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Click To Bind: Microwave-Assisted Solid-Phase Synthesis of Peptoids Incorporating Pyridine–Triazole Ligands and Their Copper(II) Complexes

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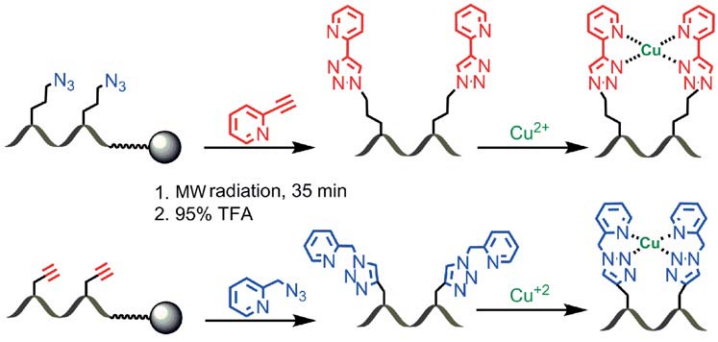

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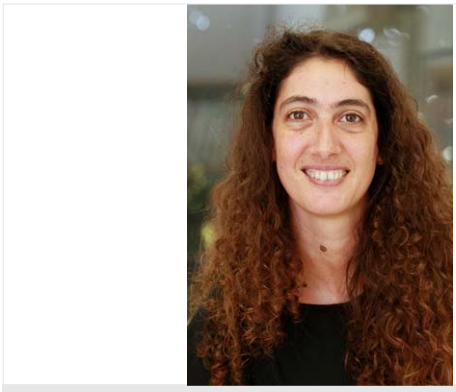
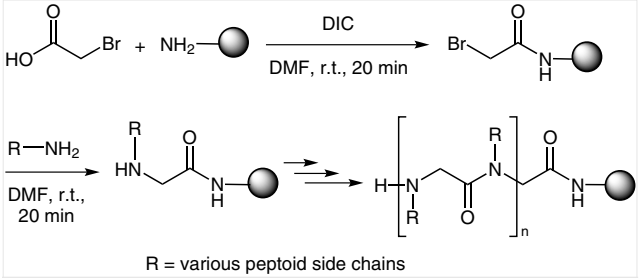
Abstract We describe a fast and efficient incorporation of the ligands 2-(1*H*-1,2,3-triazol-4-yl)pyridine and 2-(1*H*-1,2,3-triazol-1-ylmethyl)-pyridine into N-substituted glycine peptoid oligomers by the azide–alkyne cycloaddition (click) reaction on a solid support under microwave irradiation. Peptoids bearing these ligands formed stable complexes with copper(II).

Key words click reactions, cycloadditions, triazoles, solid-phase synthesis, peptides

