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Structural Impact of Coordinating a Helical 2,6-Pyridyl Diamide with Divalent Metals

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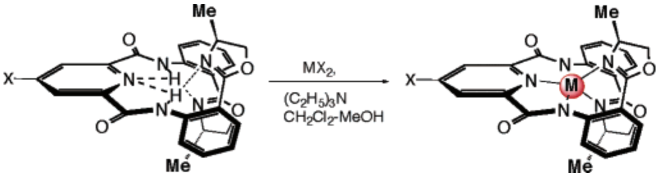
ABSTRACT



The structural consequences of coordinating 2,6-bis[2-((4*S*)-4-methyl-4,5-dihydro-1,3-oxazol-2-yl)phenyl]carbamoylpyridines, 2, with divalent metals such as Cu(II), Ni(II), and Zn(II) are reported. Metal coordination occurs under mild conditions in a manner that preserves the helical bias of the parent ligand in the solid state and in solution. ^{1}H NMR line-shape analysis indicates that metal coordination increases the helical interconversion barrier, thus rigidifying the dynamic helicity of 2.

The structural preorganization imparted by coordination of multiple ligands around a metal center often serves to assist the formation and to increase the stability of protein tertiary structures.[1] The superficial resemblance of dendrimer structures to that of globular proteins, which has been noted in even the earliest reports of dendrimer chemistry,[2] suggests that the selective coordination of metals to dendrimers will also have important structural and functional consequences.[3] Metal ions have been selectively incorporated into dendritic structures within the branches, at the periphery[4] and at the core[5] to create catalysts,[6] sensors,[7] and electronic and photonic materials.[8] Metal-mediated ligand assembly has also been employed as a strategy to construct dendritic branching centers[9] and to bring together coordinating dendrons to form a dendrimer.[10] However, the effect of metal coordination on the conformational properties of dendrimers has been limited to a recent report that depsipeptide dendrimers experience a diastereoselective folding transition, localized near the central core, upon metal complexation.[11]

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10.1021/ol062086s CCC: $33.50

Our interest in understanding the impact of metal coordination on the conformational properties of dendrimers was piqued by prior efforts to coordinate multiple Cu(II) centers to pyridine-2,6-dicarboxamide dendrons.[12] The parent dendrons, based on **1** in Figure 1, adopt compact, helical conformations due to the syn−syn conformational preference of the pyridine-2,6-dicarboxamide repeat unit.[13] In these systems, the helical antipodes experience a highly dynamic equilibrium that interconverts the *M* and *P* conformations quickly with barriers too low to be measured by NMR. However, coordination of Cu(II) to these systems produced a kinetically stable, nondynamic conformational state to be present at room temperature, in contrast to the parent dendrons. These particular systems did not yield to full structural characterization due to difficulties in acquiring X-ray quality crystals and the paramagnetic nature of the copper metal. However, we have recently measured a barrier of 12.3 kcal/mol in THF-d_8 for a related pyridine-2,6-diamide dendron displaying terminal oxazolines (**2**) using NMR line-shape analysis.[14] This system exhibits a highly biased *P*-type helical conformation in solution and in the solid state. The increased helical interconversion barrier, crystallinity, and potential coordination capability of **2** greatly facilitates structural studies. Therefore, this work focuses on understanding the conformational consequences of coordinating biamide **2** to a metal center.

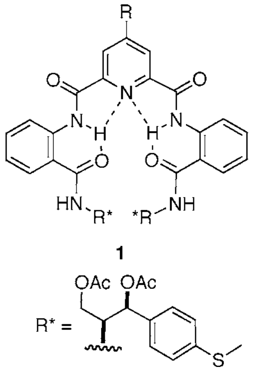

Figure 1. Amide- and oxazoline-terminated dendrons.

