Water-Soluble Chiral Metallopeptoids

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ABSTRACT:

Metal ions play a significant role in the activity of biological systems including catalysis, recognition and folding. Therefore, introducing metal ions into peptidomimetic oligomers is a potential way for creating biomimetic metal complexes toward applications in sensing, recognition, drug design and catalysis. Herein we report the design, synthesis and characterization of water-soluble chiral N-substituted glycine oligomers, "peptoids," with one and two distinct intramolecular binding sites for metal ions such as copper and cobalt. We demonstrate for the first time the incorporation of the chiral hydrophilic group (S)-(+)-1-methoxy-2-propylamine (Nsmp) within peptoid sequences, which provides both chirality and water solubility. Two peptoids, a heptamer, and a dodecamer bearing two and four 8-hydroxyquinoline (HQ) groups respectively as metal-binding ligands, were synthesized on solid support using the submonomer approach. Using UV-titrations and ESI-MS analysis we demonstrate the creation of a novel metallopeptoid bearing two metal ions in distinct binding sites via intramolecular chelation. Exciton couplet circular dichroism (ECCD) demonstrated chiral induction from the chiral non-helical peptoids to the metal centers. © *2015 Wiley Periodicals, Inc. Biopolymers (Pept Sci) 104: 577–584, 2015.*

Keywords: peptoid; chirality; metallofoldamer; copper

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INTRODUCTION

A highly promising approach for the design of synthetic materials that resemble biopolymers structure and function is the use of peptidomimetics such as β-peptides,[1–3] peptoids,[4,5] and other biotic foldamers.[6–8] Among these, peptoids—*N*-substituted glycine oligomers, reveal a range of biological activities such as metal coordination,[9–18] interaction with therapeutically relevant proteins,[5] and enantioselective catalysis.[19,20] In addition, peptoids were designed as biomimetic materials to be used as antifouling and antimicrobial agents, lung surfactants and more.[5] Although peptoids are incapable of forming hydrogen bonding because the nitrogen atom is substituted, they can fold into helical secondary structures by incorporating bulky chiral side chains into the oligomer sequence.[21–33] Helical secondary structure of peptoids is forced due to local steric and stereoelectronic interactions and mostly resembles that of the polyproline-type I helix, with a pitch of three residues per turn.[22] Peptoids can be efficiently synthesized by the submonomer approach,[34] which involves two main steps: *N,N*-diisopropylcarbodiimide (DIC)-mediated acylation with haloacetic acid, followed by amine displacement with a primary amine to form *N*-substituted glycine. This two-step sequence is repeated iteratively until the desired oligomer is obtained (see Scheme 1). The use of primary amines as building blocks enables specific tuning of the peptoids properties (e.g., chirality, polarity, metal-coordination ability, and water solubility) via the introduction of different side chains at desired positions. In the context of metal coordination, we note that exploring the interactions between metal ions and peptide mimics can lead to the generation of unique functional biomimetic materials. Currently, reported examples of metallopeptoids include: (1) Zn(II)-binding peptoids which

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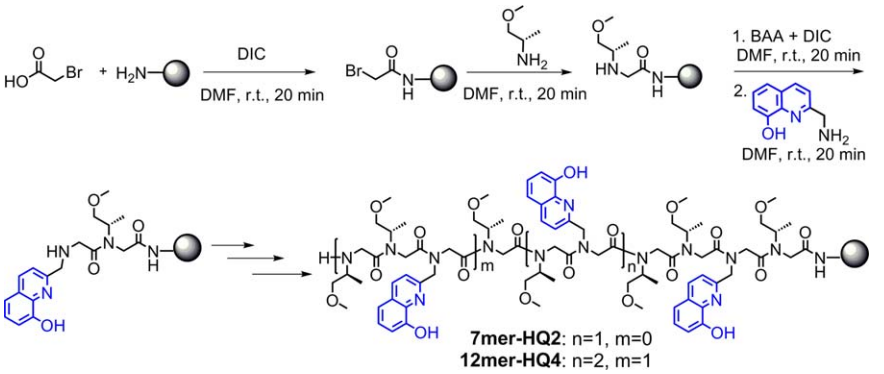

SCHEME 1 Solid-phase "submonomer" peptoid synthesis.

were designed to mimic the zinc finger motif found in biopolymers,[9] (2) Cu(II)- and Co(II)-binding chiral peptoids bearing one or two 8-hydroxyquinoline (HQ) ligands,[10] (3) Cu(II) complexes of chiral peptoids bearing pyridine-triazole residues,[11] (4) short achiral water-soluble peptoids designed specifically for the binding of chromium(VI),[12] (5) cyclic achiral water-soluble metallopeptoid complexes of lanthanides and alkali metal ions,[13–18] and (6) Au(0) nanoparticles (NPs)[35] and Ag(0) NPs assemblies[36] stabilized by peptoid oligomers. Metallopeptoids, which are both chiral and water-soluble, however, have not been described yet. A few other peptide mimics that bind metal ions were also reported, such as a β-peptide hairpin that coordinates Zn(II)[37] and a Cd(II) β-peptide bundle.[38]

Lipophilicity should be an important property of peptidomimetics designed for applications that require water solubility, such as drug design, the purification of drinking water, biphasic catalysis, and more. Water solubility can be achieved by the incorporation of polar hydrophilic pendant groups within the peptoid sequence.[39] Several examples of peptoids incorporating water-soluble functional groups were described in the literature,[12,40–42] for applications such as the solid-phase extraction of Cr(VI) from contaminated water sources[12] and phase transfer catalysis.[15] Typically, hydrophilic residues introduced to peptoid sequences include functional groups such as amines (primary and secondary), thiols, carboxylic acids, and ethers. All of these groups, with the exception of ethers, need to be protected before their incorporation, and have the potential to bind metal ions; therefore their use for the design of metal-binding peptoids is limited. The ether groups that were incorporated, however, were not chiral. Therefore, introducing new polar chiral groups that are commercially available, compatible to the peptoid synthesis and do not require additional protecting synthetic steps is desired.

