptoid nonamer that contains bulky, α-chiral side chains (Figure 4b).[117] Blackwell's group developed new strategies for controlling peptoid conformation that utilize local noncovalent interactions to regulate backbone amide rotameric equilibria.[107,121,123] They demonstrated a unique acyclic peptoid reverse-turn conformation with all-*trans*-amide backbone through the installation of *N*-aryl side chains capable of hydrogen bonding with the backbone (Figure 4c).[110] The hydrogen-bond donors of *N*-hydroxy side chains enable a sheet-like secondary structure to form[118] (Figure 4e), and the combination of two structure inducing units, alternating *N*-aryl and *N*-alpha-chiral monomers, induces a ribbon-like structure[119] (Figure 4f). Combined, these studies provide considerable control over the backbone conformation and side-chain functionality and can be used as the basis to design peptoids for specific applications.

Protein-Mimetic Architectures. Structured peptoids have been used as scaffolds to position a variety of reactive cofactors to generate protein-like functions. For example, Kang *et al.* employed a peptoid helix as a scaffolding material to construct a precisely defined cofacial array of porphyrins for potential application as

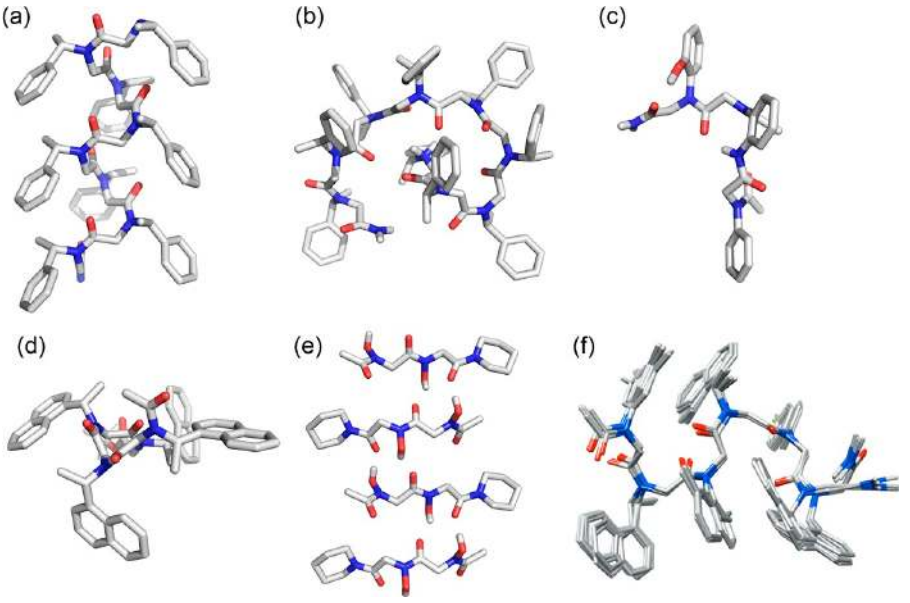

Figure 4. Variety of peptoid secondary structures have been identified. (a) Model of a peptoid helix from a homopolymer of *N*-(*S*)-(1-phenylethyl)glycine (Nspe) as first predicted by molecular mechanics,[112] (b) peptoid threaded loop structure of $(Nspe)_9$ as determined by solution-phase 2D NMR,[117] (c) *N*-aryl peptoid reverse turn,[110] (d) *N*-(*S*)-(1-naphthylethyl)glycine-based peptoid helix looking down along the helix axis,[106] (e) *N*-hydroxyamide sheet-like structures,[118] as determined by X-ray crystallography, (f) alternating *N*-aryl/*N*-1-naphthylethyl peptoid ribbon structure.[119] Atom designations: red = oxygen; blue = nitrogen; gray = carbon.

molecular wires (Figure 5a).[124] Kirshenbaum's group synthesized a family of catalytic peptoids by the attachment of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), a well-known catalyst for oxidative transformations to various sites along the spine of helical peptoids (Figure 5b).[125] They discovered that the enantioselectivity of the catalytic peptoids depends on the handedness of the asymmetric environment derived from the helical scaffold, the position of the catalytic center along the peptoid backbone, and the degree of conformational ordering of the peptoid scaffold.

Hydrophobic collapse is a predominant driving force in the folding of polypeptide chains into compact globular structures.[126] Thus, there has been much activity in studying the impact of hydrophobic sequence patterning to create folded polypeptoid structures with well-defined hydrophobic cores. Combinatorial libraries of amphiphilic peptoid helices with three-fold periodicity have been screened for their ability to pack together into discrete multihelical bundles.[56] These sequences were subsequently covalently linked together to form single-chain helical bundle sequences that folded into a compact multihelical structure.[18] More recently, a structure-dependent function has been introduced into the helical bundle motif by incorporating functional groups at defined positions to create a high affinity selective zinc binding site (Figure 5c).[19] By introducing a pair of thiol and imidazole side chains into a peptoid two-helix bundle, a convergent binding site was created which mimics the natural zinc finger domains found in DNA-binding proteins. This is one of the first tertiary folds created from a completely non-natural single-chain polymer that is capable of specific molecular recognition.

