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PAPER

C-Branched chiral (racemic) macrocyclic amino acids: structure of their Ni(II), Zn(II) and Cu(II) complexes†

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A new procedure for the synthesis of macrocyclic embedded bis-α-amino acids and their use as cation-ligands is described. These compounds are able to form stable Cu(II), Zn(II) and Ni(II) complexes as long as they have a flexible tether between the two nitrogen atoms. For a given macrocycle, the X-ray diffraction studies revealed diastereomerically pure complexes having different geometries depending on the metal ion.

Introduction

Polyazamacrocycles and macrocycles containing mixed donor atoms (*i.e.* N, O) **1** are well known for their ability to bind metal ions.[1,2] To broaden their chelating abilities and thence the scope of their applications, these structures frequently incorporate functionalized pendant arms linked to the nitrogen atoms (Fig. 1), generally carboxylic acids or their derivatives[3] (**2**–**4**), amines,[4] and more rarely phosphonic[5] and sulfonyl groups.[6] These structural modifications modulate the selectivity of a given chelating cavity from first-row transition divalent metal ions to the lanthanides.[7] The versatility of these structures as metal binding agents has been exploited in different fields ranging from antitumor agents,[8] biomedical applications (among others, contrast agents and shift reagents in magnetic resonance imaging (MRI) based techniques)[9] to luminescent sensors in optical methods.[7h–l,10]

By contrast, the analogous C-branched polyazamacrocyclic cavities have been hardly studied. The few structures reported are generally azacyclophanes such as **5**–**7**,[11] analogous to conformationally constrained α-amino acids and of great interest as synthetic receptors to probe the binding mode of bioactive molecules (Fig. 2).[12] However, the use of these chiral cavities to complex metal ions has not been reported.

The search for new small molecule chelating agents is an interesting area of research, as they constitute one of the future promising strategies for treating diseases associated with localized metal accumulation.[13] Metals such as iron, copper, and zinc play complicated roles in human health and disease. While all three metals are essential nutrients utilized as various protein cofactors, their misappropriation within cells and tissues can lead to significant damage that has been linked to Parkinson's, Alzheimer's, and other neurodegenerative diseases.[13,14]

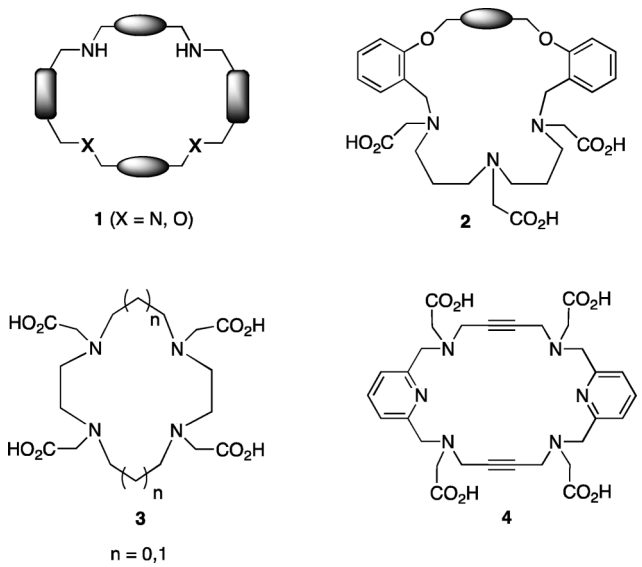

Fig. 1

Our ongoing work devoted to preparing different macrocyclic structures having specific properties[15] by peripheral functionalization[16] of preformed macrocyclic di- and polyimines, led us to devise the synthesis of a series of novel chiral macrocycles **8** (Fig. 2) which are constrained bis-α-aminoacids[17] having the structural features to bind metal ions (that is, a framework with mixed N,O donor atoms) and C-linked carboxylate groups as branched arms.[18] In this work we also study their ability to form

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C-NMR spectra of new compounds **11**–**16**. Crystallographic Information Files (CIF) for compounds **8a-Ni(II)**, **8a-Zn(II)**, and **8a-Cu(II)**. CCDC reference numbers 819737–819739. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/c1dt10539f

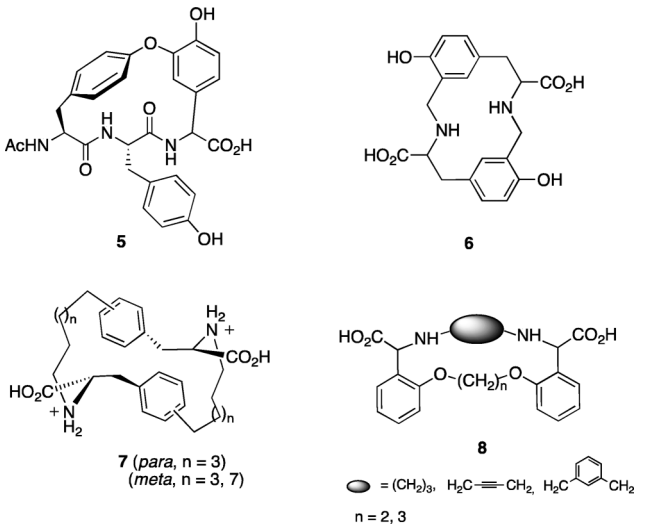


Fig. 2

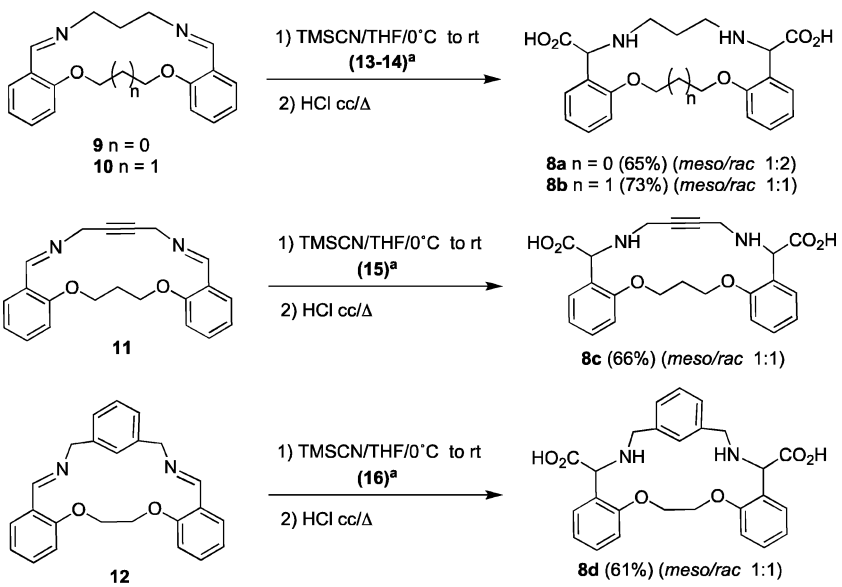
complexes with Ni(II), Zn(II) and Cu(II), and discuss their X-ray structures.