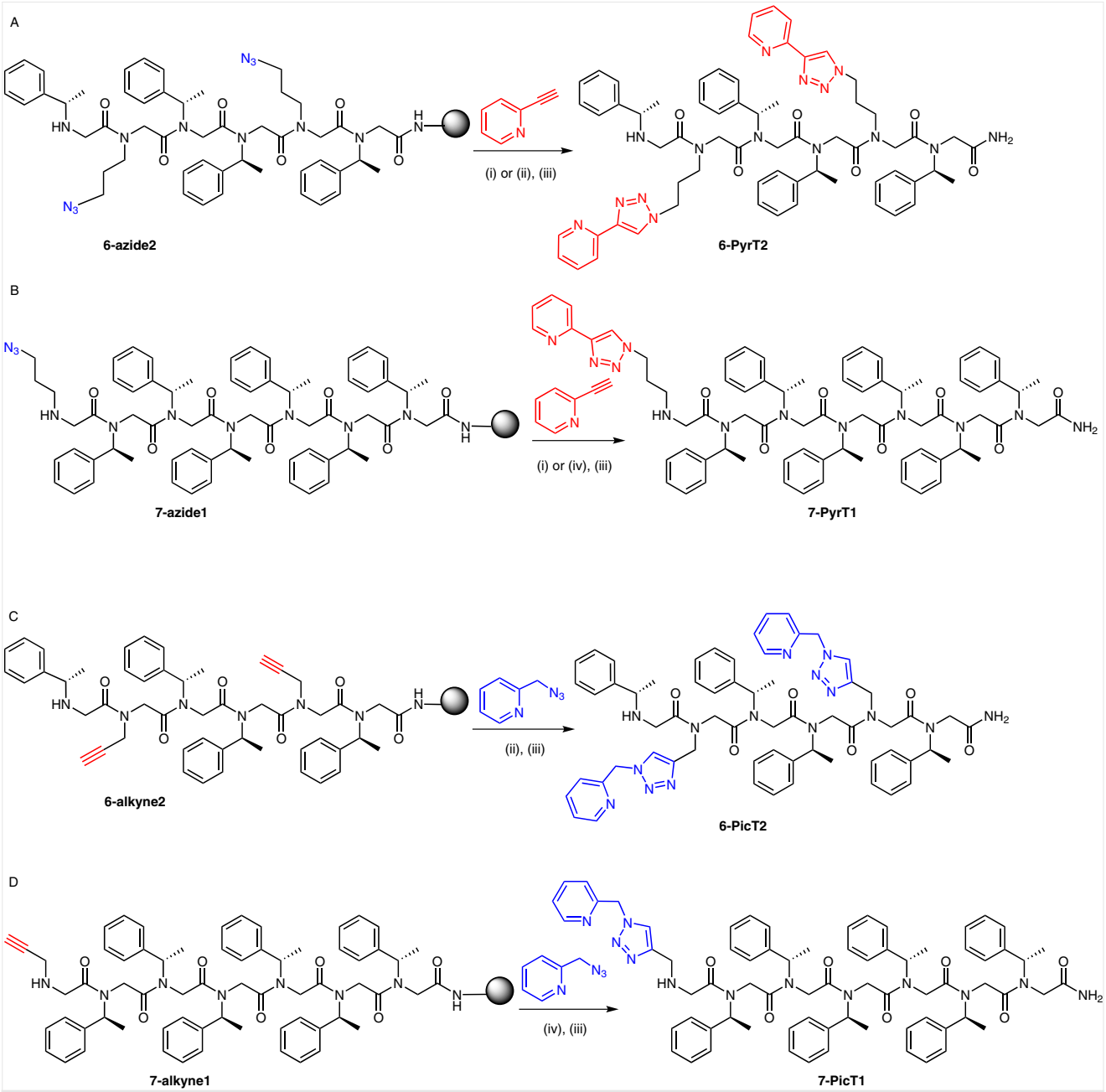
Peptoids (N-substituted glycine oligomers) have emerged as an important class of peptide mimics because of their structural and functional attributes.[1] One such attribute is the ability of some sequences to form well-defined folded architectures in solution, including helices (with a helical pitch of about three residues per turn), cycles, and turns.[2] In addition, peptoids exhibit a range of biological activities, such as coordination of metals, interactions with therapeutically relevant proteins,[1] and selective catalysis.[3] Also, peptoids have been designed as biomimetic materials and used as antifouling and antimicrobial agents, lung surfactants, and more.[1] Peptoid oligomers can be synthesized efficiently on a solid support by using primary amines as synthons (the submonomer method; Scheme 1), permitting ready incorporation of various side chains along their backbones.[4] The inclusion of pendent functional groups can be also accomplished in two steps by copper(I)-catalyzed azide–alkyne [3+2]-cycloaddition (click) reactions on solid supports. First, the alkyne or azide group is incorporated into a primary amine and, secondly, the functional group, attached to an azide- or alkyne-coupling partner reacts with the bound peptoid in the presence of click reagents. These solid-phase reactions are typically performed at room temperature for 15–72 hours.[5]



Galia Maayan was born in 1974 and studied Chemistry at Tel Aviv University and at The Weizmann Institute of Science, Israel. She was a postdoctoral research associate with Prof. Michael D. Ward and Prof. Kent Kirshenbaum in the Molecular Design Institute at New York University (USA) and with Prof. George Christou in the Department of Inorganic Chemistry at the University of Florida (USA). In the spring of 2012, she joined the Schulich Faculty of Chemistry at the Technion, Israel as an assistant professor. The research in her lab focuses on the interactions between biomimetic oligomers and metal species (ions, nanoparticles) for applications in folding, recognition, catalysis and hydrogen production.