Globule formation driven by hydrophobic collapse is considered to be central to the protein-folding problem.[127,128] There is keen interest in understanding how the sequence pattern of hydrophobic and polar residues impacts folding.[129,130] One of the most extensive theoretical efforts has been performed by Khokhlov and Khalatur, who demonstrated that copolymers with blocky (or protein-like) distributions of monomers form more stable globules than corresponding random sequences where the monomers are more evenly distributed throughout the chain.[131] An "HP model" was used to simplify the set of interactions in polypeptides, in which only two types of monomers, hydrophobic (H) and polar (P), are considered. In an effort to explore the impact of hydrophobic sequence patterning on globule formation in the absence of other competing factors (*e.g.*, chirality, intrachain hydrogen bonding), we recently designed protein-like polypeptoid HP sequences and explored their coil to globule transitions (Figure 6a).[132] We synthesized two HP polypeptoid 100mer sequences: one was designed to be "protein-like" and contained longer stretches of both the hydrophobic and polar monomers; the other "repeating" sequence contained the shortest possible stretches of both monomers. It was shown that the protein-like sequence collapsed into a tighter globule with smaller gyration radius in aqueous solution than that formed by the repeating sequence. In addition, the coil to globule transition of the protein-like sequence was sharper, more cooperative, and exhibited a significantly higher unfolding free energy than that of the repeating sequence molecule

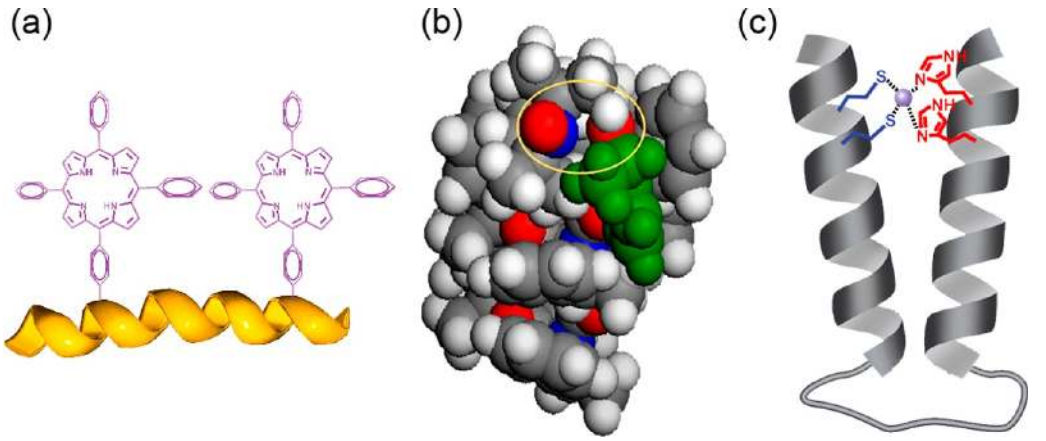

Figure 5. Several structured peptoids have been structurally modified with reactive moieties to introduce function. (a) Porphyrin groups were conjugated to a peptoid helix to study electron transfer.[124] (b) Energy-minimized structure of a TEMPO-functionalized catalytic peptoid with the docked substrate 1-phenylethanol (green);[125] hydrogen = white, oxygen = red, nitrogen = blue. (c) Peptoid two-helix bundles functionalized with thiols and imidazoles have been identified that selectively bind zinc ion with nanomolar affinity.[19]

(Figure 6b). Nile Red fluorescence showed an increased emission peak from the protein-like sequence, indicating that the larger blocks of H and P monomers along the protein-like chain allowed it to fold into a more compact globule. The study helped to prove that the concept of hydropobic sequence patterning extends to non-natural polymers and provides insight into the design of a new generation of robust protein-mimetic materials.

Murnen *et al.* used a model polypeptoid system to study the effect of charge distribution on polyelectrolyte conformation in aqueous solutions.[133] They synthesized polypeptoids containing different densities of ionizable groups along the chain and investigated the persistence length by small-angle neutron scattering. It was shown that, at low ionic strengths, the polypeptoid with closer charge placements had a higher persistence length due to the increased level of electrostatic repulsion between ionized groups. At higher ionic strengths, both polymers showed a decrease in persistence length that was inversely proportional to NaOH concentration, in agreement with previous theoretical and experimental results. These studies enrich our understanding of the fundamental behavior of polypeptoids in solution and begin to establish design rules that govern the relationship between monomer sequence and chain conformation.

Control over Thermal Properties in the Solid State. As the tools for polymer synthesis grow ever more sophisticated, fundamental questions in polymer science can now be probed with new functional designs at the molecular level.[134−137] Synthesis methods that offer precision architectural control are the key.[138−140] Traditional polymerization methods (*e.g.*, radical and anionic polymerization) offer limited levels of control over comonomer distribution. Genetic engineering techniques and metal catalysts have been explored for high levels of control.[6,138,141] However, biologically inspired polymers, particularly polypeptoids, provide perhaps the most convenient platform. Their sequence specificity and monodispersity make the polypeptoid system an excellent platform to elucidate the behavior and structure−property relationships within a family of polymers with complex, tunable intra/interchain interactions.

Rosales *et al.* have recently investigated the effects of comonomer composition and distribution on the crystallization and melting behavior of polypeptoids in the solid state.[11] Peptoid polymers were shown to be stable to very high temperatures (300 °C) and able to crystallize. A direct comparison of a polypeptoid and its exact polypeptide structural isomer was made. The two 15mer chains had the exact same side chain (an *n*-butyl group) and differed only by their point of side-chain attachment to the main chain (nitrogen *vs* α-carbon). Differential scanning calorimetry indicated that the polypeptoid exhibited a reversible melting transition, whereas no melting peak was observed in the polypeptide due to the stabilization resulting from main-chain hydrogen bonding (Figure 7). Side-chain size was also systematically varied in a series of homopolymers, and it was observed that the addition of two aliphatic carbons to each side chain depressed the melting transition by almost 15 °C. The crystallinity was readily controlled through the insertion of defects at precise locations along the polymer backbone, as well. It was demonstrated that melting point decreases with increasing defect content due to the inclusion of defects in the crystal lattice, which is consistent with Flory's theory of crystallization. Thus, sequence specificity is leading to an increased understanding of the impact of defect size and frequency on the thermal behavior.

