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ARTICLE

Enhancing Molecular Diversity of Peptoid Oligomers Using Amino Acid Synthons

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We report the use of unprotected amino acids as submonomer reagents in the solid-phase synthesis of *N*-substituted glycine peptoid oligomers. Subsequent coupling of an amine, alcohol, or thiol to the free carboxylate of the incorporated amino acid provides access to peptoids bearing amides, esters, and thioesters as side chain pendant groups and permits further elongation of the peptoid backbone. The palette of readily obtained building blocks suitable for solid-phase peptoid synthesis is substantially expanded through this protocol, further enhancing the chemical diversity and potential applications of sequence-specific peptoid oligomers.

Introduction

Peptidomimetic oligomers offer an opportunity to innovate abiotic chemical species that recapitulate the sophisticated structures and functions of biomolecules. Such biomimetic strategies enable extraordinary chemical diversity accompanied by conformational ordering. Our investigations are focused on peptoids, a family of *N*-substituted glycine oligomers capable of addressing a broad range of therapeutic,[1-22] materials,[23-32] and catalysis[33-39] applications. Peptoids were initially developed as a means to generate combinatorial libraries for drug discovery using a simple modular synthesis.[40] We aim to explore new peptoid side chain constituents to access oligomers of greater complexity in order to enable enhanced functions or to reinforce folding propensities.

Peptoids feature some similarities with polypeptides, including the presence of backbone amide linkages between the monomer units. Nevertheless, they are distinct from peptides as peptoid side chain groups are displayed on the backbone amide nitrogen atom, rather than the α-carbon (Figure 1). Submonomer solid-phase synthesis is the most common approach for generating peptoids,[41, 42] in which iterative rounds of bromoacetylation and nucleophilic displacement by a primary amine are used to generate each monomer unit (Scheme 1). Each monomer side chain is therefore installed using a primary amine synthon. Because of the ready availability of diverse primary amines, hundreds of building blocks have already been utilized for peptoid synthesis.[43]

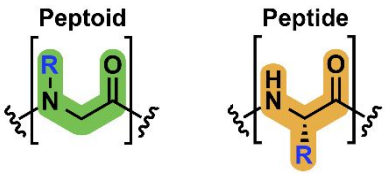
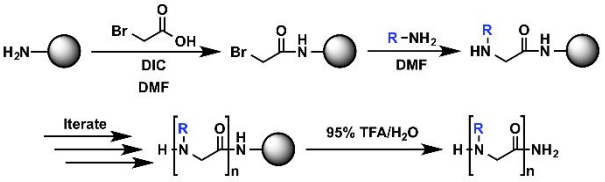


Figure 1. Comparison of peptoid and peptide primary structures.

Access to this level of chemical diversity has made peptoids a highly attractive class of oligomers. Nevertheless, it would be advantageous to enhance further the range of peptoid chemical diversity and tunability using simple synthetic approaches. A variety of synthetic procedures have been developed to elaborate the incorporation of new peptoid side chain types.[44-53] In addition, post-synthetic modifications of specific peptoid side chains have been used to introduce complex chemical moieties.[54-56]

The peptoid backbone is intrinsically achiral, it lacks hydrogen bond donors, and it can exhibit increased conformational heterogeneity associated with *cis*/*trans* amide bond isomerization.[57-59] Because of this increased flexibility, a large area of peptoid research is focused on how specific side chain types,[60-73] oligomer sequences,[74, 75] chain lengths,[76] solvent compositions,[77-79] covalent or dative bond constraints,[80-82] or stereoelectronic interactions[83-85] influence the backbone *cis*/*trans* isomerization or propensity for secondary structure formation.

Peptoids with branched side chains, particularly those with *N*-α-chiral aromatic groups, have been extensively investigated



Scheme 1. General submonomer scheme for peptoid oligomer synthesis on solid-phase support (depicted by spheres).

