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Dynamic Covalent Assembly of Peptoid-Based Ladder Oligomers by Vernier Templating

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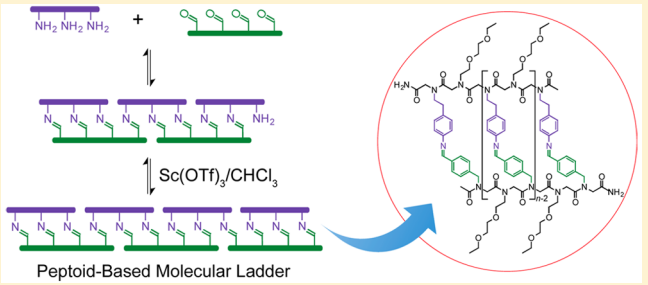
Supporting Information

ABSTRACT: Dynamic covalent chemistry, in conjunction with template-directed assembly, enables the fabrication of extended nanostructures that are both precise and tough. Here we demonstrate the dynamic covalent assembly of peptoid-based molecular ladders with up to 12 rungs via scandium(III)-catalyzed imine metathesis by employing the principle of Vernier templating, where small precursor units with mismatched numbers of complementary functional groups are coreacted to yield larger structures with sizes determined by the respective precursor functionalities. Owing to their monomer diversity and synthetic accessibility, sequence-specific oligopeptoids bearing dynamic covalent pendant groups were employed as precursors for molecular ladder fabrication. The generated structures were characterized using matrix-assisted laser desorption/ionization mass spectrometry and gel permeation chromatography, confirming successful molecular ladder fabrication.



INTRODUCTION

A long-standing challenge in molecular self-assembly is the ability to construct sophisticated yet strong nanoscale objects and devices with exacting structural control. Large, naturally occurring supramolecular structures, such as viral capsids and microtubules, emerge from the self-assembly of relatively small subunits;[1,2] however, these assembly processes are often based upon weak intermolecular interactions such as hydrogen bonding, π-stacking, or van der Waals interactions.[3] One consequence of the relative weakness of these transient interactions is that the assembled structures are often fragile and susceptible to thermal or mechanical degradation.[4−6] Recently, interest in utilizing dynamic covalent chemistry (DCC) to mediate self-assembly reactions has emerged because they afford error-correction mechanisms necessary for the selective fabrication of intricate nanostructures while retaining the robustness of covalent bonding. In these dynamic covalent interactions, molecular species undergo dynamic exchange and reorganization processes through the reversible formation and breakage of covalent connections to achieve thermodynamic equilibrium.[7−9] Consequently, DCC-based approaches have been utilized to construct a variety of macromolecular architectures, including covalent organic frameworks,[10,11] macrocycles,[12−15] molecular cages,[16−20] and molecular ladders and grids.[21−23]

Despite the recent advances in self-assembly for "bottom-up" construction techniques, approaches to achieve hybridization registry between large, complementary oligomers and polymers have long been challenging owing to kinetic trapping, even for those employing noncovalent interactions. Moreover, the fabrication of large structures typically requires templates of equivalent sizes, which themselves are difficult to synthesize[24,25] owing to the intractability of sequence-specific polymer synthesis.[26] A recently described self-assembly approach to address the limitations of conventional template assembly employs the coreaction of oligomeric precursors with unequal numbers of complementary functional groups.[24−32] This process, known as Vernier templating, results in assembled structures where each component precursor only participates in as many interactions as its number of reactive functional groups allows, whereas the total number of interaction sites on the Vernier complex is equal to the lowest common multiple of the functionality on the respective precursors. Thus, this templated molecular fabrication approach curtails the kinetic trapping that would otherwise impede the selective assembly of long precursor strands and affords a facile route to the generation of large constructs from relatively small, oligomeric precursors.[24−32] Implementations of Vernier templating have utilized several different mechanisms. For example, metal−ligand interactions between transition metals and porphyrin-based oligomers have been employed to assemble a variety of structures, including triple-stranded Vernier complexes,[29] and macrocycles that, upon subsequent ligation, yielded large structures containing different numbers of porphyrin units.[24,30,31] Additionally, several groups[26,32] have demonstrated the Vernier-templated assembly of length-programmed DNA nanostructures. Notably, these Vernier templating self-assembly

