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Synthesis and Characterization of Cu^{II} Complexes with Amino Acid Substituted Di(2-pyridyl)amine Ligands

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The two-step syntheses of the substituted di(2-pyridyl)-amine ligands (dpa), dpa-CH_2CO_2H (**1**) and dpa-$PhCO_2H$ (**2**), are described. Ligands **1** and **2** are successfully coupled to the amino acid phenylalanine, yielding the derivatives **4** and **6**, respectively. Four $Cu^{II}(dpa)_2$ complexes, [Cu(dpa-$CH_2CO_2tBu)_2(NO_3)_2$] (**3_{Cu}**), [Cu(dpa-CH_2CO-$PheOMe)_2$-$(H_2O)_2](NO_3)_2$·2MeOH (**4_{Cu}**), [Cu(dpa-$PhCO_2Me)_2$ $(MeOH)_2$]-$(ClO_4)_2$ (**5_{Cu}**) and [Cu(dpa-PhCO-$PheOMe)_2(ClO_4)_2$] (**6_{Cu}**) have been prepared and characterized, including their single crystal X-ray structures. Fluorescence emission at UV (for **3** and **4**) or blue (for **5** and **6**) wavelengths of the free ligands is preserved in the corresponding Cu complexes, although with lower intensity. X-band EPR spectra of **4_{Cu}** and **6_{Cu}** both revealed one axial Cu^{II} signal with hyperfine and superhyperfine splittings. Complexes **4_{Cu}** and **6_{Cu}** are chiral inorganic complexes with amino acid bioconjugates that may serve as nucleoside analogs in modified peptide nucleic acids (PNA).

Introduction

Inorganic nucleic acid derivatives and structural mimics have received increased attention in recent years[1] in view of their potential applications in biological and material sciences. Electrostatic attraction has been used to coat the exterior of nucleic acids with metals,[1a] and metal complexes have been inserted into double-stranded DNA (dsDNA) duplexes by intercalation and threading.[2] In contrast, metal ions have been incorporated *inside* the core of the nucleic acid duplex by replacing hydrogen bonds with metals that covalently link the nucleobases. Inclusion of metals in this manner changes the properties of the dsDNA duplex. For example, Lee et al. abstracted protons from the nucleobases of a DNA duplex at high pH, and replaced some of these H atoms with Zn cations.[3] The resulting duplex had improved electrical conductivity that was attributed to the metal-linked base pairs. Analogously, two thymine nucleobases have been shown to form a neutral complex upon complexation of a Hg^{II} ion.[4] Using this coordination chemistry, dsDNA duplex formation by metal coordination of multiple Hg^{II} ions along the oligonucleotide has been demonstrated. Nucleobases have also been replaced by synthetic ligands to adjust the binding affinity of metal ions. A number of common metal binding ligands and a variety of metal ions and oligomeric backbones (i.e. sugar phosphate and pseudo-peptide) have also been reported.[5–18]

Di(2-pyridyl)amine (dpa) is a well-known ligand for a range of transition metals, and structural studies on these complexes have been reported.[19] Metal dpa complexes have been used as homogeneous or heterogeneous catalysts in a number of chemical transformations including hydrolytic or oxidative DNA cleavage,[20] hydrolytic cleavage of amino acid esters,[21] oxidation of alcohols,[22] ring-opening metathesis polymerization,[23] Heck reactions,[24] and various asymmetric reactions.[25] Dpa based luminescence has been utilized for the development of new materials.[26] Given these properties of metal dpa complexes, development of methods for incorporation of the ligand into synthetically modified nucleic acids, nucleobases analogs, or bioconjugates will lead to broad applications in bioinorganic systems.

We have recently described heterocyclic ligand-containing aminoethyl glycine (aeg) oligomers,[5b,14] chains that are charge-neutral mimics of the sugar phosphate backbone of DNA. Our aeg oligomers crosslink by coordination of transition-metal ions and are synthetic inorganic structural analogs of dsDNA in which all hydrogen-bonded base pairs are replaced by metal coordination bonds. In previous studies, the aeg backbone has been successfully substituted with the acetic acid derivatives of the py,[5b,14a–5e] bpy,[14a,14c,14e] tpy,[14e] phtpy[14g] or hq[14f] ligands shown in Figure 1. Herein we extend this chemistry by introducing the fluorescent dpa ligands **1** and **2** and attach the ligands to an amino acid. Two of these ligands are crosslinked by coordination

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to one Cu^{II} ion to form the chiral inorganic building block that could be used to replace nucleosides in modified peptide nucleic acid (PNA).[27]

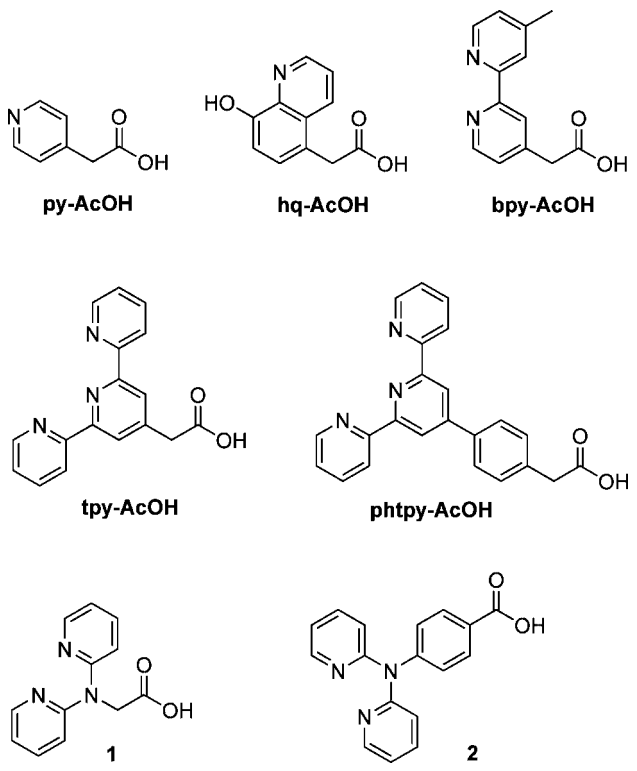


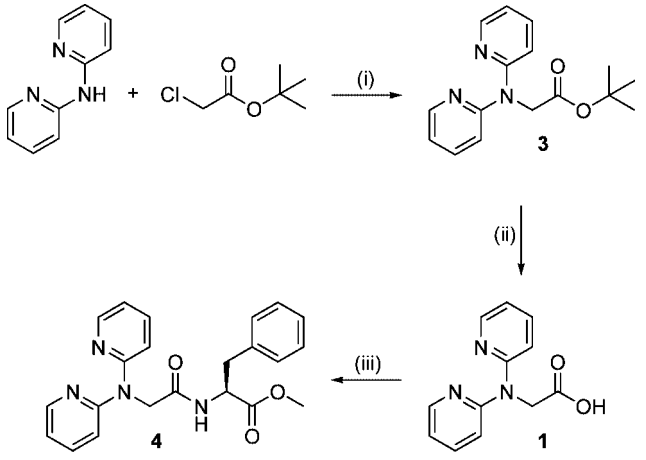
Figure 1. The heterocyclic acetic acid derivatives previously used for the synthesis of aeg-oligoligandosides[5b,14] and the dpa derivatives **1** and **2** prepared in this study.