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because of their tendency to promote formation of polyproline type I helical secondary structures.[60, 62, 74-78, 86] These reports established that bulky branched side chains can be used as structure-inducing residues that favor *cis* amide bond conformations. Accordingly, *N*-α-chiral aromatic side chains have been used in a variety of peptoids to develop robust structure-function relationships.[2, 33, 87, 88] However, ordered peptoid oligomers generally require a distinct set of side chain types to impart folding, and another set of side chain types to establish functional attributes, resulting in the current dichotomy between structure-inducing and functional side chains.[89]

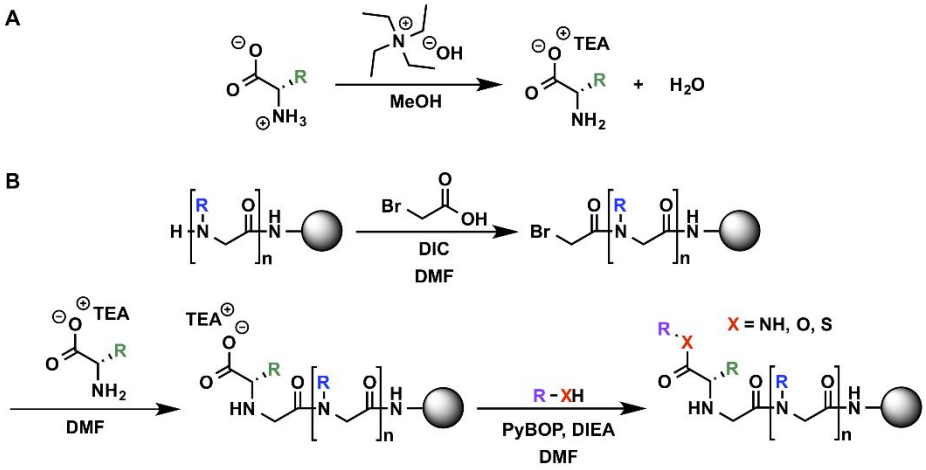
As peptoids are increasingly used for therapeutic applications, diversifying the set of available structure-inducing submonomers for peptoid synthesis (beyond bulky, chiral primary amines) will benefit rational design efforts. Emblematic of this approach, *N*-α-chiral aromatic side chains modified to display various functional groups as aryl substituents were investigated as helix-inducing submonomers.[90] Further development of useful peptoid side chains that exhibit an influence on the peptoid backbone architecture has featured the use of submoomer reagents such as *N*-aryl amines,[61] *N*-alkoxy amines,[63] *N*-acyl hydrazide,[64] *N*-hydroxyl amines,[65] and *N*-imino/alkylimino glycines,[71] all of which induce trans amide bond geometries. The use of triazolium,[66] *tert*-butylamines,[67, 70] fluorinated ethylamines,[68] *N*-α-gem-dimethylated glycines,[70] and cationic alkyl ammoniums[69] as submonomers generally induce cis amide bond geometries. Similar conformational propensities have been observed for β-peptoid monomers.[91] Several of these submonomer reagents provide an opportunity to induce peptoid conformational order without the requirement to display hydrophobic, aromatic moieties. In addition, metal binding using appropriate side chain ligands can be a successful strategy for folding peptoids.[88, 92, 93]

Interestingly, α-amino acids are a readily available source of diverse *N*-α-chiral primary amines for peptoid synthesis with capability to enforce conformational ordering. Peptoid homo-oligomers of (*S*)-*N*-(1-carboxy-2-phenylethyl)glycine were synthesized using L-phenylalanine *tert*-butyl ester as the primary amine submonomer and were shown to adopt a pH-dependent secondary structure after side chain deprotection.[94] Additionally, L-alanine *tert*-butyl ester has been used to generate (*S*)-*N*-(1-carboxyethyl)glycine peptoid monomers, which in conjunction with *N*-α-chiral aromatic side chains resulted in robust, water-soluble peptoid helices.[77] The Fuller group has used this method to incorporate multiple amino acid synthons into peptoids to impart water solubility and to study conformational switching as well as to develop pH sensors.[95, 96] Various amino acid derivatives have also been synthesized by first coupling an amine to the carboxylic acid group of Cbz protected L-alanine which, following deprotection, can be used as an amine submonomer in peptoid synthesis.[87]

Here, we describe an efficient route to expand the chemical diversity and complexity of peptoids using branched, chiral side chains. Unprotected α-amino acids are first incorporated into peptoids as amine submonomers. Then, prior to elongating the oligomer, an amine, alcohol, or thiol is coupled to the carboxylic acid within the side chain. Inexpensive and readily available reagents are used to synthesize each peptoid side chain on solid-support, thus embellishing the straightforward peptoid submonomer synthesis protocol to assemble more elaborate peptoids without prior submonomer synthesis or installation of protecting groups.