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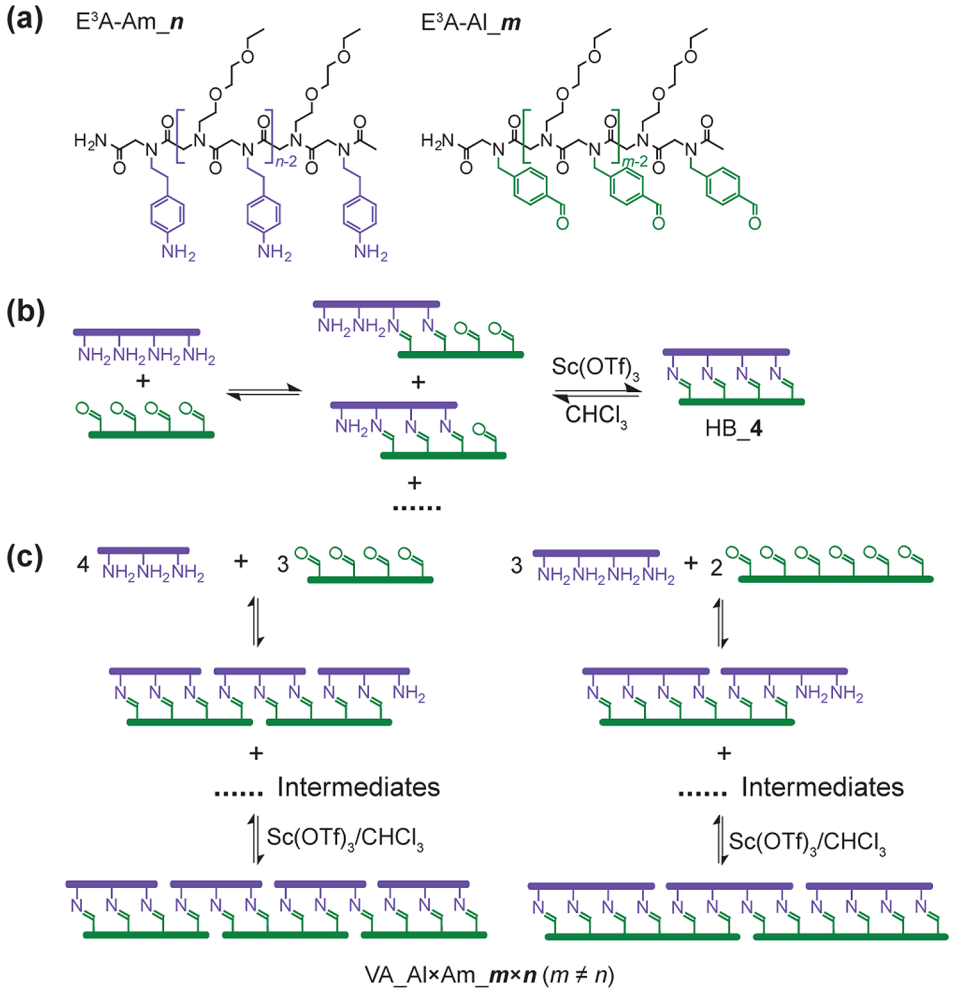
Scheme 1. Dynamic Covalent Assembly of Peptoid-Based Molecular Ladders[a]



[a](a) Structures of linear oligopeptoids bearing pendant amine (E³A-Am_*n*) and aldehyde (E³A-Al_*m*) functional groups. (b) Dimerization of complementary peptoid oligomers with commensurate functionalities (HB_*n*, where HB is "hybrid"). (c) Vernier-templated assembly of complementary oligopeptoids with non-commensurate functionalities into molecular ladders with $m \times n$ rungs (VA_Al × Am_$m \times n$, where VA is "Vernier assembly").

approaches reported to date have relied upon relatively weak intermolecular interactions. In contrast, the alternative approach of DCC-mediated Vernier templating provides an avenue for the construction of large and tough assemblies with well-defined sizes.

The rearrangement of imine bonds, generated by the condensation of aldehyde and amine functional groups, via imine metathesis was selected here for the self-assembly of molecular ladders as it is a well-characterized dynamic covalent interaction that has been extensively applied to the synthesis of equilibrium reaction mixtures.[33] Moreover, Lewis acids have been found to efficiently catalyze imine metathesis, such that the subsequent rapid bond rearrangement allows equilibrium to be attained on appropriate time scales.[34] Finally, the directionality of the imine bond precludes homodimerization, enabling its utilization in the fabrication of complex, asymmetric constructs.[22] We employ scandium(III)-catalyzed imine metathesis to mediate the dynamic covalent assembly of peptoid-based molecular ladders through both dimerization and Vernier templating by coreacting oligomeric precursors of commensurate and noncommensurate lengths, respectively. To the best of our knowledge, this work represents the first demonstration of Vernier-templated self-assembly via DCC.

RESULTS AND DISCUSSION

Dimerization of Complementary $n \times n$ Oligopeptoids. Peptoids or poly(*N*-substituted glycine)s, a class of peptidomimetic, sequence-specific polymers[35] that are readily synthesized from a diverse range of primary amine-based monomers, were employed here to enable the rapid prototyping of precursor strands for subsequent ladder assembly. Oligomeric peptoid sequences incorporating pendant aldehyde and amine functional groups were prepared using the "submonomer" solid-phase peptoid synthesis approach,[36] where a peptoid chain is grown via sequential addition reactions one unit at a time using an automated peptide synthesizer. These peptoid sequences were synthesized as alternating co-oligomers consisting of dynamic covalent monomer residues, utilizing monomers bearing benzaldehyde- and aniline-based functional groups protected with acid-labile groups to prevent unwanted side reactions during solid-phase synthesis, interspersed with inert residues. Whereas the aldehyde and amine functional groups allow the hybridization of complementary peptoid chains