Nanostructure Based on Microphase Separation of Polypeptoids. In addition to thermal processability and chain shape, the sequence specificity of polypeptoids also allows for tenability of other physical properties, such as the interaction strength between two blocks of a diblock copolymer. Rosales *et al.* synthesized sequence-defined

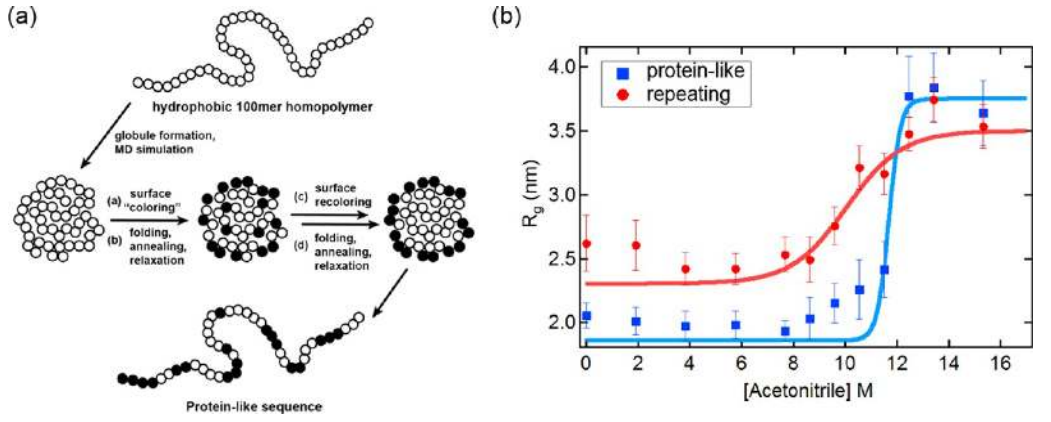

Figure 6. (a) Protein-like polypeptoid sequences were designed using an iterative computational process involving successive rounds of globule formation using all-atom molecular dynamics simulation followed by the addition and redistribution of polar residues on the globule surface.[133] White circles represent the hydrophobic monomer with a methyl side chain; black circles represent the polar monomer with a carboxylate side chain. (b) Protein-like sequence exhibited greater folding cooperativity by equilibrium acetonitrile titration and formed a more compact globule as determined by small-angle X-ray scattering.

diblock copolymers *via* azide–alkyne click chemistry using polystyrene and sequence-specific polypeptoids with *N*-2-methoxyethyl side chains, ranging from exactly 18 to 48 monomers in length.[142] These polystyrene–polypeptoid (S-Nme) block copolymers readily self-assembled into hexagonally packed and lamellar morphologies, in good agreement with the classical block copolymer phase diagram. *N*-(2-Phenylethyl)glycine (Npe) residues, which have a styrene-like side chain, were introduced throughout the polar polypeptoid block to increase the compatibility with the polystyrene block. As the strength of segregation decreased, there was a decrease in the order–disorder transition temperature, as well as a slight increase in the domain spacing by 0.8–1 nm. The polystyrene–polypeptoid block copolymers provide a tunable platform for further studies on the effect of composition and sequence design on self-assembly of block copolymers.

Nanostructures Based on the Solution Self-Assembly of Polypeptoids. The flexible synthesis of peptoids enables the precise exploration of sequence space to explore the solution self-assembly behavior of polypeptoid-based copolymers.[56] Zuckermann's group recently discovered a family of polypeptoid sequences that self-assemble into robust, water-soluble, precisely ordered nanosheets by systematic screening of different amphiphilic sequence patterns.[143] The key to generate sheet-forming sequences is to enforce a two-fold periodic sequence pattern, alternating between an aromatic hydrophobic monomer [*N*-(2-phenylethyl)-glycine (Npe)] and one of two oppositely charged ionic polar monomers [*N*-(2-aminoethyl)glycine (Nae) and *N*-(2-carboxyethyl)glycine (Nce)] (Figure 8). This results in the assembly of parallel, fully extended polypeptoid chains into a highly ordered, planar bilayer structure, hundreds of micrometers in length and width, and only 3 nm thick. Subsequently, the nanosheets were functionalized by incorporating a

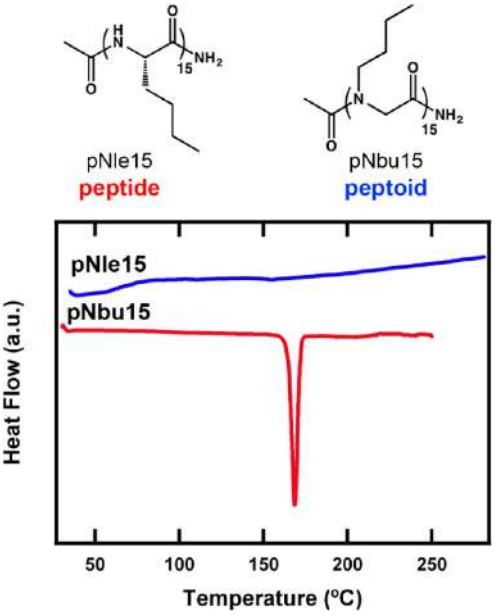

Figure 7. Comparison of the solid state melting behavior of two polymer region isomers by differential scanning calorimetry. A 15mer of norleucine shows no observable melting transition, while a 15mer of *N*-butylglycine, which has the same side chain, shows a well-defined melting transition. The difference is attributed to the lack of hydrogen bond donors in the peptoid backbone.[11]

streptavidin-binding peptide sequence cyclo-[CHPQFC]- at the N-terminus of each peptoid. It was confirmed that the protein-binding ligand was displayed on the sheet surface as desired by binding to fluorescently labeled streptavidin.