Results and discussion

We first investigated the incorporation of unprotected amino acids as submonomers in peptoid oligomer synthesis. An immediate difficulty with these amines is that their zwitterionic nature limits solubility in the organic solvents typically used for solid-phase synthesis, such as *N*,*N*-dimethylformamide (DMF). Zuckermann and co-workers overcame similar difficulties during the introduction of 2-aminoethane-1-sulfonic acid (taurine) as a peptoid submonomer reagent by using tetraethylammonium hydroxide to estabish solubility and nucleophilicity of the amino acid as the tetraethyl ammonium (TEA) salt (Scheme 2A).[97] The TEA salt complex could then be successfully used in peptoid synthesis following the standard submonomer protocol shown in Scheme 1, although without successful oligomer elongation after taurine incorporation. We adopted this scheme of using TEA salts to install an expanded variety of unprotected amino acid submonomers into peptoids.



Scheme 2. (A) TEA salt and free base formation using a zwitterionic amino acid and 1 equiv. tetraethylammonium hydroxide. (B) Amide, ester, and thioester formation on peptoid amino acid side chains *via* PyBOP activation of the carboxylic acid on-resin. Following this modification, subsequent peptoid backbone elongation is accomplished using the general synthetic scheme shown in Scheme 1.

We initiated our efforts with peptoid trimer **1** in which two of the monomers bear the common *N*-methoxyethyl and *N*-benzyl peptoid side chains while the third residue was synthesized using the L-phenylalanine TEA salt. We found that 20 equiv. of the amino acid TEA salt is sufficient to displace bromide with shaking for 1 h at 35 °C. The crude RP-HPLC trace of peptoid **1** in Figure 2 shows successful submonomer incorporation into the peptoid backbone to generate the (*S*)-*N*-(1-carboxy-2-phenylethyl)glycine monomer with good purity. MS confirmed the chemical identity of **1** (Table S1), which was isolated from the resin and purified with 75% overall yield. The lack of a protecting group within this (*S*)-*N*-(1-carboxy-2-phenylethyl)glycine side chain would typically complicate immediate oligomer extension. This necesitated chemical modification of the carboxylic acid group in the side chain prior to continuing the oligomer synthesis.

Amine coupling to the carboxylic acid of the peptoid amino acid side chain is easily achieved using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as the coupling reagent for *in situ* activation (Scheme 2B). Typically, 1.5 equiv. of PyBOP, 5 equiv. of diisopropylethylamine (DIEA), and 5 equiv. of amine are shaken with the modified resin in DMF to activate the acid and form the amide bond. The coupling reaction is generally complete within 1 h, but extending the reaction time improves incorporation of hindered or electronically deactivated amines, such as anilines. For example, treatment of peptoid **1** with the secondary amine morpholine along with PyBOP and DIEA validated this coupling scheme with the formation of peptoid **2**, in which the (*S*)-*N*-(1-carboxy-2-phenylethyl)glycine side chain was converted to the corresponding amide. The crude RP-HPLC trace in Figure 2 shows complete conversion from **1** to **2** with >95% crude purity, which was then isolated in 69% overall yield. With the carboxylate side chain now converted to an amide, subsequent backbone elongation could be conducted using standard amine submonomers to form peptoid pentamer **3**, which was also synthesized in >95% crude purity and confirmed by MS (Table S1). The crude RP-HPLC trace of **3** shown in Figure 2 shows the high conversion for each step, and the final product **3** was isolated with 44% overall yield after a total of 13 reaction steps on resin. In addition to standard primary amines used as peptoid side chains, this strategy allows the use of secondary amines, thus dramatically increasing the number of available building blocks.

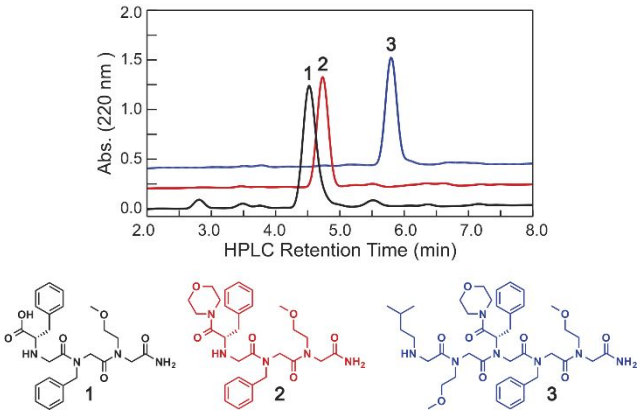


Figure 2. Overlaid RP-HPLC traces of crude products for peptoid oligomers **1** (black), **2** (red), and **3** (blue) incorporating a single substituted L-phenylalanine amino acid side chain, which was then subject to side chain amidation, and subsequent oligomer elongation.

