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TACN–Amino Acid Conjugates and Their Copper(II) Complexes

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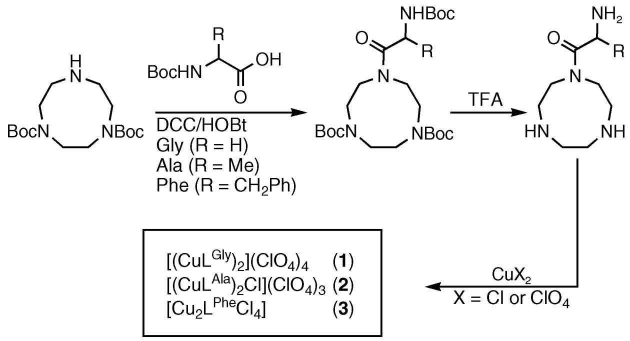
Triazacyclononane (TACN) was coupled to glycine (L^{Gly}), alanine (L^{Ala}), and phenylalanine (L^{Phe}) via standard solution phase peptide coupling techniques. Copper(II) complexes of these new ligand–amino acid conjugates, $[(CuL^{Gly})_2](ClO_4)_4$ (**1**), $[(CuL^{Ala})_2Cl](ClO_4)_3$ (**2**), and $[Cu_2L^{Phe}Cl_4]$ (**3**), were synthesized and characterized. The X-ray crystal structures of **2** and **3** were determined. Complex **2** is a dimeric species where L^{Ala} bridges between copper ions via its two TACN amine nitrogen atoms to one copper while the Ala terminal amine and carbonyl oxygen bind to the other copper. Complex **3** is bimetallic but only contains one L^{Phe} ligand that bridges between the copper ions.

Coordination chemistry in metalloproteins is dominated by amino acids since amino acid side chains and backbone heteroatoms entail the majority of ligands available to coordinate to metal ions.[1] Small molecule models of metal sites in metalloproteins are an integral part of bioinorganic chemistry, and the design of new ligands to model challenging structural and/or functional motifs plays an important role in the development of new model complexes.[2] Most model complexes use non-amino-acid ligands that mimic various aspects of the ligand environment found in the protein. Our laboratory is developing a new class of ligand–peptide conjugates where small peptides are coupled to "standard" ligands. Here we report our initial successes in coupling the tridentate ligand 1,4,7-triazacyclononane (TACN) with amino acids to form ligand–amino acid conjugates.[3] The synthesis and characterization of copper(II) complexes of these new ligands are also reported.[4]

Scheme 1. Syntheses of Ligands L^{Gly}, L^{Ala}, and L^{Phe} and Complexes **1**–**3**



Our general synthetic approach for creating ligand–peptide conjugates relies on coupling functionalized ligands to the O-terminus of Boc-protected amino acids or oligopeptides (Boc = *N-tert*-butoxycarbonyl).[5,6] The ligand–peptide conjugate can then be deprotected and purified. Ligands L^{Gly}, L^{Ala}, and L^{Phe} were synthesized according to Scheme 1 by coupling the secondary amine nitrogen of Boc_2TACN[7] to the acid group of Boc-protected amino acids glycine (Gly), alanine (Ala), or phenylalanine (Phe), respectively.[8]

Because of our interest in copper-containing metalloproteins,[9] we set off to synthesize copper complexes of ligands L^{Gly}, L^{Ala}, and L^{Phe} to explore the coordination chemistry of these new ligand–amino acid conjugates. Copper complexes $[(CuL^{Gly})_2](ClO_4)_4$ (**1**), $[(CuL^{Ala})_2Cl](ClO_4)_3$ (**2**), and $[Cu_2L^{Phe}Cl_4]$ (**3**) were synthesized in methanol by combining the ligand with a copper(II) salt.[10] Cupric perchlorate hexahydrate was used to synthesize **1** and **2**, whereas cupric chloride was used to synthesize **3**. Complexes **1** and **2** are dimeric with a 2:2 ligand–metal stoichiometry. The dimeric formulation for