Results and Discussion

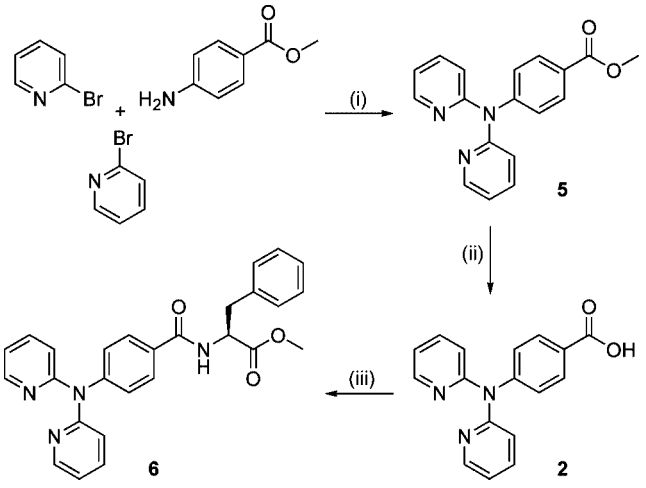
Dpa Ligands and Amino Acid Conjugates

In contrast to the other ligands shown in Figure 1, dpa has not yet been used extensively in the synthesis of nucleoside analogs or bioconjugates. This is likely due to the difficult derivatization of the central amine atom. In the literature two different routes are frequently used for the synthesis of the aromatic amines like **1** and **2**: the Pd-catalyzed Buchwald–Hartwig amination[28,29] and the Ullmann condensation,[30,31] often catalyzed by Cu^{II} salts. The Buchwald–Hartwig amination is strongly affected by electron-withdrawing substituents [like the *p*-methoxycarbonyl group in Scheme 2, reaction (i)],[32] while the Ullmann condensation needs aggressive conditions (high temperatures and extended reaction times), to produce only moderate yields.[30]

The Ullmann condensation was used to prepare key intermediates **3** and **5** according to Scheme 1 and Scheme 2, respectively. The ester **3** was synthesized by substitution of the commercially available dpa with *tert*-butyl bromoacetate in DMSO with KOH and catalytic KI to give the purified ester **3** in 47% yield. Deprotection of the ester proceeded smoothly to give the free acid **1** (91% yield). The synthesis of ester **5** included the construction of the dpa framework by condensation of *p*-aminobenzoic acid with two equivalents of 2-bromopyridine, K_2CO_3, and co-catalysts KI, $Cu(SO_4)_2$ and phenanthroline, to give the pure compound in 52% yield. Ester **5** was deprotected in standard conditions to yield the free acid **2** (89%).



Scheme 1. Synthesis of the aliphatic side chain dpa derivatives **1**, **3** and **4**: (i) KOH, KI (cat.), DMSO/2 h, room temp. (47%); (ii) TFA, TIS, DCM/10 h, room temp. (91%); (iii) HBTU, HOBt, H-Phe-OMe·HCl, DIPEA/20 h, 0 °C→room temp. (51%).



Scheme 2. Synthesis of the aromatic side chain dpa derivatives **2**, **5** and **6**: (i) K_2CO_3, KI (cat.), $Cu(SO_4)_2{\cdot}5H_2O$ (cat.) phen (cat.), neat/7 h, 200 °C (52%); (ii) 1 M NaOH/16 h, room temp. (89%); (iii) HBTU, HOBt, H-Phe-OMe·HCl, DIPEA/20 h, 0 °C→room temp. (56%).

The ability of the ligands **1** and **2** to react in amide condensations was tested by reaction with the primary amine group of acid-protected phenylalanine according to Scheme 1 and Scheme 2. The corresponding products **4** and **6** were obtained, strongly indicating the viability of **1** and **2**, respectively, for the construction of dpa-substituted aeg oligomers.

Interestingly, the ^1H NMR ($CDCl_3$) spectra of the phenylalanine conjugates **4** and **6** contain different features. The amide proton in **6** is found below 7 ppm, as expected for an amide proton not involved in H-bonding. In contrast the

amide proton in **4** is shifted above 7 ppm, which is indicative of H-bonding that likely is a result of the formation of the cyclic conformation of **4** in Figure 2. A hydrogen bond between the amide proton and the central dpa nitrogen atom causes the formation of a five-membered ring. This cyclic conformation is not possible for the rigid conjugate **6**.

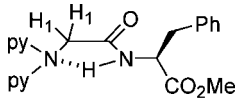


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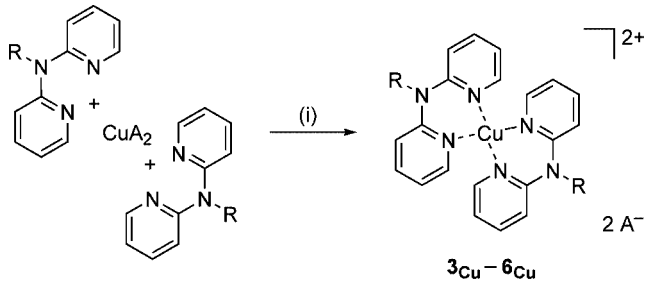
Figure 2. The cyclic conformation of dpa - amino acid conjugate **4** in $CDCl_3$ solution.

Dpa Metal Complexes

The complexes $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$ have been obtained in moderate to good yields (50–75%) by mixing methanolic solutions of ligands **3** or **4** with Cu^{II} nitrate and ligands **5** or **6** with Cu^{II} perchlorate as shown in Scheme 3. Time of flight positive ion electrospray (TOF-ES+) mass spectra of $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$ contain the molecular ion peaks for the $[CuL_2]^+$ complex, where L is the corresponding ligand **3**–**6**.



$\mathbf{3_{Cu}}$ – $\mathbf{6_{Cu}}$

$\mathbf{3_{Cu}}$, R = -CH_2CO_2tBu, A = NO_3^-
$\mathbf{4_{Cu}}$, R = -CH_2CO-PheOMe, A = NO_3^-
$\mathbf{5_{Cu}}$, R = -*p*-$C_6H_4CO_2$Me, A = ClO_4^-
$\mathbf{6_{Cu}}$, R = -*p*-C_6H_4CO-PheOMe, A = ClO_4^-

Scheme 3. Synthesis of the $[Cu(dpa)_2]$ complexes $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$: (i) MeOH, Δ (50–75%).

Optical absorbance and emission spectroscopy were also used to characterize the Cu complexes. The UV/Vis absorbance and fluorescence spectroscopic data of complexes $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$ are compared to those of the free ligands **3**–**6** in Table 1. Absorption spectra of the ligands and the Cu complexes contain characteristic peaks at high energy that are due to the π–π* transition of the aryl groups ($\lambda < 320$ nm). Additional peaks in the spectra of $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$ are found at 375–390 nm and above 600 nm. Both the ligands and the metal complexes are emissive; the UV (for **3** and **4**) or blue (for **5** and **6**) fluorescent emission of the free ligands is attributed to π*–π relaxation in the dpa ligand.[32] The red shift of the emission bands in the aromatic side chain ligands **5** and **6** is a result of the conjugation with the adjacent phenyl ring. In contrast, the emission bands are preserved in the Cu complexes, but are weaker in intensity than in the corresponding free ligands, as has been reported for other $[Cu(dpa)_2]^{2+}$ complexes.[33]

Table 1. Compilation of spectroscopic data.

	λ_{max}/nm[a]		
	λ_{abs}	λ_{ex}	λ_{em}
3	228, 306	296	360
4	228, 303[b]	278	304
5	223, 311	324	432
6	225,[b] 311	318	414
$\mathbf{3_{Cu}}$	296, 379,[c] 621[c]	280	305
$\mathbf{4_{Cu}}$	296, 376,[c] 594[c]	279	304
$\mathbf{5_{Cu}}$	315, 390,[c,b] 679[c,d]	324	434
$\mathbf{6_{Cu}}$	309, 391,[c] 678[c,d]	317	415

[a] The maxima (λ_{max}) of absorption (λ_{abs}), excitation (λ_{ex}) and emission (λ_{em}) were measured in methanol. [b] Shoulder. [c] These signals were measured in methanol/water = 1:1 solvent mixture due to low solubility in methanol. [d] very broad peak.

X-band EPR spectra of $\mathbf{4_{Cu}}$ and $\mathbf{6_{Cu}}$ (0.5 mM in frozen solution of a 1:1 water/methanol mixture) both show a well-resolved axial Cu^{II} signal with large separation of $g_{\|}$ and $g_{\perp}$ (Figures S9 and S10 and quantitative details in the supporting information; for supporting information see also the footnote on the first page of this paper). This observation is expected for a compound containing electronically identical Cu^{II} atoms separated by a distance of at least 6 Å[14a,34a] and is consistent with the geometry found by X-ray crystallography, see below. In addition, the EPR spectra show hyperfine splitting due to coupling of the unpaired electron with the copper nucleus (I = 3/2 for ^{63}Cu and ^{65}Cu) and superhyperfine splitting due to coupling with the directly coordinated nitrogen nuclei (I = 1 for ^{14}N and I = 1/2 ^{15}N).[34b,34c]

X-ray Crystallography

Single crystals suitable for X-ray analysis could be obtained for all four complexes in this study. Precipitation from a methanol solution was successful for $\mathbf{5_{Cu}}$, diffusion of diethyl ether in the methanol solution of the complex was used for $\mathbf{3_{Cu}}$, while slow evaporation from methanol solution was applied for $\mathbf{4_{Cu}}$ and $\mathbf{6_{Cu}}$.[35] Single crystals of the complexes were grown directly from the reaction mix-

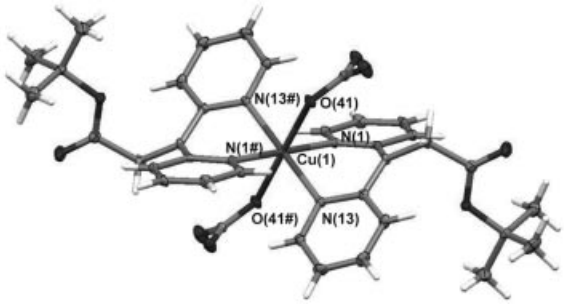


Figure 3. X-ray single crystal structure of $\mathbf{3_{Cu}}$ (thermal ellipsoids at 50% probability).

ture at room temperature; the solved crystal structures are shown in Figures 3, 4, 5 and 6, and the selected bond lengths and angles are collected in Table 2.