Results and discussion

The synthesis of the bis-α-aminoacids **8** was carried out starting from the corresponding macrocyclic diimines **9–12** as shown in Scheme 1. Thus, diimines **9–12** were transformed into the corresponding bis-aminonitriles **13–16** by a double Strecker reaction,[19] at room temperature using trimethylsilyl cyanide (TMSCN) as the cyanide source. Compounds **13–16** were obtained in quantitative yields directly from the reaction crude, and as diastereomeric mixtures. In all cases their IR spectra showed weak CN stretching bands in the range 2227–2230 cm^{-1}, characteristic of α-aminonitriles.[20] Compounds **13–16** are slightly unstable and were used in the next step without further purification (see experimental section for details).[21] The assignment of the stereochemistry of the *meso* and racemic isomers in each case, was carried out by the study of the CH signals in the ^{1}H-NMR spectra in the presence of Eu(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] Eu(hfc)$_3$. After the addition of this chiral shift reagent, the splitting of the CH singlets at 4.84, 4.83, 5.20 and 4.91 ppm (compounds **13–16**, respectively) was clearly observed, in concordance with the expected behavior for *RR*/*SS* (racemic) isomers. However, in all cases, the CH signals at 5.02, 5.01, 5.33 and 4.98 ppm (compounds **13–16**, respectively), remained unaltered as expected for the *RS*/*SR* (*meso*) form. The addition of the lanthanide hardly affects the rest of the signals in the NMR spectra, which points to the coordination of the Eu(III) with the carboxylate groups outside the macrocycle.[7b]

Bis-aminonitriles **13–16** were hydrolyzed by refluxing in HCl to the corresponding bis-α-aminoacids **8a–d** which were obtained as diastereomeric mixtures of hydrochlorides, with yields ranging from 61–73% (Scheme 1). The stereochemistry of the *meso*/racemic isomers of compounds **8a–d** was again established by means of ^{1}H-NMR experiments in the presence of Eu(hfc)$_3$. In all cases, the *meso*/racemic isomeric ratios were identical to those of the previous aminonitriles, indicating that there was no epimerization of the stereogenic centers during the acid treatment. As an example, Fig. 3 shows the Eu(hfc)$_3$ ^{1}H-NMR experiment with bis-α-aminoacid **8a**. The addition of the chiral shift reagent provoked the shielding of both CH signals but only the splitting of the more deshielded CH singlet (racemic isomer).

The ability of the macrocyclic bis-α-aminoacids **8a–d** to form complexes with divalent metal cations was next addressed. The complexes were formed by treating solutions of equimolar amounts of the corresponding bis-aminoacid with Ni(II), Zn(II) and Cu(II) salts, at pH 8 at room temperature. Bis-α-aminoacids **8a** and **8b** having flexible tethers between the amino groups, were able to form stable complexes with all the divalent metals



[a] *bis*-aminonitriles **13-16**, obtained in quantitative yields, were used in step 2) without further purification

Scheme 1

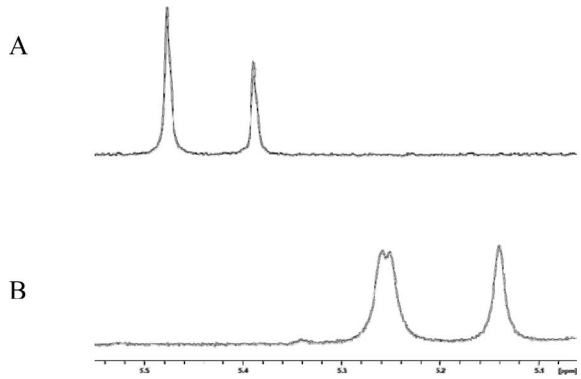


Fig. 3 (A) ^{1}H-NMR (D_2O, 295 K) spectrum (CH signals) of **8a**. (B) ^{1}H-NMR (D_2O, 295 K) spectrum (CH signals) of **8a** after the addition of $Eu(hfc)_3$.

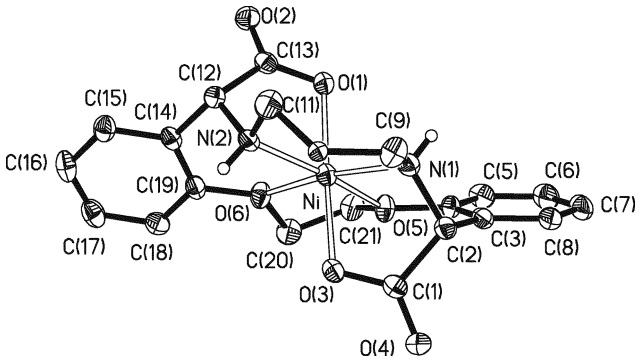


Fig. 5 Molecular diagram of complex **8a-Ni(II)**. Selected bond lengths (Å) and angles (deg): Ni–O(1) = 2.0311(17), Ni–O(3) = 2.0376(17), Ni–O(5) = 2.1339(18), Ni–O(6) = 2.1356(18), Ni–N(1) = 2.036(2), Ni–N(2) = 2.022(2); O(1)–Ni–O(3) = 177.19(7), N(1)–Ni–O(6) = 167.52(8), N(2)–Ni–O(5) = 165.36(8). Ellipsoids 50% probability level.

tested, whereas bis-α-aminoacids **8c** and **8d** bearing rigid tethers, failed. The characterization of the metal complexes was made by ESI-MS spectra (positive mode) which showed in all cases the corresponding $[M+Na]^+$ and $[M+H]^+$ peaks with the expected isotopic distribution (see for example Fig. 4).

Further information about the structure of the metal complexes formed was gained by X-ray diffraction analysis. Suitable crystals were obtained by slow crystallization at room temperature from solutions of complexes **8a-Ni(II)** ($MeOH/CH_3CN/H_2O$), **8a-Zn(II)** ($MeOH/H_2O$) and **8a-Cu(II)** ($MeOH/H_2O$). In each case only crystals of a pure diastereomeric complex were obtained and the analysis of their structures revealed different coordination modes, depending on the nature of the metal. Thus, for **8a-Ni(II)** the crystals correspond to the racemic complex and the metal complex is a distorted octahedron involving the nitrogen atoms of the macrocyclic ring, the oxygen atoms of the carboxylates and the oxygen atoms of the ether groups (Fig. 5). Bond distances fall in the range 2.02–2.13 Å, typical for Ni(II) in an octahedral environment.

An extended view of the structure of **8a-Ni(II)** (Fig. 6) shows that the molecules of this complex are associated by means of intermolecular hydrogen bonds between the hydrogen atoms of the NH groups and the nickel-bonded oxygen atoms of the carboxylates (O(1) and O(3)) to generate infinite chains. Each of the non-bonded oxygen atoms of the carboxylates (O(2) and O(4)) are associated by means of hydrogen bonds to two crystallization water molecules.