Chiral induction to metal centers has shown to be a significant analytical tool for recognition and sensing,[43,44] and can provide useful structural information.[45–51] Additional applications that can benefit from chiral induction to metal complexes are enantioselective catalysis and drug design. Chiral induction to metal centers is directly related to an efficient transfer of chiral information from a chiral unit, e.g., chiral ligands, or chiral helices that can often be found in folded macromolecules.[52] Currently, there is only one example of chiral induction in metallopeptoids.[10] In this work, two helical peptoids bearing one and two HQ pendant groups each, were prepared and characterized by circular dichroism (CD) spectroscopy. Upon metal binding, transmission of the stereogenic character of the helical peptoids to the metal center has occurred, as was reflected by the CD changes in the absorbance bands corresponding to the metal complexes. Although these results are a unique example of chiral induction to metal centers in peptoids, it was not determined whether the chirality of the metal centers arises from the peptoid helicity or simply from the fact that these oligomers are chiral. Aiming to probe this point, we have decided to design chiral non-helical peptoid oligomers bearing at least two HQ pending groups for intramolecular binding of Cu^{2+} and Co^{2+}. To prevent folding of the peptoids to helical structure we sought to incorporate chiral non-bulky monomers in the other positions along the sequence. Moreover, to add hydrophilicity to the designed peptoids aiming to obtain water-soluble metal-binding peptoids, we decided to use chiral non-bulky pendant groups, which are also hydrophilic. Thus, the monomer of choice was (*S*)-1-methoxy-2-propylamine (Nsmp).

Herein, we describe the design, synthesis and characterization of two linear water-soluble chiral non-helical peptoids, the heptamer **7mer-HQ2** bearing two HQ pendent groups for intramolecular binding of one metal ion and the dodecamer **12mer-HQ4** bearing four HQ groups for intramolecular binding of two metal ions (Figure 1). We found that upon metal binding, chiral metal centers are formed as revealed by CD measurements, demonstrating induction of chirality from chiral non-helical peptoid scaffolds to embedded metal centers.

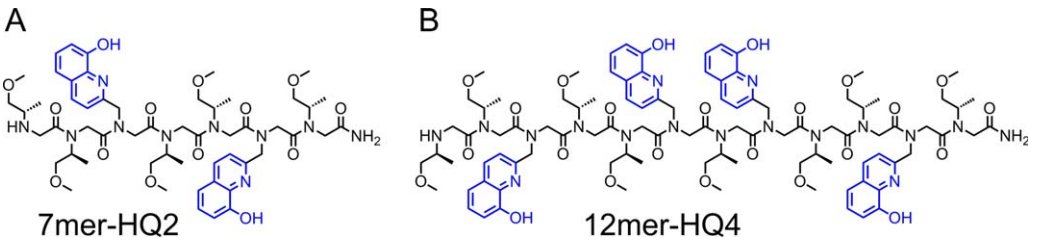

FIGURE 1 Chemical structures of peptoid oligomers (A) **7mer-HQ2** and (B) **12mer-HQ4**.

MATERIALS AND METHODS

Synthesis and Purification of the Peptoid Oligomers 7mer-HQ2 and 12mer-HQ4

Solid-phase synthesis of peptoid oligomers was performed in fritted syringes on Rink amide resin using a variation of a previously reported peptoid submonomer protocol.[34] In a typical oligomer synthesis, 100 mg of resin with a loading level of 0.82 mmol·g^{-1} was swollen in 4 mL of dichloromethane (DCM) for 40 min. Following swelling, the F_{moc} protecting group was removed by treatment with 2 mL of 20% piperidine in dimethylformamide (DMF) for 20 min. After deprotection and after each subsequent synthetic step, the resin was washed three times with 2 mL of DMF, 1 minute per wash. Peptoid synthesis was carried out with alternating bromoacylation and amine displacement steps. For each bromoacylation step, 20 equiv bromoacetic acid (1.2*M* in DMF, 8.5 mL g^{-1} resin) and 24 equiv DIC (neat, 2 mL g^{-1} resin) were added to the resin, and the mixture was mixed for 20 min. After washing, 20 eq. of the required amine (1.0*M* in DMF) were added to the resin and mixed for 20 min. This two-step addition cycle was modified as follows: after incorporation of 8-hydroxy-2-quinolinemethylamine, 0.17 mL of a 1.2*M* solution of bromoacetic acid, 0.04 mL of neat DIC and 0.29 mL of DMF were added to the resin and mixed at room temperature for 20 minutes.[53] When the desired sequence was achieved, the peptoid products were cleaved from the resin by treatment with 95% trifluoroacetic acid (TFA) in water (50 mL g^{-1} resin) for 30 minutes. After filtration, the cleavage mixture was concentrated by rotary evaporation under reduced pressure for large volumes or under a stream of nitrogen gas for volumes less than 1 mL. Cleaved samples were then re-suspended in 50% acetonitrile in water and lyophilized to powders. Peptoids were purified by preparative High performance liquid chromatography (HPLC) using a C18 column. Products were detected by UV absorbance at 230 nm during a linear gradient conducted from 5% to 95% solvent B (0.1% TFA in HPLC grade acetonitrile) over solvent A (0.1% TFA in HPLC grade water) in 50 minutes with a flow rate of 5 mL min^{-1}. Analytical data for **7mer-HQ2**: HPLC: t_R = 4.5 min; linear gradient: 5–95% solvent A over solvent B in 10 minutes with a flow rate of 0.7 mL min^{-1}. MS (ESI): m/z = 1091.3 calc for $C_{54}H_{78}N_{10}O_{14}$ [M]+; found: 1092.2 (Advion expression CMS). Analytical data for **12mer-HQ4**: HPLC: t_R = 5.5 min; linear gradient: 5–95% solvent A over solvent B in 10 minutes with a flow rate of 0.7 mL min^{-1}. MS (ESI): m/z = 1907.2 calc for $C_{96}H_{131}N_{17}O_{24}$ [M]+; found: 1907.2 (Advion expression CMS).