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through imine formation and exchange reactions, inert residues were incorporated to improve assembled ladder solubility. Upon cleavage from the solid support resin and protecting group deprotection by treatment with trifluoroacetic acid (TFA), the generated oligomeric peptoids were purified by preparative reversed-phase high performance liquid chromatography (HPLC) and purity and molecular weights characterized by analytical HPLC, NMR, and electrospray ionization (ESI) mass spectrometry, respectively (Figures S2−S5). The dynamic covalent reactants incorporated on the synthesized peptoid oligomers were either exclusively aldehyde or amine functional groups to avoid potential premature aldehyde/amine condensation reactions that would preclude oligomer purification. Preliminary hybridization experiments of peptoids incorporating benzylamine or 2-methoxyethylamine as inert spacer residues resulted in rapid formation of a precipitate after complementary oligomer mixing, indicating poor solubility of the assembled structures. Fortunately, utilizing 2-(2-ethoxyethoxy)ethylamine (E^3A) as the spacer residue was found to afford solubility of both the unhybridized oligomers and the subsequent assembled molecular ladders in chloroform, and thus was employed as the alternating comonomer for the peptoid sequences throughout this study. Structures of the synthesized peptoid co-oligomers E^3A-Al_***m*** and E^3A-Am_***n***, where ***m*** and ***n*** refer to the number of repeat units for the aldehyde- and amine-bearing oligomers, respectively, are shown in Scheme 1(a).

The dynamic covalent assembly of complementary oligomeric peptoid sequences with commensurate lengths n into n-rung molecular ladders was initially examined. Here, aldehyde- and amine-functionalized peptoid sequences E^3A-Al_***m*** and E^3A-Am_***n***, where ***m*** = ***n***, were added in a 1:1 stoichiometric ratio to chloroform with a catalytic amount of scandium(III) triflate (Scheme 1(b)), and the reaction mixture was stirred at room temperature overnight. No precipitate or cloudiness was observed throughout the course of the reaction, indicating good solubility of the resultant ladder structures and an absence of particulate, cross-linked polymer. The reaction mixture was directly analyzed by matrix-assisted laser desorption/ionization (MALDI) mass spectrometry, performed with 2-(4-hydroxyphenylazo)benzoic acid (HABA) as the matrix, and gel permeation chromatography (GPC) with chloroform/methanol/triethylamine (94/4/2, v/v/v) as the eluent. Finally, sodium triacetoxyborohydride was added to the reaction mixture to reduce the interstrand imine groups to secondary amines, irreversibly fixing the assembled structures and MALDI mass spectrometry was again performed. Attempts to characterize the reduced molecular ladders by GPC proved unsuccessful owing to insufficient signal intensities from both UV and differential refractive index (DRI) detectors.

MALDI mass spectra of the crude and reduced peptoid dimerization reaction mixtures are shown in Figure 1(a) and Figure S11, respectively. These mass spectra indicate only a single product from each dimerization reaction, where the observed dominant peaks correspond to the desired molecular ladder structures HB_**3**, **4**, and **6**, demonstrative of the successful formation of the desired ladder structures which are the only reasonable products equivalent to the observed molecular weights. Although the $[M + Na]^+$ ion predominates in each of these mass spectra, minor peaks attributable to $[M + H]^+$ and $[M+K]^+$ ions are also observed. Peaks which could be assigned to misaligned or out-of-register products, anticipated to arise at m/z values of +18 (i.e., the molecular weight of the

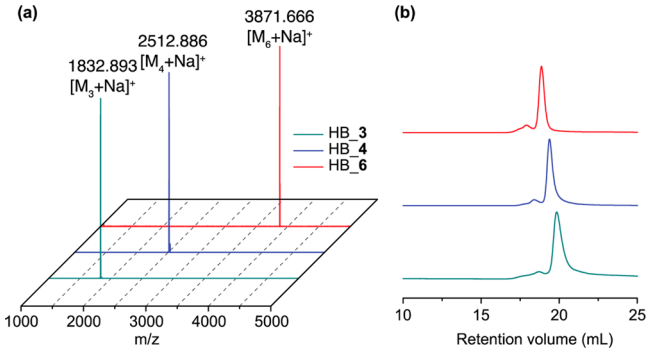

Figure 1. Molecular ladders formed by dynamic covalent oligopeptoid dimerization. (a) MALDI mass spectra of the crude reaction mixtures. Calculated molecular weights: $[M_{HB\_3}+Na]^+$ = 1832.927 g/mol; $[M_{HB\_4}+Na]^+$ = 2512.286 g/mol; $[M_{HB\_6}+Na]^+$ = 3871.002 g/mol. (b) GPC traces for crude reaction mixtures. The traces are normalized to the height of the largest peak. HB_**3**, V_r = 19.82 mL, M_n = 2270 g/mol, PDI = 1.01; HB_**4**, V_r = 19.37 mL, M_n = 2870 g/mol, PDI = 1.01; HB_**6**, V_r = 18.87 mL, M_n = 3770 g/mol, PDI = 1.01 (polystyrene standards).

