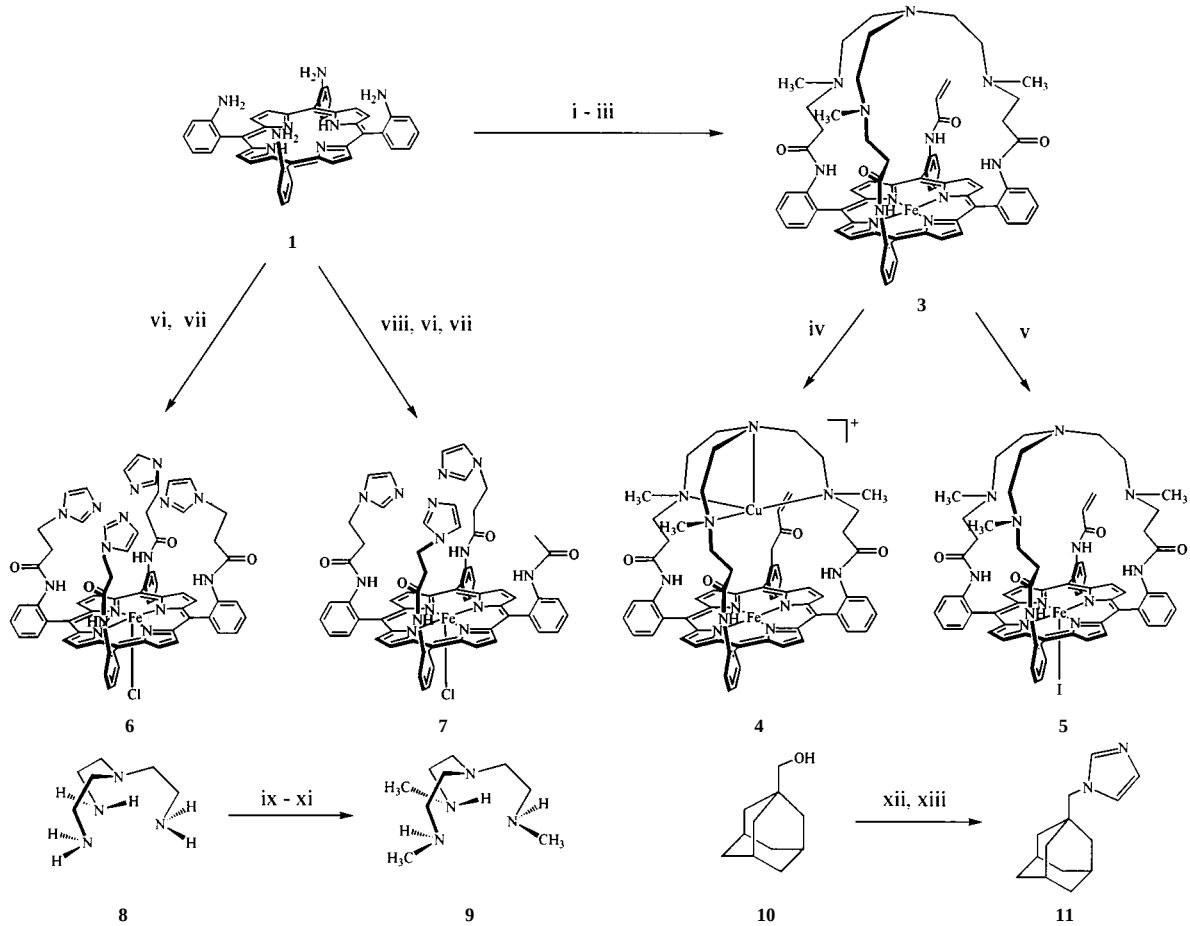
# Covalently supported porphyrins as ligands for the preparation of heme $a_3/Cu_B$ binuclear active site analogues of heme–copper terminal oxidases and metallation under mild conditions

**Jin-Ook Baeg and R. H. Holm***

*Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, USA*

**New covalently supported binucleating porphyrins have been prepared as potential structural and/or functional ligands for the iron–copper (heme $a_3/Cu_B$) active sites of heme–copper oxidases, and the introduction of iron and copper into one porphyrin under mild reaction conditions has been developed.**