Synthesis of Metal Complexes

In a typical synthesis, a solution of peptoid oligomers (0.001–0.002 mmol) in water (0.25 mL) was treated with metal salt (copper acetate or cobalt acetate) and the mixture was stirred for 2 hours. A colored solid (pale orange for cobalt complexes and pale green for copper complexes) was precipitated after the addition of NH_4PF_6 (0.02 mL of a 1*M* aqueous solution). The precipitate was isolated by centrifugation, washed twice with water and lyophilized overnight.

UV–Vis Spectroscopy

Titration experiments of the peptoid oligomers **7mer-HQ2** and **12mer-HQ4** with the metal ions Co^{2+} and Cu^{2+} were followed by UV–VIS measurements. In a typical experiment, 10 μL of a peptoid solution (2.5 or 5 m*M* in H_2O) were diluted in 3 mL H_2O solution (to get 8.5 or 17 μM) and then sequentially titrated with 2 μL aliquots of a metal ion (5 m*M* in H_2O), in multiple steps, until the binding was completed.

Circular Dichroism

Approximately 500 μL solutions (5 m*M* in H_2O) of lyophilized **7mer-HQ2** or **12mer-HQ4** powders were prepared immediately before CD measurements. CD spectra of metal-free peptoids were obtained from 10 μM water solutions followed by the addition of metal ions solutions. The metal solutions were added as follows: to the solution of **7mer-HQ2** 1.2 eq. of Cu^{2+} acetate (7.2 µL, 5 m*M* in water) or 10 eq. of Co^{2+} acetate (30 µL, 10 m*M* in water) were added to achieve saturation, and to the solution of **12mer-HQ4** 2.2 eq. Cu^{2+} acetate (13.2 µL, 5 m*M* in water) or 6.4 of eq. Co^{2+} acetate (19.2 µL, 10 m*M* in water) were added to achieve saturation. Subsequently, the samples were measured again and the spectra of the metallopeptoids were acquired. CD scans were performed at 25 °C. The spectra were obtained by averaging four scans per sample in a fused quartz cell (path length = 1 cm). Scans were performed over the 360–180 nm region using 50 nm/min scan rate.

EPR

EPR spectra were recorded on a Bruker EMX-10/12 X-band (ν = 9.4 GHz) digital EPR Spectrometer. All spectra were recorded at room temperature from solid state samples with (2,2,6,6-Tetramethyl-1-piperidinyl)oxidanyl (TEMPO, g = 2.0059) in an inner tube for determination of the g-factor. Spectra processing and simulation were performed with Bruker WIN-EPR and SimFonia Software.

RESULTS AND DISCUSSION

Design and Synthesis of Peptoid Oligomers

Peptoid heptamer **7mer-HQ2** and dodecamer **12mer-HQ4** bearing five and eight (*S*)-methoxy-2-propyl side chains

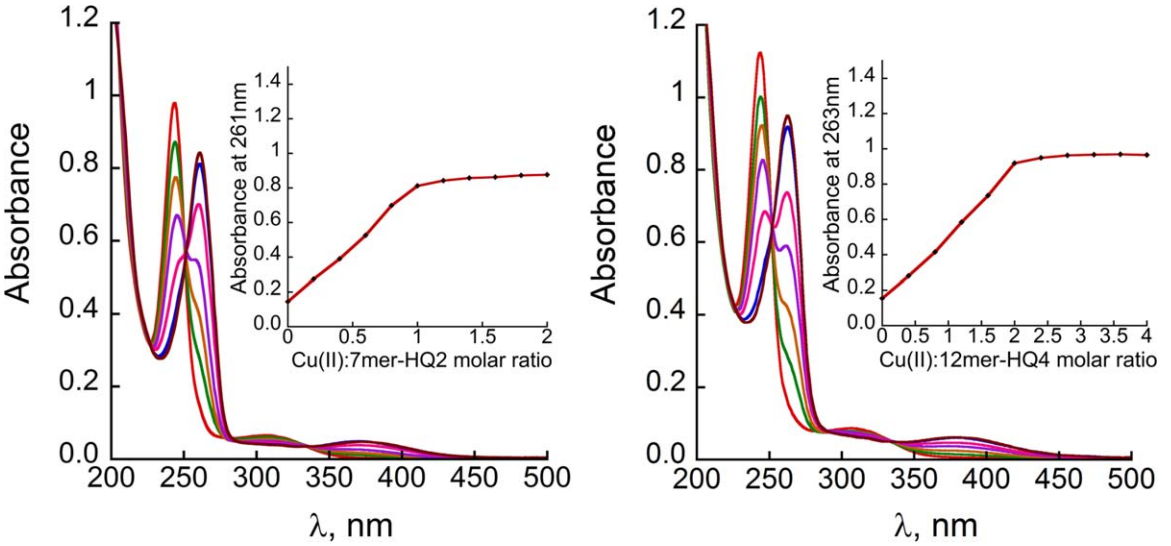

FIGURE 2 UV–Vis spectra and Job plots for titration of (left) **7mer-HQ2** and (right) **12mer-HQ4** with Cu^{2+}.