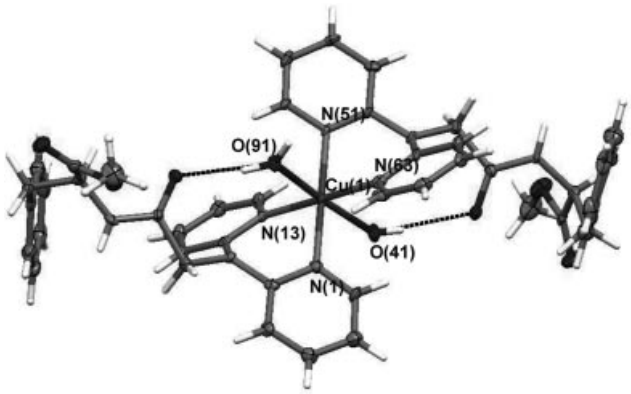


Figure 4. X-ray single crystal structure of $\mathbf{4_{Cu}}$ dication (thermal ellipsoids at 30% probability). The nitrate counterions and methanol solvent molecules are omitted for clarity.

Table 2. Selected bond lengths [Å] and angles [°] for $\mathbf{3_{Cu}}$-$\mathbf{6_{Cu}}$.

	$\mathbf{3_{Cu}}$	$\mathbf{4_{Cu}}$	$\mathbf{5_{Cu}}$	$\mathbf{6_{Cu}}$
Cu(1)–N(1)	1.994(2)	2.011(6)	2.007(2)	2.006(7)
Cu(1)–N(51)	–	2.029	–	2.008(7)
Cu(1)–N(13)	2.005(2)	2.029(6)	1.982(2)	2.015(7)
Cu(1)–N(63)	–	1.980(6)	–	2.007(6)
Cu(1)–O(41)	2.467(2)	2.451(5)	2.472(2)	2.452(7)
Cu(1)–O(91)	–	2.411(6)	–	2.477(8)
N(1)–Cu(1)–N(13)	85.10(7)	85.3(2)	85.67(9)	86.0(3)
N(51)–Cu(1)–N(63)	–	86.4(2)	–	84.7(3)
N(1)–Cu(1)–O(41)	96.98(6)	91.4(2)	89.58(9)	93.1(2)
N(1)–Cu(1)–O(91)	–	84.8(3)	–	88.5(2)
N(13)–Cu(1)–O(41)	89.74(7)	93.4(3)	93.43(9)	81.1(3)
N(13)–Cu(1)–O(91)	–	85.5(2)	–	87.3(3)
N(1)–C(6)–C(8)–C(13)	–8.8	3.4	7.2	5.2
N(51)–C(56)–C(58)–C(63)	–	–2.8	–	2.1
α [plane A/plane A′][a]	43.6	53.4, 50.0	37.0	34.8, 36.9
β [plane B/plane C][a]	38.1	35.6, 36.7	39.0	35.4, 41.5
χ [plane D/plane Ph][a]	–	–	73.7	87.4, 79.6

[a] See Figure 7 for explanation.

The crystal structures of $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$ share a number of common features that for clarity are described using $\mathbf{3_{Cu}}$ as the example (Figure 3). The structure unambiguously confirms

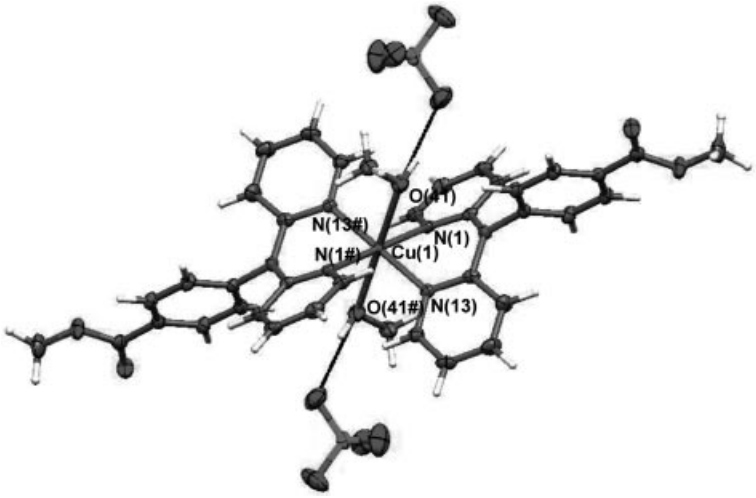


Figure 5. X-ray single crystal structure of $\mathbf{5_{Cu}}$ (thermal ellipsoids at 50% probability).

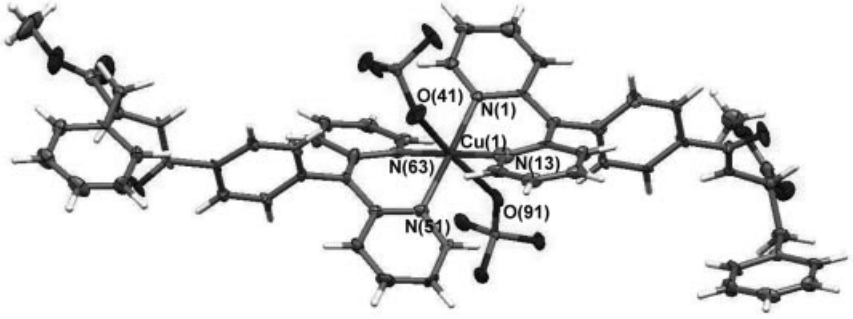


Figure 6. X-ray single crystal structure of $\mathbf{6_{Cu}}$ (thermal ellipsoids at 50% probability).

the [Cu(dpa)$_2$] stoichiometry as well as the bidentate nature of the dpa ligand, in which only the py nitrogen atoms coordinate to the Cu and the central dpa amine atom is not involved in metal chelation. The N_4O_2 coordination polyhedron is Jahn–Teller distorted square pyramidal. Four N atoms from the two dpa ligands coordinate to the Cu in the equatorial plane, *d*(Cu–N) = 1.99 and 2.01 Å, while nitrate counterions occupy the apical positions, *d*(Cu–O) = 2.47 Å. The bite angle of the dpa ligand (85.1°) indicates that there is only minimal strain in the six-membered chelate ring. Because the counterions or solvent molecules occupy apical positions, differences exist in the structures: these are nitrates in $\mathbf{3_{Cu}}$, perchlorates in $\mathbf{6_{Cu}}$, water in $\mathbf{4_{Cu}}$, and methanol in $\mathbf{5_{Cu}}$.

Selected geometrical parameters are summarized in Figure 7. The dpa moiety in $\mathbf{3_{Cu}}$ is not planar, and the angle α between the py rings is found to be 43.6°. In addition the central dpa chelate ring B is not coplanar with the coordination plane C and the angle between B and C is 38.1°. The conformation of the phenyl side chain with respect to the dpa moiety defined by the χ angle, specific to $\mathbf{5_{Cu}}$ and $\mathbf{6_{Cu}}$, is shown in Figure 7.[36] In both $\mathbf{5_{Cu}}$ and $\mathbf{6_{Cu}}$ χ is rather large, >70°, resulting in a "twisted" conformation in these complexes.