H_2O condensation product) for each unreacted amine/aldehyde pair, or to unreacted peptoid oligomers were not observed in any of these mass spectra. Moreover, higher molecular weight species, potentially resulting from the coreaction of more than two peptoid strands (i.e., $(E^3$A-Al_***m***$)_x(E^3$A-Am_***n***$)_y$, where ***m*** = ***n*** and $x + y > 2$), were not observed. Near-exclusive formation of the desired ladder structures was further confirmed by GPC chromatograms showing one major peak preceded by very small peaks potentially attributable to low concentrations of higher molecular weight species (see Figure 1(b)). In each case, by comparing to low dispersity polystyrene standards, the elution volumes confirm the molecular weights corresponding to the resultant molecular ladders. Furthermore, deconvolution of the experimental GPC chromatograms revealed that the obtained molecular ladders were uniform with dispersities approaching 1 (see Figure S14 and Table S5). Interestingly, although the GPC chromatograms suggest the presence of small amounts of higher molecular weight, out-of-registry byproducts in the reaction mixtures, no corresponding evidence for these byproducts is apparent in the MALDI mass spectra. A previous examination of the dynamic covalent assembly of single-stranded precursors into n-rung molecular ladders[22] using m-phenylene-ethynylene-based oligomers proved only moderately successful as the molecular ladder assembly became kinetically trapped at four rungs.[23] Thus, ladders containing five or more rungs were unable to be synthesized in high yield owing to the inadequate error-correction of misaligned, out-of-register byproducts.[23] In contrast to this previous investigation, the success of our peptoid-based oligomer hybridization even for 6-rung ladders, the longest examined here using commensurate length precursor strands, suggests that the flexibility of the peptoid backbone likely helps curtail kinetic trapping while the close spacing between dynamic covalent residues affords cooperative binding, improving hybridization selectivity and enabling formation of the desired product. Although our utilization of peptoid oligomers backbone improves upon the previously described approach employing m-phenylene-ethynylene oligomers, thermodynamically disfavored but kinetically trapped products will necessarily be generated for sufficiently long precursor oligomers; thus, we investigated Vernier

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templating as a facile approach to achieve large molecular ladders from the dynamic covalent assembly of small oligomeric species.

Vernier-Templated Assembly of Complementary *m* × *n* Oligopeptoids. The Vernier template-directed assembly of molecular ladders was similarly investigated via application of Sc(III)-catalyzed metathesis of interstrand imine bonds. As before, aldehyde- and amine-functionalized peptoid oligomers were added to chloroform such that the stoichiometric ratio of dynamic covalent reactants was 1:1; however, in this case, the functionalities of the peptoids E^3A-Al_***m*** and E^3A-Am_***n*** in the reaction mixture were not commensurate (i.e., $m \neq n$) (Scheme 1(c)). In the presence of a catalytic amount of scandium(III) triflate, the reaction mixture was stirred at room temperature for 1 week and analyzed by both MALDI mass spectrometry and GPC. The self-assembly of four different oligomer combinations were examined: VA_Al × Am_**3** × **4** (i.e., trialdehyde/tetraamine), VA_Al × Am_**4** × **3** (tetraaldehyde/triamine), VA_Al × Am_**4** × **6** (tetraaldehyde/hexaamine), and VA_Al × Am_**6** × **4** (hexaaldehyde/tetraamine). These combinations were selected as each reaction was anticipated to yield 12-rung molecular ladder products, based on the lowest common multiple of both 3 × 4 and 4 × 6. Notably, although the ladders VA_Al × Am_**3** × **4** and VA_Al × Am_**4** × **3** share the same molecular weight, and the ladders VA_Al × Am_**4** × **6** and VA_Al × Am_**6** × **4** similarly share the same molecular weight, the different numbers of E^3A solubilizing groups incorporated into the constituent peptoid strands results in different molecular weights between the Vernier-templated trimer/tetramer and tetramer/hexamer systems despite both yielding 12-rung molecular ladders.

MALDI mass spectra of the crude and reduced hybridization reaction mixtures utilizing noncommensurate length precursor strands shown in Figure 2(a) and Figure S12, respectively, demonstrate major peaks assignable to the desired 12-rung ladder structures with observed molecular weights equivalent to the expected values, demonstrating the success of this dynamic covalent approach to Vernier-templated self-assembly. Notably, in addition to the desired product, the mass spectra also indicate the presence of partially assembled intermediates. For example, mass spectra of the trimer and tetramer peptoid coreactions revealed peaks corresponding to partially assembled intermediates of $(E^3A\text{-Al\_}\mathbf{3})_3(E^3A\text{-Am\_}\mathbf{4})_2$ for the trialdehyde/tetraamine system, and $(E^3A\text{-Al\_}\mathbf{4})_2(E^3A\text{-Am\_}\mathbf{3})_3$ and $(E^3A\text{-Al\_}\mathbf{4})_2(E^3A\text{-Am\_}\mathbf{3})_2$ for the tetraaldehyde/triamine system. Similarly, for the tetramer and hexamer peptoid coreactions, additional peaks in the mass spectra are assignable to the intermediate $(E^3A\text{-Al\_}\mathbf{4})_2(E^3A\text{-Am\_}\mathbf{6})_1$ for the tetraaldehyde/hexamine system, and $(E^3A\text{-Al\_}\mathbf{6})_1(E^3A\text{-Am\_}\mathbf{4})_2$ for the hexaaldehyde/tetraamine system.