respectively and two and four 8-hydroxy-2-quinolinemethyl (HQ) respectively, were synthesized on Rink amide resin using a variation of a previously reported peptoid submonomer protocol (Scheme 1). Typically, *N*-alkyl-substituted glycine units are generated by the iteration of successive short bromoacetylation and amine displacement steps (see Scheme 1). After incorporation of HQ the bromoacetylation step was modified (concentrations of reagents were reduced) to make the reaction more efficient and prevent side reactions such as alkylation of the heterocyclic nitrogen.[52] The products were cleaved from the resin with aqueous TFA, analyzed by analytical high-performance liquid chromatography (HPLC), purified by preparative HPLC, and their sequences were confirmed by electrospray mass spectrometry (ESI-MS). Our design goal was to generate water-soluble chiral peptoids that can bind one or two metal ions in an intramolecular manner. Heptamer **7mer-HQ2** contains two HQ groups at positions *i* and *i+3* such that they are in optimal distance to facilitate an intramolecular binding toward the formation of 1:1 peptoid:metal complexes[10] (see Scheme 1). Dodecamer **12mer-HQ4** contains four HQ ligands at positions *i* and *i+3* for intramolecular binding of two metal ions toward the formation of 1:2 peptoid:metal complexes with two distinct binding sites that are located at a distance of two monomers from each other (see Scheme 1). (*S*)-1-Methoxy-2-propyl side chains provide both chirality and water solubility to the designed peptoids.

UV-Titration and Metal Complexation

Metal-free **7mer-HQ2** and **12mer-HQ4** exhibit absorption bands near $\lambda = 244$, 309 nm and $\lambda = 244$, 307 nm respectively in water. Upon addition of copper acetate, binding of Cu^{2+} produced new absorption bands at $\lambda = 261$, 372 nm and $\lambda = 263$, 379 nm for **7mer-HQ2** and **12mer-HQ4**, respectively (Figure 2). Job plots constructed from UV titrations of the peptoids with copper acetate were consistent with a 1:1 **7mer-HQ2**Cu complex and a 1:2 **12mer-HQ4**$(Cu)_2$ complex that demonstrate the formation of an intramolecular tetracoordinated complex (Figure 2). The peptoid-to-metal ratio was verified further by electrospray mass spectrometry MS-ESI (Supporting Information Table S1) and no evidence for the formation of higher order complexes (e.g., 2:2 complexes) was detected. Upon addition of cobalt(II) acetate new absorption bands at $\lambda = 261$, 370 nm and $\lambda = 261$, 375 nm for **7mer-HQ2** and **12mer-HQ4**, respectively appeared (Supporting Information Figures S11 and S12). MS-ESI analysis of metal complexes demonstrated the mass of the intramolecular complex **7mer-HQ2**Co with a ratio of peptoid:metal 1:1 and the intramolecular complex **12mer-HQ4**$(Co)_2$ with a ratio of peptoid:metal 1:2 (Supporting Information Table S1). Using the ratios that were confirmed by the ESI-MS measurements, metal complexes were synthesized in a larger scale. Thus, the peptoid solutions were each treated with a metal salt and the solution was stirred for two hours, followed by the addition of a counter ion that resulted in precipitation of the metal complexes. The metallopeptoid complexes were washed with cold water and dried by lyophilization.

Near UV CD Spectra

Typical CD spectra of helical peptoids is characterized by double minima near 200 and 220 nm in organic solvents such as

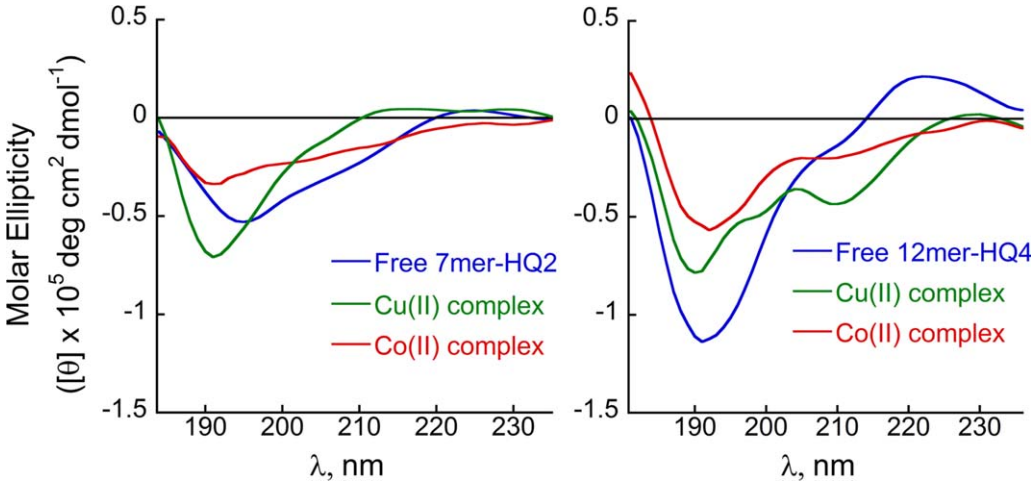

FIGURE 3 Near UV CD spectra of **7mer-HQ2** and **12mer-HQ4** and their metal complexes in 10 μ*M* concentration at 25 °C.