Scheme 1 Solid-phase synthesis of peptoid oligomers by the submonomer method



Scheme 2 Solid-phase synthesis of the peptoid oligomers by the submonomer method and their copper(I)-catalyzed azide–alkyne [3+2] cycloaddition (click) reaction. *Reagents and conditions*: (i) resin-bound peptoid (100 mg), anhyd EtCH(Me)OH–DMF–py (6:3.6:2.4 v/v/v), coupling partner (21 equiv), ascorbic acid (212 mg, 20 equiv.), DIPEA (478.6 μL, 50 equiv.), CuI (410 mg, 40 equiv), r.t., 4 d; (ii) microwave radiation, 150 W, 60 °C, 30 min; (iii) 95% TFA–H_2O; (iv) as for (ii) but with a reaction time of 35 min.

As part of our effort to study the interactions of metal ions with peptoid oligomers,[6] we sought to develop efficient synthetic procedures for the incorporation of metal-binding ligands into peptoid sequences. With this aim, we previously designed and synthesized various peptoid sequences bearing the multidentate ligands 2,2′:6′,2″-terpyridine, 1,10-phenanthroline, and 8-hydroxyquinoline, and we demonstrated their coordination to metal ions and to metal nanoparticles.[6,7] Here, we report our studies on the incorporation of two other bidentate ligands, 2-(1*H*-1,2,3-triazol-4-yl)pyridine (**PyrT**) and 2-(1*H*-1,2,3-triazol-1-ylmethyl)pyridine (**PicT**), into chiral helical peptoids by a microwave-assisted click reaction, and we describe the formation of their copper(II) intramolecular and intermolecular complexes.

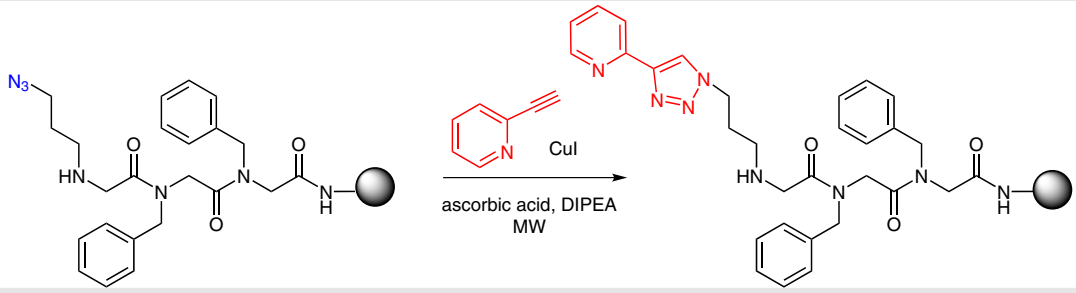
Our design goal was to generate two types of peptoid sequences: (i) helical oligomers having two bidentate ligands at positions *i* and *i+3b*, so that they face each other, facilitating intramolecular binding and the formation of 1:1 peptoid–metal complexes, and (ii) helical oligomers bearing one bidentate ligand, suitable for forming intermolecular 2:1 peptoid–metal complexes. To this end, we decided to first synthesize a peptoid hexamer bearing two **PyrT** ligands (**6-PyrT2**) and a peptoid heptamer having one such ligand (**7-PyrT1**). Our plan was to generate these two oligomers from the corresponding peptoids **6-azide2** and **7-azide1** by using the 2-ethynylpyridine as a coupling partner in a click reaction on a solid support (Scheme 2, A and B). Chiral *S*-phenylethyl groups (Nspe) were introduced at the other N-positions to enforce a helicity resembling that of a polyproline Type I helix, with a pitch of roughly three residues per turn.

As shown in Scheme 2, the peptoids **6-PyrT2** and **7-PyrT1** were obtained in two steps. First, oligomers **6-azide2** and **7-azide1** were synthesized by solid-state methods with (3-azidopropyl)amine and (*S*)-(−)-(1-phenylethyl)amine as synthons, employing the submonomer protocol.[4] At the end of the synthesis, samples of the peptoids were cleaved from the solid support and analyzed by HPLC, and their molecular weights were confirmed by electrospray mass spectrometry. Secondly, **6-azide2** and **7-azide1** were dissolved in a mixture of butan-2-ol, *N*,*N*-dimethylformamide, and pyridine then treated with 2-ethynylpyridine, ascorbic acid, *N*,*N*-diisopropylethylamine, and copper(I) iodide under the previously reported conditions for a solid-phase click reaction of peptoids.[5b] Monitoring of the reaction by HPLC, showed that full conversion at room temperature was achieved only after four days.

