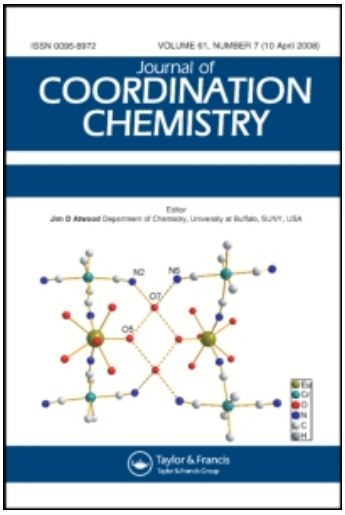

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Synthesis and spectroscopic characterization of a porphyrin-dibenzimidazole dinucleating ligand and its cobalt-copper heterodinuclear complex as a cytochrome *C* oxidase active site model

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Online publication date: 12 May 2010

To cite this Article Lu, Weibing , Lv, Qingye , Wang, Cunxin and Zhou, Xiaohai(2003) 'Synthesis and spectroscopic characterization of a porphyrin-dibenzimidazole dinucleating ligand and its cobalt-copper heterodinuclear complex as a cytochrome *C* oxidase active site model', Journal of Coordination Chemistry, 56: 16, 1383 — 1390
To link to this Article: DOI: 10.1080/00958970310001636462
URL: http://dx.doi.org/10.1080/00958970310001636462

J. Coord. Chem., Vol. 56, No. 16, 10 November 2003, pp. 1383–1390

SYNTHESIS AND SPECTROSCOPIC CHARACTERIZATION OF A PORPHYRIN–DIBENZIMIDAZOLE DINUCLEATING LIGAND AND ITS COBALT–COPPER HETERODINUCLEAR COMPLEX AS A CYTOCHROME *C* OXIDASE ACTIVE SITE MODEL

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(Received 16 December 2002; In final form 6 October 2003)

A new dinucleating ligand consisting of a tetraphenylporphyrin derivative covalently linked with di(2-benzimidazolylmethyl)imine and its homodinuclear Co–Co and heterodinuclear Co–Cu complexes were synthesized and spectroscopically characterized. The heterobimetallic Co–Cu complex, a cytochrome *c* oxidase active site model, can be obtained by a simple metathesis reaction of the homodinuclear complex with the metal salt in high yield.

Keywords: Dinucleating ligand; Homodinuclear; Heterodinuclear; Cytochrome *c* oxidase; Model compound

INTRODUCTION

Metalloenzymes have received much attention because of their vital roles in biological processes. Among various polymetallic metalloenzymes, cytochrome *c* oxidase (CcO) is of special interest. CcO, the terminal enzyme of the respiratory chain in aerobic organisms, catalyzes the 4 H^+, 4 e^- reduction of O_2 to water without leakage of partially reduced toxic intermediates such as H_2O_2 to cell [1]. X-ray crystallographic studies [2–4] demonstrate that the O_2-binding/activating site in CcO consists of a myoglobin-type iron center (heme a_3) and a copper atom (Cu_B) coordinated to three histidine ligands.

In recent years, with extensive study of some carefully designed functional analogues [5–25] of CcO, considerable progress has been made in elucidating the catalytic mechanism of O_2 reduction to water at the heterodinuclear heme a_3/Cu_B site of CcO. Many issues remain uncertain, however, among which the role of the copper in the catalytic process is the key subject under debate. Construction of artificial modeling systems

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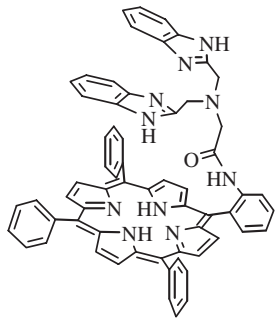
ISSN 0095-8972 print: ISSN 1029-0389 online © 2003 Taylor & Francis Ltd
DOI: 10.1080/0095897031000163646 2



3

FIGURE 1 The proposed structure of the dinucleating ligand **3**.

of CcO is an essential and effective strategy, which may not only potentially address the mechanism issue but also allow the study of structure–catalytic activity relationships.