methanol and acetonitrile.[23,24] In water, these double minima were noted to absorb near 197 and 212 nm.[40] Helical secondary structure of peptoids is forced due to local steric and stereoelectronic interactions and mostly resembles that of the polyproline-type I helix, with a pitch of three residues per turn.[22] Peptoids **7mer-HQ2** and **12mer-HQ4** were designed to be non-helical and thus, we expected that the peptoids will not exhibit double minima in solution. Indeed, our CD measurements support this assumption; metal free peptoid **7mer-HQ2** exhibits one minimum around 195 nm in low intensity, demonstrating that the peptoid is unstructured in solution. After addition of Cu^{2+}, a small increase in the CD magnitude and a small UV shift of the signal were recorded. After addition of Co^{2+} a small decrease in the CD magnitude and a small UV shift of the signal were reordered as well. For both metal complexes there are no substantial changes in the secondary structure compared with the peptoid **7mer-HQ2** (Figure 4). Metal free peptoid **12mer-HQ4** exhibit one minimum around 191 nm and after the addition of Co^{2+} the CD magnitude decreases. Surprisingly, after the addition of Cu^{+2} acetate both a decrease in the CD magnitude around 191 nm and an increase near 210 nm were recorded, revealing a double minima, which may indicate an increase in conformational order of the peptoid (Figure 4). The differences between the spectra of Co^{2+} and Cu^{2+} complexes may exist due to different geometries that have an impact on the overall three dimensional structure of the peptoids. The difference in the CD spectra of **7mer-HQ2**(Cu) and **12mer-HQ4**$(Cu)_2$ might results from the number of binding sites in the two peptoids and consequently the number of Cu^{2+} ions in the peptoid-metal complex. Peptoid **7mer-HQ2** has one Cu^{2+} ion while **12mer-HQ4** has two Cu^{2+} ion bound in intramolecular manner; therefore it is anticipated that the stabilization of a folded structure will be stronger in the longer peptoid.

Far UV CD Spectra and Exciton Couplet CD (ECCD)

As mentioned above, the CD measurements suggest that peptoid oligomers **7mer-HQ2** and **12mer-HQ4** are not helical in solution. Therefore, any changes in the CD spectra between 240-280 nm, the area corresponding to the absorbance of the metal complexes, will imply that chiral induction to the metal center in metallopeptoids is attributed to the chirality of the oligomers and not to their helicity. Metal free peptoids **7mer-HQ2** and **12mer-HQ4** exhibit one positive band around 249 nm in low intensity. According to our UV measurements, this absorbance corresponds to the HQ ligand. This ligand is achiral and therefore the appearance of its absorbance band in the CD spectra means that there is chiral induction from the chiral peptoid to HQ. Metal binding to **7mer-HQ2** and **12mer-HQ4** produced new peaks between 240 and 280 nm, which reflects the transmission of the stereogenic character of the peptoid chiral groups to the metal centers. These changes imply that indeed the chiral induction to the metal centers in metallopeptoids is attributed to the chirality of the oligomers and not to their helicity.

7mer-HQ2 Cu and **12mer-HQ4**$(Cu)_2$ metal complexes exhibit exciton couplets with a maximum signal at 270 nm and minimum at 257 nm crossing $\varepsilon = o$ near 262 nm with roughly twice as high CD intensity for the latest due to the existence of twice as many HQ groups in **12mer-HQ4** as in **7mer-HQ2**. The metal complexes **7mer-HQ2**Co and **12mer-HQ4**$(Co)_2$

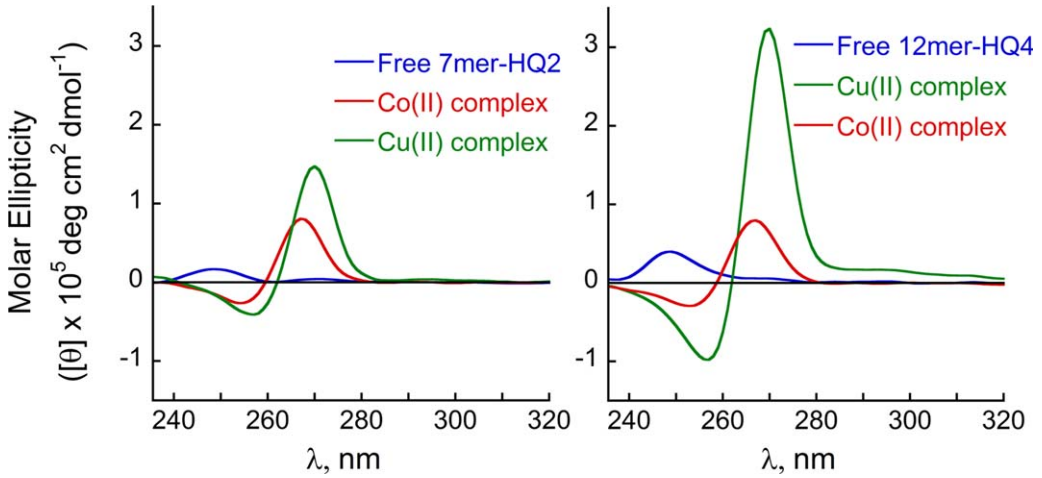

FIGURE 4 Far UV CD spectra of **7mer-HQ2** and **12mer-HQ4** and their metal complexes in 10 μ*M* concentration at 25 °C.