While the early nanosheet designs involved the interaction of two oppositely charged peptoids, it was recently discovered that a single polymer strand combining all three monomers (aromatic positive and negative) arranged in the same two-fold sequence pattern can also form nanosheets.[144] Two sequences were designed that obey the two-fold amphiphilic periodicity rule: one with charged residues alternately

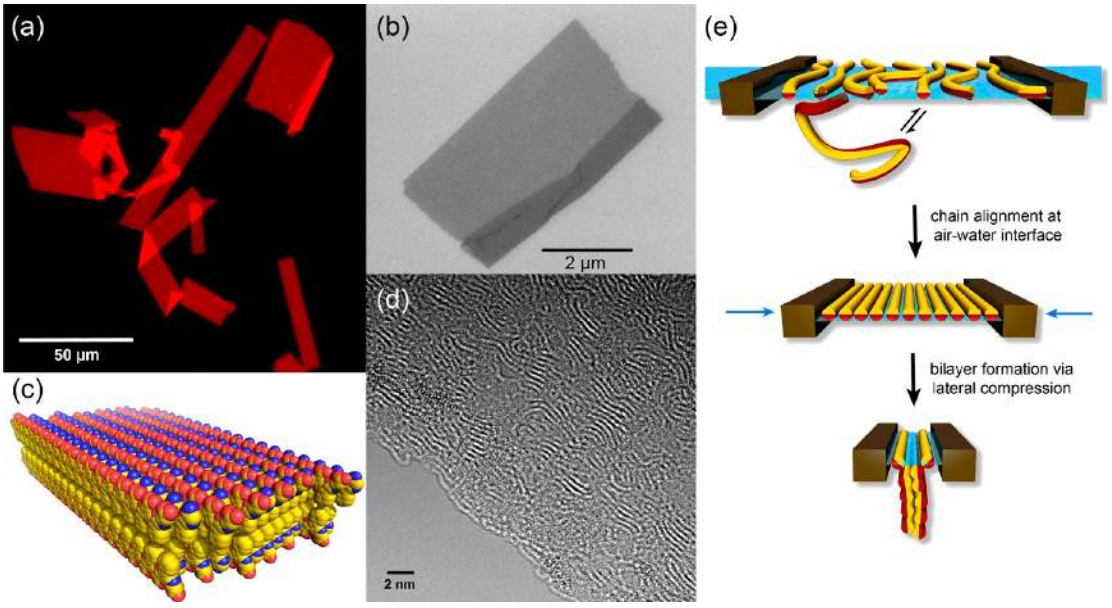

Figure 8. Two-dimensional crystalline nanosheet bilayers assemble in dilute aqueous solution from an amphiphilic peptoid sequence with a two-fold periodicity.[143] The peptoid nanosheets sheets (a) are free-floating in solution as observed by fluorescence microscopy (stained with Nile red); (b) have very sharp, straight edges as observed by scanning electron microscopy; and (c) are composed of fully extended polymer chains lined up side-by-side in a bilayer. (d) Individual aligned polymer chains are directly observed by aberration-corrected TEM. (e) Peptoid nanosheets are formed by a unique assembly mechanism involving the formation of an ordered monolayer at the air−water interface, followed by a buckling event induced by lateral compression of the monolayer to produce a stable bilayer.[145]

positive and negative (alternating pattern); the other with charges segregated in positive and negative halves of the molecule (block pattern). The two structural motifs displayed differing sensitivities to pH and to denaturation by acetonitrile. The block charge pattern design was shown to be more stable, which was consistent with expectations based on theoretical considerations of the molecules' electrostatic interactions.

Moreover, it was demonstrated that the key intermediate in nanosheet formation is an ordered monolayer at the air−water interface (Figure 8e).[145] Due to the amphiphilicity of these peptoids, a small but important fraction of the dissolved compound spontaneously adsorbs to the air−water interface to form a monolayer. Monitoring of the surface pressure isotherm in a langmuir trough reveals distinct stages of the compression/expansion cycle. As lateral compression begins, a collapse pressure is eventually reached, after which continued compression produces nanosheets that appear in the aqueous subphase. The peptoid monolayer reaches a solid phase upon compression that eventually buckles, bringing two hydrophobic faces irreversibly together into a bilayer. The interfacial contact between the two adjacent hydrophobic polyaromatic faces creates a highly stabilized, water-soluble nanosheet bilayer coated by a zwitterionic polar surface. Upon expansion, peptoid from solution gradually re-forms the surface monolayer so that the cycle can be repeated. The cycle can in fact be repeated hundreds of times until over 90% of the peptoid has been converted into nanosheets. This is the first example of a non-natural sequence-specific polymer that could fold into a well-defined protein-like material. The peptoid nanosheets form under physiological conditions, are only two molecules thick, have a chemically defined interior and exterior, and are among the largest two-dimensional organic crystals known. They are a highly engineerable 2D nanomaterial platform that can potentially serve as the basis to address a variety of problems including biosensing, membrane-based separations, drug delivery, and templates to grow inorganic materials.