Exposure of bisoxazoline **2** to Cu(OTf)$_2$ or Ni(OAc)$_2$ in the presence of triethylamine in 9:1 CH_2Cl_2/MeOH at room temperature afforded the corresponding dark green copper and brown nickel complexes in 69% and 87% yields, respectively (Figure 2). The rapid coordination of **2** by these divalent metals in the presence of a weak base contrasts with bisamide **1** that required full deprotonation with NaH for complexation to proceed at ambient temperature. The neutrality of these complexes permitted efficient purification by silica gel chromatography.

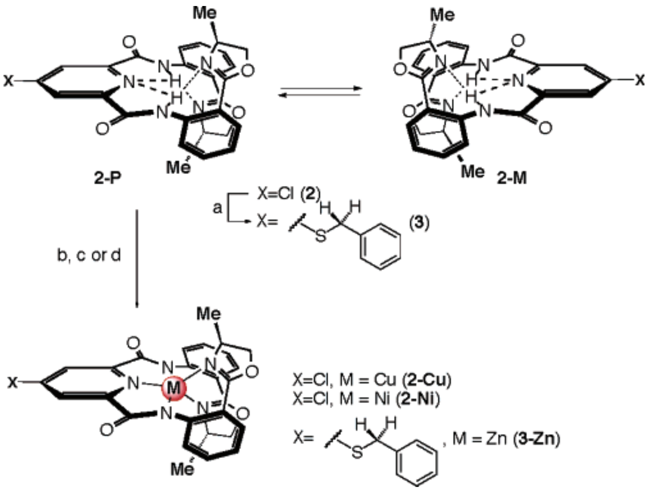

Figure 2. Key: (a) NaH, $PhCH_2SH$, THF, 72%; (b) Cu(OTf)$_2$, CH_2Cl_2−MeOH (9:1), $(C_2H_5)_3N$, 69% (for **2-Cu**); (c) Ni(OAc)$_2$, CH_2Cl_2−MeOH (9:1), $(C_2H_5)_3N$, 87% (for **2-Ni**); (d) $(C_2H_5)_2Zn$, toluene, rt (for **3-Zn**).

The apparent paramagnetism of the complexes precluded use of ^1H NMR for structural characterization. However, electrospray mass spectrometry and X-ray crystallography of the isolated Cu and Ni complexes were consistent with the expected structures (Supporting Information). Green (for **2-Cu**) and brown (for **2-Ni**) orthorhombic crystals in space group $P2_12_12_1$ were obtained by crystallization from CH_2Cl_2/EtOAc (Figure 3).[15] Both metal complexes exhibited a

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(15) **2-Cu**: $C_{27}H_{22}ClCuN_5O_4$, Mo Kα radiation, $T = 200$ K, orthorhombic, $P2_12_12_1$, $a = 9.4787(1)$ Å, $b = 9.6895(1)$ Å, $c = 27.4742(3)$ Å, $V = 2523.34(5)$ Å^3, $Z = 4$, 5788 unique reflections, R1(F) = 0.029, wR2(F^2) = 0.062 (all data). **2-Ni** + $CHCl_3$: $C_{27}H_{22}ClNiN_5O_4$, Mo Kα radiation, $T = 200$ K, orthorhombic, $P2_12_12_1$, $a = 10.0378(1)$ Å, $b = 17.8225(1)$ Å, $c = 19.2315(3)$ Å, $V = 3440.49(5)$ Å^3, $Z = 4$, 7883 unique reflections, R1(F) = 0.046, wR2(F^2) = 0.099 (all data). A second solvent molecule of $CHCl_3$ is badly disordered.