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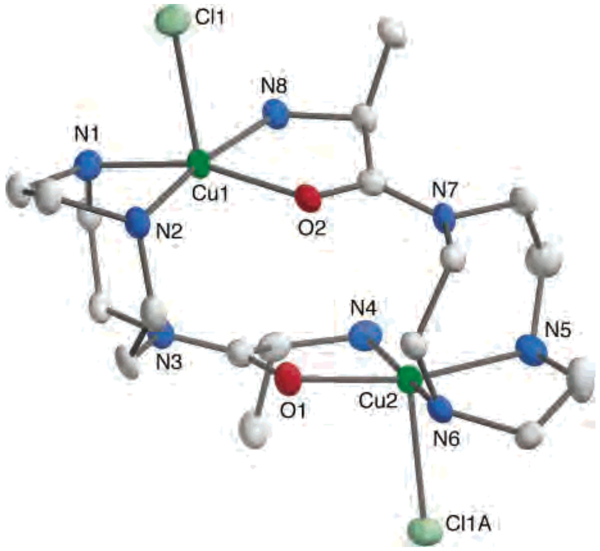

Figure 1. Representation of the X-ray structure of **2** as 50% thermal ellipsoids. H atoms have been omitted for clarity. Selected bond distances (Å): Cu1−O2, 1.998(3); Cu1−N2, 1.999(3); Cu1−N1, 2.031(3); Cu1−N8, 2.057(3); Cu1−Cl1, 2.508(1); Cu2−N6, 1.984(3); Cu1−O1, 1.999(3); Cu2−N4, 2.007(3); Cu2−N5, 2.025(3); Cu2−Cl1A, 2.526(1).

1 and **2** was determined in solution by ESI-MS. For **1** in CH_3CN: $m/z = 797$ $[M - ClO_4]^+$, $m/z = 348$ $[M - CuL^{Gly}(ClO_4)_3]^+$. For **2** in CH_3CN: $m/z = 825$ $[M - Cl]^+$, $m/z = 761$ $[M - ClO_4]^+$, $m/z = 362$ $[M - CuL^{Ala}Cl(ClO_4)_2]^+$. The dimeric form of **2** was verified in the solid state by X-ray crystallography.

The crystal structure of **2** confirmed that it is composed of bimetallic species where two copper(II) ions are bridged via two L^{Ala} ligands to form a 4+ cation (Figure 1).[11,12] The charge is balanced by one bridging chloride anion[13] and three outer sphere perchlorate anions. The chloride links molecules of **2** in the crystal lattice by bridging between Cu1 from one dimer and Cu2 from an adjacent dimer.

The TACN portion of the L^{Ala} ligand binds to Cu1 via two amine nitrogens, but the amide nitrogen is not coordinated.[14] The Cu1⋯N3 distance of 2.96 Å in **2** stands in contrast to the rare examples of copper complexes with coordinated tertiary amides (2.16−2.49 Å).[3a−c] These amide-coordinated species are sensitive to C−N bond cleavage,[3b−c,6] while **2** is stable in methanol. The stability of the amide C−N bonds in **2** can be attested to the fact that the metal is not coordinated by the amide N atom. The Ala portion of the same ligand coordinates to the other copper atom in **2**, Cu2, via the terminal amine nitrogen and the carbonyl oxygen atom.[15] The second ligand in the bimetallic complex is related via a noncrystallographic pseudo-C_2 axis to the first ligand; thus, two L^{Ala} ligands bridge between the copper atoms in **2**.

The coordination geometry around each copper is closest to square pyramidal, with a N_3O ligand set in the equatorial plane and a chloride ligand in the axial position ($\tau = 0.16$ and 0.10 for Cu1 and Cu2, respectively).[16] The chloride anions bridge between bimetallic moieties [$\angle$Cu−Cl−Cu = 158.25(5)°] to create linear chains of molecules along the crystallographic *b* axis (see Figure S5). The intra- and intermolecular Cu⋯Cu distances in **2** are long (> 4.9 Å), making any significant magnetic coupling between copper(II) ions unlikely, an assertion corroborated by the typical axial EPR spectrum of **2** ($g_\perp = 2.08$, $g_\| = 2.39$, $A^{Cu}{}_\| = 120$ G).[8]

Unlike the dimeric 2:2 ligand−metal ratio of **1** and **2**, in the solid state **3** has a 1:2 ligand−metal stoichiometry (vide infra). Attempts to synthesize the 1:1 or 2:2 ligand−copper complex using L^{Phe} were unsuccessful, with exclusive formation of **3** even when excess L^{Phe} was used. Attempts to synthesize copper complexes with L^{Phe} using cupric perchlorate were also unsuccessful. The inability of L^{Phe} to form symmetrical dimers with $Cu(ClO_4)_2$, as L^{Gly} and L^{Ala} do in **1** and **2**, may be a consequence of steric interactions of the bulkier Phe side chains.