exhibit an exciton couplet with a maximum signal at 267 nm and a minimum at 253 nm crossing $\varepsilon = 0$ near 260 nm and with CD magnitude similar in both cases. We note that the CD magnitude of the cobalt complexes is much lower than the corresponding copper complexes. A possible reason for the similarity in the CD magnitude between **7mer-HQ2**Co and **12mer-HQ4**$(Co)_2$, despite the fact that the intensity of **12mer-HQ4**$(Co)_2$ should be double the intensity of **7mer-HQ2**Co might be due to lower solubility of **12mer-HQ4**$(Co)_2$ complex in water compare to **7mer-HQ2**Co. Results of the same experiment in MeOH/H_2O 4:1 solutions support this assumption, revealing that the intensity of the CD signal at 267 nm is as twice as high in magnitude than the corresponding CD intensity of **7mer-HQ2**Co complex in the same solution mixture (Supporting Information Figures S13 and S14). As for the differences in ECCD between the two metal ions, we can clearly see higher intensity of Cu^{2+} complexes compare to Co^{2+} complexes of both peptoids with a slight shift to UV region for the later (Figure 3). It was previously demonstrated both by calculation analysis and empirical experiments that the intensity and the wavelength of exciton couplets depend on the dihedral angle between the two chromophores.[46] As the angle between the chromophores increases, the CD magnitude decreases and slightly shifts toward the UV region.[46] Herein we propose that dihedral angles between the chromophores in our metallopeptoids are directly related to the coordination geometrical angles in the metal centers because the two chromophores in the metallopeptoids are the HQ ligands that are connected through metal-coordination bonds rather than via covalent bonds. Therefore, based on the observed exciton couplets, we can

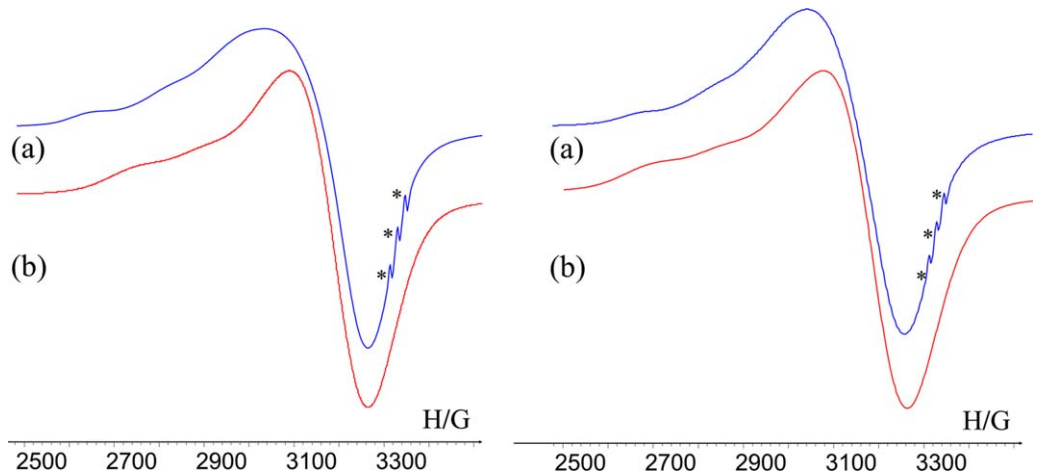

FIGURE 5 Room temperature X-band EPR spectra in solid state (a) and the corresponding simulated spectra (b) of (left) **7mer-HQ**Cu and (right) **12mer-HQ4**$(Cu)_2$. Reference-TEMPO (marked by *), $g = 2.0058$.

suggest that there is a difference in the coordination geometries between Cu^{2+} and Co^{2+} peptoid complexes and this hypothesis is currently under investigation in our lab by both empirical and computational methods.

EPR Studies

Peptoid-Cu(II) complexes were characterized by EPR. The X-band EPR spectra of solid, powdered samples of **7mer-HQ2**Cu and **12mer-HQ4**$(Cu)_2$ were measured at room temperature (Figure 5). EPR signals clearly indicated the presence of a Cu^{2+} and the Hamiltonian parameters obtained from the spectra of **7mer-HQ2**Cu and **12mer-HQ4**$(Cu)_2$ were $g\| = 2.235$ and 2.250, $g\perp = 2.080$ and 2.086, and $A\| = 157$ G and 150 G, respectively (Supporting Information Table S2). The two peptoids are expected to form tetragonal complexes when bound to Cu^{2+}; hydroxyquinoline usually adopts trans-planar configuration when Cu(hydroxyquinolate)$_2$ is formed.[54,55] However, in the intramolecular Cu^{2+} complexes, the peptoid scaffold may prohibit a square planar geometry because of the steric interactions with the peptoid backbone.[10] It was previously suggested that the empirical quotient $(g\|)/(A\|)$ $cm^{-1} \times 10^4$ is a good parameter for determining the coordination geometry of Cu^{2+} complexes; it ranges between 105 and 135 for square-planar structures and indicate tetrahedral distortion when higher than 135.[56] Thus, the calculated value of the quotient $(g\|)/(A\|)$ $cm^{-1} \times 10^4$ of the complex $(\mathbf{HQ})_2$Cu, which is known to adopt a square planar geometry is 134,[57] while the calculated values of the quotient $(g\|)/(A\|)$ $cm^{-1} \times 10^4$ from our EPR measurements are 137 and 143 for **7mer-HQ2**Cu and **12mer-HQ4**$(Cu)_2$, respectively (Supporting Information Table S2). These results support our assumption that the peptoid backbone affects the coordination geometry and suggest that the coordination geometry of both these complexes exhibit tetrahedral distortion from the expected square planar.