Polymer sequence control was also used to investigate the solution assembly of diblock copolypeptoids. Zuckermann and co-workers developed a comparatively simpler model system that allowed controlled engineering of self-assembled structures in aqueous solution.[146] An amphiphilic diblock copolypeptoid system [*N*-(2-phenylethyl)glycine]$_{15}$-*b*-[*N*-(2-carboxyethyl)glycine]$_{15}$ was synthesized with one hydrophobic block of *N*-2-phenylethyl side chains and one chargeable hydrophilic block of *N*-2-carboxyethyl side chains. Upon dissolution in aqueous solution at pH 6.5, this peptoid hierarchically self-assembled into nanosheets, which further self-assembled into superhelical structures with a diameter of 624 $\pm$ 69 nm and lengths ranging from 2 to 20 μm (Figure 9). Moreover, it was shown that increasing of overall length of the each polymer block resulted in a similar superhelical structure, but with an increase in the lamellar spacing. This is consistent with the conversion of nanosheets into superhelices. Helix formation only occurred in a pH range where the carboxylates were

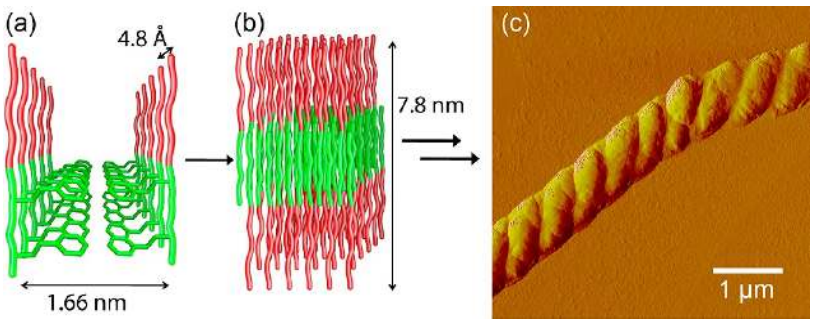

Figure 9. Model of the proposed mechanism for the formation of a superhelix from an amphiphilic diblock copolypeptoid.[145] Green represents the hydrophobic portion of the chain, and red represents the hydrophilic block. (a) Chains initially organize with the aromatic groups facing each other. This spacing (1.66 nm) along with the distance between two chains laterally (4.8 Å) was verified by X-ray scattering. (b) Chains further arrange into extended two-dimensional nanosheets with a height of 7.8 nm, which further assemble into superhelices as imaged by AFM (c).

between 1/2 and 2/3 charged, where there was a balance between reduced electrostatic repulsion and good water solubility. The superhelices are remarkably homochiral despite the achiral nature of all components.

For a deeper understanding of the superhelix internal structure and the role of charge location and density in the self-assembly, specific chemical modifications in the form of closely related analogues were made. To investigate the interplay of ionic interactions and hydrogen bonding of the 2-carboxyethyl side chain in the self-assembly of the superhelices, a nonionic side chain, *N*-(2-methoxyethyl)glycine, and a hydrogen bond donor/acceptor side chain, *N*-(2-carboxamidoethyl)-glycine, were used as hydrophilic blocks. Neither sequence could self-assemble into organized structures, demonstrating that ionic interactions are indeed necessary for helix self-assembly to occur.

Control over sequence patterning between hydrophobic and cationic side chains was shown to be critical in the formation of spherical nanoparticles with DNA and RNA for use as intracellular delivery vehicles.[7] Many of the peptoids synthesized were capable of condensing plasmid DNA into small particles and protecting it from nuclease degradation, but only a repeating triplet motif (cationic−hydrophobic−hydrophobic) was found to exhibit transfection activity in cell culture experiments. The most active peptoid was a 36mer that contained 12 cationic aminoethyl side chains. This peptoid condensed plasmid DNA into uniform spherical nanoparticles 50−100 nm in diameter and mediated the transfection of a number of cell lines in the presence of fetal calf serum with good efficiency. A small library of lipid−peptoid conjugates (lipitoids) was subsequently synthesized.[147] The complexes with DNA showed a spherical shape with a diameter of ∼100 nm. The most active compound had the same repeating triplet motif (cationic−aromatic−aromatic) but with a much shorter main chain. The compound exhibited much higher transfection efficiencies, was active in the presence or absence of serum, could transfect primary cells, and could deliver siRNA.[20] Further examination is needed to reveal hidden structure−activity relationships in both system.[21]

Goodman and co-workers synthesized collagen peptidomimetics as an alternative to natural collagen (Figure 10a).[148,149] The peptoid residue *N*-isobutylglycine (Nleu), a structural mimic of leucine, has been successfully incorporated into a series of collagen mimetics composed of Gly-Pro-Nleu, Gly-Nleu-Pro, and Gly-Nleu-Nleu trimer repeat units. The incorporation of unnatural peptoid residues in these collagen sequences exhibited potent and specific biological activity and enhanced biostability against enzymatic degradation. Furthermore, the use of achiral peptoids simplified synthetic strategies by reducing racemization problems. Interestingly, a single peptoid-containing trimer repeat unit, boc-Gly-Nleu-Nleu, was found to form a crystalline complex with calcium ions (Figure 10b).[150] The discovery of template-assembled collagen mimetics and metal-binding ability has laid the foundation for new opportunities in the design of novel collagen-mimetic complexes.