In this article, we present the synthesis and characterization of a porphyrin-di(2-benzimidazolylmethyl)imine (IDB) dinucleating ligand (Fig. 1), as well as a synthetic pathway leading to the corresponding homodinuclear Co–Co and heterobimetallic Co–Cu complex of this ligand.

EXPERIMENTAL

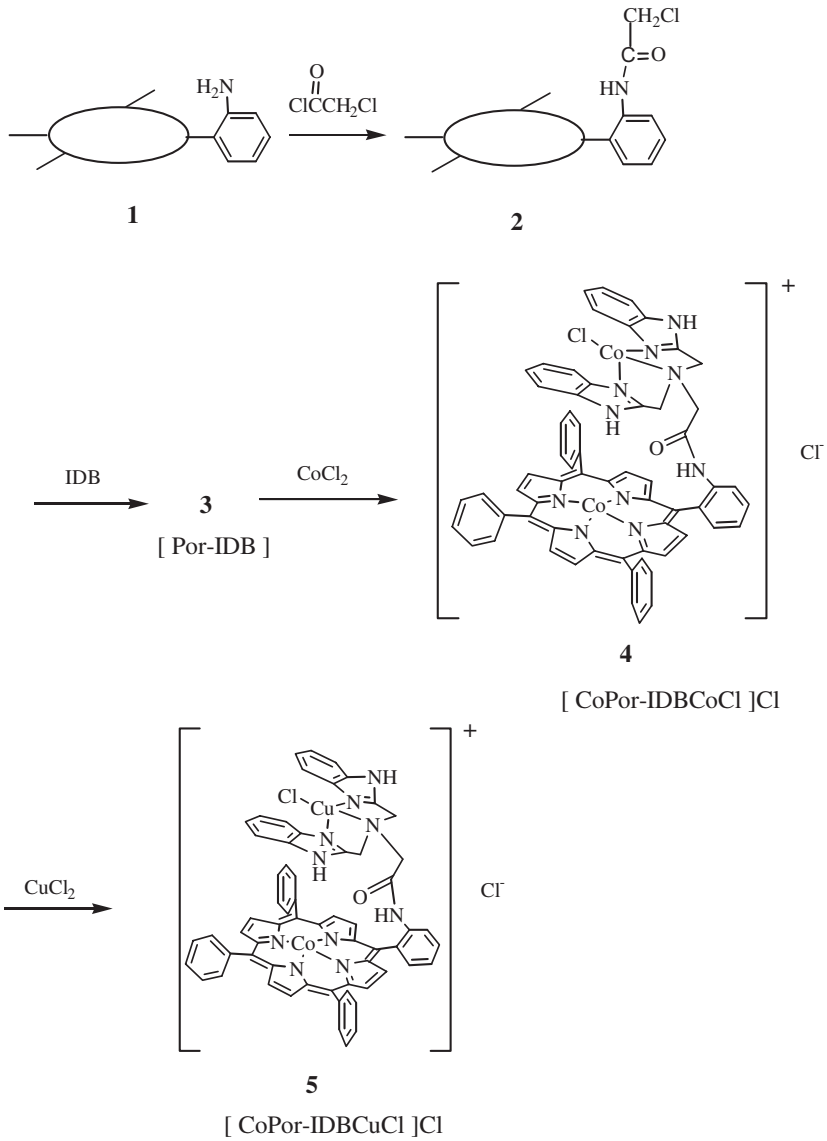
Materials and Apparatus

^{1}H NMR spectra were recorded on a Varian-Mercury300 spectrometer with TMS as internal standard. UV-Vis spectroscopy was performed using a Shimadzu UV-240 spectrophotometer. C, H, and N elemental analyses were determined by a Perkin-Elmer 240B elemental analyzer and metal content was determined with an HP 7500a ICP-MS (Agilent) System. IR spectra were recorded on a Shimadzu FT-IR-8100 spectrophotometer (KBr pellets). MS spectra were recorded on a Finnigan LCQ ESI-MS spectrometer or a ZAB-HF-3F MS instrument. X band ESR spectra were recorded on an ER 200-D-SRC 10 12 spectrometer. Cyclic voltammograms were recorded on a CHI model 660A electrochemical workstation with a three-electrode system: Pt disk, working electrode; Pt wire, counter electrode; and saturated calomel electrode (SCE), reference electrode. The working and counter electrodes were cleaned ultrasonically in HNO_3, acetone, and doubly distilled water sequentially prior to use. High purity argon gas was used to deaerate the solutions throughout the electrochemical experiment.

DMF was dried with 4A molecular sieves and redistilled under argon. Pyrrole was purchased from Fluka and redistilled prior to use. All other chemicals were purchased from commercial sources and used as received without further purification. IDB was prepared by a literature method [26]. 5-(*o*-Aminophenyl)-10,15,20-triphenylporphyrin was prepared according to a literature procedure [27].

Synthesis

The synthetic route to the final model complex is shown in Scheme 1.



SCHEME 1 Synthetic route to the model complex **5**.

Preparation of Precursor 2