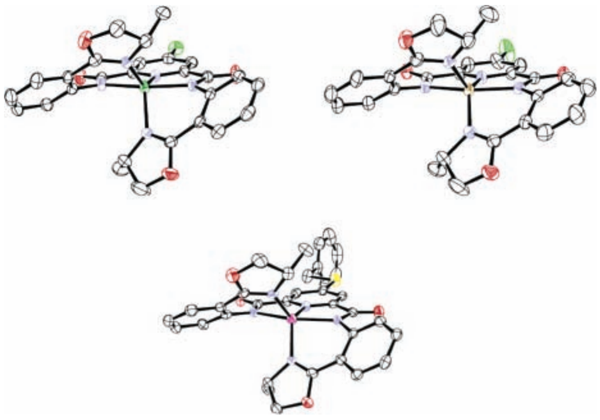

Figure 3. X-ray structures of **2-Cu** (green) and **2-Ni** (brown) and **3-Zn** (from toluene) (purple).

five-coordinate species consisting of the planar tridentate pyridyl diamide with the oxazoline nitrogens occupying axial positions. A *P*-helical conformational preference was exhibited by both complexes, identical to the preference observed for parent dendron **2**.[14]

Coordination contracted the $N_{amide}-N_{amide}$ distances of the pyridyl diamide from 4.569 Å in the parent bisamide **2** to average distances of 3.937 Å in **2-Cu** and 4.032 Å in **2-Ni**. Whereas a decrease in the $N_{amide}-N_{pyr}$ distance from 2.688 Å to 2.526 Å in **2-Cu** and to 2.548 Å in **2-Ni** occurred upon coordination, the $N_{amide}-N_{oxaz}$ distances increased from 2.693 Å to 2.828 in **2-Cu** and to 2.817 Å in **2-Ni**. The average $Cu\cdots N_{amide}$, $Cu\cdots N_{pyr}$, and $Cu\cdots N_{oxaz}$ distances were 1.998, 1.926, and 2.067 Å in **2-Cu** and 2.060, 1.975, and 1.995 Å in **2-Ni**. Five-coordinate complexes similar to **2-Cu** and **2-Ni** have also been observed in other Cu(II) and Ni(II) complexes.[16]

To determine the effect of coordination on the helical interconversion barrier by NMR line-shape analysis, a set of diastereotopic protons were introduced to the complex. This was achieved by appending a thiobenzyl function to bisamide **2** prior to metalation with diethylzinc, which provided diamagnetic complex **3-Zn** as a crystalline solid. NMR line-shape analysis of the AB quartet arising from the methylene hydrogens of the thiobenzyl group in Zn complex **3-Zn** was performed in several solvents. Increasing temperature caused the AB quartet to gradually coalesce into a singlet consistent with the progressive averaging of the two protons undergoing A−B exchange due to an $M \Leftrightarrow P$ helical interconversion (Figure 4). The helical inversion barriers ($\Delta G^{\ddagger}$), calculated using the coalescence temperature method,[17] were significantly higher than that of the parent ligand[14] in all solvents examined (Table 1). The measured barriers were highly sensitive to solvent, ranging from 12.4 to 19.1 kcal/mol.[18] However, we were unable to correlate the solvent dependence with factors such as the dielectric constant, dipole moment, donor number, or viscosity of the solvents.