In the case of **8a-Zn(II)** the crystals of the *meso*-complex reveal a distorted trigonal bipyramid geometry around the metal center, with N(1) and O(3) occupying the apical positions (N(1)–Zn–O(3) 171.96(15)), and N(2), O(1) and the water molecule (O(7)) in the equatorial plane (Fig. 7). In this case the ether oxygen atoms of the ligand do not coordinate to the metal and the zinc atom is placed outside the cavity formed by the macrocyclic ligand. There are intramolecular O···H bonds between both ether oxygen atoms (O(6) and O(5)) and the hydrogen atom of one of the NH groups (H(22)). An extended view of the structure (Fig. 8) indicates also intermolecular interactions between the other NH-hydrogen atom of the molecule (H(21)) and the oxygen atom O(1) of the neighboring molecule, and between an OH-hydrogen atom of the coordinated water molecule O(7) and the oxygen O(2) of the neighboring molecule to generate infinite chains.

The X-ray structure of **8a-Cu(II)** (Fig. 9) consists of two Cu(II) centres bridged by two oxygen atoms of the carboxylate groups. The dimer exhibits a (μ_2-oxo) Cu(1)O_2Cu(1A) ring with

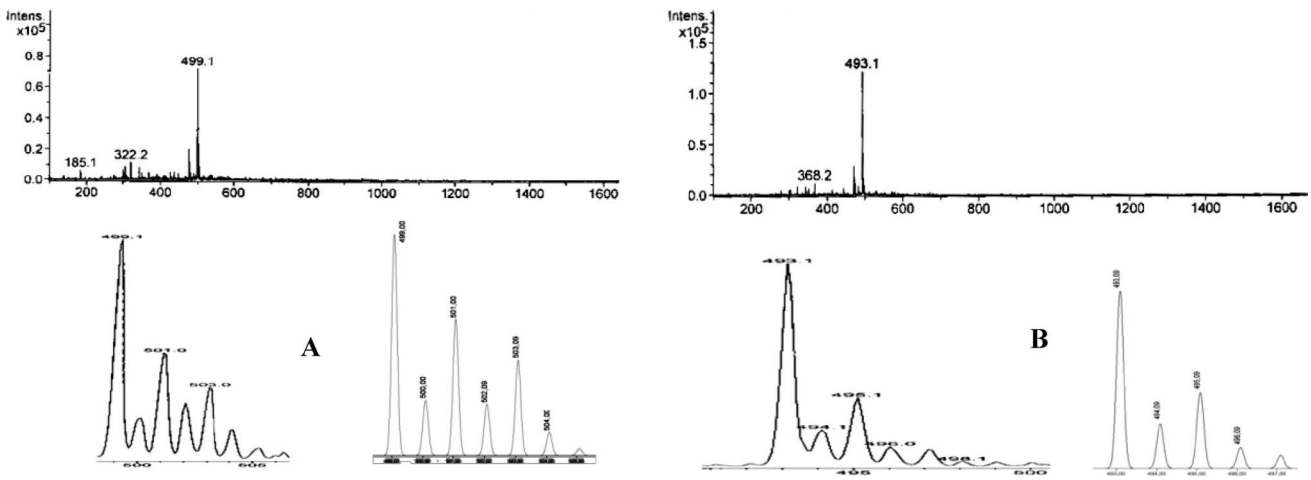


Fig. 4 (A) Experimental (left) and theoretical (right) isotopic distribution of $[M+Na]^+$ of **8b-Zn(II)** complex. (B) Experimental (left) and theoretical (right) isotopic distribution of $[M+Na]^+$ of **8b-Ni(II)** complex.

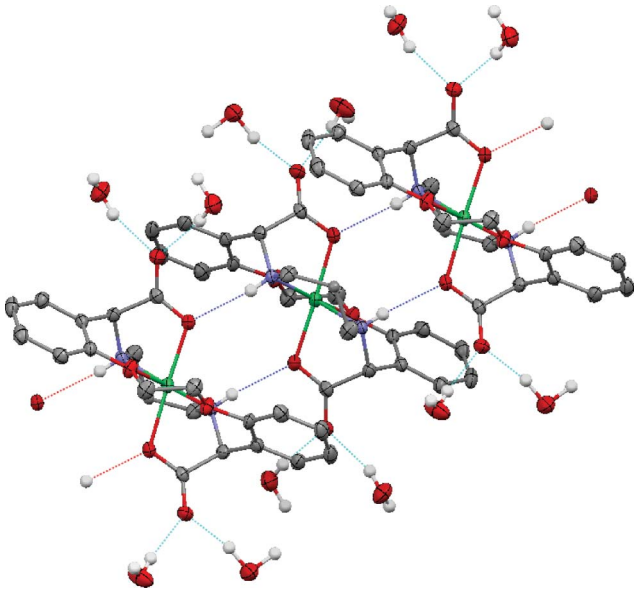


Fig. 6 Crystal packing of **8a-Ni(II)** showing the H bonding pattern (blue atoms, N; red, O; green, Ni). Hydrogen atoms not involved in hydrogen bonding as well as water crystallization molecules not involved in hydrogen bonding with the complex have been omitted for clarity.

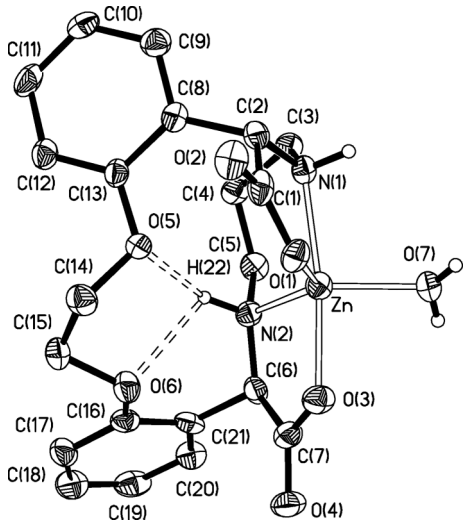


Fig. 7 Molecular diagram of complex **8a-Zn(II)**. Selected bond lengths (Å) and angles (deg): Zn–O(1) = 2.003(3), Zn–O(3) = 2.018(3), Zn–O(7) = 2.018(3), Zn–N(1) = 2.100(4), Zn–N(2) = 2.072(4); N(1)–Zn–O(3) = 171.96(15), O(1)–Zn–N(2) = 129.61(15), N(2)–Zn–O(7) = 116.00(16), O(1)–Zn–O(7) = 114.39(14), N(1)–Zn–O(1) = 80.41(15), N(1)–Zn–O(7) = 96.09(15), N(1)–Zn–N(2) = 95.00(15), O(3)–Zn–O(1) = 95.55(14), O(3)–Zn–O(7) = 91.91(15), O(3)–Zn–N(2) = 82.17(14) .Ellipsoids 50% probability level.