Essential to the elucidation of the mechanism of dioxygen reduction to water and its inhibition at the binuclear heme $a_3/Cu_B$ active sites of heme–copper oxidases[1–5] is the construction of a functional enzyme analogue system. This can presumably be achieved by synthesizing covalently supported binucleating heme ligands whose iron–copper arrangement approaches the enzyme active site stereochemistry. Collman *et al.*[6–9] have reported the synthesis of several such ligands by a congruent Michael multiple addition method, including one ligand whose $Co^{II}$–$Cu^{I}$ derivative shows catalytic activity in the four-electron reduction of dioxygen to water.[9,10] These systems primarily contain 1,4,7-triazacyclononane-, cyclen-, or cyclam-adapted copper binding sites. Our previous investigations of binuclear heme–Cu bridged assemblies have featured a variety of unsupported bridges suitable for structural and electronic elucidation.[11–20] To extend our investigation to reactivity with dioxygen and inhibiting ligands such as cyanide, we have undertaken the design and synthesis of covalent binucleating ligands and their complexes capable of sustaining various Fe–X–Cu bridges. Here we report the preparation of three new porphyrin ligands, using Michael addition methodology for one of them, with structural features somewhat different than those previously described.[6–9]




**Scheme 1** *Reagents and conditions*: i, $H_2C$=CHCOCl, $Et_3N$, $CH_2Cl_2$, 46%; ii, $[Fe(OH_2)_6][BF_4]_2$, 2,6-dimethypyridine, THF, 90%; iii, **9**, $CH_2Cl_2$, MeOH, 48 h, 32%; iv, $[Cu(MeCN)_4]PF_6$, THF, 24 h, 70%; v, $I_2$, THF, 12 h, 82%; vi, **15**, $SOCl_2$, DMF, 20 h, 60%; vii, $FeSO_4$, HOAc, $O_2$, NaOH, HCl, 57–60%; viii, MeCOCl, $Et_3N$, $CH_2Cl_2$, 2 h, 50%; ix, PhCHO, 1 N HCl, benzene, molecular sieves, $NaBH_3CN$, 85%; x, $HCO_2H$, HCHO, 110 °C, 12 h, 76%; xi, $Pd(OH)_2$ on carbon, MeOH, $H_2$ (1 atm), 60 °C, 20 h, 90%; xii, $PBr_3$, quinoline, bromobenzene, 24 h, 165 °C, 65%; xiii, sodium imidazolate, $Me_2SO$, 150 °C, 20 h, 84%

Synthetic pathways for ligands and complexes are depicted in Scheme 1.† Reactions were carried out at ambient temperature unless noted otherwise. A key starting material, as in related work,[6–8] is *meso*-α,α,α,α-tetrakis(*o*-aminophenyl)porphyrin **1**.[21] Treatment of **1** with acryloyl chloride and triethylamine in dichloromethane affords the corresponding tetrakis(acryloylamidophenyl)porphyrin **2**[6] (46%). The new tetraamine **9** was prepared in three steps from tris(2-aminoethyl)amine **8** in 58% overall yield. Reaction of **8** with benzaldehyde in dry benzene containing ethereal 1 M HCl and molecular sieves, followed by reduction with $NaBH_3CN$, gave tris[2-(benzylamino)ethyl]amine **12** (85%). Subsequent reaction of **12** with formic acid and formaldehyde solution afforded tris[2-(benzylmethylamino)ethyl]amine **13** (76%). Palladium hydroxide catalyzed the selective debenzylation of **13** under 1 atm of dihydrogen at room temperature for 20 h to afford **9** (90%). Iron(II) was inserted into **2** at room temperature by reaction of $Fe[BF_4]_2$ in the presence of 2,6-dimethylpyridine to give [$Fe^{II}$(**2**)] (90%). Metal insertion under these mild conditions is necessary to minimize undesirable porphyrin isomerization. In the next step, reaction of the Michael acceptor [$Fe^{II}$(**2** −2H)] with tetraamine **9** in dichloromethane for 48 h gave the covalently capped iron(II) porphyrin **3** (32%, $\lambda_{max}$ 426 nm, *m/z* 1133) with a vacant tetraaza binding site. The free ligand of **3** ($\lambda_{max}$ 424 nm, *m/z* 1079) was obtained by the same reaction in comparable yield using **2**. Treatment of **3** with 1 equiv. of $[Cu(MeCN)_4]PF_6$ in THF for 24 h afforded the binuclear $Fe^{II}$–$Cu^{I}$ assembly **4** (70%, $\lambda_{max}$ 426 nm, *m/z* 1196). Complex **3** was readily oxidized by excess iodine in THF to give the iron(III) complex **5** (82%, $\lambda_{max}$ 417 nm, *m/z* 1260) in which the iodide ligand is presumed to occupy an axial position on the unhindered heme face as shown. The EPR spectrum shows **5** to be high spin ($g_{\|}$ = 2.03, $g_{\perp}$ = 5.73; acetonitrile, 10 K).