In an attempt to reduce the reaction time, we decided to develop a new procedure for the cycloaddition reaction by using microwave irradiation. We synthesized an achiral peptoid trimer as a model to be tested under various radiation conditions (Scheme 3). Initially, we chose moderate conditions in which the temperature was below the boiling point of our solvent and which would not decompose the peptoid. Thus, the resin-bound peptoid (10 mg) was treated with the same reagents as described above in the presence of microwave irradiation (150 W) at 60 °C for 30 minutes. A conversion of >99% was obtained, as determined by HPLC. Excited by these results we attempted to optimize the conditions by reducing the temperature to 30 °C and using reaction times of 30, 15, or 5 minutes. Again, conversions of >99% were obtained in all three reactions.

We therefore decided to use 150 W microwave irradiation at 30 °C with 10 mg of **6-azide2** or **7-azide1**, and to perform the click reaction with 2-ethynylpyridine for five minutes. In the case of **7-azide1**, full conversion to **7-PyrT1** was achieved after five minutes, whereas in the case of **6-azide2**, only about a 65% conversion into **6-PyrT2** occurred after five minutes at 30 °C. Increasing the reaction time under the same reaction conditions produced no marked increase in the conversion, whereas increasing the temperature to 60 °C produced a full conversion after five minutes. We then generated another batch of **7-azide1** and **6-azide2** on 100 mg of resin and performed the click reaction for five minutes under the same conditions, but at temperatures of 30 °C and 60 °C, respectively. This time, when the reaction was scaled up, full conversion was not achieved under these conditions; it was, however, achieved when the temperature was 60 °C for both **6-azide2** and **7-azide1**, with reaction times of 30 and 35 minutes, respectively.

High-performance liquid chromatograms of the crude **6-azide2** and **7-azide1** are shown in Figure 1 (top, black), and those of **6-PyrT2** and **7-PyrT1** are presented in the Supporting Information (Figure S3, top). Overall, we succeeded in reducing the reaction time significantly from four days to 30–35 minutes. Pleased by these results, we decided to apply these reaction conditions to a second pair of peptoids, **6-alkyne2** and **7-alkyne1**, in order to obtain the oligomers **6-PicT2** and **7-PicT1** by reacting them with 2-(azidomethyl)pyridine as a coupling partner (Scheme 2,C and D). High-performance liquid chromatograms of the crude **6-alkyne2** and **7-alkyne1** are shown in Figure 1 (bottom, black) and those of the **6-PicT2** and **7-PicT1** presented in the Supporting Information (Figure S3, bottom). After the second step, oligomers **6-PyrT2**, **7-PyrT1**, **6-PicT2**, and **7-PicT1** were cleaved from the solid support and purified by HPLC to leave no detectable impurities (>98% purity). High-



Scheme 3 Microwave-assisted solid-phase click reaction of a model peptoid trimer. Full conversion was achieved with 10 mg resin-bound peptoid by using 150 W microwave irradiation at 30 °C for 5 minutes.

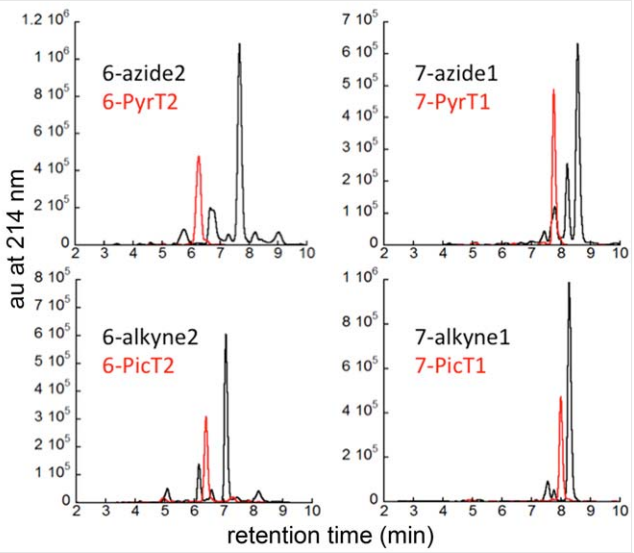


Figure 1 High-performance liquid chromatograms (214 nm) of the peptoid oligomers before (black, crude peptoids) and after (red, purified peptoids) the click reaction