a Cu···Cu separation of 3.4959(18) Å and bridging angles of 81.4(2)° (O(3)–Cu–O(3A)) and 98.6(2)° (Cu(1)–O(3)–Cu(1A)). The geometry around each copper center can be described as a distorted octahedron. The equatorial positions are occupied by the nitrogen atoms N(1) and N(2) (Cu(1)–N(1) 1.998(6), Cu(1)–N(2) 1.974(6) Å) and by the carboxylate oxygen atoms O(3) and O(4) (Cu(1)–O(3) 1.947(5), Cu(1)–O(4) 1.919(6) Å). The axial positions are occupied by the ether atom O(1) and a bridging carboxylate oxygen of the neighbouring ligand bonded to Cu(1A) (Cu(1)–

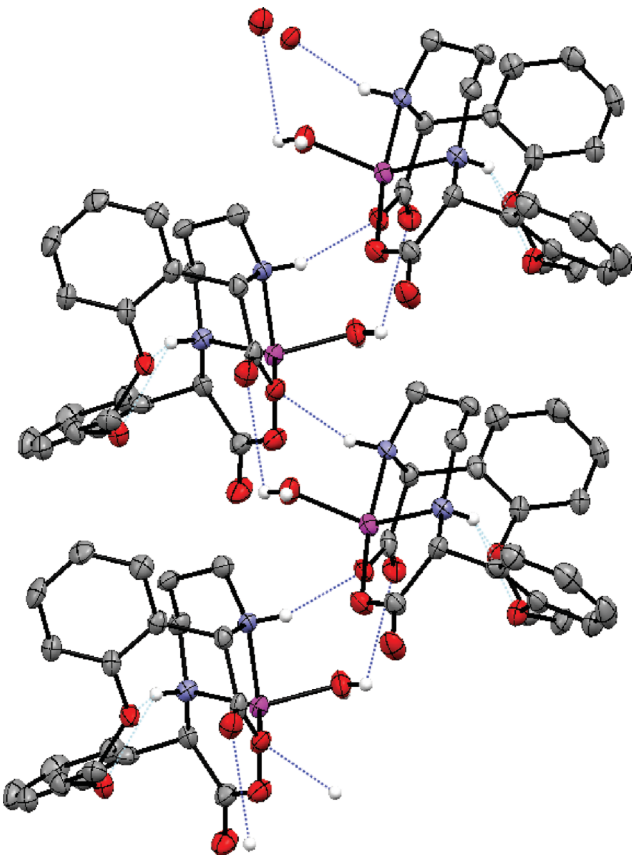


Fig. 8 Crystal packing of **8a-Zn(II)** showing the H bonding pattern (blue atoms, N; red, O; purple, Zn). Hydrogen atoms not involved in hydrogen bonding as well as solvent crystallization molecules have been omitted for clarity.

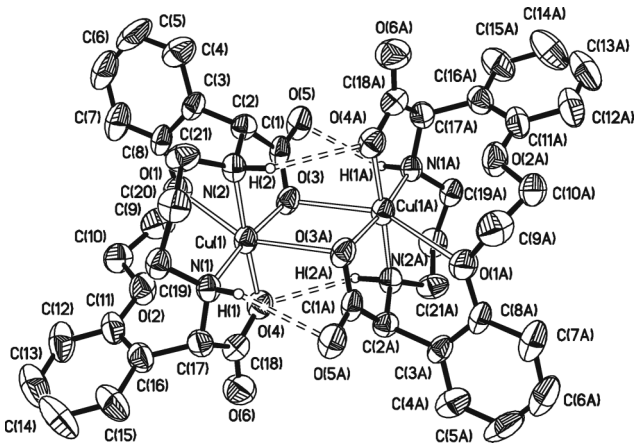


Fig. 9 Molecular diagram of complex **8a-Cu(II)**. Selected bond lengths (Å) and angles (deg): Cu(1)–O(3) = 1.947(5), Cu(1)–O(4) = 1.919(6), Cu(1)–N(1) = 1.998(6), Cu(1)–N(2) = 1.974(6), Cu(1)–O(3A) = 2.627(5), Cu(1)–O(1) = 2.744(7), Cu(1)···Cu(1A) = 3.4959(18); O(3)–Cu(1)–N(1) = 172.3(2), O(4)–Cu(1)–N(2) = 176.6(2), O(4)–Cu(1)–N(1) = 85.1(2), N(1)–Cu(1)–N(2) = 98.1(2), O(1)–Cu(1)–O(3A) = 153.3(2). Ellipsoids 50% probability level.

O(1) = 2.744(7), Cu(1)–O(3A) = 2.627(5) Å). The neighbouring ligands are connected by means of hydrogen bonding between the hydrogen atom of N(1) and the non-coordinating carboxylate

oxygen atom O(5) and between the hydrogen atom of N(2) and the carboxylate oxygen atom O(4). An extended view of the structure (Fig. 10) also indicates intermolecular interactions between the hydrogen atom of N(1) and the non-coordinating carboxylate oxygen atom O(5) of the neighbouring dimer, generating infinite chains.[22]

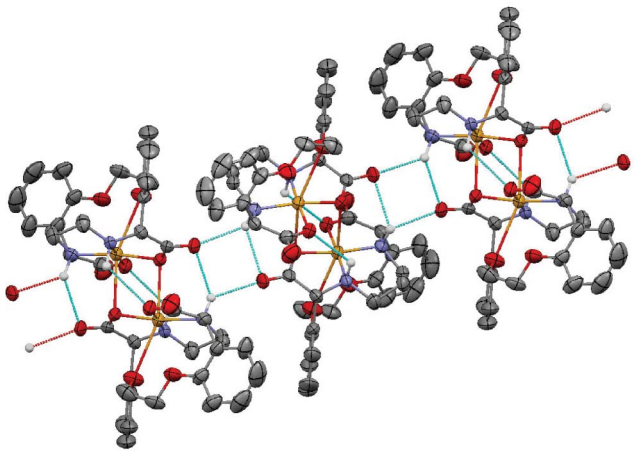


Fig. 10 Crystal packing of **8a-Cu(II)** showing the H bonding pattern (blue atoms, N; red, O; orange, Cu). Hydrogen atoms not involved in hydrogen bonding as well as solvent crystallization molecules have been omitted for clarity.

