

Amino Acid-Derived Ligands for Transition Metals: Catalysis via a Minimalist Interpretation of a Metalloprotein

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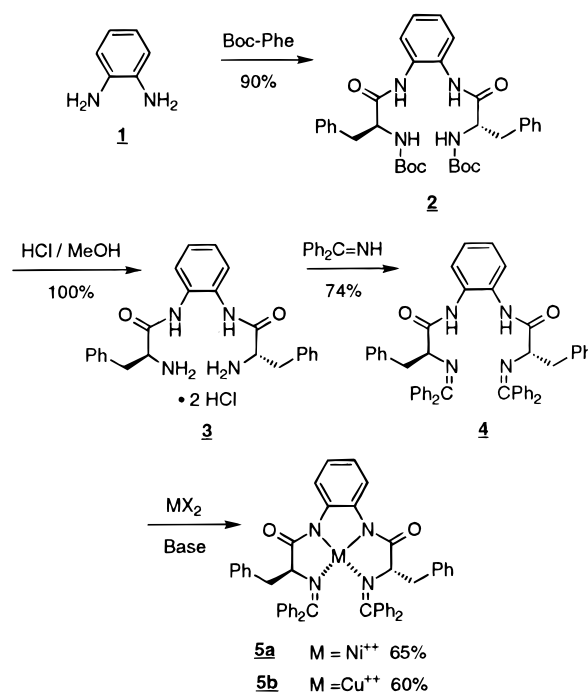
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Chemists and enzymologists have attempted to understand and duplicate the incredible efficiency of metalloproteins for over 70 years now.¹ Of particular interest are the metalloporphyrins which display a wide variety of chemical reactivity, principally due to their ability to complex almost any of the transition metals.² Most of the metalloporphyrin chemistry has been developed in a “self-governing field,” far removed from the practical constraints imposed by the requirements of catalysis and organic synthesis.³ Exquisitely powerful and selective catalysts have been designed based on the porphyrin ring system,⁴ but the lengthy synthesis required to produce these metal-binding moieties may preclude their widespread use as practical chemical catalysts.⁵ A more direct approach is to use the peptide backbone to bind metals^{6a} or a peptide-derived macrocycle.^{6b,c}

Since the majority of amino acids in a typical protein are structural in nature, and thus far removed from the active site, it should be possible to replace them with a simple achiral diamine which would serve to bring only two optically active amino acid residues into close proximity to form a simplified “active site.”⁷ A short, chemically efficient synthesis of the ligand system with chirality incorporated from the amino acids should be possible, and a variety of transition metal-binding geometries should be accessible. This allows for development of a variety of catalysts. Creation of new symmetry elements centered on the metal would be ideal⁸ and should allow for the efficient transfer of chirality to the substrate upon catalysis. While only C₂-symmetric tetradentate complexes⁹ will be described in this paper, many other geometries are possible with the introduction of other linkers and more functionalized amino acids capable of metal binding.¹⁰

The synthesis of the Ni^{II} and Cu^{II} complexes **5a** and **5b** is depicted in Scheme 1. Phenylenediamine (**1**) was doubly acylated with Boc-L-phenylalanine with various condensation

Scheme 1



agents (DCC or BOP) to provide the Boc-protected bis-amide **2** in excellent yield. The Boc groups were quantitatively removed with HCl in methanol to yield crystalline **3**, which was treated with diphenylketimine to yield the Schiff base **4**.¹¹ Reaction of **4** with NiBr₂ in refluxing MeOH in the presence of the Et₃N provided the deep maroon, crystalline complex **5a** which was air-stable and water-stable and was readily chromatographed on SiO₂. This low-spin complex was characterized by ¹H-NMR and provided crystals suitable for single-crystal X-ray analysis. Similarly, reaction of **4** with CuCl₂ in DMF at room temperature with the much stronger base DBU provided brown crystals of **5b** after flash chromatography on SiO₂. This paramagnetic complex was subjected to EPR analysis.

A single crystal of **5a** was subjected to X-ray analysis, and a preliminary structure (*R* ≈ 8%) was obtained (Figure 1). Two molecules, a totally symmetric molecule **5a'**, possessing a C₂ axis, and an unsymmetric molecule **5a''** were observed in the unit cell, differing predominantly by rotation about one ^αC–^βC bond in a phenylalanine residue. Thus, the solid-phase X-ray data strongly supported the NMR data obtained in CDCl₃ solution. In addition to rotation about the phenylalanine side chain, the two conformations differed in metal geometry as well (Table 1). In both molecules the Ni–N=CPh₂ bond lengths

(8) The idea for these complexes sprang from work in which [7]-helicenes bearing terminal cyclopentadienyl anions were used to introduce optical activity into transition metals: (a) Dewan, J. C. *Organometallics* **1983**, *2*, 83–88. (b) Sudhakar, A.; Katz, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 179–181. (c) Gilbert, A. M.; Katz, T. J.; Geiger, W. E.; Robben, M. P.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3199–3211. (d) Dai, Y.; Katz, T. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2109–2111. (e) Kawamoto, T.; Hammes, B.S.; Haggerty, B.; Yap, G. P. A.; Rheingold, A. L.; Borovik, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 285–286.

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(10) In a similar fashion L-Phe has been reacted with ethylenediamine, propylenediamine, 1,3-diaminonaphthalene, and diaminomaleonitrile (DAMN) to produce other tetradentate ligands. *o*-Phenylenediamine has been reacted with L-Ser and L-His to produce hexadentate ligands. This work will be reported in full elsewhere.