To a refluxed solution of 5-(*o*-aminophenyl)-10,15,20-triphenylporphyrin, **1** (157 mg, 0.25 mmol), in benzene, a solution of chloroacetyl chloride (0.1 cm^3, 1.25 mmol) in the same solvent (5 cm^3) was added over a 10-min period. The reaction mixture was stirred under reflux for another 30 min, cooled and washed with saturated aqueous sodium carbonate. The organic layer was separated, dried with anhydrous sodium sulfate, and filtered. After removal of the solvent from the filtrate under reduced pressure, the desired compound was obtained. Further purification was performed by recrystallization from CH_3Cl/CH_3OH to afford the precursor **2** (yield 123 mg, 70%).

IR(cm^{-1}): 3317, 3047, 2910, 2843, 1676(C=O), 1614, 1521, 1467, 1441, 1344; MS(ESI): 705.2(M); UV-Vis($CHCl_3$): 420, 512, 546, 585, 647; ^1H NMR($CDCl_3$): 8.82(m, 8H, H_β), 8.22(m, 6H, H_{ar}), 8.08(d, 2H, H_{ar}), 7.79(m, 9H, H_{ar}), 7.59(t, 2H, H_{ar}), 3.43(s, 2H, CH_2), −2.72(s, 2H, pyrrole NH).

Preparation of Dinucleating Ligand 3

2 (141 mg, 0.2 mmol), IDB (554 mg, 2 mmol) and anhydrous potassium carbonate (200 mg) were thoroughly mixed in DMF and stirred at 110°C for 24 h under N_2, then the mixture was concentrated to a smaller volume under reduced pressure, poured into distilled water, and filtered. The residue was dissolved in a minimum amount of CH_2Cl_2 and chromatographed on a column of silica gel using CH_2Cl_2/CH_3OH (9 : 1) as the eluent. The second red band eluted off the column was the dinucleating ligand **3**. Recrystallization from chloroform/hexane gave pure **3** (yield 123 mg, 65%).

IR(cm^{-1}): 3311, 3054, 2920, 2851, 1663(C=O), 1597, 1531, 1437; MS(ESI): 947.5(M + H); 687(CoTPP + NH + H); 629(TPP + NH); UV-Vis($CHCl_3$): 244, 275, 282, 420, 513, 554, 588, 644; ^1H NMR($CDCl_3$): 8.92(m, 8H, H_β), 8.77∼8.76(m, 6H, H_{ar}), 7.94(m, 3H, H_{ar}), 7.71∼7.72(m, 8H, H_{ar}), 7.54(m, 10H, H_{ar}), 6.34(s, 1H, CONH), 3.70(s, 4H, $2CH_2$), 1.90(s, 2H, CH_2), −2.72(s, 2H, pyrrole NH); Anal. Calcd. for $C_{62}H_{46}N_{10}O$(%): C, 78.65; H, 4.86; N, 14.80. Found: C, 78.19; H, 5.17; N, 15.24.