The structures of the metal complexes **8a-Ni(II)**, **8a-Zn(II)** and **8a-Cu(II)** are a good example of how a chiral macrocycle can modulate its binding properties depending not just on the size of the cavity, or the number and type of the donor atoms, but also on the geometry imposed by their stereogenic centers. Thus, in the octahedral racemic-**8a-Ni(II)** all N,O donor atoms are involved in a hexacoordinate complex, placing the metal inside the cavity. By contrast, the *meso*-complexes **8a-Zn(II)** and **8a-Cu(II)**, having the same cavity size and donor atoms, show arrangements that place the metal outside the macrocycle. Examples of both, coordination and non-coordination of the ether oxygen atoms with the metal, have been reported for Ni(II) complexes derived from *N*-branched (*N*-CH_2CH_2OH and *N*-CH_2CONH_2) macrocycles[23] having size cavities and N,O mixed donor atoms as in **8a**.[24] The formation of different diastereomeric complexes depending on the metal ion could constitute an *a la carte* method for the separation of the isomeric cavities **8**. To test this point, crystals of the **8a-Cu(II)** complex were treated with KOH (20% w/w in water) and after acidulation and filtration of the salts formed, pure macrocycle *meso*-**8a** could be obtained (the ^{1}H-NMR spectrum showed the characteristic singlet at 5.42 ppm for this isomer).

Conclusions

An efficient approach for the synthesis of C-branched macrocycles with (N,O) mixed donor atoms is described. Starting from macrocyclic diimines and by means of a Strecker reaction and subsequent hydrolysis, macrocyclic bis-α-aminoacids **8** were prepared in good yields. These new compounds are small chiral (racemic) molecules analogous to constrained α-aminoacids and have shown their ability to form complexes with Cu(II), Zn(II) and Ni(II). The structures of the metal complexes racemic-**8a-Ni(II)**, *meso*-**8a-Zn(II)** and *meso*-**8a-Cu(II)** are a good example of how a chiral macrocycle can modulate its metal binding properties depending not just on the size of the cavity, or the number and type of the donor atoms, but also on the geometry imposed by their stereogenic centers, leading to different diastereomerically pure complexes. As far as we are aware, these are the first metal complexes derived from C-branched polyazamacrocyclic cavities reported in the literature.

Experimental

General procedures

Diimines **9** and **10** were prepared following the previously reported procedures.[25] ^{1}H NMR and ^{13}C NMR spectra were recorded at 22 °C on Bruker Avance 300 (300.1 and 75.4 MHz) or Bruker 200-AC (200.1 and 50 MHz) spectrometers. Chemical shifts are given in ppm relative to $CDCl_3$ (^{1}H, 7.27 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm); D_2O (^{1}H, 4.60 ppm), and D_2O/Na_2CO_3 (^{13}C, 165.0 ppm). IR spectra were taken on a Bruker Tensor 27 (MIR 8000–400 cm^{-1}) spectrometer. Mass spectra were recorded on a QSTAR pulsar I, (hybrid analyzed QTOF, applied biosystems) (ESI), or a MAT 95 XP ThermoFinnigan (FAB) apparatus. $CH_2Cl_2$was distilled from calcium hydride and THF from sodium-benzophenone. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. All commercially available organic reagents were used without further purification.

Caution: HCN is produced by reaction of trimethylsilyl cyanide (TMSCN) with acid, water or protic solvents. All reactions using this reagent should be carried out using the adequate precautions in well ventilated hoods.

Diimine 11. Was obtained as yellow oil (1.05 g, 90%) by refluxing 1,3-bis(2-formylphenyl)-1,3-dioxapropane (1.0 g, 3.7 mmol)[25] and (0.3 g, 3.7 mmol) 1,4-diamine-2-butyne in 500 cm^3 MeOH for 24 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 2H, CH═N), 7.92 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 2H, ArH), 7.42–7.36 (m, 2H, ArH), 7.07–6.96 (m, 4H, ArH), 4.69 (s, 4H, CH_2–N), 4.24 (t, J = 5.9 Hz, 4H, CH_2O), 2.36 (q, J = 5.9 Hz, 2H, CH_2). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 158.2 (C═N), 158.0, 131.9, 127.5, 125.8, 121.7, 114.0 (ArC), 82.8 (C), 67.3 (CH_2O), 47.3 (CH_2N), 28.5 (CH_2). IR (Film) ν_{max} 3070, 2891, 2217, 1640, 1597, 1293, 1240, 1108, 1058, 754 cm^{-1}. ESI-MS: 333.1 $[M+H]^+$.

Diimine 12. Was obtained as pale yellow oil (1.27 g, 93%) by refluxing 1,2-bis(2′-formylphenyl)-1,3-dioxaethane (1.0 g, 3.56 mmol)[25] and α,α′-diamine-*m*-xylene (0.48 g, 3.56 mmol) in 500 cm^3 MeOH for 24 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 2H, CH═N), 7.84 (d, J = 7.6 Hz, 2H, ArH), 7.36–7.28 (m, 2H, ArH), 7.20 (m, 4H, ArH) 7.06–6.95 (m, 4H, ArH), 4.67 (s, 4H, CH_2O), 4.34 (s, 4H, CH_2–N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8 (C═N), 157.5, 138.1, 131.6, 128.5, 128.1, 127.9, 127.6, 125.2, 121.1, 110.9 (ArC), 65.8 (CH_2O), 64.3 (CH_2N). IR (Film) ν_{max} 3018, 2935, 1634, 1598, 1485, 1450, 1290, 1242, 1111, 1062, 751 cm^{-1}.

General procedure for the synthesis of bis-aminonitriles 13–16

To a solution of the corresponding diimine in anhydrous THF, under an argon atmosphere and at 0 °C, TMSCN was added in a 1 : 3 molar ratio. The reaction mixture was stirred at 0 °C for

30 min, then at room temperature for 20 h, quenched at 0 °C with NH_4Cl (10 cm^3, sat. soln.) and extracted with CH_2Cl_2 (2 × 100 cm^3). The combined organic extracts were washed with water, brine and dried over $MgSO_4$. The solution was filtered and the solvent was removed under vacuum. Bis-aminonitriles **13–16** were obtained in nearly quantitative yields as unstable oils and were used in the following step without further purification.

Bis-aminonitrile 13. From 0.64 g (2.1 mmol) of diimine **9** and 0.8 cm^3 (6.3 mmol) TMSCN, bis-aminonitrile **13** was obtained in quantitative yield (0.75 g) as pale yellow oil and as a 1 : 2 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53–7.34 (m, 4H, ArH), 7.06–6.85 (m, 4H, ArH), 5.02 (s, 0.7H, CH, *meso*), 4.84 (s, 1.3H, CH, racemic), 4.44 (s, 4H, CH_2O), 3.01–2.90 (m, 2H, CH_2N), 2.76–2.65 (m, 2H, CH_2N), 1.89–1.79 (m, 2H, CH_2).^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 155.4, 130.7, 130.5, 129.5, 129.1, 122.9, 122.8, 121.9 (ArC), 118.6, 118.7 (CN), 111.1, 110.0 (ArC), 65.9, 65.5 (CH_2O), 51.9, 51.1 (CH_2N), 47.5, 46.1 (CH), 25.5, 25.0 (CH_2). IR (KBr) ν_{max} 3309, 3018, 2929, 2229 (w), 1597, 1494, 1453, 1249, 1113, 1060, 753 cm^{-1}.