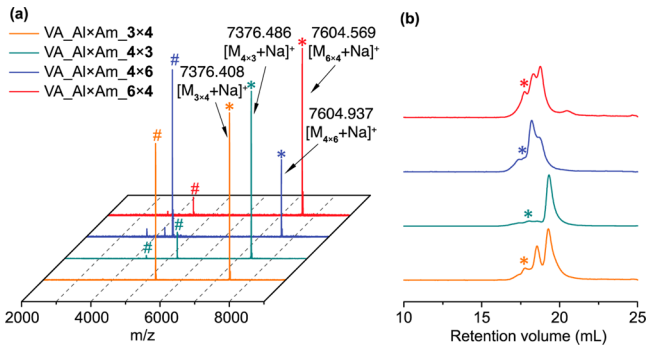

Figure 2. Vernier-templated assembly of molecular ladders. (a) MALDI mass spectra of the crude reaction mixtures. The target ladder structures are labeled with * symbols, and the intermediates are labeled with #. Calculated molecular weights for the target ladders: $[M_{3\times4}+Na]^+ = [M_{4\times3}+Na]^+ = 7376.810$ g/mol; $[M_{4\times6}+Na]^+ = [M_{6\times4}+Na]^+ = 7604.946$ g/mol. Intermediates are identified as $(E^3A\text{-Al\_}\mathbf{3})_3(E^3A\text{-Am\_}\mathbf{4})_2$; $(E^3A\text{-Al\_}\mathbf{4})_2(E^3A\text{-Am\_}\mathbf{3})_3$, $(E^3A\text{-Al\_}\mathbf{4})_2(E^3A\text{-Am\_}\mathbf{3})_2$; $(E^3A\text{-Al\_}\mathbf{4})_2(E^3A\text{-Am\_}\mathbf{6})_1$; $(E^3A\text{-Al\_}\mathbf{6})_1(E^3A\text{-Am\_}\mathbf{4})_2$. (b) GPC traces for crude reaction mixtures (PS standards). The traces are normalized to the height of the largest peak. The target ladder structures are labeled with * symbol. VA_Al × Am_**3** × **4**, V_r = 17.78 mL, M_n = 7270 g/mol, PDI = 1.04; VA_Al × Am_**4** × **3**, V_r = 17.81 mL, M_n = 7120 g/mol, PDI = 1.05; VA_Al × Am_**4** × **6**, V_r = 17.72 mL, M_n = 7700 g/mol, PDI = 1.06; VA_Al × Am_**6** × **4**, V_r = 17.73 mL, M_n = 7650 g/mol, PDI = 1.01.

Further evidence of Vernier assembly was obtained from GPC as performed on the crude reaction mixtures (see Figure 2(b)). Here, the multiple observed peaks correspond both to the desired 12-rung molecular ladders and to the partially assembled intermediates. These reaction mixture chromatograms were deconvoluted by automated peak fitting (see Figure S15), enabling peaks attributable to the multiple species in the mixtures to be resolved. By determining the potential structures that could be formed during the assembly process, we assigned the resolved peaks to the desired Vernier ladders and specific intermediate structures (see Tables S6–S9). The area percentages of the desired ladder structures as determined from GPC peak deconvolution were relatively low (~6.5–14.7%, Tables S6–S9), and no correlation was observed between the precursor oligomer lengths and the 12-rung molecular ladder yield. The resolved peaks assigned to the desired Vernier ladder structures exhibit uniformity with molecular weights closely corresponding to the expected values. However, as the partially assembled intermediates as determined by GPC peak deconvolution are not wholly consistent with those present in the MALDI mass spectra, we could not rule out the presence of additional, out-of-registry ladder complexes. Despite the extended reaction times and excellent registry observed for the dimerization of complementary *n* × *n* oligopeptoids, the attained mixtures, composed of the desired Vernier ladders and partially assembled intermediates, may result from sluggish strand exchange among the generated molecular ladders. To further examine the origin of this slow elimination of out-of-registry intermediates, we monitored the scrambling of molecular ladders by mass spectrometry.

Molecular Ladder Scrambling by Strand Exchange. The Vernier-templated assembly described here involves multiple, simultaneous reactions, including transimination and imine metathesis, to facilitate bond rearrangements and yield the most thermodynamically favored products. As indicated above, in addition to the desired Vernier ladders, we observed the continued presence of intermediate species in the reaction mixtures even after extended reaction times. To determine if the existence of intermediate species is a result of the respective reactions having not reached equilibrium, we performed kinetic studies of peptoid-based molecular ladder scrambling through two different approaches: transimination between a tetraamine-bearing peptoid and a 4-rung molecular ladder (Scheme 2), and imine metathesis between two different 4-rung molecular ladders (Scheme 3). These tetrafunctional oligomeric species were selected because there are at most four interactions among individual strands in the Vernier assemblies. Here, we employed