CONCLUSIONS

This work describes the design, synthesis and characterization of chiral water-soluble peptoid oligomers bearing HQ ligands and their corresponding metallopeptoids. We demonstrate the incorporation of a new monomer within the sequences, which provided both hydrophilicity and chirality to the peptoids. We described for the first time the formation of a dinuclear metallopeptoid from one peptoid oligomer by an intramolecular metal binding of two Cu^{2+} or Co^{2+} ions. We also demonstrated that chiral induction from peptoid oligomers to embedded metal centers occurs due to the peptoids chirality and not to the peptoids helicity. Though a variety of metallo-peptides are reported in the literature, we believe that the range of properties and applications, such as chemical and biological sensing, selective catalysis, drug design and more can be extended by the design of biomimetic metallopeptoids. The ease of peptoid synthesis and their versatile backbone as well as their stability and biocompatibility make them excellent candidates for exploring their interactions with metal ions toward various biomimetic applications. Further efforts that are currently undergoing in our laboratory target selective metal binding of two (or more) different metal ions in distinct binding sites along the peptoid backbone, as well as the induction of helicity solely by metal complexation.

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REFERENCES

1. Cheng, R. P.; Gellman, S.; DeGrado, W. F. Chem Rev 2001, 101, 3219–3232.
2. Seebach, D.; Gardiner, J. Acc Chem Res 2008, 41, 1366–1375.
3. Johnson, L. M.; Gellman, S. H. Methods in Enzymology; Elsevier Inc., 2013; Chapter 19.
4. Sun, J.; Zuckermann, R. N. ACS Nano 2013, 7, 4715–4732.
5. Seo, J.; Lee, B. C.; Zuckermann, R. N. Comprehensive Biomaterials; Elsevier 2011, Vol. 2, pp. 53–76.
6. Foldamers; Hecht, S.; Huc, I., Eds. Wiley-VCH, 2007.
7. Maayan, G. Eur J Org Chem 2009, 5699–5710.
8. Metallofoldamers; Maayan, G.; Albrecht, M. Eds. John Wiley& Sons, Ltd 2013.
9. Lee, B. C.; Chu, T. K.; Dill, K. A.; Zuckermann, R. N. J Am Chem Soc 2008, 130, 8847–8855.
10. Maayan, G.; Ward, M. D.; Kirshenbaum, K. Chem Commun 2009, 56–58.
11. Zabrodski, T.; Baskin, M.; Prathap, J. K.; Maayan, G. Synlett 2014, 25, A–F.
12. Knight, A. S.; Zhou, E. Y.; Pelton, J. G.; Francis, M. B. J Am Chem Soc 2013, 135, 17488–17493.
13. Maulucci, N.; Izzo, I.; Bifulco, G.; Aliberti, A.; De Cola, C.; Comegna, D.; Gaeta, C.; Napolitano, A.; Pizza, C.; Tedesco, C.; Flot, D.; De Riccardis, F. Chem Commun 2008, 3927–3929.
14. De Cola, C.; Licen, S.; Comegna, D.; Cafaro, E.; Bifulco, G.; Izzo, I.; Tecilla, P.; De Riccardis, F. Org Biomol Chem 2009, 7, 2851.
15. Della Sala, G.; Nardone, B.; De Riccardis, F.; Izzo, I. Org Biomol Chem 2013, 11, 726–731.
16. Izzo, I.; Ianniello, G.; De Cola, C.; Nardone, B.; Erra, L.; Vaughan, G.; Tedesco, C.; De Riccardis, F. Org Lett 2013, 15, 598–601.
17. De Cola, C.; Fiorillo, G.; Meli, A.; Aime, S.; Gianolio, E.; Izzo, I.; De Riccardis, F. Org Biomol Chem 2014, 12, 424.
18. Tedesco, C.; Erra, L.; Izzo, I.; De Riccardis, F. CrystEngComm 2014, 16, 3667–3687.
19. Maayan, G.; Ward, M. D.; Kirshenbaum, K. Proc Natl Acad Sci USA 2009, 106, 13679–13684.