To further expand the scope of this on-resin side chain elaboration, we next attempted to couple alcohols to the carboxylic acid moiety of a peptoid amino acid side chain to yield esters (Scheme 2B X = O). It has been previously reported that (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP)-activated benzotriazolyl esters can react with amines to form amides but not with alcohols to form esters.[98] Instead, the more electrophilic phosphonium intermediate formed prior to the benzotriazolyl ester reacts with alcohols. We opted to use PyBOP for formation of esters to avoid the by-products of the BOP reagent. To encourage

reaction between the alcohol and the phosphonium intermediate, we incubated the resin with the alcohol reagent immediately prior to addition of the activating agent (see Experimental section). However, we found that the slow esterification rate led to undesired diketopiperazine (DKP) formation from oligomer dimerization, as observed by MS and RP-HPLC. This intermolecular reaction can occur between the terminal secondary amines on each oligomer backbone with the PyBOP-activated acid side chains on neighboring oligomers prior to reaction with alcohol while on-resin (Figure S1). The use of low loading level resins could potentially mitigate this reaction. As an alternative strategy, we used a a large concentration of the alcohol nucleophile to favor ester formation. The amino acid modified resin is pre-incubated with 120 equiv. of alcohol and 5 equiv. of DIEA in DMF for 5 min. Then, 1.5 equiv. of PyBOP is added to the reaction vessel with shaking for 1 h at room temperature. This strategy was demonstrated on peptoid **1**, where after incorporation of L-phenylalanine, 1-butanol was used as the nucleophile for ester formation to synthesize **4**. RP-HPLC traces in Figure 3 show complete consumption of **1** and formation of **4** with 66% crude purity while the DKP side product is observed as the second major product at ~6.7 min retention time. Following side chain esterification with 1-butanol, backbone elongation gave high conversion to peptoid pentamer **5** with 59% crude purity as evaluated by RP-HPLC. However, the DKP product persisted, suggesting that the intermolecular reaction occurs on-resin. Overall, peptoids **4** and **5** were synthesized bearing (*S*)-*N*-(1-carboxy-2-phenylethyl)glycine butyl ester monomers with 47% and 44% isolated yields, respectively.

In a similar fashion, thiols could be coupled to the peptoid amino acid side chains using this PyBOP strategy (Scheme 2B, X = S). Formation of the thioesters was facile and followed the same protocol as for ester formation except that only 5 equiv. of thiol were needed due to greater nucleophilicity. Again, using **1** with an incorporated L-phenylalanine monomer, cyclohexanethiol could be coupled to the carboxylic acid using

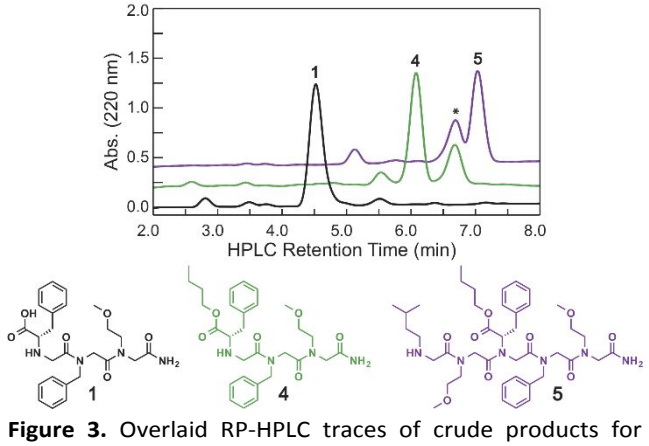


Figure 3. Overlaid RP-HPLC traces of crude products for peptoid oligomers **1** (black), **4** (green), and **5** (purple) incorporating a single substituted L-phenylalanine amino acid side chain at position three, subsequent side chain esterification, and oligomer elongation. *Indicates a DKP side product formed during esterification of peptoids **4** and **5**.