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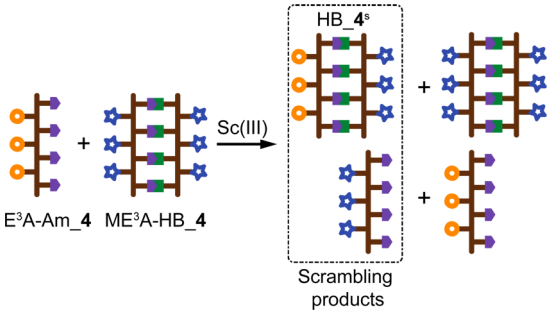
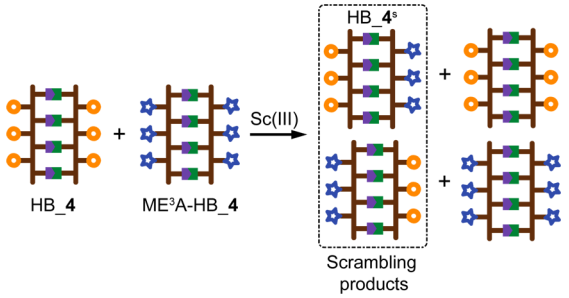
Scheme 2. Scrambling between a Single Strand and a 4-Rung Molecular Ladder[a]



[a]Upon mixing of a tetrafunctional single strand and a 4-rung molecular ladder, strand exchange proceeds until an equilibrium mixture of single strands and molecular ladders is afforded.

Scheme 3. Scrambling between Two Different 4-Rung Molecular Ladders[a]



[a]Upon mixing of the different 4-rung molecular ladders, strand exchange proceeds until an equilibrium mixture of molecular ladders is afforded.

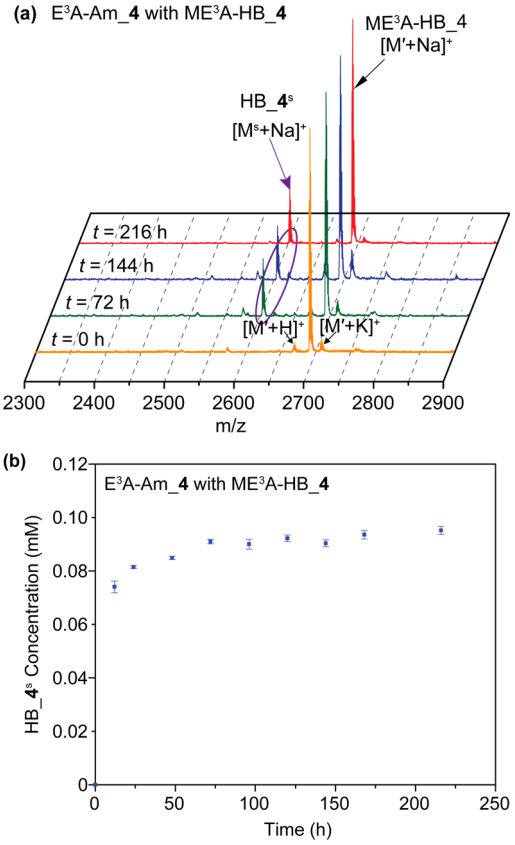


Figure 3. Scrambling between a tetraamine peptoid strand and a peptoid-based, 4-rung molecular ladder. (a) MALDI mass spectra of scrambling via transimination between E^{3}A-Am_**4** and ME^{3}A-HB_**4** at different time points; here, HB_**4**^{s} denotes a scrambled molecular ladder composed of E^{3}A-Am_**4** and ME^{3}A-Al_**4** strands. (b) Concentration of HB_**4**^{s} versus time during molecular ladder scrambling.

precursor peptoid oligomers bearing different spacer residues such that, upon molecular ladder scrambling, molecular weights of the generated scrambled products differs from their parent molecular ladders, enabling facile detection by MALDI mass spectrometry.[23]

Strand exchange by transimination was examined by utilizing a single-stranded tetra-amine peptoid E^{3}A-Am_**4** in conjunction with ME^{3}A-HB_**4**, a peptoid-based, 4-rung molecular ladder incorporating 2-(2-(2-methoxyethoxy)ethoxy)-ethylamine (ME^{3}A) as the spacer residue (see Figure S16). E^{3}A-Am_**4** and ME^{3}A-HB_**4** were added in a 1:1 stoichiometric ratio to chloroform with a catalytic amount of scandium(III) triflate and mixed at room temperature. Aliquots of the reaction mixture were examined directly by MALDI mass spectrometry over the course of 9 days to determine the rate and extent of ladder scrambling.

MALDI mass spectra of the tetraamine/4-rung molecular ladder reaction mixture (Figure 3(a)) demonstrate peaks attributable to both the parent molecular ladder ME^{3}A-HB_**4** and its scrambled product HB_4^s, generated by the transimination reaction between ME^{3}A-HB_**4** and E^{3}A-Am_**4**. As shown in Figure 3(b), this transimination-mediated strand exchange proceeds rapidly, and scrambling products were observed after 12 h; indeed, the concentration of the scrambled ladder product plateaus after approximately 72 h, indicating that equilibrium is reached well within the extended reaction time frame of the Vernier-templated syntheses.