The crystal structure of **3** revealed a bimetallic complex that is different than **2** (Figure 2).[11,17] Here, L^{Phe} bridges between the two copper(II) ions in a manner similar to **2** with the TACN ring binding to Cu1 through the amine N atoms in a bidentate fashion and the Phe portion of the ligand binding to Cu2 through the terminal amine and the carbonyl O atom. However, unlike the symmetric binding mode in **2**, the coordination sphere around each copper(II) ion in **3** is completed by two chloride ligands.

The coordination geometry around both copper(II) ions is square planar,[18] with an N_2Cl_2 ligand set around Cu1 and

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(10) Analytical data for **1**−**3** (see Supporting Information for full details). **1**: 0.18 g, 40% yield. Anal. Calcd for **1**·$2H_2O$, $C_{16}H_{40}Cl_4Cu_2N_8O_{20}$: C, 20.59; H, 4.32; N, 12.00. Found: C, 20.04; H, 4.33; N, 11.08. **2**: 0.28 g, 60% yield. Anal. Calcd for **2**, $C_{18}H_{40}Cl_4Cu_2N_8O_{14}\cdot CH_3NO_2\cdot H_2O$: C, 24.26; H, 4.82; N, 13.51. Found: C, 23.53; H, 4.88; N, 12.53. **3**: 0.136 g, 50% yield. Anal. Calcd for **3**, $C_{15}H_{24}Cl_4Cu_2N_4O$: C, 33.04; H, 4.44; N, 10.27. Found: C, 32.78; H, 4.91; N, 10.21.

(11) Data collection was performed on a Bruker Apex CCD diffractometer with Mo Kα radiation (0.71073 Å) at 143 K for **2** and 120 K for **3**. See Supporting Information for full details.

(12) X-ray data for **2**: $C_{18}H_{40}Cl_4Cu_2N_8O_{14}\cdot CH_3NO_2\cdot H_2O$, $M = 940.52$, orthorhombic, space group $P2_12_12_1$, $a = 9.996(1)$ Å, $b = 17.432(2)$ Å, $c = 20.285(2)$ Å, $V = 3534.7(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.767$ g/cm^3. All non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were included with idealized parameters except the hydrogen atoms on N1, N2, N4, N5, N6, N8, and O17, which were located and refined with fixed temperature factors. Full-matrix least-squares refinement on F^2 converged with R1 = 0.0505, wR2 = 0.1334, GOF = 1.051 for 6919 independent reflections with $I > 2\sigma(I)$ and 492 parameters.

(13) The most likely origin of the chloride is either contamination in the ligand or in the cupric perchlorate.

(14) This is not surprising in light of the poor coordinating ability of tertiary amides. See Greenberg, A. In *The Amide Linkage*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-Interscience: New York, 2000, pp 47−84.

(15) This type of chelating binding mode for amino acids is relatively common and, in particular, has been reported for copper(II) amino acid species. (a) Tan, X. S.; Fujii, Y.; Sato, T.; Nakano, Y.; Yashiro, M. *Chem. Commun.* **1999**, 881−882. (b) Castellano, E. E.; Piro, O. E.; Casado, N. M. C.; Brondino, C. D.; Calvo, R. *J. Chem. Crystallogr.* **1998**, *28*, 61−68.

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(17) X-ray data for **3**: $C_{15}H_{24}Cl_4Cu_2N_4O$, $M = 545.26$, monoclinic, space group $P2_1$, $a = 7.5158(6)$ Å, $b = 7.5207(6)$ Å, $c = 17.9669(15)$ Å, $\beta = 100.012(1)°$, $V = 1000.1(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.811$ g/cm^3. All non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were included with idealized parameters. Full-matrix least-squares refinement on F^2 converged with R1 = 0.0221, wR2 = 0.0492, GOF = 1.005 for 3795 independent reflections with $I > 2\sigma(I)$ and 235 parameters.