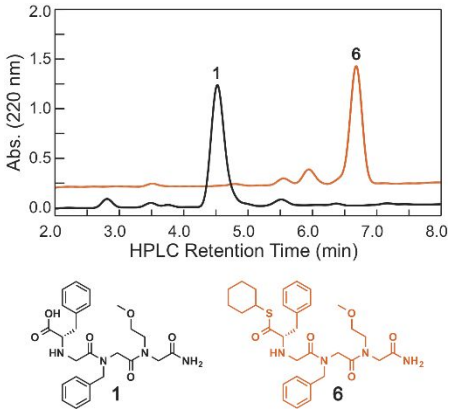


Figure 4. Overlaid RP-HPLC traces of crude products for peptoid oligomers **1** (black) and **6** (orange) incorporating a single substituted L-phenylalanine amino acid side chain at position three and subsequent side chain thioester formation.

PyBOP and DIEA to give **6** (Figure 4). The crude RP-HPLC trace of peptoid trimer **6** possessing an (*S*)-*N*-(1-carboxy-2-phenylethyl)glycine cyclohexyl thioester peptoid side chain demonstrates the success of this thioester formation with 85% crude purity and an isolated 47% yield. Unfortunately, subsequent peptoid backbone elongation of **6** did not result in the desired oligomer. This is likely due to the increased electrophilicity of the thioester present in the side chain, which is exposed to excess amounts of nucleophiles during the peptoid elongation. As a result, amino acid peptoid side chains bearing thioester moieties are limited to the *N*-terminal position of the peptoid oligomer. Even so, an *N*-terminal peptoid side chain bearing a thioester may prove useful for several interesting applications, including a possible variation of native chemical ligation.[99, 100]

To explore the scope of these methods further, a representative library of linear hexamers was created with each oligomer incorporating four substituted amino acid peptoid side chain positions (structures **7-16**, Figure 5). After cleavage from the resin, each of these peptoids was readily purified by RP-HPLC and characterized by MS (Table S1). Peptoid hexamers **7-11** were synthesized using only amine synthons to modify the amino acid side chains to amides, conveniently yielding a set of unprecedented peptoid side chains. Both primary and secondary amines can be employed to introduce various functional groups including alkynes, ethers, trifluoromethyl groups, aryl halides, cycloalkanes, and heterocycles, as well as protected amines, alcohols, or carboxylic acids that can then be deprotected during the resin cleavage step. Benzyl alcohol, trifluoroethanol, and 1-butanol were used to demonstrate the scope of alcohol coupling, forming the side chain esters in peptoids **12**, **15**, and **16**. This reaction was limited to primary alcohols, whereas secondary and tertiary alcohols were not successfully used in this side chain esterification, likely due to increased steric bulk. Further optimization may expand the scope of alcohols that can be used for side chain esterification.Cyclohexanethiol, 2-furanmethanethiol and 1-butanethiol were also successfully coupled, generating peptoids

13-**16** with *N*-terminal thioester side chains. Thioesterification of the carboxylate side chains was observed with high conversion, and the greater nucleophilicity relative to alcohols allowed for the use of primary as well as secondary thiols. Although the overall isolated yields of purified **7**-**16** are relatively low (ranging from 2-10%), this strategy for synthesizing complex peptoids is advantageous given: a) the syntheses required 18 total reaction steps on resin, b) the lack of protecting groups used, c) only solid-phase synthesis techniques are needed, and d) the significant bulk and elaborate character of the side chains incorporated on short oligomer products. Overall, the average yield of the 18 individual reactions ranged from 80% to 88%, which is sufficient for many applications and can easily be scaled by using more resin. The low overall yields could be due to the bulky nature of these side chains which may hinder further coupling on the peptoid backbone. Notably, the crude yield of **7**-**16** ranged from 10% to 63%, suggesting that incomplete resin cleavage rather than poor conversion diminished yields and may necessitate future optimization. Alternatively, the intermolecular DKP formation (see Figure S1) may also influence yields which could potentially be alleviated by use of low loading level resins.