Bis-aminonitrile 14. From 1.0 g (3.1 mmol) of diimine **10** and 1.25 cm^3 (9.3 mmol) TMSCN, bis-aminonitrile **14** was obtained in quantitative yield (1.16 g) as pale yellow oil and as a 1 : 1 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.26 (m, 4H, ArH), 7.06–6.86 (m, 4H, ArH), 5.01 (s, 1H, CH *meso*), 4.83 (s, 1H, CH racemic), 4.42–4.28 (m, 4H, CH_2O), 2.94–2.67 (m, 4H, CH_2N), 2.35–2.28 (m, 2H, CH_2), 1.76–1.65 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.3, 156.2, 130.7, 130.6, 129.4, 128.9, 124.8, 124.2, 121.7, 121.4, 121.1 (ArC), 119.1, 118.9 (CN), 114.5, 114.1 (ArC), 66.7, 65.9 (CH_2O), 51.2, 49.9 (CH), 46.2, 46.1 (CH_2N), 29.8, 29.6, 28.3 (CH_2). IR (KBr) ν_{max} 3310, 3018, 2930, 2230 (w), 1597, 1495, 1453, 1371, 1249, 1110, 1060, 938, 754 cm^{-1}.

Bis-aminonitrile 15. From 1.2 g (3.1 mmol) of diimine **11** and 1.25 cm^3 (9.3 mmol) TMSCN, bis-aminonitrile **15** was obtained in quantitative yield (1.19 g) as pale yellow oil and as a 1 : 1 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.46 (m, 1H, ArH), 7.40–7.33 (m, 3H, ArH), 7.08–6.95 (m, 4H, ArH), 5.33 (s, 1H, CH *meso*), 5.20 (s, 1H, CH racemic), 4.34–4.26 (m, 4H, CH_2O), 3.64 (s, 2H, CH_2–N), 3.59 (s, 2H, CH_2N), 2.43–2.31 (m, 2H, CH_2).^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 155.6, 130.8, 130.7, 130.5, 129.1, 128.8, 124.8, 123.6, 121.7, 121.6 (ArC), 118.6, 118.5 (CN), 113.1, 113.0 (ArC), 80.8, 80.7 (C), 65.1, 65.0 (CH_2O), 48.5, 47.9 (CH), 36.7, 36.6 (CH_2N), 29.1, 29.0 (CH_2). IR (KBr) ν_{max} 3329, 3017, 2931, 2226 (w), 1599, 1492, 1451, 1245, 1114, 1061, 751 cm^{-1}.

Bis-aminonitrile 16. From 0.8 g (2.5 mmol) of diimine **12** and 0.92 cm^3 (7.5 mmol) TMSCN, bis-aminonitrile **16** was obtained in quantitative yield (1.05 g) as pale yellow oil and as a 1 : 1 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.47 (m, 2H, ArH), 7.40–7.21 (m, 6H, ArH), 7.08–7.00 (m, 2H, ArH), 6.95–6.89 (m, 2H, ArH), 4.98 (s, 1H, CH *meso*), 4.91 (s, 1H, CH racemic), 4.43–4.35 (m, 4H, CH_2–O), 4.07–3.85 (m, 4H, CH_2–N). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 155.3, 138.3, 138.2, 130.4, 130.3, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 127.2, 123.2, 123.0, 121.4 (ArC), 118.9, 118.8 (CN), 67.8, 67.7 (CH_2O), 51.0, 51.8 (CH_2N), 47.8, 47.5 (CH). IR (KBr) ν_{max} 3315, 3020, 2936, 2229 (w), 2217, 1598, 1495, 1450, 1243, 1110, 1058, 751 cm^{-1}.

General procedure for the synthesis of bis-aminoacids 8a–d

Concentrated aqueous HCl (12 M) (15–20 cm^3) was added over the freshly prepared bis-aminonitrile. The mixture was heated at 50–60 °C for 2 h and then water (20 cm^3) was added and the resultant mixture was refluxed for 4 h. The solution was filtered and the solvent removed under reduced pressure. The solid obtained was washed with acetone and dried. Bis-aminoacids **8a–d** were obtained as hydrochlorides, and as a mixture of *meso*/racemic isomers.

Bis-α-aminoacid 8a. Following the general procedure, 635 mg (65% from imine **9**) bis-α-aminoacid **8a** was obtained as a pale pink solid and as a 1 : 2 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (200 MHz, D_2O) δ 7.57–7.50 (m, 2H, ArH), 7.38–7.33 (m, 2H, ArH), 7.23–7.08 (m, 4H, ArH), 5.48 (s, 1.3H, CH, racemic), 5.42 (s, 0.7H, CH, *meso*), 4.65–4.50 (m, 4H, CH_2O), 3.16–2.87 (m, 4H, CH_2N), 2.61–2.43 (m, 1H, CH_2), 2.20–1.98 (m, 1H, CH_2). ^{13}C NMR (75 MHz, D_2O/Na_2CO_3) δ 180.4, 180.3 (C═O), 161.4, 161.0, 135.9, 135.8, 135.4, 135.2, 128.0, 127.9, 126.4, 126.3, 117.1, 117,0 (ArC), 71.8, 71.4 (CH_2O), 66.2, 66.0 (CH), 50.0, 49.9 (CH_2N), 29.3, 29.2 (CH_2). IR (KBr) ν_{max} 3410, 3126, 2936, 1734, 1632, 1495, 1452, 1403, 1330, 1252, 1117, 766 cm^{-1}. ESI-MS: 401.3 $[M+H]^+$; HRMS (ESI): calc for $C_{21}H_{24}N_2O_6$: 400.1634; found 400.1631.

Bis-α-aminoacid 8b. Following the general procedure, 1.1 g (73% from imine **10**) bis-α-aminoacid **8b** was obtained as a pale pink solid and as a 1 : 1 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (200 MHz, D_2O) δ 7.52–7.05 (m, 8H, ArH), 5.32 (s, 1H, CH, racemic), 5.29 (s, 1H, CH, *meso*), 4.40–4.05 (m, 4H, CH_2O), 3.07–2.50 (m, 4H, CH_2N), 2.20–1.60 (m, 4H, CH_2). ^{13}C NMR (75 MHz, D_2O/Na_2CO_3) δ 179.4, 179.2 (C═O), 161.8, 161.5, 136.2, 136.0, 135.7, 135.3, 128.8, 127.8, 127.1, 126.4, 119.0, 118,3 (ArC), 72.2, 69.8 (CH_2O), 65.8, 65.6 (CH), 51.6, 48.9 (CH_2N), 33.8, 32.6, 29.3, 29.2 (CH_2). IR (KBr) ν_{max} 3265, 2883, 1753, 1635, 1598, 1560, 1485, 1240, 1110, 1031 cm^{-1}. ESI-MS: 415.2 $[M+H]^+$; HRMS (ESI): calc for $C_{22}H_{26}N_2O_6$: 414.1791; found 414.1784.