Polyethylene Glycol Mimetic Peptoids. Polyethylene glycol- (or polyethylene oxide)-mimetic materials have been widely investigated and used for a variety of applications. In particular, PEGylated peptide/protein-based biopharmaceuticals often exhibit enhanced proteolytic stability, reduced rates of renal clearance, and an enhancement of therapeutic efficacy. However, the polydispersity or heterogeneity of PEG preparations results in polymer-like product distributions, which require a complicated purification processing and result in heterogeneous preparations. Barron *et al.* have exploited polymers of *N*-(2-methoxyethyl)glycine as an excellent PEG-mimetic material because of its similar chemical structure and more homogeneous product distribution.[151] They attached an *N*-2-methoxyethyl glycine (Nmeg) oligomer covalently to a short therapeutic peptide, which showed neither ideal solubility nor serum stability.[152] Upon the incorporation of just one Nmeg monomer, comparable therapeutic efficacy relative to the parent peptide was observed but with a prolonged half-life. Longer Nmeg oligomer chains were shown to interfere with peptide

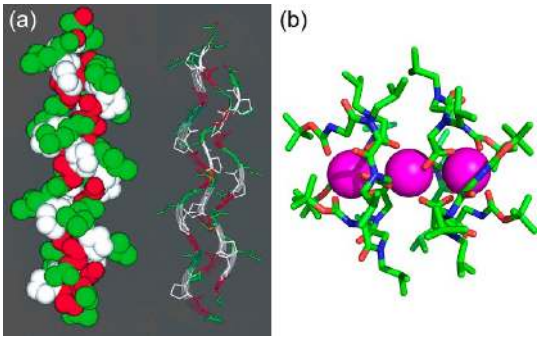

Figure 10. Peptoid monomers have been substituted into the triplet repeat sequence of collagen to create collagen-mimetic materials.[148,149] (a) Calculated lowest energy triple-helical conformation of Ac-(Gly-Pro-Nleu)$_4$-NH$_2$ represented as a heavy atom CPK model (left) and as a stick model (right). For the stick model, the backbone ribbon diagram is shown for each of the three chains, which are staggered by one residue. The Gly, Pro, and Nleu residues are color coded red, white, and green, respectively. Nleu = *N*-isobutylglycine. (b) Peptoid-containing trimer motif, boc-Gly-Nleu-Nleu, used in the study of collagen mimics was found to form a crystalline complex with calcium ions.[150]

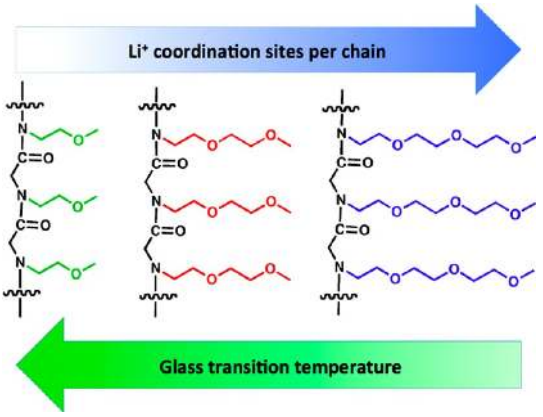

Figure 11. Three new comb-like PEO-mimetic polypeptoid homopolymers were studied as potential solid polymer electrolytes.[36] The polypeptoids with longer ethylene oxide side-chain materials are excellent PEO-mimetic materials that exhibit rapid segmental motion and are capable of complexing lithium ions.

binding to the target protein. They also reported a new class of antifouling peptidomimetic polymers based on a Nmeg 20mer. This polymer showed excellent protein resistance, and its ability to resist fouling could be maintained for several months under frequent challenge with fresh serum and cells.[153] Van Zoelen *et al.* designed polypeptoid−polystyrene diblock copolymer thin films with the help of fluorinated side chains in the peptoid sequence for antifouling coating applications.[154]

In recent years, poly(ethyleneoxide) (PEO)-based materials have received a great deal of interest for use as battery solid polymer electrolyte applications, due to their high ionic conductivity. Sun *et al.* recently designed and synthesized a class of well-defined PEO-mimetic homopolypeptoids to investigate their ability to serve as electrolytes with small amounts of dissolved lithium ion in the solid state. A series of analogues were prepared with varying numbers of ethylene oxide (EO) units in the side chains (Figure 11).[36] Subtle variation of the side chain enabled the systematic study of the relationship between polymer structure and activity. All peptoids in the series were amorphous, and the glass transition temperature (T_g) values of these polypeptoids decreased with increasing side-chain EO unit length. The ionic conductivity behavior of the complex of these polypeptoids and Li[N(SO_2CF_3)$_2$] salt was also explored. The optimum ionic conductivity of 2.6×10^{-4} S/cm was achieved for poly(*N*-2-(2-(2-methoxyethoxy)ethoxy)-ethylglycine)−Li salt complex at 100 °C, which is 2 orders of magnitude higher than previously reported for comb-like PEO-mimetic polypeptides. This is because the lack of hydrogen bond donors along the peptoid main chain results in a flexible backbone, allowing for increased segmental motion of the polymer chains. Taken together, the conductivity data as a function of temperature and lithium ion concentration show that the conductivity of the system is strongly correlated to the changes in glass transition temperature and not to changes due to other factors such as complexation with salt or the length of the pendant $(EO)_n$ chains. It was demonstrated that the polypeptoid is an ideal model system for understanding the thermodynamic and kinetic properties associated with ion solvation and mobility, due to their precise monomer sequence, absolute monodispersity, and fine-tuned structure. Information from this study helped identify the critical structural attributes of the polymer design, which may ultimately be prepared by a cheaper method (see below).

Polypeptoids by Solution Polymerization. The ring-opening polymerization (ROP) of *N*-carboxyanhydrides (NCA), which is typically used to produce polypeptides, has also been recently used to synthesize polypeptoids from N-substituted monomers.[155] Due to synthetic accessibility, early research mainly focused on poly(*N*-methyl glycine),[156−158] also referred to as polysarcosine. Because of its excellent biocompatibility and water solubility,[159] polysarcosine has been used as the hydrophilic block in amphiphilic block copolymers for the application of controlled release drug delivery.[160−164] In the polymerization of polypeptoids, N-substitution plays a crucial role and is thus distinct from the polymerization mechanism of polypeptides. The steric effect of the nitrogen substituent limits propagation *via* the C5 nucleophilic attack mechanism,[165] making polypeptoid polymerization more efficient.