performance liquid chromatograms of the purified **6-PyrT2**, **7-PyrT1**, **6-PicT2**, and **7-PicT1** are shown in Figure 1 (red). The molecular weights measured by electrospray mass spectrometry were consistent with the expected values for all four peptoids (Table 1 and Supporting Information).

Table 1 Molecular Masses and Purities of the Crude Peptoid Oligomers, and Their Conversions into the Corresponding Click Products and Copper Complexes

Product	Molecular mass		Purity (%)	Conv. (%)
	Calculated	Found (*m*/*z*)		
6-azide2	942.1	942.1	80	
6-PyrT2	1148.3	1149.0	80	>99
6-PyrT2 Cu	1211.9	1209.8	–	quant[a]
7-azide1	1124.4	1124.1	63	
7-PyrT1	1227.5	1228.0	35	>99
(**7-PyrT1**)$_2$Cu	2518.5	2518.0	–	quant[a]
6-alkyne2	852.0	851.9	84	
6-PicT2	1120.3	1120.8	92	>99
6-PicT2 Cu	1183.8	1183.0	–	quant[a]
7-alkyne1	1079.4	1079.9	91	
7-PicT1	1213.4	1213.8	85	>99
(**7-PicT1**)$_2$Cu	2490.3	1244.2[b]	–	quant[a]

[a] Conversions into the Cu^{2+} complexes are as obtained from the synthesis.
[b] *m*/2*z*.

With these four peptoids in hand, we investigated some of their metal-binding properties. The bidentate ligands 2-(1*H*-1,2,3-triazol-4-yl)pyridine and 2-(1*H*-1,2,3-triazol-1-ylmethyl)pyridine are versatile chelators and their complexes with copper(II),[8,9] silver(I),[8,9] iron(II),[10] platinum(II),[8,11,12] palladium(II),[8,10,13] ruthenium(II),[8,14–16] and rhenium(I)[17] have been previously reported by other groups. Some of these complexes have shown potential for applications in medicine or materials science. Because we were studying biomimetic oligomers and were interested in biologically relevant metal ions, we chose to examine the coordination of copper(II) to our peptoids. The binding of copper(II) to the peptoids was initially evaluated by isothermal titration calorimetry. We titrated solutions of each of the peptoids with small aliquots of copper(II) acetate solution and measured the association constant K_A in two different solvents: methanol and acetonitrile. The results, as calculated by independent curve fitting, are summarized in Table 2. First, the results show that complex formation is facilitated in methanol in comparison with acetonitrile. Also, larger K_A values were obtained for the hexamer complexes than for the heptamer complexes. This suggests that, as with other metal-binding peptoids,[6b] two binding modes are possible. In the case of the hexamers, intramolecular binding occurs, leading to the formation of the 1:1 peptoid–copper(II) complexes **6-PyrT2**Cu and **6-PicT2**Cu, whereas in the case of the heptamers, binding occurs in an intermolecular fashion to give the 2:1 peptoid–copper(II) complexes (**7-PyrT1**)$_2$Cu and (**7-PicT1**)$_2$Cu.

Table 2 Association Constants K_A of the Peptoid–Copper(II) Complexes as Calculated by Independent Curve Fitting

Compound	Methanol	Acetonitrile
6-PyrT2 Cu	3.318×10^6	3.071×10^6
(**7-PyrT1**)$_2$Cu	3.725×10^5	3.103×10^5
6-PicT2 Cu	1.680×10^6	1.206×10^6
(**7-PicT1**)$_2$Cu	6.970×10^5	4.698×10^5

The solid complexes were prepared in quantitative yield,[18] and their identities were verified by mass spectrometry (see Table 1). The MS data supports our hypothesis that 1:1 peptoid–metal complexes are formed in the case of **6-PyrT2** and **6-PicT2**, and 2:1 complexes are formed in the case of **7-PyrT1** and **7-PicT1** (see Supporting Information).