Bis-α-aminoacid 8c. Following the general procedure, 1.18 g (66% from imine **11**) bis-α-aminoacid **8c** was obtained as a pale pink solid and as a 1 : 1 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (300 MHz, D_2O) δ 7.39–6.88 (m, 8H, ArH), 5.37 (s, 1H, CH, racemic), 5.27 (s, 1H, CH, *meso*), 4.29–4.08 (m, 4H, CH_2O), 3.75 (s, 2H, CH_2N), 3.74 (s, 2H, CH_2N), 2.19–2.08 (m, 2H, CH_2). ^{13}C NMR (125 MHz, D_2O/Acetone d_6) δ 170.4, 170.2 (C═O), 157.1, 133.1, 132.9, 130.1, 129.4, 123.0, 122.9, 119.1, 114.8, 113,9 (ArC), 79.0, 78.8 (C), 67.5, 65.7 (CH_2O), 57.8, 57.3 (CH), 35.5, 35.4 (CH_2N), 29.4, 28.5 (CH_2). IR (KBr) ν_{max} 3387, 2944, 2803, 1746, 1652, 1598, 1559, 1494, 1248, 1100, 1049 cm^{-1}. ESI-MS: 425.1 $[M+H]^+$; HRMS (ESI): calc for $C_{23}H_{25}ClN_2O_6$:460.1401; found 460.1414.

Bis-α-aminoacid 8d. Following the general procedure, 700 mg (61% from imine **12**) bis-α-aminoacid **8d** was obtained as a pale yellow solid and as a 1 : 1 (*meso*/racemic) diastereomeric mixture. ^{1}H NMR (300 MHz, D_2O) δ 784 (s, 1H, ArH), 7.56–7.37 (m, 6H, ArH), 7.23–7.10 (m, 5H, ArH), 5.43 (s, 1H, CH, racemic), 5.31

(s, 1H, CH, *meso*), 4.44–4.14 (m, 8H, CH_2O + CH_2N). ^{13}C NMR (75 MHz, D_2O/Na_2CO_3) δ 179.5 (C═O), 159.5, 159.3, 139.0, 138.8, 133.3, 132.8, 132.7, 132.4, 132.1, 128.9, 128.3, 125.2, 124.8, 117.1, 116.0 (ArC), 71.2, 70.9 (CH_2O), 63.2, 63.1 (CH), 52.9, 52.7 (CH_2N). IR (KBr) ν_{max} 3392, 2929, 2813, 1743, 1652, 1558, 1494, 1251, 1112, 1049 cm^{-1}. ESI-MS: 463.1 $[M+H]^+$. HRMS (ESI): calc for $C_{26}H_{26}N_2O_6$ ($[M+H]^+$): 462.1791; found 462.1790.

General procedure for the synthesis of metal complexes

A solution of the corresponding bis-aminoacid hydrochloride **8a–d** in water was adjusted to pH 8.5 with 10% NaOH. Then, a solution of the corresponding metallic salt in 2–3 cm^3 of water was added, slowly, dropwise, maintaining the pH 8.5 by successive additions of 5% NaOH and 5% HCl. The molar ratio aminoacid/metal salt was 1 : 1. After the addition, the solution was adjusted to pH 7 and the mixture was kept in the refrigerator overnight. The solution was filtered (0.45 μm membrane) and the solvent was removed under vacuum, to yield the metal complexes, which were analyzed by ESI-MS or FABMS.

Cu(II)-8a. Following the general procedure, from bis-α-aminoacid 8a (0.41 mmol, 200 mg) and $CuCl_2{\cdot}2H_2O$ (0.41 mmol, 68 mg). The Cu(II) complex was obtained as a dark blue solid (145 mg, 75%). ESI-MS: 484.0 $[M+Na]^+$, 461.9 $[M+H].^+$ IR (KBr) ν_{max} 3405, 3215, 2951, 1617, 1601, 1492, 1384, 1245, 1110, 834 cm^{-1}. HRMS (ESI): calc for $C_{21}H_{22}N_2O_6Cu$: 461.0774; found 461.0785.

Cu(II)-8b. Following the general procedure, from bis-α-aminoacid **8b** (0.42 mmol, 200 mg) and $CuCl_2{\cdot}2H_2O$ (0.42 mmol, 70 mg). The Cu(II) complex was obtained as a dark blue solid (140 mg, 72%). ESI-MS: 498.0 $[M+Na]^+$, 476.0 $[M+H]^+$. IR (KBr) ν_{max} 3415, 3210, 2921, 1618, 1603, 1494, 1384, 1244, 1111, 833 cm^{-1}. HRMS (ESI): calc for $C_{22}H_{24}N_2O_6Cu$: 475.0930; found 475.0942.

Zn(II)-8a. Following the general procedure, from bis-α-aminoacid **8a** (0.41 mmol, 200 mg) and $Zn(NO_3)_2{\cdot}6H_2O$ (0.41 mmol, 120 mg). The Zn(II) complex was obtained as a pale yellow solid (123 mg, 65%). ^1H NMR (700 MHz, D_2O/MeOD) δ 7.59-7-38 (m, 4H, ArH), 7.30-7.07 (m, 4H, ArH), 4.70-4.44 (m, 4H, CH_2O), 3.24-3.03 (m, 2H, CH_2N), 3.02-2.90 (m, 2H, CH_2N), 2.73-2.64 (m, 2 H, CH_2). ^{13}C NMR (176 MHz, D_2O/MeOD) δ 181.3, 179.6 (C=O), 158.6, 156.3, 136.6, 133.4, 132.3, 131.2, 128.6, 125.5, 123.3, 122.7, 114.5, 114.0 (ArC), 70.0, 68.9 (CH_2O), 66.0, 63.5 (CH), 48.6, 45.8 (CH_2N), 28.2 (CH_2). FABMS: 482.5 $[M+H_2O+H]^+$. IR (KBr) ν_{max} 3446, 3133, 2935, 1643, 1609, 1495, 1384, 1248, 1118, 835 cm^{-1}. HRMS (ESI): calc for $C_{21}H_{22}N_2O_6Zn$: 462.0769; found 462.0761.

Zn(II)-8b. Following the general procedure, from bis-α-aminoacid **8b** (0.42 mmol, 200 mg) and $Zn(NO_3)_2{\cdot}6H_2O$ (0.42 mmol, 124 mg). The Zn(II) complex was obtained as a pale yellow solid (140 mg, 70%). ^1H NMR (700 MHz, D_2O/MeOD) δ 7.53-6.98 (m, 8H, ArH), 4.54-4.45 (m, 1H, CH_2O), 4.44-4.31 (m, 2H, CH_2O), 4.28-4.19 (m, 1H, CH_2O) 3.13-2.64 (m, 4H, CH_2N), 2.54-2.36 (m, 2H, CH_2), 2.14-2.02 (m, 2 H, CH_2). ^{13}C NMR (176 MHz, D_2O/MeOD) δ 179.7, 178.4 (C=O), 158.2, 155.3, 134.9, 131.8, 130.8, 129.7, 126.0, 122.9, 120.5, 119.1, 112.9, 111.6 (ArC), 74.1, 67.9 (CH_2O), 64.7, 61.6 (CH), 48.3, 44.8 (CH_2N), 28.8, 26.3 (CH_2). ESI-MS: 499.1 $[M+Na]^+$, 477.1 $[M+H]^+$. IR (KBr) ν_{max} 3441, 3140, 2925, 2853, 1632, 1601, 1493, 1384, 1250, 1111, 835, 760 cm^{-1}. HRMS (ESI): calc for $C_{22}H_{24}N_2O_6Zn$: 476.0926; found 476.0927.