Recently, Luxenhofer *et al.*[166,167] used a primary amine to initiate a series of peptoid polymerizations with alkyl side chains (Figure.12). They investigated the polymerization kinetics and showed that it occurs in a living manner. The polymer molecular weights are well-controlled and obey a Poisson distribution. A series of amphiphilic block copolypeptoids with different aliphatic side chains as hydrophobic blocks were

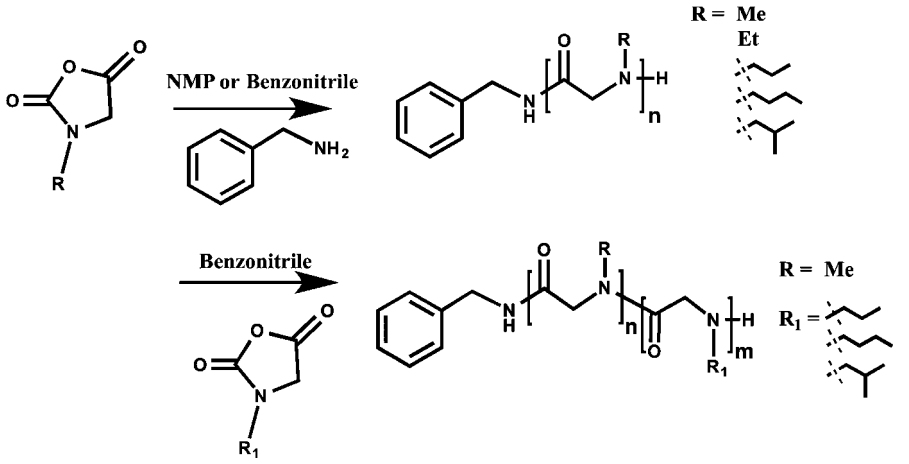

Figure 12. Peptoid polymers can be synthesized by living ring-opening polymerization of N-substituted *N*-carboxyanhydride monomers with a primary amine as an initiator.[166,167] Diblock copolymers can also be readily prepared.

then prepared by successive ROP of N-substituted NCAs, and a hydrophobic dye was used as model for drug delivery applications. It was observed that the efficiency of encapsulation is dependent on the side-chain structure. Block copolypeptoids with poly(*N*-*n*-butylglycine) as hydrophobic block show lower critical micelle concentrations and higher capacity for hydrophobic components, which would be beneficial for many applications. They also reported a systematic study of the thermal properties of aliphatic polypeptoids bearing short side chain (C1−C5) with polymerization degrees in the range of 10 to 100. As expected, the side-chain and main-chain lengths can influence the thermal properties of the polypeptoids.[168] Recently, they reported the preparation of poly(β-peptoids) by living ring-opening polymerization of N-substituted NCAs.[169] Zhang's group[38,170−172] has explored N-heterocyclic carbine (NHC)-mediated polymerization of N-substituted NCA monomers (Figure 13). It was reported that the molecular weight and polymerization rate could be well-controlled in solvents with low dielectric constants. Interestingly, they found that a cyclic topology is maintained throughout the entire process of polymerization due to existence of zwitterionic intermediates. Moreover, with different end-capping reagents, either cyclic or linear polymer chains could be obtained. The cyclic structure was verified by AFM after post-polymerization modification of poly(ethylene glycol).[173] They also investigated the self-assembly properties and thermoresponsive behavior of cyclic copolypeptoids.[174] With the amphiphilic diblock cyclic copolymer cyclo-[poly(*N*-methylglycine)-*b*-poly(*N*-decylglycine)] or c-(pNMG-b-pNDG), cylindrical micelles were obtained in methanol, and it was demonstrated the transition from spherical to cylindrical micelle is due to crystallized core of the micelle. A cloud point temperature (T_{cp}) in the range of 20−60 °C was observed with the random cyclic copolypeptoids cyclo-[poly(*N*-ethylglycine)-r-poly(*N*-butylglycine)] or c-(pNEG-r-pNBG). The linear random copolypeptoid analogue show higher T_{cp} by ∼5 °C than the cyclic polymers irrespective of copolymer compositions, which behave differently from the benchmark thermoresponsive polymer PNIPAM. Furthermore, they found that cyclic poly(*N*-decylglycine) can exhibit side-chain and main-chain-coupled crystallization behavior.[172] Schlaad and co-workers[175,176] recently synthesized well-defined polypeptoids by ROP of *N*-allylglycine NCA under homo- or heterophase conditions and obtained high molecular weight glycopeptoids through the post-modification of poly(*N*-allylglycine)s with glucose utilizing UV light in combination with photoinitiators.