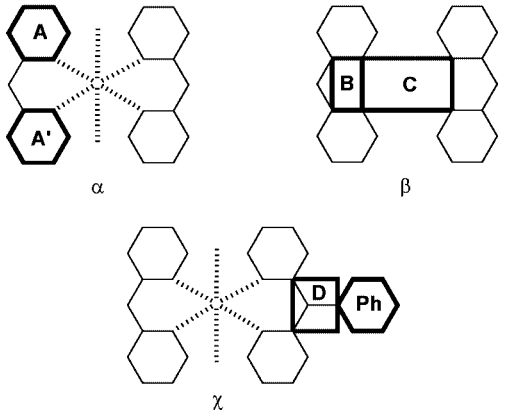


Figure 7. Selected geometrical parameters in [Cu(dpa)$_2$] complexes are defined as α (angle between the planes A and A′), β (angle between B and C), and χ (angle between the planes H and Ph).

In $\mathbf{3_{Cu}}$ and $\mathbf{5_{Cu}}$ no significant intermolecular contacts are found, except the hydrogen bond between the coordinated methanol and a perchlorate counterion in $\mathbf{5_{Cu}}$. The inorganic nucleoside pair analogs $\mathbf{4_{Cu}}$ and $\mathbf{6_{Cu}}$ have more interesting intermolecular interactions. In $\mathbf{4_{Cu}}$ the amide oxygen atom of the dpa ligand coordinates to the water molecule in the apical position by hydrogen bonding. In addition, π-stacking is found between dpa ligands from neighboring molecules, which causes chains to form along the *a* crystallographic axis (Figure S11 in the electronic supporting information). Dpa π-stacking allows the Cu atoms of neighboring complexes to come as close as 8.2 Å. In $\mathbf{6_{Cu}}$, short contacts include hydrogen bonding between the coordinated perchlorate counterion of one molecule and the phenylalanine amide proton of the neighboring molecule. There is also weak π-stacking between the py substituent from one molecule with the phenyl substituent of Phe from its neighbor. These contacts cause the formation of chains along the *c* axis in the crystal of $\mathbf{6_{Cu}}$ (Figure S12 in the electronic supporting information). As a result, the Cu–Cu separation in these chains is 12.1 Å. The large separation of the copper centers in $\mathbf{4_{Cu}}$ and $\mathbf{6_{Cu}}$ is in accordance with the EPR spectra discussed above.

Conclusions

The two new bidentate heterocyclic nitrogen ligands **3** and **5** have been prepared using the Ullmann reaction in at least 47% yield. The ester groups in **3** and **5** have been hydrolyzed in standard conditions to give the acids **1** and **2**, respectively. Ligands **1** and **2** have a carboxylic functional group that allows their use in conjugation with biological molecules. To confirm this, the bioconjugates **4** and **6** with the amino acid H-Phe-OMe have been prepared following Scheme 1 and Scheme 2.

The Cu complexes $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$ have been synthesized and fully characterized, including their X-ray single crystal structures. In addition to confirming the 1:2 metal to ligand stoichiometry, the X-ray structures reveal square bipyramidal geometries for all four complexes in this study. Both the free ligands and their corresponding Cu complexes are fluorescent.

Conjugates of metal complexes with amino acids or peptides have a number of biological applications,[37,38] including artificial catalysts or enzymes for biochemical reactions.[39] In this paper, we present complexes with an 1:2 metal/ligand stoichiometry that can serve as inorganic analogs of nucleic acids.[5b,14] Our current efforts are focused on the development of chiral inorganic nucleic acid models based on the aeg-oligoamide chemistry.

Experimental Section

General Remarks: Chemicals were used without further purification except where indicated. UV/Vis absorption spectra were measured in 1-cm quartz cuvettes in a double-beam spectrophotometer (Varian Cary 500). Excitation and emission spectra were recorded with a Photon Technologies International fluorimeter. Positive-ion time of flight electrospray mass spectrometry (TOF ES+) was performed using a Mariner mass spectrometer (Perseptive Biosystems). For fragments containing copper only the isotopomer of the highest intensity was described. NMR spectra were collected with a 360-MHz spectrometer (Bruker AV 360). Chemical shifts, δ/ppm, indicate a downfield shift from tetramethylsilane, TMS, the internal standard. Coupling constants, *J*, are given in Hz. X-band EPR spectra were obtained using a 9.5-GHz Bruker eleXsys 500 spectrometer equipped with a liquid helium cryostat. The experiments were performed in a frozen solution (0.5 mM in methanol/water = 1:1) at 20 K, with a modulation frequency of 100 kHz and a modulation amplitude of 5 G. The *g* factors were calculated as $g = 714.484\ \nu/B_0$, were ν is the microwave frequency in GHz and B_0 the magnetic field in gauss.

Dpa-CH_2CO_2tBu (3): KOH (3.0 g, 53.6 mmol, 4.6 equiv.) was added to the solution of dpa (2.0 g, 11.7 mmol) in dimethyl sulfox-

ide (DMSO, 40 mL) and the resulting suspension was stirred overnight at room temperature. KI (200 mg, 1.2 mmol, 0.1 equiv.) and *tert*-butyl chloroacetate (4 × 0.5 mL, 14.0 mmol, 1.2 equiv.) were added. The reaction was stirred for additional 2 h and the resulting mixture was extracted with diethyl ether (3 × 50 mL). The organic extracts were dried with Na_2SO_4, filtered and the ether removed under reduced pressure to give a brown oil. The crude product was purified by column chromatography (silica, hexane/ethyl acetate = 8:2). Yield: 1.56 g (47%), pale yellow oil. M_r (calcd. for $C_{16}H_{19}N_3O_2$) = 285.34, MS (TOF ES+): *m*/*z* = 324.5 $[M + K]^+$, 308.5 $[M + Na]^+$, 286.5 $[M + H]^+$, 230 $[M - OtBu]^+$. HR MS (TOF ES+): exp. 286.1549 and calcd. 286.1556 for $[C_{17}H_{12}N_3O_2]^+$. ^1H NMR ($CDCl_3$): δ = 8.32 (ddd, $^3J_{HH}$ = 1.0, 2.0 and 5.0 Hz, 2 H, $H_{py\text{-}6}$), 7.53 (ddd, $^3J_{HH}$ = 2.0, 7.2 and 8.4 Hz, 2 H, $H_{py\text{-}4}$), 7.22 (dt, $^3J_{HH}$ = 1.0 and 8.4 Hz, 2 H, $H_{py\text{-}3}$), 6.87 (ddd, $^3J_{HH}$ = 1.0, 5.0 and 7.2 Hz, 2 H, $H_{py\text{-}5}$), 4.83 (s, 2 H, H_1), 1.42 (s, 9 H, H_{OtBu}) ppm. ^{13}C NMR ($CDCl_3$): δ = 175.26 (C=O), 156.75 ($C_{py\text{-}2}$), 148.24 ($C_{py\text{-}6}$), 137.14 ($C_{py\text{-}4}$), 117.24 ($C_{py\text{-}5}$), 113.87 ($C_{py\text{-}3}$), 80.93 ($C_{q\text{-}tBu}$), 50.63 (C_1), 28.03 (C_{Me}) ppm.

Dpa-CH_2CO_2H (1): Dpa-Ac-O*t*Bu (**3**, 1.5 g, 5.26 mmol) was dissolved in a mixture of dichloromethane (DCM, 12 mL), TIS (0.6 mL) and TFA (12 mL), stirred at room temperature and the reaction monitored by TLC (silica, hexane/ethyl acetate = 8:2). After the disappearance of the starting material (10 h), the DCM was evaporated under reduced pressure and cold ether (–20 °C) was added to the residue. After 1 h at –20 °C, the precipitate was collected by filtration. Yield: 1.10 g (91%) of an off-white solid. M_r (calcd. for $C_{12}H_{11}N_3O_2$) = 229.23. MS (TOF ES+): *m*/*z* = 230.1 $[M + H]^+$, 252.1 $[M + Na]^+$. HR MS (TOF ES+): exp. 230.0921 and calcd. 230.0930 for $[C_{17}H_{12}N_3O_2]^+$. ^1H NMR ([D$_6$]DMSO): δ = 8.30 (ddd, $^3J_{HH}$ = 0.8 and 5.0 Hz, 2 H, $H_{py\text{-}6}$), 7.72 (dq, $^3J_{HH}$ = 2.0 and 8.5 Hz, 2 H, $H_{py\text{-}4}$), 7.29 (dt, $^3J_{HH}$ = 0.8 and 8.5 Hz, 2 H, $H_{py\text{-}3}$), 7.02 (dq, $^3J_{HH}$ = 0.8 and 5.0 Hz, 2 H, $H_{py\text{-}5}$), 4.82 (s, 2 H, H_1) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 170.96 (C=O), 155.22 ($C_{py\text{-}2}$), 146.83 ($C_{py\text{-}6}$), 137.99 ($C_{py\text{-}4}$), 117.33 ($C_{py\text{-}5}$), 113.70 ($C_{py\text{-}3}$), 48.91 (C_1) ppm.