Metal-free **6-PyrT2** and **7-PyrT1** showed absorption bands near λ = 241 nm and 280 nm in acetonitrile. Upon addition of copper(II) acetate, binding of copper(II) produced an enhancement of the absorption band at λ = 241 and a new absorbance band at λ = 285 nm (Figure 2, top). Metal-free **6-PicT2** and **7-PicT1** exhibited absorption bands near λ = 261 nm in acetonitrile, which were also enhanced upon addition of copper(II) acetate. In addition, binding of copper(II) produced an additional enhancement of the absorbance at λ = 278–310 nm (Figure 2, bottom). ESI

MS measurements were consistent with the formation of 1:1 **6-PyrT2**Cu and **6-PicT2**Cu complexes, and 2:1 (**7-PyrT1**)$_2$Cu and (**7-PicT1**)$_2$Cu duplexes, indicative of intramolecular and intermolecular tetracoordinated complexation, respectively.

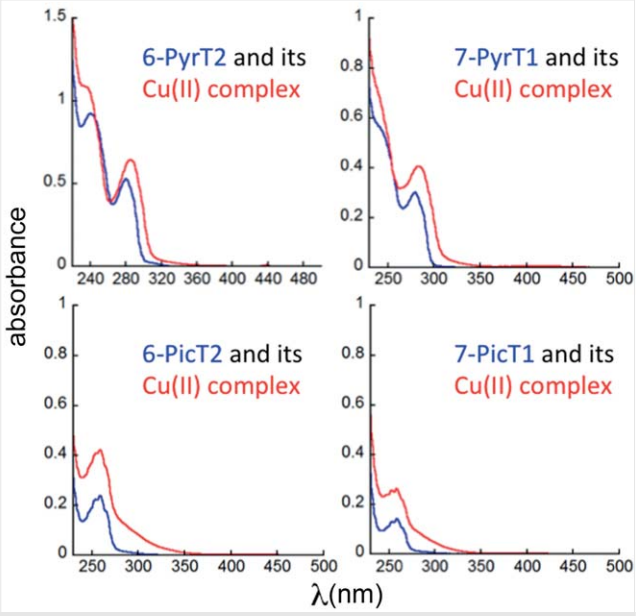


Figure 2 UV–vis spectra for the peptoid oligomers (47 μM solution in acetonitrile, blue lines) and of their copper(II) complexes (47 μM solution in acetonitrile, red lines)

All four copper(II) complexes were also characterized by means of EPR spectroscopy. The x-band EPR spectra of solid powdered samples of **6-PyrT2**Cu, **7-PyrT1**Cu, **6-PicT2**Cu, and **7-PicT1**Cu were measured at room temperature (Supporting Information, Figures S16–S19). The EPR signals clearly showed the presence of a Cu(II) magnetic dimer. The Hamiltonian parameters obtained from the spectra of **6-PyrT2**Cu, **7-PyrT1**Cu, **6-PicT2**Cu, and **7-PicT1**Cu were g|| = 2.200, 2.194, 2.213, and 2.212; g⊥ = 2.064, 2.061, 2.063 and 2.070; and A|| = 168.4, 171, 171.7, and 171.7 G, respectively (Supporting Information, Table S1). All four ligand are expected to form tetragonal complexes with copper(II); these are typically square-planar when copper(II) is directly bound to four nitrogen atoms. The EPR results support this assumption; the quotient (g||)/(A||) ($cm^{-1} \times 10^4$), which has been shown to range from about 105 to 135 for square-planar structures,[19] was 130.6, 128.3, 128.9, and 128.8 for **6-PyrT2**Cu, **7-PyrT1**Cu, **6-PicT2**Cu, and **7-PicT1**Cu, respectively (see Supporting Information).