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(2) (a) *Porphyryns and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Amsterdam, 1975. (b) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1979.

(3) Meunier, B. *Bull. Soc. Chim. Fr.* **1986**, 578–594.

(4) Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401–1449.

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(7) Several groups have used cyclic dipeptides (diketopiperazines) as asymmetric catalysts. We like to think of these small peptides as “microenzymes.” Cf.: (a) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181–185. (b) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740–6741. (c) Lipton, M.; Iyer, M. S.; Gigstad, K.M.; Namdev, N. D. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911. With the incorporation of a metal binding site it is natural to refer to these moieties as “micro-metalloenzymes.”

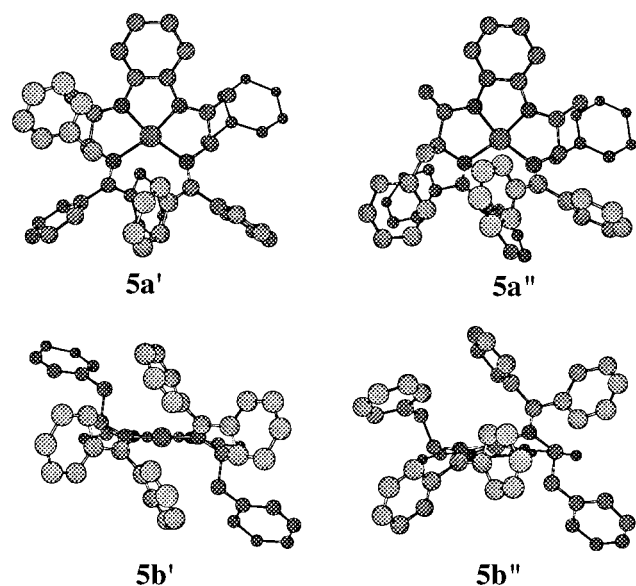


Figure 1.

Table 1

	5a'	5a''
Selected Bond Lengths (Å)		
Ni–N(1)	1.99	1.98
Ni–N(2)	1.88	1.87
Ni–N(3)	1.87	1.83
Ni–N(4)	1.98	1.93
Selected Bond Angles (deg)		
N(1)–Ni–N(2)	81.5	85.0
N(2)–Ni–N(3)	85.6	83.2
N(3)–Ni–N(4)	82.5	82.0
N(1)–Ni–N(4)	110.4	110.7
rms dev from plane (Å)	0.020	0.119

were somewhat longer than the Ni–N–C=O bond lengths, and the complexes are more trapezoidal, relative to porphyrin complexes, which tend to be more planar and strictly square. While the symmetric **5a'** showed almost no deviation from square planarity, the four nitrogens in **5a''** showed a noticeable tetrahedral distortion—0.119 Å rms deviation overall from the ideal plane. The Ph₂C=N– groups were observed to be “stacked” in both cases, a factor which undoubtedly adds to the “helical twist” about the metal.

Complex **5b** was purified by flash chromatography and recrystallization and subjected to electron spin resonance spectroscopy at 9.447 GHz. The EPR parameters were evaluated from a combination of glass and liquid-state spectra.¹²

Simulation of the spectra based on QPWA is in progress. From preliminary data we can conclude that the complex is qualitatively similar to Cu^{II} tetraphenylporphyrin complexes, but with increased tetrahedral distortion from square planarity.¹³ Strong evidence for the helical nature of these complexes was provided by the unusually large optical rotation upon insertion of the metal.¹⁴

Since several groups showed previously that Ni^{II} can catalyze the epoxidation of olefins,¹⁵ the epoxidation of simple *cis*- and *trans*-olefins was examined using complex **5a** and commercial bleach (NaOCl) as an oxidant. No attempt was made to optimize the reactions. The *trans*-epoxides were observed as the major product in every case, regardless of the starting olefin geometry. While the ee's were not large (~4%), turnover numbers of 12–14 were observed with *trans*-β-methylstyrene and **5a**, indicating that the ligand system can function under the conditions of catalysis. Most likely, the epoxidation does not occur on the metal,^{14d} but is mediated by the hypochlorite oxidation product *OCl.

Several other ligands constructed from various diamines and amino acids have also been prepared using the same methodology outlined above. The insertion of other transition metals and the examination of the catalytic activity of the resulting complexes are also in progress. Since these catalysts are formed easily in four steps from readily available chiral starting materials, it is anticipated that they will find widespread applications.

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(12) Glass: $g_{\parallel} \approx 2.18$ MHz and $A_{\parallel} \approx 625$ MHz. Liquid: $g_{av} = 2.093$ MHz and $A_{av} \approx 284$ MHz, and $g_{\perp} = 2.05$ MHz and $A_{\perp} \approx 114$ MHz. Assuming the hyperfine interaction with Cu^{II} is isotropic, the magnitude is 37–42 MHz.

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(14) **4**: $[\alpha]_D = -156^{\circ}$ ($c = 0.560$ g/100 mL of CHCl₃). **5a**: $[\alpha]_D = -494^{\circ} \pm 11^{\circ}$ ($c = 0.002875$ g/100 mL of CHCl₃). **5b**: $[\alpha]_D = -2020^{\circ} \pm 140^{\circ}$ ($c = 0.001875$ g/100 mL of CHCl₃). This last rotation is reminiscent of the helicenes in terms of the large degree of optical activity: Laarhoven, W. H.; Prinsen, W. J. C. *Topics Current Chem.* **1984**, *125*, 63.

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