Dpa-CH_2CO-PheOMe (4): Dpa acetic acid (**1**, 229 mg, 1 mmol), was suspended in acetonitrile (30 mL) and cooled to 0 °C with an ice bath. HBTU (379 mg, 1 mmol) and diisopropylethylamine (DIPEA, 875 μL, 5 mmol) were added. After the clear solution was stirred for 1 h at 0 °C, H-Phe-OMe·HCl (216 mg, 1 mmol) was added. The reaction mixture was allowed to reach room temperature and the stirring was continued for 20 h. After that period, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (50 mL), washed with sodium hydrogen carbonate (satd. aq., 3 × 50 mL) and the organic extract was dried with sodium sulfate, filtered and evaporated under reduced pressure. The crude product was subjected to column chromatography (silica, hexane/ethyl acetate = 2:8) to yield a colorless oil (200 mg, 51%). M_r (calcd. for $C_{22}H_{22}N_4O_3$) = 390.44, MS (TOF ES+): *m*/*z* = 391.2 $[M + H]^+$, 413.2 $[M + Na]^+$. HR MS (TOF ES+): exp. 391.1802 and calcd. 391.1770 for $[C_{22}H_{23}N_4O_3]^+$. ^1H NMR ($CDCl_3$): δ = 8.32 (ddd, $^3J_{HH}$ = 1.0, 2.0 and 5.0 Hz, 2 H, $H_{py\text{-}6}$), 7.85 (d, $^3J_{HH}$ = 8.0 Hz, 1 H, NH_{amide}), 7.58 (ddd, $^3J_{HH}$ = 2.0, 7.5 and 9.5 Hz, 2 H, $H_{py\text{-}4}$), 7.14–7.07 (m, 5 H, 2 $H_{Ph\text{-}m}$, 1 $H_{Ph\text{-}p}$ and 2 $H_{py\text{-}3}$), 6.96–6.91 (m, 4 H, 2 $H_{Ph\text{-}o}$ and 2 $H_{Py\text{-}5}$), 4.90 (td, $^3J_{HH}$ = 6.0 and 8.0 Hz, 1 H, $H_{Phe\text{-}a}$), 4.84 (d, $^3J_{HH}$ = 16.5 Hz, 1 H, H_{1a}), 4.71 (d, $^3J_{HH}$ = 16.5 Hz, 1 H, H_{1b}), 3.63 (s, 3 H, H_{OMe}), 3.11–2.99 (m, 2 H, $H_{Phe\text{-}\beta}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 171.65 (C_{ester}), 170.57 (C_{amide}), 156.33 ($C_{py\text{-}2}$), 148.32 ($C_{py\text{-}6}$), 137.59 ($C_{ph\text{-}i}$), 135.89 ($C_{py\text{-}4}$), 129.22 ($C_{phe\text{-}m}$), 128.21 ($C_{phe\text{-}o}$), 126.78 ($C_{phe\text{-}p}$), 117.92 ($C_{py\text{-}5}$), 114.42 ($C_{py\text{-}3}$), 53.07 (C_1), 52.71 (C_{OMe}), 52.09 ($C_{Phe\text{-}\alpha}$), 37.85 ($C_{Phe\text{-}\beta}$) ppm.

Dpa-$PhCO_2$Me (5): Methyl *p*-aminobenzoic acid (2 g, 13.23 mmol), 2-bromopyridine (2.5 mL, 26.11 mmol), potassium carbonate (2 g), potassium iodide (200 mg), copper(II) sulfate pentahydrate (200 mg) and phenanthroline (200 mg) were mixed in a 100-mL round-bottomed flask and heated at 200 °C for 7 h. After the reaction mixture was cooled down to room temperature, it was partitioned between water (150 mL) and ethyl acetate (150 mL). The water layer was further extracted with ethyl acetate (2 × 150 mL). The combined organic extracts were dried with sodium sulfate, filtered and evaporated at reduced pressure. The crude product was subjected to column chromatography (Ø 2.5 cm, silica, 75 g), a hexane/ethyl acetate gradient (5:5 → 2:8) was used as eluent. Yield: 2.0 g (52%), pale yellow oil. M_r (calcd. for $C_{18}H_{15}N_3O_2$) = 305.33. MS (TOF ES+): *m*/*z* = 306.1 $[M + H]^+$. HR MS (TOF ES+): exp. 306.1261 and calcd. 306.1243 for $[C_{18}H_{16}N_3O_2]^+$. ^1H NMR ($CDCl_3$): δ = 8.36 (ddd, $^3J_{HH}$ = 1.0, 2.0 and 5.0 Hz, 2 H, $H_{Py\text{-}6}$), 7.79 (d, $^3J_{HH}$ = 9.0 Hz, 2 H, $H_{Ph\text{-}3,5}$), 7.60 (ddd, $^3J_{HH}$ = 2.0, 7.5 and 8.5 Hz, 2 H, $H_{py\text{-}4}$), 7.16 (d, $^3J_{HH}$ = 9.0 Hz, 2 H, $H_{Ph\text{-}2,6}$), 6.99–7.04 (m, 4 H, $H_{py\text{-}5}$ and $H_{py\text{-}3}$), 3.89 (s, 3 H, H_{OMe}) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.14 (C=O), 157.68 ($C_{py\text{-}2}$), 149.30 ($C_{Ph\text{-}1}$), 148.90 ($C_{Py\text{-}6}$), 137.86 ($C_{Py\text{-}4}$), 130.96 ($C_{Ph\text{-}3,5}$), 125.83 ($C_{Ph\text{-}2,6}$), 124.98 ($C_{Ph\text{-}4}$), 119.14 ($C_{Py\text{-}5}$), 117.88 ($C_{Py\text{-}3}$), 52.61 (C_{OMe}) ppm.

Dpa-$PhCO_2$H (2): Ligand **5** (2.0 g, 6.55 mmol) was dissolved in methanol (20 mL), 1 M NaOH (aq., 1.6 g in 20 mL) was stirred room temperature added and monitored by TLC (silica, hexane/ethyl acetate = 3:7). After the disappearance of the starting material (16 h), the reaction mixture was neutralized with HCl and the solvents evaporated to dryness. The residue was partitioned between water (150 mL) and ethyl acetate (150 mL), and the aqueous layer was further extracted with ethyl acetate (2 × 150 mL), dried with sodium sulfate, filtered and evaporated at reduced pressure. Yield: 1.63 g (89%), off white solid. The crude product was used without further purification. M_r ($C_{17}H_{13}N_3O_2$) = 291.30. MS (TOF ES+): *m*/*z* = 292.1 $[M + H]^+$, 314.1 $[M + Na]^+$. HR MS (TOF ES+): exp. 292.1100 and calcd. 292.1086 for $[C_{17}H_{14}N_3O_2]^+$. ^1H NMR ([D$_6$]-DMSO): δ = 8.22 (m, 2 H, $H_{py\text{-}6}$), 8.85 (d, $^3J_{HH}$ = 8.5 Hz, 2 H, $H_{Ph\text{-}3,5}$), 7.66 (ddd, $^3J_{HH}$ = 2.0 Hz, 2 H, $H_{py\text{-}4}$, 7.5 and 8.5), 7.03–6.92 (m, 6 H, $H_{Ph\text{-}2,6}$, $H_{Ph\text{-}2,6}$ and $H_{py\text{-}5}$) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 167.32 (C=O), 157.28 ($C_{py\text{-}2}$), 148.61 ($C_{Ph\text{-}1}$), 148.41 ($C_{Py\text{-}6}$), 138.23 ($C_{Py\text{-}4}$), 130.58 ($C_{Ph\text{-}3,5}$), 127.30 ($C_{Ph\text{-}4}$), 124.89 ($C_{Ph\text{-}2,6}$), 119.19 ($C_{Py\text{-}5}$), 117.63 ($C_{Py\text{-}3}$) ppm.