Preparation of the Homodinuclear Complex 4

Under N_2 gas, **3** (94.6 mg, 0.1 mmol) and $CoCl_2 \cdot 6H_2O$ (238 mg, 1 mmol) in DMF (20 cm^3) were refluxed for 30 min. After cooling, the mixture was poured into water and filtered. The precipitate was dried overnight under vacuum, dissolved in a minimum of $CHCl_3$, and chromatographed on a column of silica gel with $CHCl_3$/EtOH(13 : 1) as eluent. The first red band eluted off the column was collected and the solvent was evaporated under vacuum. The residue was recrystallized twice from $CHCl_3$/EtOH to provide **4** (yield 94 mg, 83%).

IR(cm^{-1}): 3319, 3053, 2924, 2851, 1660(C=O), 1599, 1537, 1449, 1005(N–Co); MS(FAB): 1097(M − Cl); 1062(M − 2Cl); 670(CoTPP − H); 686(CoTPP + NH); 628(TPP + NH); 336(CoIDB); 277(IDB); UV-Vis($CHCl_3$): 240, 412, 518; Anal. Calcd. for $Co_2C_{62}H_{44}N_{10}Cl_2O$(%): C, 65.67; H, 3.88; N, 12.36; Co, 10.41. Found C, 66.12; H, 3.71; N, 12.74; Co, 10.07.

Preparation of the Heterodinuclear Complex 5

To a stirred solution of **4** (110 mg, 0.1 mmol) in 20 cm^3 of $CHCl_3$, a solution of cupric dichloride dihydrate (69 mg, 0.4 mmol) in 10 cm^3 of CH_3OH was added. The mixture was stirred under reflux for 4 h and the solvent was removed under reduced pressure to leave a solid, which was washed with distilled water to remove excess $CuCl_2$ and dried under vacuum. The resultant residue was dissolved in $CHCl_3$ and purified by chromatography on a silica-gel column with $CHCl_3$/CH_3OH (7 : 1) as eluent. The red fraction was collected and evaporated to dryness to obtain the heterodinuclear complex **5** (yield 101 mg, 89%).

IR(cm^{-1}): 3317, 3054, 2921, 2851, 1657(C=O), 1597, 1532, 1448, 1006(N–Co); MS(FAB): 1101(M − Cl); 1066(M − 2Cl); 714(CoTPP + NH + CO); 686(CoTPP + NH); 340(CuIDB); 277(IDB); UV-Vis($CHCl_3$): 240, 414, 522; Anal. Calcd. for $CoCuC_{62}H_{44}N_{10}Cl_2O \cdot H_2O$(%): C, 64.33; H, 3.98; N, 12.11; Co, 5.10; Cu, 5.58. Found C, 64.03; H, 3.74; N, 12.26; Co, 5.71; Cu, 5.23.

RESULTS AND DISCUSSION

Synthesis

Access to heterodinuclear porphyrin complexes by a simple and high-yield pathway is of special interest because of the potential of such complexes in modeling the active site of polymetallic metalloenzymes. However, to our knowledge, preparation of heterodinuclear complexes is generally tedious, requiring separation of homo- and heterodinuclear species, and always with low yield. Here, metallation of the dinucleating ligand **3** by excess cobalt afforded the homodinuclear complex **4**. Then substitution of cobalt in the IDB moiety of **4** with copper gave the heterodinuclear complex **5** in very high yield. This method of preparation of a heterobimetallic complex by a metathesis reaction between different metals may provide a potential strategy for the preparation of heterodinuclear complexes in excellent yields.