Ligand binding by complexes **3**–**5** at the iron site could introduce ligands internal to the tetraaza cavity or on the unhindered face. To direct ligands to the desired internal venue, an exceptionally bulky axial base, incapable of residing in the cavity, has been prepared. Selective bromination of 1-adamantylmethanol using $PBr_3$ gave 1-bromomethyladamantane **14** (65%). Reaction of **14** with equimolar sodium imidazolate in $Me_2SO$ at 150 °C yielded the *N*-adamantylimidazole **11** (84%).

Spectroscopic evidence has supported the coordination of three imidazole groups from histidyl residues by $Cu_B$,[1,2,5] a matter recently confirmed by the X-ray structures of two enzymes in the oxidized form.[3,4] To our knowledge, no binucleating porphyrin having this type of binding potentiality with copper is available, the closest approach being those with pyrazolyl binding sites.[22] We have sought binucleating ligands of this sort from the reactions of **1** and the acyl chloride of 3-(*N*-imidazolyl)propionic acid **15**.[23] Treatment of **1** with an excess (5 equiv.) of **15** and $SOCl_2$ in DMF for 20 h produced the free base of **6** (60%, $\lambda_{max}$ 421 nm, *m/z* 1163). In another experiment, **1** was monoprotected by reaction with 1 equiv. of acetyl chloride in dichloromethane for 2 h to give the triphenyl(*o*-methylamidophenyl)porphyrin, which was resolved from an isomeric mixture by preparative TLC (acetone–chloroform, 3 : 7 v/v; 50%). This compound was subjected to reaction with 4 equiv. of **15** and $SOCl_2$ in DMF to give the desired free base of **7** (58%, $\lambda_{max}$ 420, *m/z* 1083) containing three imidazole groups. Both free bases could be metalated by the $FeSO_4$/HOAc method:[24] **6** [60%, $\lambda_{max}$ 425 nm, *m/z* 1252]; **7** [57%, $\lambda_{max}$ 424 nm, *m/z* 1172].

In summary, we have prepared three new types of binucleating porphyrin ligands and their iron complexes capable of covalently supporting Fe–X–Cu bridges. The ligand of **3**–**5** furnishes a trigonal four-coordinate tetraaza binding site, one feature of which is direction of the magnetic orbital of $Cu^{II}$ toward a bridging ligand such as dioxygen, hydroxide or cyanide, thereby optimizing magnetic coupling of the iron atom across the bridge.[20] Complex **6** is favorable to planar coordination by $Cu^{II}$, while **7** provides the tris(imidazole) binding site of the native oxidases. The binding sites in **3**–**5** and **7** are necessarily displaced off a perpendicular through the iron atom normal to the heme plane, as is the case for two crystalline oxidases.[3,4] The sterically demanding ligand **11** has been developed as a promotor of the bridging *vs*. terminal ligand binding mode.

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## Notes and References

* E-mail: holm@chemistry.harvard.edu

† Full experimental details will be published in due course. All new compounds were fully characterized by spectroscopic methods. UV–VIS spectra were measured in THF. Masses quoted are from FAB or electrospray mass spectral measurements and apply to the principal ion $(M + H)^+$. Stated yields refer to isolated compounds.


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