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Research paper

Intramolecular hydroxylation of a tetrabenzimidazole-based dicopper complex

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ABSTRACT

The synthesis of bis(N-methylbenzimidazol-2-yl)methane serves as the entry point for the preparation of a tetrabenzimidazole-based binucleating ligand. A cupric complex of the former compound was prepared to compare its properties to those of the dicopper complexes of the tetrabenzimidazole derivative. In the latter case, the reaction of the binucleating ligand with cupric trifluoromethylsulfonate in air results in intramolecular C—H activation with concomitant hydroxylation, presumably by an *in situ* formed copper-oxygen reactive intermediate. This reactivity highlights the relevance of benzimidazole-based scaffolds in biologically inspired copper-oxygen systems.

1. Introduction

Nitrogen-based heterocycles represent an important class of compounds due to their σ-donor and π-acceptor properties towards transition metals, which vary considerably based on the identity of the heterocycle. The presence of histidine as imidazole donor in the active site of metalloenzymes is thus required to tune the properties of metal ions such as copper. In this fashion, the biologically and chemically relevant $Cu^{2+/+}$ redox couple is involved in electron transfer processes, and in the selective oxidation of a wide range of organic substrates [1]. Within the context of dioxygen activation for substrate oxidations at metalloenzymatic active sites, both mono- and bimetallic scaffolds have been developed by nature, with histidine as ubiquitous nitrogen-based donor [2]. Among these enzymes, dopamine β-monooxygenase has a monocopper active site defined by two histidine imidazoles and one methionine-derived thioether donor [3]. Despite the tentative nature of its assignment, a potentially bimetallic site is exemplified by particulate methane monooxygenase, featuring a proposed binuclear active site where one copper ion is bound by two histidine-derived imidazoles, and the other one by only one histidine residue acting as a bidentate ligand through the imidazole moiety and the amino terminus, in the structural motif known as *histidine brace*; the Cu—Cu distance in the binuclear site is 2.6 Å [4].

Recently, our group has developed mono- [5], and bimetallic [6] copper complexes inspired by the active sites of histidine-rich copper metalloenzymes. To this end, we have exploited 2-substituted benzimidazoles to assemble chelating ligands for $Cu^{2+/+}$ complexes inspired by the active site of dioxygen-activating metalloenzymes. The choice of nitrogen heterocycle is based on the pK_a value of protonated 2-methylbenzimidazole (**BzIm**, pK_a 6.10) [7], which is very close to that of the imidazolium moiety in histidine (pK_a 6.17) [8], and the relatively high association constant of **BzIm** with Cu^{2+} (log K 4.43) [9]. Relatively few literature reports exist regarding the use of benzimidazoles as histidine analogs inspired by the active site of O_2-activating metalloenzymes when compared to their pyridine-based counterparts, with the exception of the seminal work by the group of Casella [10]. Here, we report the synthesis of binucleating tetrabenzimidazole ligands, as well as the copper complexes of its bisbenzimidazole precursor and the oxidation byproduct of the latter (see Chart 1).

2. Experimental

2.1. Reagents and techniques

All reagents and solvents for syntheses were obtained from commercial sources. We attempted to prepare bis(N-methylbenzimidazol-2-yl)methanone (**BBMO**) following the procedure described by Miranda [11], albeit with very low yields. Reactions and manipulations were carried out under an inert atmosphere

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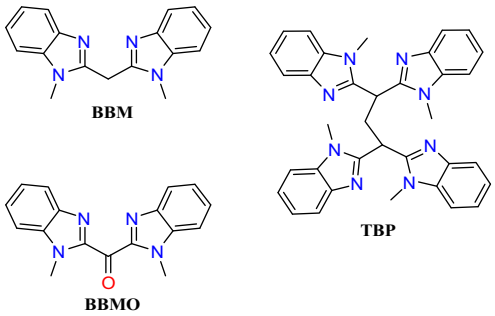

Chart 1. Ligands employed.