Dpa-PhCO-Phe-OMe (6): Dpa *p*-benzoic acid (**2**, 220 mg, 0.75 mmol), was suspended in DCM (30 mL) and cooled to 0 °C with an ice bath. HBTU (284 mg, 0.75 mmol), HOBt (125 mg, 0.75 mmol) and DIPEA (700 μL, 4 mmol) were added. After the clear solution was stirred for 1 h at 0 °C, H-Phe-OMe·HCl (165 mg, 0.75 mmol) was added. The reaction mixture was allowed to reach room temperature and the stirring was continued for 20 h. After that period, the reaction mixture was washed with sodium hydrogen carbonate (satd. aq., 3 × 50 mL) and the extracts was dried with sodium sulfate, filtered and evaporated under reduced pressure. The crude product was subjected to column chromatography (silica, hexane/ethyl acetate = 2:8) to yield an off-white solid (190 mg, 56%). M_r (calcd. for $C_{27}H_{24}N_4O_3$) = 452.50. MS (TOF ES+): *m*/*z* = 453.2 $[M + H]^+$, 475.2 $[M + Na]^+$. HR MS (TOF ES+): exp. 453.1932 and calcd. 453.1940 for $[C_{27}H_{25}N_4O_3]^+$. ^1H NMR ($CDCl_3$): δ = 8.33 (ddd, $^3J_{HH}$ = 1.0, 2.0 and 5.0 Hz, 2 H, $H_{py\text{-}6}$), 7.68 (d, $^3J_{HH}$ = 9.0 Hz, 2 H, $H_{Ph\text{-}3,5}$), 7.58 (ddd, $^3J_{HH}$ = 2.0, 7.5 and 9.5 Hz, 2 H, $H_{py\text{-}4}$), 7.31–7.06 (m, 7 H, $H_{Ph\text{-}3,5}$, $H_{Ph\text{-}m}$, $H_{Ph\text{-}p}$ and $H_{py\text{-}3}$), 7.01–6.95 (m, 4 H, $H_{Ph\text{-}o}$ and $H_{Py\text{-}5}$), 6.49 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, NH_{amide}), 4.90 (td, $^3J_{HH}$ = 5.5 and 7.5 Hz, 1 H, $H_{Phe\text{-}\alpha}$), 3.75 (s, 3 H, H_{OMe}), 3.27 (dd, $^3J_{HH}$ = 5.5 and 14.0 Hz, 1 H, $H_{Phe\text{-}\beta1}$), 3.27 (dd, $^3J_{HH}$ = 5.5 and 14.0 Hz, 1 H, $H_{Phe\text{-}\beta2}$) ppm.

^{13}C NMR ($CDCl_3$): δ = 171.95 (C_{ester}), 166.18 (C_{amide}), 157.62 ($C_{py\text{-}2}$), 148.76 ($C_{Ph\text{-}1}$), 148.23 ($C_{py\text{-}6}$), 137.80 ($C_{Ph\text{-}i}$), 135.78 ($C_{py\text{-}4}$), 129.78 ($C_{Ph\text{-}4}$), 129.25 ($C_{phe\text{-}m}$), 128.56 ($C_{Ph\text{-}3,5}$), 128.37 ($C_{phe\text{-}o}$), 127.10 ($C_{phe\text{-}p}$), 125.58 ($C_{Ph\text{-}2,6}$), 118.95 ($C_{py\text{-}5}$), 117.62 ($C_{py\text{-}3}$), 53.33 (C_{OMe}), 52.29 ($C_{Phe\text{-}\alpha}$), 37.73 ($C_{Phe\text{-}\beta}$) ppm.

Caution: *Perchlorate salts are potentially explosive and should be handled with great care!*

Cu Complexes, General Procedure: Solutions containing the corresponding ligand or Cu salt were briefly heated to boiling before adding the Cu salt solution to the ligand solution reaction mixture was filtered hot and cooled to room temperature. If precipitation was observed, the vial was closed and left at room temperature for the indicated period (method 1). If no precipitation occurred, the vial was placed in a container with diethyl ether (10 mL), closed, and left at room temperature for the indicated period (method 2), or the vial was left open for slow evaporation of the solvent (method 3). In all cases the product was isolated by filtration and dried in air.

[Cu(dpa-CH_2CO_2tBu)$_2$(NO$_3$)$_2$] ($\mathbf{3_{Cu}}$): Ligand **3** (62.7 mg, 0.22 mmol), $Cu(NO_3)_2{\cdot}2.5H_2O$ (23 mg, 0.10 mmol) and methanol (10 + 5 mL) were used, method 2. After standing for 7 d, the product was collected by filtration. Yield: 38 mg (50%) of dark brown crystals, X-ray quality. M_r (calcd. for $C_{32}H_{38}N_8O_{10}Cu$) = 758.24. MS (TOF ES+): *m*/*z* = 286 [ligand **3** + H]$^+$, 317 [M – 2NO$_3$]$^{2+}$, 410 [M – NO$_3$ – ligand **3**]$^+$, 633 [M – 2NO$_3$]$^+$. HR MS (TOF ES+): *m*/*z* = exp. 633.2210 and calcd. 633.2251 for [$C_{32}H_{38}N_6O_4{}^{63}Cu$]$^+$.

[Cu(dpa-CH_2CO-PheOMe)$_2$(H$_2$O)$_2$](NO$_3$)$_2{\cdot}$2MeOH ($\mathbf{4_{Cu}}$): Ligand **4** (39 mg, 0.11 mmol), $Cu(NO_3)_2{\cdot}2.5H_2O$ (12 mg, 0.05 mmol) and methanol (10 + 5 mL) were used, method 3. After standing for 5 d, the product was collected by filtration. Yield: 40 mg (75%) of violet-blue crystals, X-ray quality. M_r (calcd. for $C_{46}H_{56}N_{10}O_{16}Cu$) = 1068.54; M (TOF ES+): 391.2 [ligand **4** + H]$^+$, 413.2 [ligand **4** + Na]$^+$, 453.1 [M – 2NO$_3$ – ligand **4**]$^+$, 843.3 [M – 2NO$_3$]$^+$, 866.4 [M – 2NO$_3$ + Na]$^+$. HR MS (TOF ES+): exp. 843.2717 and calcd. 843.2680 for [$C_{44}H_{44}N_8O_6{}^{63}Cu$]$^+$; X-band EPR (9.370 GHz): $g_\parallel$ = 2.17, $A_\parallel = 189\times10^{-4}$ cm^{-1}, $g_\perp$ = 2.05.

[Cu(dpa-PhCO$_2$Me)$_2$(MeOH)$_2$](ClO$_4$)$_2$ ($\mathbf{5_{Cu}}$): Ligand **5** (33.6 mg, 0.11 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (18.5 mg, 0.05 mmol) and methanol (5 + 5 mL) were used, method 1. After standing for 1 d, the product was collected by filtration. Yield: 35 mg (75%) of dark brown crystals, X-ray quality. M_r (calcd. for $C_{36}H_{30}Cl_2N_6O_{12}Cu$) = 873.11; M (TOF ES+): 306.1 [ligand **5** + H]$^+$, 328.1 [ligand **5** + Na]$^+$, 369.2 [M – 2 ClO$_4$ – ligand **5**], 673.2 [M – 2 ClO$_4$]$^+$. HR MS (TOF ES+): exp. 673.1627 and calcd. 673.1625 for [$C_{36}H_{30}N_6O_4{}^{63}Cu$]$^+$.

[Cu(dpa-PhCO-PheOMe)$_2$(ClO$_4$)$_2$] ($\mathbf{6_{Cu}}$): Ligand **6** (37.3 mg, 0.0825 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (13.9 mg, 0.0375 mmol) and methanol (10 + 5 mL) were used, method 3. After standing for 7 d, the product was collected by filtration. Yield: 27 mg (62%) of green-brown crystals, X-ray quality. M_r (calcd. for $C_{54}H_{48}Cl_2N_8O_{14}Cu$) = 1167.46. MS (TOF ES+): *m*/*z* = 453.2 [ligand **6** + H]$^+$, 475.2 [ligand **6** + Na]$^+$, 967.3 [M – 2 ClO$_4$]$^+$. HR MS (TOF ES+): exp. 967.2982 and calcd. 967.2993 for [$C_{54}H_{48}N_8O_6{}^{63}Cu$]$^+$; X-band EPR (9.370 GHz): $g_\parallel$ = 2.24, $A_\parallel = 160\times10^{-4}$ cm^{-1}, $g_\perp$ = 2.07.