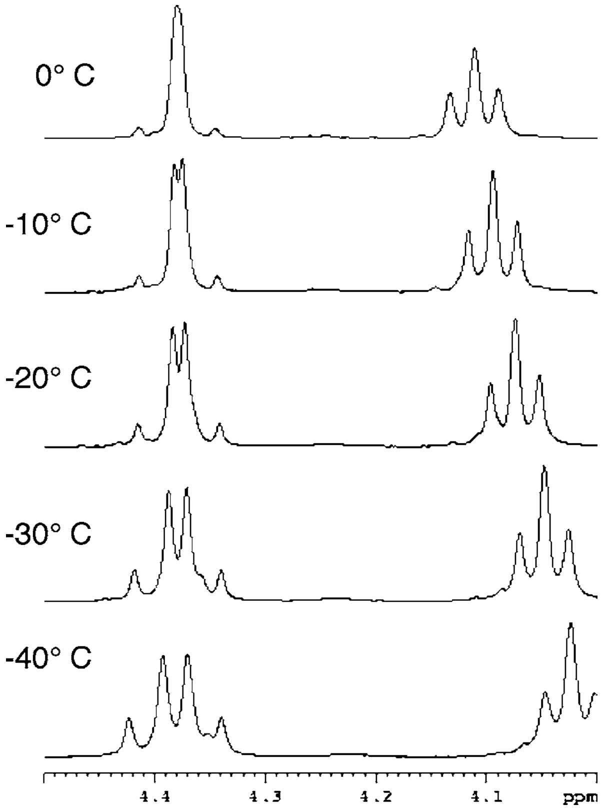

Figure 4. Representative temperature-dependent ^1H NMR spectra of **3-Zn** in pyridine-d_5.

Table 1. Helical Inversion Barrier of **3-Zn** as a Function of Solvent

solvent	$\Delta G^{\ddagger}$ (kcal/mol)	solvent	$\Delta G^{\ddagger}$ (kcal/mol)
DMSO-d_6	19.1	toluene-d_8	15.1
THF-d_8	>17.2[a]	pyridine-d_5	14.1
$CDCl_3$	>17.0[a]	CD_3CN	12.4
acetone-d_6	--[b]	CD_3NO_2	--[b]

[a] This value of the inversion barrier represents a lower limit because the coalescence temperature was higher than the bp of solvent. [b] Splitting of the methylene singlet was not observed in these solvents, even at the solvent freezing point.

To probe the potential of solvent to interact with the zinc center in **3-Zn**, X-ray structures were determined using

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[16] For x-ray structures of related metal complexes of the pyridine-2,6-dicarboxamide unit, see: (a) Yu, Q.; Baroni, T. E.; Liable-Sands, L.; Rheingold, A. L.; Borovik, A. S. *Tetrahedron Lett.* **1998**, *39*, 6831. (b) Kawamoto, T.; Hammes, B. S.; Ostrander, R.; Rheingold, A. L.; Borovik, A. S. *Inorg. Chem.* **1998**, *37*, 3424. (c) Kawamoto, T.; Hammes, B. S.; Haggerty, B.; Yap, G. P. A.; Rheingold, A. L.; Borovik, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 285. (d) Kawamoto, T.; Prakash, O.; Ostrander, R.; Rheingold, A. L; Borovik, A. S. *Inorg. Chem.* **1995**, *34*, 4294.

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[18] For examples of solvent-dependent conformational dynamics in metal complexes, see: (a) Coggin, D. K.; Gonzalez, J. A.; Kook, A. M.; Stanbury, D. M.; Wilson, L. J. *Inorg. Chem.* **1991**, *30*, 1115. (b) Fujiwara, T.; Yamamoto, Y. *Inorg. Nucl. Chem. Lett.* **1975**, *11*, 635.

crystals formed by crystallization from CD_3CN or toluene-d_8. Both solvents provided clear, monoclinic crystals, space group $P2_1$, with an asymmetric unit containing two molecules differing only in the orientation of the thiobenzyl substituent[19] (Figure 3 and Supporting Information). Each five-coordinate Zn complex displayed a preference for the *P*-helix in the solid state, virtually identical to **2-Cu** and **2-Ni** structures. The cocrystallized solvents did not exhibit any coordinative interactions with the metal centers.

The conformational preference of the metal complexes in solution was probed by circular dichroism (CD) spectroscopy. Coordination to Cu(II), Ni(II), and Zn(II) induced a red shift of the $\pi \rightarrow \pi^*$ transition associated with the 2-acylaminophenyl oxazoline chromophore from 309 (**2**) to 341 (**2-Cu**), 351 (**2-Ni**), or 343 nm (**3-Zn**) in the UV−vis spectrum. CD spectra of **2-Cu**, **2-Ni**, and **3-Zn** exhibited positive excitonic couplets centered at ca. 350 nm (Figures 5 and 6). Time-dependent density functional methods (TDDFT) methods were applied to **2-Cu** and **2-Ni**, using the three-parameter Lee−Yang−Parr (B3LYP) functional and the 6-31G* basis set to calculate the direction of the transition dipole moment associated with these transitions (Supporting Information) (Figure 5).[20] Using the calculated electric transition dipole moments, the positive couplet indicates that a *P* helical preference is adopted in solution identical to that of the parent bisamide (**2**).[21]