Electronic Spectra

As depicted in Fig. 2, the electronic spectra of complexes **3**, **4**, and **5** all exhibit relatively strong absorption in the region 190–330 nm, which can be easily ascribed to the presence of benzimidazole moieties because complexes **1** and **2**, without the IDB moiety, show almost no absorption in this region. It can be seen that the spectrum of complex **3** shows three peaks in the region 190–330 nm, while in the spectra of complexes **4** and **5** there is only one sharp peak at $\lambda = 240$ nm. This kind of change implies the successful insertion of Co and Cu into the IDB moiety of **4** and **5**. Furthermore, the spectrum of the heterodinuclear complex **5** is very similar to that of the homodinuclear complex **4**.

Mass Spectroscopy

The mass spectrum of complex **4** gives a peak at m/z 1097 which corresponds to the complex ion, $[CoPor–IDBCoCl]^+$; the mass spectrum of complex **5** shows a peak at m/z 1101, corresponding to the ion, $[CoPor–IDBCuCl]^+$. Complexes **4** and **5** each give an additional MS peak, m/z 1062 and m/z 1066. These peaks can be assigned to $[CoPor–IDBCo]^{2+}$ and $[CoPor–IDBCu]^{2+}$ by loss of Cl^- from $[CoPor–IDBCoCl]^+$ and $[CoPor–IDBCuCl]^+$, respectively.

ESR Spectroscopy

Preparing a single crystal of the Co–Cu complex **5** to obtain detailed information about the coordination geometry at Cu(II) proved to be unsuccessful and, unfortunately, the ESR spectrum of the Co–Cu complex is too complicated to interpret, possibly because

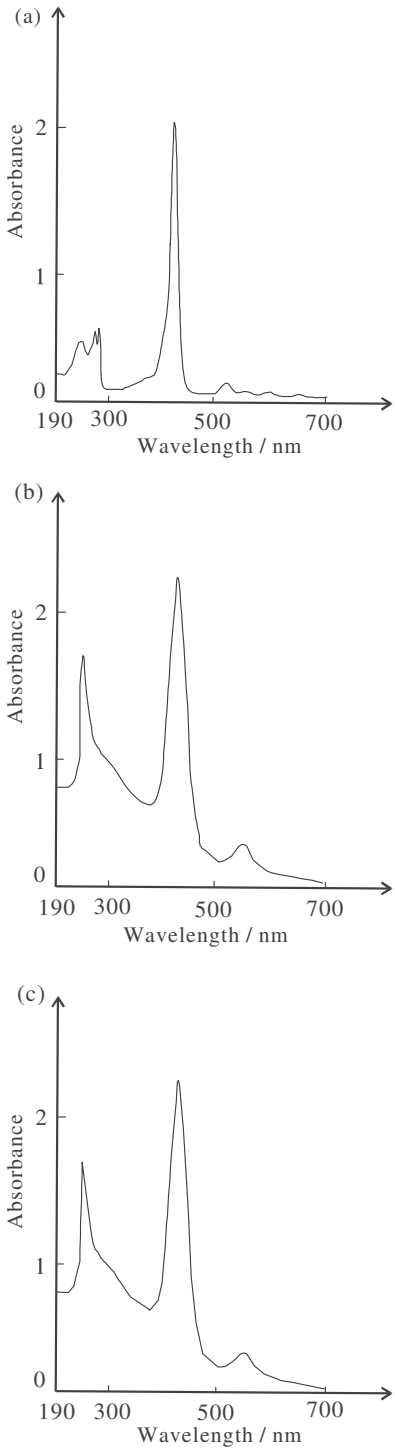


FIGURE 2 Electronic spectra of **3**, **4**, and **5** in chloroform. (a) **3**, [Por–IDB]; (b) **4**, [CoPor–IDBCoCl]Cl; (c) **5**, [CoPor–IDBCuCl]Cl.