X-ray Crystallographic Data Collection and Refinement: A dark blue single crystal of $\mathbf{3_{Cu}}$, a blue crystal of $\mathbf{4_{Cu}}$ and dark green specimens of $\mathbf{5_{Cu}}$ and $\mathbf{6_{Cu}}$ were coated with paratone freezing oil, picked up with nylon loops and mounted in the nitrogen cold stream of the diffractometer. Intensity data were collected using a Bruker AXS APEX diffractometer equipped with a Mo-target rotating anode X-ray source and a graphite monochromator (Mo-K_α radiation, λ = 0.71073 Å). Data reduction (including intensity integration, background, Lorentz and polarization corrections) was performed by use of the Bruker software package. The structure was solved by direct methods (SHELXS)[40] and refined by the full-matrix, least-squares method based on F^2 against all reflections (SHELXL).[41] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed geometrically and were refined by use of the riding model. Crystallographic data of $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$ are listed in Table 3.

Table 3. Crystallographic data for $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$.

	$\mathbf{3_{Cu}}$	$\mathbf{4_{Cu}}$	$\mathbf{5_{Cu}}$	$\mathbf{6_{Cu}}$
Empirical formula	$C_{32}H_{38}CuN_8O_{10}$	$C_{46}H_{56}CuN_{10}O_{16}$	$C_{38}H_{38}Cl_2CuN_6O_{14}$	$C_{54}H_{48}Cl_2CuN_8O_{14}$
Formula weight	758.25	1068.54	937.19	1167.46
T [K]	293(2)	133(2)	93(2)	105(2) K
λ [Å]	0.71073	0.71073	0.71073	0.71073
Crystal size [mm]	0.08 × 0.05 × 0.01	0.20 × 0.18 × 0.07	0.12 × 0.11 × 0.05	0.09 × 0.03 × 0.03
Crystal system	monoclinic	triclinic	monoclinic	monoclinic
Space group	*C*2/*c*	$P\bar{1}$	$P2_1/n$	$P2_1$
a [Å]	19.953(6)	8.2409(15)	11.440(5)	9.530(7)
b [Å]	10.109(3)	11.778(2)	13.457(6)	27.68(2)
c [Å]	17.502(5)	12.749(2)	12.735(6)	9.909(8)
α [°]	90	82.676(3)	90	90
β [°]	102.839(5)	84.052(3)	99.963(10)	103.438(16)
γ [°]	90	81.784(3)	90	90
V [Å^3]	3441.9(17)	1210.2(4)	1930.9(14)	2542(3)
Z	4	1	2	2
$\rho_{calcd.}$ [g cm^{-3}]	1.463	1.466	1.612	1.525
$\mu_{Mo\text{-}K\alpha}$ [mm^{-1}]	0.704	0.534	0.784	0.614
θ range [°]	2.09 ≤ 28.34	2.51 ≤ 28.21	2.21 ≤ 28.45	2.11 ≤ 28.38
Data collected	15906	11582	15262	19198
Independent data	4233 [*R*(int) = 0.0503]	9445 [*R*(int) = 0.0231]	4804 [*R*(int) = 0.0593]	11952 [*R*(int) = 0.0980]
GOF on F^2[a]	1.024	1.019	1.058	1.093
Final R_1 (obsd. data)[b]	0.0455	0.0680	0.0561	0.1192
Final wR_2 (all data)[c]	0.1026	0.1632	0.1294	0.2702
Largest diff. p/h [e Å^{-3}]	0.574/–0.521	0.584/–0.450	0.452/–0.460	1.452/–1.837

[a] GOF = $[\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)]^{1/2}$, where n = number of reflections and p = number of refined parameters. [b] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [c] $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)_2]]^{1/2}$, where $w = 1/\sigma^2(F_o^2) + (aP)^2 + bP$, $P = (F_o^2 + 2F_c^2)/3$.

CCDC-638745 to -638748 (for $\mathbf{3_{Cu}}$–$\mathbf{6_{Cu}}$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): (^{1}H and ^{13}C NMR, absorption, excitation and emission spectra, EPR spectra and crystal packing views of the amino acid bioconjugates **4** and **6**, and/or their copper complexes $\mathbf{4_{Cu}}$ and $\mathbf{6_{Cu}}$).

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[1] a) J. Richter, *Physica E* **2003**, *16*, 157–173; b) M. Shionoya, K. Tanaka, *Curr. Opin. Chem. Biol.* **2004**, *8*, 592–597; c) B. Lippert, J. Müller in *Concepts and Models in Bioinorganic Chemistry* (Eds.: H.-B. Kraatz, N. Metzler-Nolte), Wiley-VCH, Weinheim, Germany, **2006**, pp. 137–158.

[2] See for example: a) K. D. Copeland, M. P. Fitzsimons, R. P. Houser, J. K. Barton, *Biochemistry* **2002**, *41*, 343–356; b) D. R. van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, *104*, 5931–5985.

[3] a) P. Aich, S. L. Labiuk, L. W. Tari, L. J. T. Delbaere, W. J. Roesler, K. J. Falk, R. P. Steer, J. S. Lee, *J. Mol. Biol.* **1999**, *294*, 477–485; b) S. D. Wettig, D. O. Wood, P. Aich, J. S. Lee, *J. Inorg. Biochem.* **2005**, *99*, 2093–2101.

[4] a) A. Ono, H. Togashi, *Angew. Chem. Int. Ed.* **2004**, *43*, 4300–4302; b) A. A. Voityuk, *J. Phys. Chem. B* **2006**, *110*, 21010–21013.

[5] a) S. Atwell, E. Meggers, G. Spraggon, P. G. Schultz, *J. Am. Chem. Soc.* **2001**, *123*, 12364–12367; b) S. I. Kirin, K. Ohr, H. P. Yennawar, C. M. Morgan, L. A. Levine, M. E. Williams, *Inorg. Chem. Commun.* **2007**, *10*, 652–656.

[6] a) K. Tanaka, G. H. Clever, Y. Takezawa, Y. Yamada, C. Kaul, M. Shionoya, T. Carell, *Nat. Biotechnol.* **2006**, *1*, 190–194; b) G. H. Clever, T. Carell, *Angew. Chem. Int. Ed.* **2007**, *46*, 250–253.

[7] a) K. Tanaka, M. Shionoya, *J. Org. Chem.* **1999**, *64*, 5002–5003; b) K. Tanaka, A. Tengeiji, T. Kato, N. Toyama, M. Shionoya, *Science* **2003**, *299*, 1212–1213; c) H. Y. Zhang, A. Calzolari, R. Di Felice, *J. Phys. Chem. B* **2005**, *109*, 15345–15348.

[8] H. Weizman, Y. Tor, *Chem. Commun.* **2001**, 453–454.

[9] C. Brotschi, C. J. Leumann, *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 1195–1997.

[10] a) D.-L. Popescu, T. J. Parolin, C. Achim, *J. Am. Chem. Soc.* **2003**, *125*, 6354–6355; b) R. M. Watson, Y. A. Skorik, G. K. Patra, C. Achim, *J. Am. Chem. Soc.* **2005**, *127*, 14628–14639; c) R. M. Franzini, R. M. Watson, G. K. Patra, R. M. Breece, D. L. Tierney, M. P. Hendrich, C. Achim, *Inorg. Chem.* **2006**, *45*, 9798–9811.

[11] a) L. Zapata, K. Bathany, J.-M. Schmitter, S. Moreau, *Eur. J. Org. Chem.* **2003**, 1022–1028; b) J. S. Choi, C. W. Kang, K. Jung, J. W. Yang, Y.-G. Kim, H. Han, *J. Am. Chem. Soc.* **2004**, *126*, 8606–8607.

[12] L. Zhang, E. Meggers, *J. Am. Chem. Soc.* **2005**, *127*, 74–75.

[13] a) C. Switzer, D. Shin, *Chem. Commun.* **2005**, 1342–1344; b) C. Switzer, S. Sinha, P. H. Kim, B. D. Heuberger, *Angew. Chem. Int. Ed.* **2005**, *44*, 1529–1532.