Circular dichroism (CD) measurements also showed some changes upon complex formation. Solutions of all four complexes showed significant decreases in the ellipticity near 200 nm relative to the corresponding values for of the metal-free peptoids; furthermore, complexes **6-PicT2**Cu and **7-PicT1**Cu exhibited small increases in the magnitude of the CD signals near 220 nm relative to those of the metal-free peptoids. It has been previously demonstrated that *N*-(*S*)-(1-phenylethyl)glycine (Nspe) peptoids generally adopt right-handed helices with a *cis*-amide bonds, although there is a minor population of conformers containing one or more *trans*-amide bonds.[2a] It has also been shown that the CD spectra of peptoids bearing Nspe groups are characterized by bands near 190 and 200 nm, the latter of which is associated with the *trans*-amide bond conformation. These peptoids also show a band near 218 nm associated with the *cis*-amide bond conformation.[2b] Therefore, both an increase in the band near 218 nm and a decrease in the band near 200 nm are indicative that a helix with *cis*-amide bonds is the favored conformation and is actually the dominant one in solution.[2b] Our results therefore imply that all our peptoids show an increase in conformational order upon complexation to a metal. In the case of the hexamers, this increase can be attributed to conformational constraint and enhanced secondary-structure content, resulting from intramolecular metal complexation.[11,12] In the case of the heptamers, the increase might be related to the formation of duplexes that are similar to peptide bundles formed upon metal complexation.[2,10] The small increases near 220 nm shown by the complexes **6-PicT2**Cu and **7-PicT1**Cu suggest that they show greater increases in conformational order and in degree of helicity than do **6-PyrT2**Cu and **7-PyrT1**Cu, probably because of the shorter distance between the pyridine–triazole ligands and the peptoid backbone in the case of the picoline complexes.

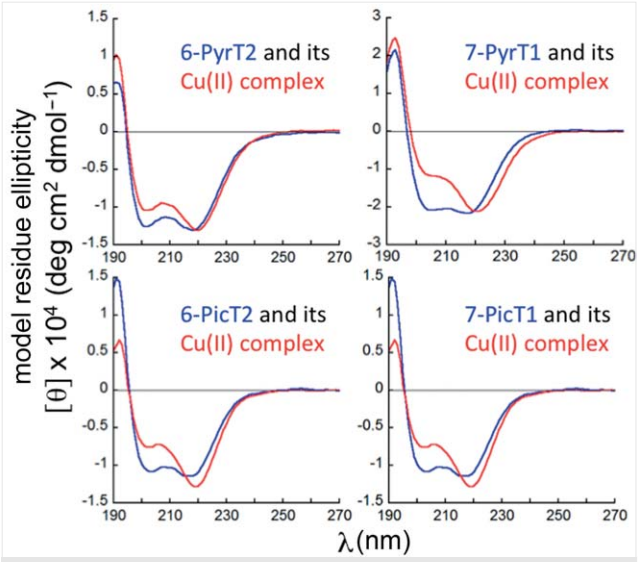


Figure 3 CD spectra of the peptoid oligomers (10 μM solution in acetonitrile, blue lines) and of their copper(II) complexes (10 μM solution in acetonitrile, red lines). The path length was 1 cm.

In summary, we have succeeded to incorporate two versatile *N*,*N* metal-binding ligands into peptoid oligomers by developing an efficient and rapid method for performing

azide–alkyne cycloaddition (click) reactions on a solid support and microwave irradiation. The new peptoid chelators were used to prepare intramolecular and intermolecular chiral helical peptoid–copper(II) complexes. We believe that this microwave-assisted strategy can be extended to the solid-phase synthesis of numerous sequences, including peptides and peptidomimetics, through the incorporation of various functional groups by means of the click reaction. We are currently exploring the binding properties of our four metal chelators with other metal ions with a view to their potential use in asymmetric catalysis and materials science.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378938.

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(18) **Copper Complexes; General Method**
The four copper(II) complexes were prepared by adding solid $Cu(OAc)_2$ (1.2 equiv.) a 5.5 M solution of **6-PyrT2** or **6-PicT2** in MeOH (1 equiv) or solid $Cu(OAc)_2$ (0.6 equiv) to a 5.5 M solution of **7-PyrT1** or **7-PicT1** in MeOH (1 equiv). The resulting solutions were stirred for 4 h and then the unreacted Cu salt was removed by filtration to give a green–blue filtrate. The solution was divided into two portions, and one portion was used for spectroscopic analysis. The other portion was evaporated under a low pressure and the solid obtained was washed with H_2O (3 × 0.5 mL), and dried under low pressure.

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