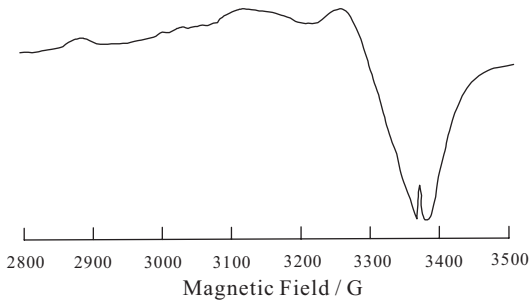


FIGURE 3 ESR spectrum of [ZnPor–IDBCuCl]Cl (0.5 mM) at 105 K in $CHCl_3$.

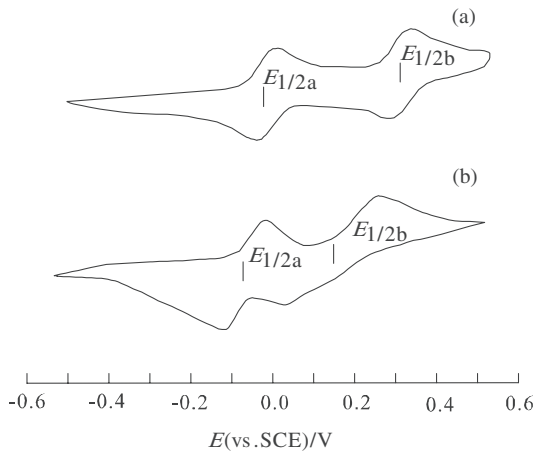


FIGURE 4 Cyclic voltammograms of (a) homodinuclear complex **4** and (b) heterodinuclear complex **5** in DMF containing 0.1 M TBAP; scan rate, 100 mV s^{-1}.

of magnetic interaction between Co(II) and Cu(II) or overlapping of the ESR signals of these two paramagnetic metals. To obviate this problem, an analogue of **5**, [Zn(II)Por–IDBCu(II)Cl]Cl was prepared according to the synthetic route for **5**. Figure 3 shows the ESR spectrum of complex [Zn(II)Por–IDBCu(II)Cl]Cl in $CHCl_3$ at 105 K, from which the ESR parameters ($g_{||} = 2.21$, $g_{\perp} = 2.02$, and $A_{||} = 137$ G) are obtained. Comparing these parameters with those of reported copper complexes [28,29], indicates that the Cu(II) ion in [Zn(II)Por–IDBCu(II)Cl]Cl is in a tetrahedral field. Zinc is not cobalt, but its introduction should not result in a change of coordination mode of the copper in the IDB moiety. So, combining this information with the mass spectrum of complex **5**, we conclude that copper in the IDB moiety of **5** is four coordinate, that is to say, in complex **5**, copper is coordinated to three tertiary nitrogen and one Cl^- ligands; a similar arrangement should apply to cobalt in complex **4** (Scheme 1).

Cyclic Voltammetry

Figure 4 shows the cyclic voltammograms of complexes **4** and **5** (3.0 mM) in DMF, which give two reversible redox waves (complex **4**, $E_{1/2a} = -0.02$ V and

$E_{1/2b} = 0.33$ V; complex **5**, $E_{1/2a} = -0.07$ V and $E_{1/2b} = 0.17$ V vs SCE). The first and second reversible waves at $E_{1/2a}$ and $E_{1/2b}$ in complex **5** correspond to the Co(II)/Co(III) and Cu(II)/Cu(I) redox couples, respectively. The two reversible waves at $E_{1/2a}$ and $E_{1/2b}$ in complex **4** correspond to the first Co(II)/Co(III) and the second Co(II)/Co(III) redox couples, respectively. The $E_{1/2a}$ value of complex **5** is nearly equal to that of **4**. Thus a different metal coordinated to IDB causes very little change in the $E_{1/2}$ value of the Co(II)/Co(III) redox couple in the porphyrin core.

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