Strand exchange via imine metathesis was also investigated between 4-rung molecular ladders bearing different spacer residues (HB_**4** and ME^{3}A-HB_**4**, see Scheme 3). Using an experimental approach similar to that employed for molecular ladder scrambling by transimination, the molecular ladder HB_**4**, composed of peptoid oligomers bearing E^{3}A spacer residues, was mixed with ME^{3}A-HB_**4** in a 1:1 stoichiometric ratio in chloroform with a catalytic amount of scandium(III) triflate at room temperature, and aliquots of the reaction mixture were examined by MALDI mass spectrometry. Although peaks attributable to the parent molecular ladders and the scrambled product are observable in the MALDI mass spectra of the two 4-rung molecular ladder imine metathesis reaction mixture (Figure 4(a)), the product concentration is low. Indeed, as shown in Figure 4(b), strand exchange between molecular ladders via imine metathesis is particularly sluggish as the concentration of the scrambled product continues to increase even after reaction for over a week, indicating that elimination of the out-of-registry intermediates generated during the Vernier assembly reaction proceeds very slowly. Thus, the strand exchange between molecular ladders via imine metathesis likely acts as the rate-determining reaction for this approach to Vernier-templated assembly.

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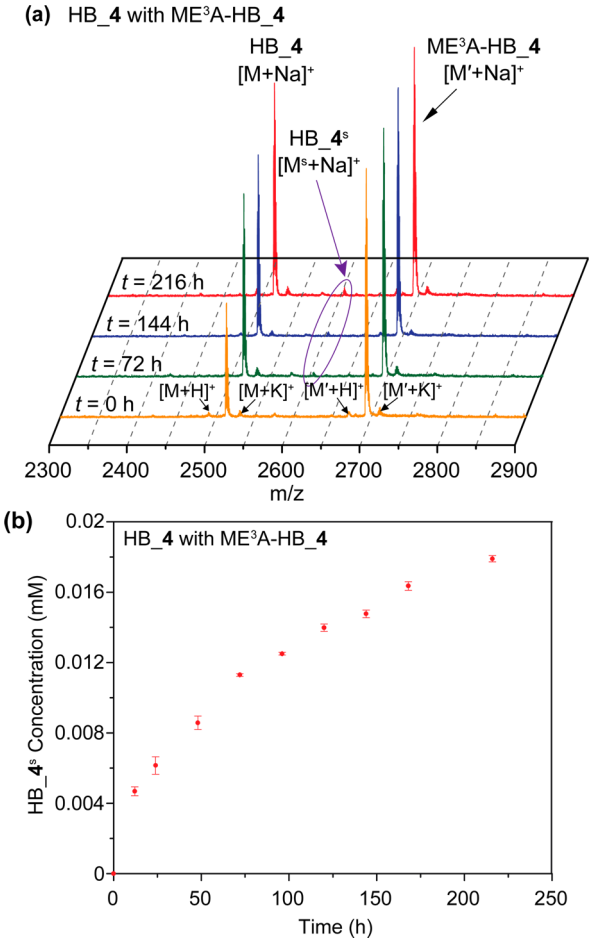

Figure 4. Scrambling between two different peptoid-based, 4-rung molecular ladders. (a) MALDI mass spectra of scrambling via imine metathesis between HB_**4** and ME^{3}A-HB_**4** at different time points; here, HB_**4**^{s} denotes scrambled molecular ladders composed either of E^{3}A-Am_**4** and ME^{3}A-Al_**4** or ME^{3}A-Am_**4** and E^{3}A-Al_**4** strands. (b) Concentration of HB_**4**^{s} versus time during molecular ladder scrambling.

CONCLUSIONS

Molecular ladders containing up to six rungs were successfully and selectively assembled by the Sc(III)-catalyzed dimerization of complementary, amine- and aldehyde-bearing oligopeptoids with commensurate lengths. Nevertheless, to curtail the kinetic trapping of thermodynamically disfavored products inevitably resulting from the hybridization of sufficiently long precursor oligomers, we utilized the Vernier-template directed, dynamic covalent self-assembly of oligomeric peptoids to create large, molecular ladder structures, the lengths of which were predetermined by the functionalities of the precursor strands. MALDI mass spectrometry and GPC, performed on the reaction mixture after 1 week reaction time, confirmed the formation of the desired ideal molecular ladder structures in addition to the presence of partially assembled intermediates. Scrambling experiments indicated that, whereas transimination between an amine-bearing peptoid and a molecular ladder proceeded rapidly, imine metathesis between two different molecular ladders had not reached equilibrium after 9 days reaction time; thus, despite the extended reaction time, the continued presence of partially assembled intermediates in the Vernier assembly mixture was attributed to the slow interladder imine metathesis.

By utilizing dynamic covalent interactions to mediate the self-assembly of complementary sequences, we believe this approach will prove particularly suitable for the fabrication of multidimensional nanostructures with unparalleled thermal, chemical, and mechanical stability. Additionally, the structural diversity and sequence-specific nature of peptoids make them excellent candidates as construction media for complex nanostructures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11251.