Ni(II)-8a. Following the general procedure, from bis-α-aminoacid **8a** (0.41 mmol, 200 mg) and $Ni(NO_3)_2{\cdot}6H_2O$ (0.41 mmol, 118 mg). The Ni(II) complex was obtained as a green solid (120 mg, 63%). ESI-MS: 479.2 $[M+Na]^+$, 457.3 $[M+H]^+$. IR (KBr) ν_{max} 3390, 3175, 2935, 1631, 1602, 1494, 1384, 1249, 1111, 834, 757 cm^{-1}. HRMS (ESI): calc for $C_{21}H_{22}N_2O_6Ni$: 456.0831; found 456.0858.

Ni(II)-8b. Following the general procedure, from bis-α-aminoacid **8b** (0.42 mmol, 200 mg) and $Ni(NO_3)_2{\cdot}6H_2O$ (0.42 mmol, 121 mg). The Ni(II) complex was obtained as a green solid (115mg, 60%). ESI-MS: 493.1 $[M+Na]^+$, 471.1 $[M+H]^+$. IR (KBr) ν_{max} 3386, 3187, 1633, 1601, 1492, 1384, 1246, 1111, 1052, 834, 757 cm^{-1}. $C_{22}H_{24}N_2O_6Ni$: 470.0988; found 470.1013

X-Ray data collection and structure refinement of complexes 8a-Ni(II), 8a-Zn(II) and 8a-Cu(II)

Crystals suitable for the X-ray diffraction were obtained by crystallization in MeOH/CH_3CN/H_2O (**8a-Ni(II)**) and MeOH/H_2O (**8a-Zn(II)** and **8a-Cu(II)**). X-Ray data were collected on a Bruker Smart APEX CCD diffractometer equipped with a normal focus, 2.4 kW sealed tube source (Mo radiation, $\lambda = 0.71073$ Å) operating at 50 kV and 30 mA. Data were collected over the complete sphere by a combination of four sets. Each frame exposure time was 10 s (**8a-Ni(II)**, **8a-Cu(II)**) or 30 s (**8a-Zn(II)**) covering 0.3° in ω. Data were corrected for absorption by using a multiscan method applied with the SADABS program.[26] The structures were solved by the Patterson method. Refinement, by full-matrix least squares on F^2 with SHELXL97,[27] was similar for all complexes, including isotropic and subsequently anisotropic displacement parameters. The hydrogen atoms were observed or calculated and refined freely or using a restricted riding model. A methylene group (C10) of **8a-Ni(II)** was found to be disordered and was refined with an isotropic model in two positions (0.5/0.5). For **8a-Ni(II)** seven molecules of water were observed in the asymmetric unit as crystallization solvent. For **8a-Zn(II)**, 2.5 (water) and 0.5 (ethanol) molecules were observed in the asymmetric unit as crystallization solvents. For **8a-Cu(II)** three molecules of water were observed in the asymmetric unit as crystallization solvent. All the highest electronic residuals were observed in the close proximity of the metal centers and make no chemical sense.

Crystal data for **8a-Ni(II)**: $C_{21}H_{22}N_2NiO_6{\cdot}7(H_2O)$, M_W 583.23, blue, prism (0.12 × 0.10 × 0.08), monoclinic, space group $P2_1/n$, a: 10.5486(10) Å, b: 16.1100(15) Å, c: 15.8867(15) Å, α: 90.00°, β: 108.0310(10)°, γ: 90.00°, V = 2567.2(4) $Å^3$, Z = 4, D_{calc}: 1.509 g cm^{-3}, $F(000)$: 1232, T = 173(2) K, μ = 0.825 mm^{-1}. 27 115 measured reflections (2θ: 3–57°, ω scans 0.3°), 6253 unique (R_{int} = 0.0933); min./max. transm. factors 0.766/0.940. Final agreement factors were R^1 = 0.0429 (3550 observed reflections, $I > 2\sigma(I)$) and wR^2 = 0.0958; data/restraints/parameters 6253/7/376; GoF = 0.892. Largest peak and hole 0.494 and –0.412 e $Å^{-3}$.

Crystal data for **8a-Zn(II)**: $C_{21}H_{24}N_2O_7Zn{\cdot}0.5(C_2H_6O){\cdot}2.5(H_2O)$, M_W 549.87, colorless, needle(0.20 × 0.06 × 0.05), monoclinic, space group $P2_1$, a: 11.7777(11) Å, b: 7.4694(7) Å, c: 14.6265(13) Å, α: 90.00°, β: 107.0520(10)°, γ: 90.00°,

V = 1230.2(2) Å^3, Z = 2, D_{calc}: 1.484 g cm^{-3}, F(000): 576, T = 173(2) K, μ = 1.056 mm^{-1}. 11 233 measured reflections (2θ: 3–58°, ω scans 0.3°), 5872 unique (R_{int} = 0.0747); min./max. transm. factors 0.857/0.925. Final agreement factors were R^1 = 0.0508 (4290 observed reflections, $I > 2\sigma(I)$) and wR^2 = 0.1263; data/restraints/parameters 5872/9/328; GoF = 0.963. Largest peak and hole 1.165 and –0.522 e Å^{-3}.

Crystal data for **8a-Cu(II)**: $C_{42}H_{44}Cu_2N_4O_{12}\cdot 3H_2O$, M_W 977.94, blue, prism (0.25 × 0.12 × 0.12), monoclinic, space group $C2/c$, a: 13.4667(13) Å, b: 21.127(2) Å, c: 16.2489(17) Å, α: 90.00°, β: 92.054(2)°, γ: 90.00°, V = 4620.1(8) Å^3, Z = 4, D_{calc}: 1.466 g cm^{-3}, F(000): 2032, T = 296(2) K, μ = 0.990 mm^{-1}. 18 880 measured reflections (2θ: 3–52°, ω scans 0.3°), 4511 unique (R_{int} = 0.1579); min./max. transm. factors 0.850/1.0. Final agreement factors were R^1 = 0.0739 (2130 observed reflections, $I > 2\sigma(I)$) and wR^2 = 0.2682; data/restraints/parameters 4511/0/285; GoF = 1.034. Largest peak and hole 1.567 and –0.382 e Å^{-3}.

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