In addition to the ring-opening polymerization (ROP) of N-substituted NCA, polypeptoids have also been synthesized by metal-catalyzed alternating copolymerization with imines and carbon monoxide (CO) as monomers.[177] Products with high molecular weights and low polydispersity have been attained with an acyl−cobalt complex as the catalyst. Similarly, several homologues of polypeptoids, referred as poly(β-peptoids)[178,179] and poly(γ-peptoids),[180] were made from copolymerization of CO and N-substituted aziridines/azetidines with metal as the catalyst. A couple of chimeras based on polypeptoids, polypeptides, polyamines, and polyesters have been synthesized with the same approach.[181−183] A urea peptoid trimer has been synthesized and conjugated to polymer main chains to obtain a polymer/urea peptoid conjugate.[184] Further, a linear poly(*N*-alkyl urea peptoid) has been prepared by step-growth polymerization.[185]

Simulation of Peptoid Structure. Advances in polypeptoid synthesis over the past 20 years have far outpaced advances in their structure prediction. The vast design space that is synthetically accessible within this compound class could be much more efficiently mined with computational tools that could predict their folding and assembly. MD simulation helped to predict the stable helical fold induced by chiral side chains. Calculations predicted a noctamer of (*S*)-*N*-(1-phenylethyl)glycine could adopt a polyproline

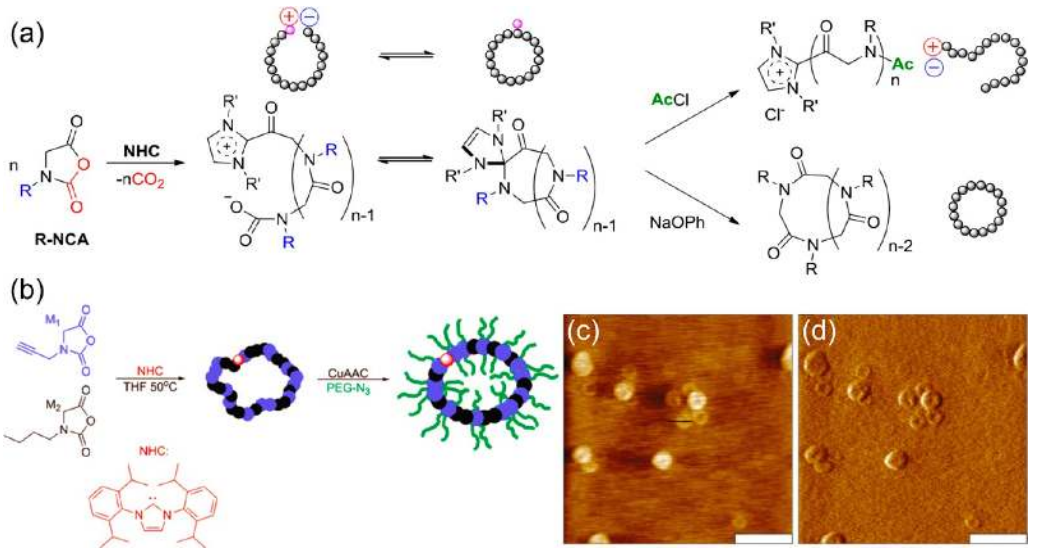

Figure 13. (a) NHC carbene-mediated polymerization of N-substituted *N*-carboxyanhydrides. Different end-capping reagents enable the preparation of linear and cyclic polypeptoids. R is the side-chain group (*e.g.*, alkyl, phenyl, or methyl groups). (b) Scheme of the formation of a big cycle of brush-like polypeptoids from click chemistry with azido-terminated PEG. (c,d) Representative AFM topographic and amplitude images of the cyclic structure (scale bar = 500 nm).

type-I helical conformation,[112] and that *N*-aryl peptoids may form polyproline type-II helices,[109] in agreement with subsequent experimental findings. A compete landscape of peptoid backbone energies was later constructed that provides a detailed understanding of the local backbone dihedral angle preferences.[186] Molecular dynamics force fields from polypeptides have been recently used with peptoids to predict the structures of several short peptoid oligomers. A combination of replica exchange molecular dynamics simulation and quantum mechanical refinement was employed in the blind structure prediction of three short peptoid sequences, which correctly predicted the pattern of *cis*/*trans* backbone amides and the structure of a cyclic peptoid nonamer to an accuracy of 1.0 Å rmsd backbone.[187] This work is a tangible milestone on the path to reliable and efficient tools for computational peptoid design.

CONCLUDING REMARKS AND OUTLOOK

In this review, we summarize the synthesis and nanoscience applications of a novel class of bioinspired non-natural polymeric material, polypeptoids, in which a wide variety of chemically diverse side chains can be incorporated. In comparison to polypeptides and other bioinspired polymers, polypeptoids offer significant advantages in stability, processability, and synthetic efficiency. Peptoids are a side-chain-dominated polymer system, which can generate polymers that can span a huge range of chemical and physical properties. Because polypeptoids lack both chirality and a hydrogen bond donor in their backbone, they offer a simplicity and freedom of design that makes them an ideal rapid prototyping system to study different principles and explore new materials properties. Polypeptoids are biomimetic materials capable of folding into specific protein-like shapes in water and exhibit potent biological activities. Polypeptoids combine the advantages of proteins and polymers and are ideally suited for discovery of highly functional biomaterials.

A major feature of polypeptoids is that the iterative solid-phase submonomer synthesis method allows for the efficient synthesis of polypeptoids of exact monomer sequence from an extremely diverse set of side-chain functionalities, derived from readily obtainable reagents. The precise sequence control and the ability to introduce a wealth of functional monomers at specific locations make it convenient to control and fine-tune intra- and intermolecular interactions simply by changing individual side chains. Two complementary peptoid polymerization techniques have been developed, allowing great versatility in the types of polymers that can be accessed synthetically. Chains of specific sequence can be made up to 50 monomers in length, and chemical ligation and polymerization techniques allow for even longer chain lengths and larger scales. All these features make polypeptoids a new promising platform in nanomaterials science. The emerging design rules for controlling peptoid structure and function, as well as the unique combination of solid-phase and solution-phase synthesis techniques available, make polypeptoids a versatile tool kit for exploiting the next generation of bioinspired polymeric materials.

Conflict of Interest: The authors declare no competing financial interest.

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