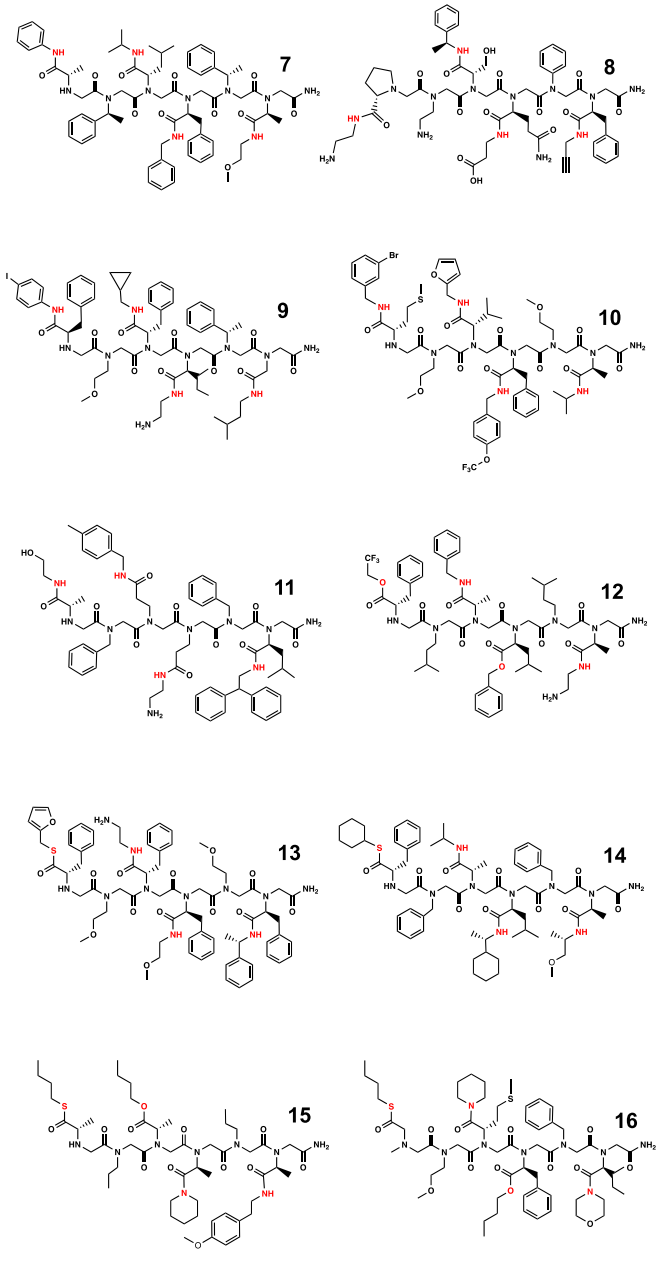


Figure 5. A library of representative peptoid oligomers **7**-**16** bearing four diverse substituted amino acids as side chains. The incorporated amino acid synthons include L-alanine, L-glutamine, glycine, L-isoleucine, L-leucine, L-methionine, L-phenylalanine, L-proline, L-serine, L-valine, D-phenylalanine, β-alanine, and sarcosine bearing either amide, ester, or thioester pendants.

Peptoids **7**-**16** were synthesized bearing an array of peptoid amino acid amide, ester, and thioester side chains. Such side chain moieties have not been previously explored, but were all synthesized on resin from commercially available reagents. A representative RP-HPLC chromatogram of peptoid **16** is shown in Figure 6 demonstrating the ability to obtain a complex peptoid primary sequence in high purity incorporating multiple defined side chain stereocenters by use of L-isoleucine, L-phenylalanine, L-methionine, and sarcosine synthons, and upon which amides, esters, and thioesters are appended using only solid-phase synthesis procedures. Peptoid **16** was isolated with 6% overall yield, corresponding to an average 86% yield for each of the 18 individual steps. The series of peptoid oligomers presented here demonstrates that a wide range of canonical amino acids can be used as peptoid submonomers including L-alanine, L-glutamine, glycine, L-isoleucine, L-leucine, L-methionine, L-phenylalanine, L-proline, L-serine, and L-valine. Preliminary results also show successful incorporation of L-tyrosine, L-cysteine, and L-histidine bearing unprotected side chains that remain intact upon amidation of these amino acid side chains and further oligomer elongation (see supporting information). Additionally, peptoids **9**, **11**, and **16** incorporate the noncanonical amino acids D-phenylalanine, *β*-alanine, and sarcosine as peptoid submonomers, respectively. Amino acids bearing protected side chains would enable incorporation of an even greater diversity of amino acids into peptoids. Altering the amino acid and the amine/alcohol/thiol in each of the substituted peptoid amino acid side chains provides multiple positions of chemical diversity within each individual side chain.