Experimental procedures for monomer and oligomer synthesis, purification, hybridization, and scrambling. Oligomer and molecular ladder characterization (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1155.
(2) Mattia, E.; Otto, S. *Nat. Nanotechnol.* **2015**, *10*, 111.
(3) Zhang, S. G. *Nat. Biotechnol.* **2003**, *21*, 1171.
(4) Lowik, D.; Shklyarevskiy, I. O.; Ruizendaal, L.; Christianen, P. C. M.; Maan, J. C.; van Hest, J. C. M. *Adv. Mater.* **2007**, *19*, 1191.
(5) Hsu, L.; Cvetanovich, G. L.; Stupp, S. I. *J. Am. Chem. Soc.* **2008**, *130*, 3892.
(6) Rajendran, A.; Endo, M.; Katsuda, Y.; Hidaka, K.; Sugiyama, H. *J. Am. Chem. Soc.* **2011**, *133*, 14488.
(7) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898.
(8) Jin, Y. H.; Yu, C.; Denman, R. J.; Zhang, W. *Chem. Soc. Rev.* **2013**, *42*, 6634.
(9) Hunt, R. A. R.; Otto, S. *Chem. Commun.* **2011**, *47*, 847.
(10) Cote, A. P.; Benin, A. I.; Ockwig, N. W.; O'Keeffe, M.; Matzger, A. J.; Yaghi, O. M. *Science* **2005**, *310*, 1166.
(11) Kuhn, P.; Forget, A.; Su, D. S.; Thomas, A.; Antonietti, M. *J. Am. Chem. Soc.* **2008**, *130*, 13333.
(12) MacLachlan, M. J. *Pure Appl. Chem.* **2006**, *78*, 873.
(13) Zhang, W.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4416.
(14) Hartley, C. S.; Moore, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 11682.
(15) Christinat, N.; Scopelliti, R.; Severin, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1848.
(16) Jin, Y. H.; Jin, A.; McCaffrey, R.; Long, H.; Zhang, W. *J. Org. Chem.* **2012**, *77*, 7392.
(17) Tozawa, T.; Jones, J. T. A.; Swamy, S. I.; Jiang, S.; Adams, D. J.; Shakespeare, S.; Clowes, R.; Bradshaw, D.; Hasell, T.; Chong, S. Y.;

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J. Am. Chem. Soc. 2015, 137, 16196−16202

Tang, C.; Thompson, S.; Parker, J.; Trewin, A.; Bacsa, J.; Slawin, A. M. Z.; Steiner, A.; Cooper, A. I. *Nat. Mater.* **2009**, *8*, 973.
(18) Rue, N. M.; Sun, J. L.; Warmuth, R. *Isr. J. Chem.* **2011**, *51*, 743.
(19) Wang, Q.; Zhang, C. X.; Noll, B. C.; Long, H.; Jin, Y. H.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 10663.
(20) Wang, Q.; Yu, C.; Long, H.; Du, Y.; Jin, Y.; Zhang, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 7550.
(21) Tanoue, R.; Higuchi, R.; Enoki, N.; Miyasato, Y.; Uemura, S.; Kimizuka, N.; Stieg, A. Z.; Gimzewski, J. K.; Kunitake, M. *ACS Nano* **2011**, *5*, 3923.
(22) Hartley, C. S.; Elliott, E. L.; Moore, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 4512.
(23) Elliott, E. L.; Hartley, C. S.; Moore, J. S. *Chem. Commun.* **2011**, *47*, 5028.
(24) O'Sullivan, M. C.; Sprafke, J. K.; Kondratuk, D. V.; Rinfray, C.; Claridge, T. D. W.; Saywell, A.; Blunt, M. O.; O'Shea, J. N.; Beton, P. H.; Malfois, M.; Anderson, H. L. *Nature* **2011**, *469*, 72.
(25) Hunter, C. *Nature* **2011**, *469*, 39.
(26) Greschner, A. A.; Bujold, K. E.; Sleiman, H. F. *Biomacromolecules* **2014**, *15*, 3002.
(27) Lindsey, J. S. *New J. Chem.* **1991**, *102*, 153.
(28) Kelly, T. R.; Xie, R. L.; Weinreb, C. K.; Bregant, T. *Tetrahedron Lett.* **1998**, *39*, 3675.
(29) Hunter, C. A.; Tomas, S. *J. Am. Chem. Soc.* **2006**, *128*, 8975.
(30) Kondratuk, D. V.; Perdigao, L. M. A.; O'Sullivan, M. C.; Svatek, S.; Smith, G.; O'Shea, J. N.; Beton, P. H.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 6696.
(31) Kondratuk, D. V.; Perdigão, L. M. A.; Esmail, A. M. S.; O'Shea, J. N.; Beton, P. H.; Anderson, H. L. *Nat. Chem.* **2015**, *7*, 317.
(32) Li, X.; Hao, C. H.; Tian, C.; Wang, P. F.; Mao, C. D. *Chem. Commun.* **2014**, *50*, 6361.
(33) Belowich, M. E.; Stoddart, J. F. *Chem. Soc. Rev.* **2012**, *41*, 2003.
(34) Giuseppone, N.; Schmitt, J. L.; Schwartz, E.; Lehn, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 5528.
(35) Zuckermann, R. N. *Biopolymers* **2011**, *96*, 545.
(36) Zuckermann, R. N.; Kerr, J. M.; Kent, S. B. H.; Moos, W. H. *J. Am. Chem. Soc.* **1992**, *114*, 10646.

DOI: 10.1021/jacs.5b11251
J. Am. Chem. Soc. 2015, 137, 16196−16202