20. Schettini, R.; Nardone, B.; De Riccardis, F.; Della Sala, G.; Izzo, I. Eur J Org Chem, 2014, 7793–7797.
21. Wu, C. W.; Kirshenbaum, K.; Sanborn, T. J.; Patch, J. A.; Huang, K.; Dill, K. A.; Zuckermann, R. N.; Barron, A. E. J Am Chem Soc 2003, 125, 13525–13530.
22. Armand, P.; Kirshenbaum, K.; Falicov, A.; Dunbrack, R. L. Jr.; Dill, K. A.; Zuckermann, R. N.; Cohen, F. E. Folding Des 1997, 2, 369–375.
23. Kirshenbaum, K.; Barron, A. E.; Goldsmith, R. A.; Armand, P.; Bradley, E. K.; Truong, K. T. V.; Dill, K. A.; Cohen, F. E.; Zuckermann, R. N. Proc Natl Acad Sci USA 1998, 95, 4303–4308.
24. Armand, P.; Kirshenbaum, K.; Goldsmith, R.A.; Farr-Jones, S.; Barron, A.E.; Truong, K.T.V.; Dill, K.A.; Mierke, D.F.; Cohen, F.E.; Zuckermann, R.N.; Bradley, E.K. Proc Natl Acad Sci USA 1998, 14, 4309–4314.
25. Wu, C. W.; Sanborn, T. J.; Zuckermann, R. N.; Barron, A. E. J Am Chem Soc 2001, 123, 2958–2963.
26. Shin, S. B. Y.; Yoo, B.; Todaro, L.; Kirshenbaum, K. J Am Chem Soc 2007, 129, 3218.
27. Wu, C. W.; Sanborn, T. J.; Huang, K.; Zuckermann, R. N.; Barron, A. E. J Am Chem Soc 2001, 123, 6778.
28. Gorske, B. C.; Bastian, B. L.; Geske, G. D.; Blackwell, H. E. J Am Chem Soc 2007, 129, 8928.
29. Shah, N. H.; Butterfoss, G. L.; Nguyen, K.; Yoo, B.; Bonneau, R.; Rabenstein, D. L.; Kirshenbaum, K. J Am Chem Soc 2008, 130, 16622.
30. Stringer, R.; Crapster, J. A.; Guzei, I. A.; Blackwell, E. J. Org Chem 2010, 75, 6068.
31. Paul, B.; Butterfoss, G. L.; Boswell, M. G.; Huang, M. L.; Bonneau, R.; Wolf, C.; Kirshenbaum, K. Org Lett 2012, 14, 926.
32. Paul, B.; Butterfoss, G. L.; Boswell, M. G.; Renfrew, P. D.; Yeung, F. G.; Shah, N. H.; Wolf, C.; Bonneau, R.; Kirshenbaum, K. J Am Chem Soc 2011, 133, 10910.
33. Roy, O.; Caumes, C.; Esvan, Y.; Didierjean, C.; Faure, S.; Taillefumier, C. Org Lett 2013, 15, 2246.
34. Zuckermann, R. N.; Kerr, J. M.; Kent, S. B.H.; Moos, W.H. J Am Chem Soc 1992, 114, 10646–10647.
35. Robinson, B. D.; Buffleben, G. M.; Langham, M. E.; Zuckermann, R. N. Biopolymers (Peptide Science) 2011, 96, 669–678.
36. Maayan, G.; Liu, L. Biopolymers (Peptide Science) 2011, 96, 679–687.
37. Lelais, G.; Seebach, D; Jaun, B.; Mathad, R. I.; Flogel, O.; Rossi, F.; Campo, M.; Wortmann, A. Helv Chim Acta 2006, 89, 361–403.
38. Miller, J. P.; Melicher, M. S.; Schepartz, A. J Am Chem Soc 2014, 136, 14726–14729.
39. Barron, A. E.; Zuckermann, R. N. Curr Opin Chem Biol 1999, 3, 681.
40. Shin, S. B. Y.; Kirshenbaum, K. Org Lett 2007, 9, 5003–5006.
41. Sanborn, T. J.; Wu, C. W.; Zuckermann, R. N.; Barron, A. E. Biopolymers 2002, 63, 12–20.
42. Seo, J.; Barron, A. E.; Zuckermann, R. N. Org Lett 2010, 12, 492–495.
43. Gidron, O.; Ebert, M. O.; Trapp, N.; Diederich, F. Angew Chem Int Ed 2014, 53, 13614–13618.
44. Petrovic, A. G.; Vantomme, G.; Negrón-Abril, Y. L.; Lubian, E.; Saielli, G.; Menegazzo, I.; Cordero, R.; Proni, G.; Nakanishi, K.; Carofiglio, T.; Berova, N. Chirality 2011, 23, 808–819.
45. Pintre, I. C.; Pierrefixe, S.; Hamilton, A.; Valderrey, V.; Bo, C.; Ballester, P. Inorg Chem 2012, 51, 4620–4635.
46. Berova, N.; Di Bari, L.; Pescitelli, G. Chem Soc Rev 2007, 36, 914–931.
47. Berova, N.; Pescitelli, G.; Petrovica, A. G.; Proni, G. Chem Commun 2009, 5958–5980.
48. Holmes, A. E.; Simpson, S. A.; Canary, J. W. Monatshefte Chem 2005, 136, 461–475.
49. Zahn, S.; Canary, J. W. J Am Chem Soc 2002, 124, 9204–9211.
50. Zhang, J.; Holmes, A. E.; Sharma, A.; Brooks, N. R.; Rarig, R. S.; Zubieta, J.; Canary, J. W. Chirality 2003, 15, 180–189.
51. Canary, J. W.; Zahn, S. Trend Biotechnol 2001, 19, 251–255.
52. Pescitelli, G.; Di Bari, L.; Berova, N. Chem Soc Rev 2014, 43, 5211–5233.
53. Maayan, G.; Yoo, B.; Kirshenbaum, K. Tetrahedron Lett 2008, 49, 335–338.
54. Palenik, G. J. Acta Cryst 1964, 17, 687.
55. Hoy, R. C.; Morriss, R. H. Acta Cryst 1967, 22, 476.
56. Sakaguchi, U.; Addison, A. W. J Chem Soc Dalton Trans 1979, 600–608.
57. Gersmann, H. R.; Swalen, J. D. J Chem Phys 1962, 36, 3221–3233.