[14] a) B. P. Gilmartin, K. Ohr, R. L. McLaughlin, R. Koerner, M. E. Williams, *J. Am. Chem. Soc.* **2005**, *127*, 9546–9555; b) K. Ohr, B. P. Gilmartin, M. E. Williams, *Inorg. Chem.* **2005**, *44*, 7876–7885; c) B. P. Gilmartin, R. L. McLaughlin, M. E. Williams, *Chem. Mater.* **2005**, *17*, 5446–5454; d) L. A. Levine, C. M. Morgan, K. Ohr, M. E. Williams, *J. Am. Chem. Soc.* **2005**, *127*, 16764–16765; e) B. P. Gilmartin, Ph. D. Thesis, Pennsylvania State University **2006**; f) L. M. Pantzar, M. S. Thesis, Pennsylvania State University **2006**; g) K. Ohr, R. L. McLaughlin, M. E. Williams, *Inorg. Chem.* **2007**, *46*, 965–974.

[15] J. Müller, D. Böhme, P. Lax, M. Morell Cerda, M. Roitzsch, *Chem. Eur. J.* **2005**, *11*, 6246–6253.

[16] A. Küsel, J. Zhang, M. A. Gil, A. C. Stueckl, W. Meyer-Klaucke, F. Meyer, U. Diederichsen, *Eur. J. Inorg. Chem.* **2005**, 4317–4324.

[17] B. R. Babu, P. J. Hrdlicka, C. J. McKenzie, J. Wengel, *Chem. Commun.* **2005**, 1705–1707.

[18] S. J. Kim, E. T. Kool, *J. Am. Chem. Soc.* **2006**, *128*, 6164–6171.

[19] a) R. E. Shepherd, Y. Chen, R. A. Kortes, M. S. Ward, *Inorg. Chim. Acta* **2000**, *303*, 30–39; b) T. D. Coombs, B. J. Brisdon, C. P. Curtis, M. F. Mahon, S. A. Brewer, C. R. Willis, *Polyhedron* **2001**, *20*, 2935–2943; c) S. P. Foxon, O. Walter, S. Schindler, *Eur. J. Inorg. Chem.* **2002**, 111–121; d) M. J. Rauterkus, S. Fakih, C. Mock, I. Puscasu, B. Krebs, *Inorg. Chim. Acta* **2003**, *350*, 355–365; e) S. Youngme, P. Phuengphai, S. Booncoon, N. Chaichit, *Polyhedron* **2004**, *23*, 1685–1694.

[20] a) V. Uma, M. Kanthimathi, J. Subramanian, B. U. Nair, *Biochim. Biophys. Acta* **2006**, *1760*, 814–819; b) C. Tu, Y. Shao, N. Gan, Q. Xu, Z. Guo, *Inorg. Chem.* **2004**, *43*, 4761–4766.

[21] A. A. Shoukry, *Transition Met. Chem.* **2005**, *30*, 814–827.

[22] a) Y. Uozumi, R. Nakao, *Angew. Chem. Int. Ed.* **2003**, *42*, 194–197; b) B. Karimi, S. Abedi, J. H. Clark, V. Budarin, *Angew. Chem. Int. Ed.* **2006**, *45*, 4776–4779.

[23] a) F. Sinner, M. R. Buchmeiser, R. Tessadri, M. Mupa, K. Wurst, G. K. Bonn, *J. Am. Chem. Soc.* **1998**, *120*, 2790–2797; b) M. R. Buchmeiser, S. Lubbad, M. Mayr, K. Wurst, *Inorg. Chim. Acta* **2003**, *345*, 145–153.

[24] J. Silberg, T. Schareina, R. Kempe, K. Wurst, M. R. Buchmeiser, *J. Organomet. Chem.* **2001**, *622*, 6–18.

[25] C. Bolm, J.-C. Frison, J. Le Paih, C. Moessner, G. Raabe, *J. Organomet. Chem.* **2004**, *689*, 3767–3777 and references cited therein.

[26] a) W. Yang, H. Schmider, Q. Wu, Y.-s. Zhang, S. Wang, *Inorg. Chem.* **2000**, *39*, 2397–2404; b) H. Zhu, M. Ströbele, Z. Yu, Z. Wang, H.-J. Meyer, X. You, *Inorg. Chem. Commun.* **2001**, *4*, 577–581; c) N. M. Shavaleev, A. Barbieri, Z. R. Bell, M. D. Ward, F. Barigelletti, *New J. Chem.* **2004**, *28*, 398–405; d) J. Lee, Q.-D. Liu, M. Motala, J. Dane, J. Gao, Y. Kang, S. Wang, *Chem. Mater.* **2004**, *16*, 1869–1877.

[27] For the incorporation of amino acids into chiral aeg backbone see: a) M. S. Robillard, S. van Alphen, N. J. Meeuwenoord, B. A. J. Jansen, G. A. van der Marel, J. H. van Boom, J. Reedijk, *New J. Chem.* **2005**, *29*, 220–225; b) I. Dilek, M. Madrid, R. Singh, C. P. Urrea, B. A. Armitage, *J. Am. Chem. Soc.* **2005**, *127*, 3339–3345.

[28] a) F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970; b) A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902; c) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609–3612.

[29] For examples of dpa syntheses using the Buchwald–Hartwig amination see ref.[25,26d]

[30] H. B. Goodbrand, N.-X. Hu, *J. Org. Chem.* **1999**, *64*, 670–674.

[31] For examples of dpa syntheses using the Ullmann condensation see ref.[19d,26a,26c]

[32] C. Seward, J. Pang, S. Wang, *Eur. J. Inorg. Chem.* **2002**, 1390–1399.

[33] H. C. Ahn, S. K. Yang, H. M. Kim, S. Li, S.-J. Jeon, B. R. Cho, *Chem. Phys. Lett.* **2005**, *410*, 312–315.

[34] a) E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563–2605; b) F. Neese, *J. Phys. Chem. A* **2001**, *105*, 4290–4299; c) H.-J. Scholl, J. Hüttermann, *J. Phys. Chem.* **1992**, *96*, 9684–9691.

[35] Only single crystals of moderate quality could be obtained for $\mathbf{6_{Cu}}$, the *R* factor is therefore relatively high. A detailed discussion of bond lenghts and angles is not possible in this case, but the data allow discussion of the coordination geometry.
[36] J.-S. Yang, Y.-D. Lin, Y.-H. Lin, F.-L. Liao, *J. Org. Chem.* **2004**, *69*, 3517–3525.
[37] a) K. Severin, R. Bergs, W. Beck, *Angew. Chem. Int. Ed.* **1998**, *37*, 1634–1654; b) R. Alberto, J. K. Pak, D. van Staveren, S. Mundwiler, P. Benny, *Biopolymers* **2004**, *76*, 324–333; c) S. I. Kirin, P. Dübon, T. Weyhermüller, E. Bill, N. Metzler-Nolte, *Inorg. Chem.* **2005**, *44*, 5405–5415; d) M. Cindrić, T. Kajfež Novak, S. Kraljević, M. Kralj, B. Kamenar, *Inorg. Chim. Acta* **2006**, *359*, 1673–1680; e) C. Schickaneder, F. W. Heinemann, R. Alsfasser, *Eur. J. Inorg. Chem.* **2006**, 2357–2363; f) M. C. Kuchta, C. Gemel, N. Metzler-Nolte, *J. Organomet. Chem.* **2007**, *692*, 1310–1314.
[38] For the interaction of metals with the peptide backbone or side chains see: a) O. Yamaguchi, A. Odani, M. Takani, *J. Chem. Soc. Dalton Trans.* **2002**, 3411–3421; b) I. Sovago, K. Osz, *Dalton Trans.* **2006**, 3841–3854.
[39] a) A. Scarso, U. Scheffer, M. Göbel, Q. B. Broxterman, B. Kaptein, F. Formaggio, C. Toniolo, P. Scrimin, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5144–5149; b) H. Zelder, A. A. Mokhir, R. Kramer, *Inorg. Chem.* **2003**, *42*, 8618–8620; c) D. Jayasinghe, H.-B. Kraatz, *Inorg. Chim. Acta* **2006**, *359*, 3054–3065.
[40] G. M. Sheldrick, *SHELXS97*, Program for the Solution of Crystal Structures, University of Göttingen, Germany, **1997**.
[41] G. M. Sheldrick, *SHELXL97*, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, **1997**.

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