Future studies will evaluate the conformational tendencies of these side chain types. We conducted a preliminary analysis of the structural influence of these new monomer units by comparing the circular dichroism spectra of compounds 1, 4 and

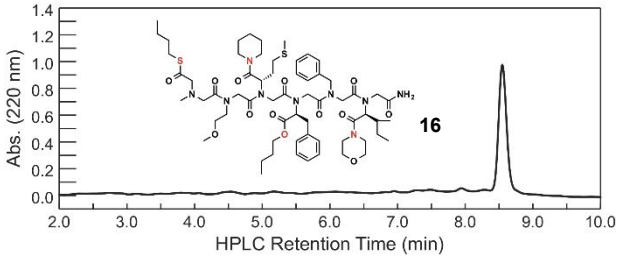


Figure 6. Representative analytical RP-HPLC trace of peptoid hexamer **16** following purification.

5 (Figure S2). The ellipticities for these oligomers were generally weak, as would be expected for oligomers with achiral backbones incorporating a discrete chiral center. Notably, we observed inversion of the sign of ellipticity for peptoid 5, suggesting that the presence of the bulky branched side chain at an internal position may establish some conformational control, as distinct from incorporating these monomer types at a terminal residue. The relationships between the sequence and structure of peptoids will continue to be an ongoing focus.

Moving forward, our synthetic technique offers many opportunities to elaborate the palette of peptoid attributes. This method introduces potential hydrogen bonding sites into the peptoid oligomer and thus may provide both structural and functional benefits. This characteristic may also be helpful in developing water-soluble, structured peptoids, since structure-inducing *N*-*α*-chiral aromatic side chains can be readily incorporated and then modified to introduce solubilizing moieties. Additionally, this work provides a possible method for conjugating a greater number of functional moieties to peptoid oligomers, such as fluorophores, dyes, peptides, or chelators, as well as moieties that can be removed, such as benzyl or allyl esters, thus acting as a method for on-resin carboxylic acid protection. This expansion of accessible peptoid chemical diversity could also aid in the generation of peptoid pro-drugs or combinatorial libraries for drug screening.[20]

Conclusions

We present an efficient and modular strategy for greatly enhancing the chemical diversity of peptoid oligomers. Our method introduces the use of readily available unprotected amino acids as submonomer reagents that can be subsequently functionalized with primary/secondary amines or alcohols. This facilitates the stepwise synthesis of peptoids bearing complex side chains, typically incorporating *N*-*α*-chiral substituents, while using commercial reagents. The protocol avoids solution-phase preparation of the corresponding primary amine submonomers and instead takes advantage of on-resin synthesis for side-chain modification. This strategy for accessing branched peptoid side chains offers the potential to explore additional chemical space of folded peptoid oligomers. Our future studies will evaluate the conformational tendencies of these side chain types. As the diversity of structure-inducing side chains continues to increase, and as more peptoid high resolution structures are deposited in the Peptoid Data Bank,[89] we can establish a more robust modular framework for the rational design of functional ordered peptoid sequences.

Experimental

Materials. All solvents and reagents were purchased from commercial sources and used without further purification. All amino acids were purchased from Fisher Scientific. Tetraethylammonium hydroxide (25% in methanol) was purchased from Sigma-Aldrich. Each amine, alcohol, and thiol was purchased from Sigma-Aldrich, Alfa Aesar, TCI America, Chem-Impex International, or CNH Technologies and used without further purification.