of dinitrogen using standard Schlenk techniques. Tetrahydrofuran (THF) was dried by refluxing over sodium/benzophenone under N_2 prior to use in reactions with *n*-BuLi. IR spectra were acquired with a Perkin Elmer 203-B FT-IR spectrophotometer in the range of 4000–400 cm^{-1} as KBr pellets. ^1H and ^{13}C NMR spectra were recorded with a JEOL Eclipse 300 spectrometer, and tetramethylsilane as internal standard. Fast Atom Bombardment mass spectra (FAB) were measured on a JEOL JMS-SX-102A spectrometer, and electrospray ionization mass spectra (ESI) were acquired with a Bruker Daltonics Esquire 6000 spectrometer with ion trap. Electron paramagnetic resonance (EPR) spectra were recorded in Joel JES-TE300 spectrometer in quartz tubes at X band frequency (9.4 GHz), at 77 K as frozen solutions.

2.2. X-ray crystallography

Single crystals of **[(TBP$_2$Cu$_2$)OTf$_4$]**, and **[(TBPO$_2$Cu$_2$)OTf]** were mounted on a Bruker SMART diffractometer, and collected by omega scans. Data were integrated with the Bruker SAINT software [12], solved with SHELXS-97 [13], and refined by full-matrix least-squares on F^2 with SHELXL-97 [14]. Weighted *R* factors, R_w, and all goodness-of-fit indicators, *S*, were based on F^2. The observed criterion of ($F^2 > 2\sigma F^2$) was used only for calculating the R factors. All non-hydrogen atoms were refined with anisotropic thermal parameters in the final cycles of refinement. Hydrogen atoms were placed in idealized positions, with C—H distances of 0.93 and 0.98 Å for aromatic and saturated carbon atoms, respectively. The isotropic thermal parameters of the hydrogen atoms were assigned the values of U_{iso} = 1.2 times the thermal parameters of the parent non-hydrogen atom. Crystals of **[(BBMO)CuCl$_2$]** and **[TBP$_2$Cu$_2$I$_2$]** were mounted on an Oxford Diffraction Gemini "A" diffractometer with a CCD area detector with $\lambda_{MoK\alpha}$ = 0.71073 Å and monochromator of graphite at 130 K. CrysAlisPro and CrysAlis RED software packages were used for data collection and integration [15]. The double pass method of scanning was used to exclude any noise. The collected frames were integrated by using an orientation matrix determined from the narrow frame scans. Final cell constants were determined by a global refinement; collected data were corrected for absorbance by using analytical numeric absorption correction using a multifaceted crystal model based on expressions upon the Laue symmetry using equivalent reflections [16]. A summary of crystallographic data is presented in Table 1.

2.3. Synthetic procedures

2.3.1. Synthesis of bis(N-methylbenzimidazol-2-yl)methane (*BBM*)

The ligand was obtained by adapting a literature method [17], from the reaction of *N*-methyl-*o*-phenylenediamine (2.63 g, 22 mmol) and diethylmalonimidate dihydrochloride (2.49 g, 11 mmol) in methanol, by heating to reflux for 14 h. After cooling to room temperature, the solution was concentrated to dryness, the solid was filtered and washed exhaustively with water and aqueous sodium carbonate solution. The product (**BBM**) was obtained as a pink solid in 35% yield (1.04 g); m.p. 208–210 °C. IR (KBr) ν_{max}/cm^{-1}: 3312, 3051, 1646, 1612, 1564, 1514, 1473, 1439, 1400, 1333, 1301, 1273, 1235, 1207, 1148, 1123, 1007, 933, 911, 882, 863, 750, 691, 647, 559, 509, 433. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.67–7.64 (m, 2 H, Ar), 7.21–7.16 (m, 6 H, Ar), 3.82 (s, 6 H, NCH_3), 4.60 (s, 2 H, CH_2).