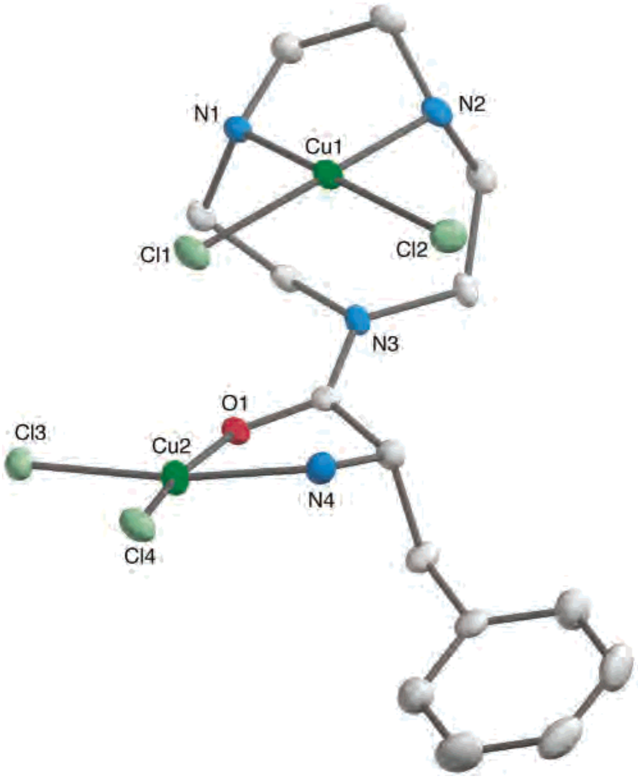

Figure 2. Representation of the X-ray crystal structure of **3** as 50% thermal ellipsoids. H atoms have been omitted for clarity. Selected bond distances (Å): Cu1−N1, 2.039(2); Cu1−N2, 2.032(2); Cu1−Cl1, 2.2729(8); Cu1−Cl2, 2.2852(8); Cu1$\cdots$N3, 2.783(2); Cu2−O1, 2.007(2); Cu2−N4, 2.004(2); Cu2−Cl3, 2.2500(8); Cu2−Cl4, 2.2392(7); Cu2$\cdots$Cl1, 3.042(1).

a $NOCl_2$ ligand set around Cu2. However, if axial interactions are considered, the geometry is closer to elongated octahedral. The axial distances involving Cu1 are shorter than the sum of their van der Waals radii [Cu1$\cdots$N3 = 2.783(2) Å, intramolecular; Cu1A$\cdots$Cl3 = 2.818(1) Å, intermolecular], suggesting weak Cu$\cdots$ligand interactions. Likewise, the axial distances involving Cu2 are also shorter than the sum of their van der Waals radii [Cu2$\cdots$Cl1 = 3.042(1) Å, intramolecular; Cu2$\cdots$Cl2A = 3.087(1) Å, intermolecular]. The bimetallic complexes, loosely linked through weak intra- and intermolecular axial bonds, consequently form chains along the crystallographic *b* axis (see Figure S7).

Evidence of the two distinct copper coordination environments for **3** in solution was provided by EPR spectroscopy. The EPR spectrum of a frozen solution of **3** clearly indicates two different copper environments based on two distinct $g_{\parallel}$ signals (Cu1, $g_{\parallel} = 2.41$, $A^{\mathrm{Cu}}{}_{\parallel} = 119$ G; Cu2, $g_{\parallel} = 2.24$, $A^{\mathrm{Cu}}{}_{\parallel} = 177$ G).[8] Whether **3** retains its bimetallic structure or dissociates is difficult to ascertain from EPR alone. However, no evidence of the bimetallic species was observed by mass spectroscopy (ESI-MS for **3** in H_2O: $m/z = 410$ $[M - CuCl_2]^+$, $m/z = 374$ $[M - CuCl_3]^+$), suggesting that in solution **3** dissociates into 1:1 L^{Phe}Cu monomers and solvated Cu^{2+}.

In summary, we have synthesized a new family of ligand−amino acid conjugates by coupling TACN to glycine, alanine, and phenylalanine. The copper(II) complexes of these ligands have been synthesized and characterized. The ligands coordinate in a bridging mode between copper ions. The TACN amines coordinate to one copper ion whereas the amino acid amine and carbonyl oxygen coordinate to the other copper ion.

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Supporting Information Available: Experimental details and characterization for L^{Gly}, L^{Ala}, L^{Phe}, and **1**−**3** (PDF); X-ray structural information for **2** and **3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The dihedral angle between the Cl1−Cu1−Cl2 plane and the N1−Cu1−N2 plane is 14°. The dihedral angle between the Cl3−Cu2−Cl4 plane and the O1−Cu2−N4 plane is 6°.