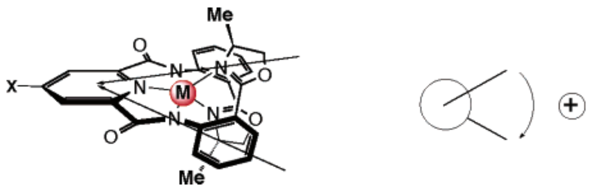

Figure 5. TDDFT-calculated direction of the transition dipole moment of the $\pi \rightarrow \pi^*$ transition of **2-Cu** and **2-Ni** complexes for the *P* helical conformation. The calculated orientation of dipole moments indicates the *P*-helix would be manifested in the CD spectra as a positive couplet.

This work demonstrates that coordination of divalent metals to pyridine-2,6-dicarboxamide dendrons creates a complex with a helical preference identical to that of the parent system in the solid state and in solution. However, coordination rigidifies the structure in a manner that affords significantly higher, solvent-dependent helical interconversion barriers. These observations provide a rationalization of how coordination to Cu(II) centers caused the dendrons in ref 12 to become conformationally “locked”.

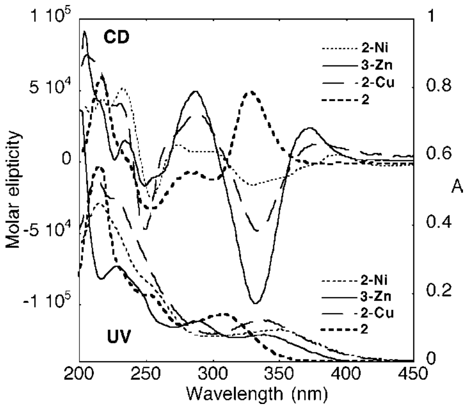

Figure 6. Circular dichroic and UV spectra of metal complexes of **2** and **3**.

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Supporting Information Available: Experimental procedures and compound characterization for all compounds. Temperature-dependent ^1H NMR spectra for **3-Zn**, TDDFT calculation details and molecular orbital plots for **2-Cu**, **2-Ni**, and **3-Zn**, and unit cells for X-ray structures of **2-Cu**, **2-Ni**, and **3-Zn**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] **3-Zn** with toluene-d_8: $2(C_{34}H_{29}ZnSN_5O_4)$ + toluene-d_8, Mo Kα radiation, $T = 150$ K, monoclinic, $P2_1$, $a = 9.3015(1)$ Å, $b = 15.6450(2)$ Å, $c = 23.0613(3)$ Å, $\beta = 95.222(4)°$, $V = 3342.01(7)$ Å^3, $Z = 2$, 11 655 unique reflections, $R1(F) = 0.058$, $wR2(F^2) = 0.102$ (all data). **3-Zn** with CD_3CN: $C_{34}H_{29}ZnSN_5O_4$ + CD_3CN, Mo Kα radiation, $T = 200$ K, monoclinic, $P2_1$, $a = 14.489(1)$ Å, $b = 9.618(1)$ Å, $c = 23.916(2)$ Å, $\beta = 91.480(4)°$, $V = 3331.7(5)$ Å^3, $Z = 4$, 11 542 unique reflections, $R1(F) = 0.047$, $wR2(F^2) = 0.090$ (all data).

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[21] Similar to **3-Zn**, the ^1H NMR spectrum of bisamide **3** revealed a single set of resonances consistent with the presence of a single diastereomer at low temperatures.