2.3.2. Synthesis of [dichloro(bis(N-methylbenzimidazol-2-yl) methane)copper] [(*BBM*)CuCl$_2$]

$CuCl_2{\cdot}2H_2O$ (8.0 mg, 0.05 mmol) was dissolved in 3 mL of methanol, the ligand (10 mg, 0.04 mmol) was added dropwise dissolved in the minimum amount of methanol, and the mixture was stirred at room temperature. After a few minutes a yellow solid started to deposit, which was filtered and dissolved in a 1:1 methanol/dichloromethane mixture, and yellow/green crystals of **[(BBM)CuCl$_2$]** were obtained by slow evaporation in 79% yield (13 mg); m.p. 243–246 °C. IR (KBr) ν_{max}/cm^{-1}: 3214, 1616, 1615, 1595, 1524, 1501, 1482, 1459, 1398, 1341, 1321, 1284, 1245, 1157, 1131, 1104, 1010, 976, 937, 899, 838, 786, 752, 689, 560, 524, 427. EPR (77 K, THF): g_x = 2.26, g_y = 2.13, g_z = 2.07. Anal. Calcd. for $C_{17}H_{16}Cl_2CuN_4{\cdot}H_2O$ (%): C, 47.62; H, 4.23; N, 13.07. Found: C, 47.18; H, 3.87; N, 12.19.

2.3.3. Synthesis of [dichloro(bis(N-methylbenzimidazol-2-yl) methanone)copper] [(*BBMO*)CuCl$_2$]

BBMO was obtained as a byproduct during the synthesis of **TBP** (see below); combining the amount obtained after several preparations of the latter compound, 20 mg of **BBMO** (0.07 mmol) in dichlorometane were mixed with $CuCl_2{\cdot}2H_2O$ (23 mg, 0.14 mmol) dissolved in methanol. After stirring for 3 h, volatiles were evaporated and the complex was recrystallized by slow evaporation of a dicloromethane/methanol solution to afford a minimum amount of **[(BBMO)CuCl$_2$]**, sufficient to obtain partial characterization; m.p. 235–236 °C. IR (KBr) ν_{max}/cm^{-1}: 3103, 2921, 1695, 1662, 1617, 1521, 1484, 1456, 1390, 1341, 1294, 1252, 1187, 1155, 1127, 1089, 1009, 972, 921, 883, 855, 743, 689, 619, 556, 533, 507, 426.

2.3.4. Synthesis of 1,1',3,3'-tetra(N-methylbenzimidazol-2-yl)propane (*TBP*)

BBM (0.33 g, 1.18 mmol) was dissolved in anhydrous THF (5 mL) and cooled to −78 °C, followed by addition of 0.84 mL of 1.6 M *n*-buthyllithium in hexanes *via* syringe, and after a few minutes the mixture was added and let warm to 0 °C for 30 min. This solution was added dropwise to a solution of 0.84 mL chloromethyl methylthioether in 5 mL of anhydrous THF at −78 °C and stirred for 16 h, while allowing to warm to room temperature slowly. The precipitate formed was filtered and washed with hot water. TBP was obtained as a green solid in 98% yield (0.35 g); m.p. 224–225 °C (dec.). IR (KBr) ν_{max}/cm^{-1}: 3368, 3056, 2947, 1660, 1616, 1497, 1443, 1331, 1278, 1240, 1152, 1126, 1006, 862, 736, 679, 614, 492, 416. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.74–7.72 (m, 4 H, Ar), 7.26–7.22 (m, 4 H, Ar), 5.33 (t, ^3J = 7.45 Hz, 2 H, CH), 3.78 (s, 12 H, NCH_3), 3.68 (t, ^3J = 7.43 Hz, 2 H, CH_2). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 75 MHz): δ 153.05 (Ar), 141.89 (Ar), 136.03 (Ar), 122.03 (Ar), 121.44 (Ar), 118.69 (Ar), 110.04 (Ar), 43.97 (CH_2), 34.54 (CH), 29.77 (CH_3). FAB$^+$ MS *m/z* (rel. intensity): 571 ([**TBP**]$^+$, 20%), 277 ([**BBM** + H]$^+$, 100%).

2.3.5. Synthesis of [tetrakis(trifluoromethylsulfonate)bis(1,1',3,3'-tetra (N-methylbenzimidazol-2-yl)propane)dicopper] [(*TBP$_2$Cu$_2$)OTf$_4$*]

TBP (0.02 g, 0.03 mmol) and $Cu(OTf)_2$ (0.03 g, 0.07 mmol) were dissolved under stirring in acetonitrile, and after only 8 min the volatiles were evaporated under reduced pressure, and the solid obtained was washed with CH_2Cl_2. The complex was obtained as