General Peptoid Synthesis. Each peptoid oligomer was synthesized on Rink amide MBHA resin (Protein Technologies Inc.) with a 0.2 mmol/g loading level. This low loading level resin was used so as to minimize formation of intermolecular side-products that were observed when using higher loading levels (data not shown). The resin (100 mg) was added to a fritted syringe (Torviq) and swelled in DMF (4 mL) for 30 min. The Fmoc protecting groups were removed by addition of 20% piperidine/DMF (3 mL). The mixture was shaken for 15 min at room temperature, drained, and then the piperidine treatment was repeated. Washing steps with DMF (5x4 mL) were performed, and then bromoacetic acid (20 equiv.; 0.4 M in DMF; 1 mL) and diisopropylcarbodiimide (DIC) (18.6 equiv.; 58.2 µL) were added, and the reaction was shaken for 30 min at room temperature (Step A). After washing with DMF (5x4 mL), the corresponding amine submonomer (20 equiv.; 0.4 M in DMF; 1 mL) was added to the resin with shaking for 30 min at room temperature (Step B). Steps A and B were then repeated until the desired peptoid oligomer length was synthesized. Prior to cleavage, the resin was washed with DMF (5x4 mL) and then dichloromethane (DCM) (5x4 mL). Cleavage from resin was performed with 95% trifluoroacetic acid (TFA) in H_2O for 20 min. The cleavage cocktail was evaporated under a stream of nitrogen gas, dissolved in 50% acetonitrile (ACN) in H_2O, frozen, and lyophilized.

Amino Acid Side Chain Incorporation. The desired unprotected amino acid (20 equiv. to resin) was first converted from the zwitterion to the free-base by dissolving in 25% tetraethylammonium hydroxide in methanol (1 equiv. to amino acid).[97] Sonication and gentle heating were used to aid in dissolution. For amino acids that were difficult to solubilize, a small excess of 25% tetraethylammonium hydroxide in methanol was added. Rotary evaporation was then used to reduce the solution to a clear, viscous oil. The amine submonomer was then dissolved in DMF to a concentration of 0.4 M (1 mL). When solubility of the amino acid tetraethylammonium salt in DMF was poor, a 5% H_2O/DMF solution was used. This amine solution was added to bromoacetylated resin and shaken for 1 h at 35 ºC to incorporate the amino acid side chain.

Amino Acid Amidation and (Thio)Esterification. Subsequent to incorporation of an amino acid tetraethylammonium salt side chain and washing with DMF (5x4 mL), the unprotected carboxylic acid was functionalized before continuing the oligomer elongation. For amidation of this moiety, PyBOP (1.5 equiv.), DIEA (5 equiv.), and the corresponding amine (5 equiv.) were added to the resin in DMF (1 mL) with shaking for 1 h at room temperature. This reaction mixture was made immediately prior to adding to the resin. For valuable amine building blocks, 1.2 equiv. were used while extending the reaction time to overnight. For (thio)esterification of this moiety, DIEA (5 equiv.) and the corresponding alcohol (120 equiv.) or thiol (5 equiv.) were added to the resin in DMF (0.5 mL). After shaking for 3 min, PyBOP (1.5 equiv.) in DMF (0.5 mL) was added to the reaction mixture without draining the DIEA

and alcohol/thiol solution, and the reaction was shaken for 1 h at room temperature. After either amidation or (thio)esterification of the amino acid side chain, the resin was washed with DMF (5x4 mL), and the oligomer synthesis was continued using the general peptoid synthetic scheme above.

Purification and Characterization of Peptoid Oligomers. A Waters AutoPurification HPLC/MS system was used for purification and characterization. Peptoid oligomers were analyzed by analytical reversed-phase (RP)-HPLC (Waters XBridge BEH300 4.6x50 mm C18 column) using a linear gradient of 5-95% ACN/H_2O (0.1% TFA) in 10 min with a 0.7 mL/min flow rate and 220 nm wavelength detection. Crude oligomers were purified by semi-preparative RP-HPLC (Peeke Scientific Ultro 250x10 mm C18 column) with a linear gradient of 5-95% ACN/H_2O (0.1% TFA) in 50 min with a 2.5 mL/min flow rate and 230 nm wavelength detection. The desired fractions were automatically detected by MS, collected, frozen, and lyophilized. Purified oligomers were again characterized by analytical RP-HPLC and MS as described above. A Waters G3 QTof MS (ZORBAX StableBond 300, C_{18}, 4.6 x 50 mm) was used for HRMS analysis on select compounds 1, 4, and 5 (see supporting Information).

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been provided in the Supplementary Information; MS characterization, analytical HPLC spectra, and synthetic methods.

Acknowledgements

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Data availability

The data supporting this article have been provided in the Supplementary Information; ESI-MS characterization, analytical HPLC/ESI-MS spectra, and synthetic methods.