The preparation of Cu(II) complexes derived from a novel pyrazole containing dinucleating ligand

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Abstract

The synthesis of the new heptadentate dinucleating ligand 2,6-bis[(bis(3,5-dimethylpyrazol-1-ylmethyl)-amino)methyl]phenol (bpamp) (**3**) is described. The preparation of Cu(II) complexes of the form $[Cu_2(bpamp)X](BF_4)_2$ where X = Cl (**8**) or N_3 (**9**) derived from this ligand is detailed. These complexes have been characterized on the basis of elemental analysis, IR spectroscopy, fast atom bombardment mass spectrometry and UV–Vis spectroscopy. The results indicate that ligand **3** coordinates to Cu(II) in a dinuclear fashion with the ligand acting as an N_6O donor set. These results are consistent with **8** and **9** existing as five-coordinate Cu(II) complexes each bound to three nitrogen atoms, an endogenous phenolate oxygen and an exogenous bridge. The spectroscopic data indicate that for **9** the azide bridges the coppers in a μ-1,1 fashion.

Introduction

There is continued interest in the synthesis of multidentate ligands and their metal complexes where the features of naturally occuring molecules are incorporated. The utility of such compounds lies in their use as models for metalloproteins, in their capacity to bind and/or activate small molecules, or in their potential catalytic abilities.

Of the large variety of multidentate ligands which have been prepared, those which incorporate nitrogen donor atoms are of interest because of their demonstrated existence in a variety of proteins. These include the iron containing protein hemerythrin [1] and the copper containing proteins hemocyanin [2] and tyrosinase [3]. Spectroscopic, chemical and crystallographic evidence suggest that the active sites are very similar in hemocyanin and tyrosinase [4]. There are two coppers per active site each ligated by two or three imidazole nitrogens from histidine residues and, in the oxidized form, a bridging oxygen. The role of these copper containing proteins is to bind and transport molecular oxygen, and in the case of tyrosinase, to also catalyze the oxidation of phenols and catechols. Notable advances in understanding the structural and chemical properties of these proteins have been achieved through the comparison of synthetic models to the naturally occurring molecules [5].

Pyrazole has been used as a mimic for the imidazole found on histidine residues because of its size, ease of preparation and simple incorporation into chelating ligands [5]. Sorrell has described the preparation of a number of pyrazole containing N_6O ligands and their Cu(II) complexes where attempts have been made to constrain the metal ions into specific orientations by changing the length of the arms between donor atoms. Copper complexes of ligands **1** and **2** shown in Fig. 1 result in considerable variation in the Cu–Cu distance ranging from 3.0 to 3.75 Å [6, 7].

In our work, we have prepared both mononuclear and dinuclear Cu(II) complexes with pyrazole containing ligand sets and have studied the catalytic properties

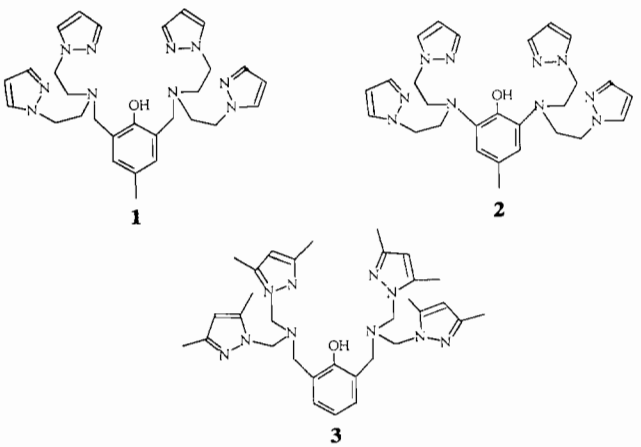

Fig. 1. Dinucleating pyrazole containing N_6O ligands.

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of these complexes. Marked variations in the reactivity were observed due to changes in geometries [8], exogeneous donors [9], bridging groups and mononuclear versus dinuclear systems [10]. In this paper, we describe the synthesis of the novel pyrazole containing ligand 2,6-bis[(bis(3,5-dimethylpyrazol-1-ylmethyl)amino)-methyl]phenol (bpamp) (**3**) which ligates as an N_6O donor where the bridging atom is a phenoxide oxygen. In addition, Cu(II) complexes of the type $[Cu_2(bpamp)X](BF_4)_2$ (X = Cl, N_3) derived from this ligand have been synthesized. These compounds have been characterized by a combination of fast atom bombardment mass spectroscopy, UV–Vis and IR spectroscopy, and these results will be discussed.

Experimental

All reagents and solvents were purchased from commercial sources and used as received unless noted otherwise. 1-(Hydroxymethyl)-3,5-dimethylpyrazole was prepared by the literature method [11]. Melting points were obtained with the use of a Fisher-Johns apparatus and are uncorrected. Chemical analyses were performed at Desert Analytical, Tucson, AZ.

Electronic spectra were performed on a Uvikon 860 spectrophotometer while IR spectra were recorded on a Nicolet 5ZDX instrument. Mass spectra were run at the Midwest Center for Mass Spectrometry in Lincoln, NE. ^{1}H NMR were recorded on a Varian T-60 instrument, or a Bruker WM 250 instrument at 250.13 MHz using $CDCl_3$ as the solvent. All chemical shifts are reported in parts per million (ppm) relative to an internal standard of Me_4Si. Kinetics were followed spectrophotometrically on a Uvikon 860 spectrophotometer by following the appearance of quinone using the 390 nm peak.

2,6-Bis(bromomethyl)anisole (4)

To a stirred solution of 30.0 g (0.22 mol) of 2,6-dimethylanisole in 400 ml of CCl_4 were slowly added 78.4 g (0.44 mol) of *N*-bromosuccinimide. Benzoyl peroxide (1.5 g) was added and the solution was refluxed for 6 h. The solution was filtered hot and the filtrate evaporated under reduced pressure. The resultant oil was crystallized from hexane to yield 39.4 g (61%) of light orange crystals, m.p. 75–76 °C (lit. 75 °C [12]). ^{1}H NMR: 4.00 (3H, s), 4.52 (4H, s), 7.22–7.45 (3H, m).

2,6-Bis(phthalimidomethyl)anisole (5)

To a stirred suspension of 48.1 g (0.26 mol) of potassium phthalimide in 400 ml of DMF were slowly added 38.0 g (0.13 mol) of **4**. The mixture was stirred for 48 h at 50 °C, cooled to room temperature and filtered. The white solid collected was crystallized from $CHCl_3$ to give 18.0 g of white crystals. Additional product was obtained by evaporating the filtrate under reduced pressure and crystallizing the residue resulting in an additional 5.0 g of product. Total yield 41%, m.p. 224–226 °C. ^{1}H NMR: 4.01 (3H, s), 4.93 (4H, s), 7.13–7.34 (3H, m), 7.65–7.89 (8H, m).

2,6-Bis(phthalimidomethyl)phenol (6)

Hydriodic acid (120 ml) was stirred while 9.20 g (0.021 mol) of compound **5** were slowly added. The resultant solution was refluxed for 5 h, cooled to room temperature and extracted with 3×50 ml $CHCl_3$. The combined extracts were successively washed with water and a 5% sodium thiosulfate solution until the coloration disappeared. The solution was dried over $MgSO_4$ and filtered. Upon evaporation of the solvent under reduced pressure, a white precipitate formed which was filtered and washed with cold water. Yield 7.51 g (87.0%), m.p. 209–212 °C. ^{1}H NMR: 4.82 (4H, s), 7.18–7.32 (3H, m), 7.65–7.89 (8H, m).

2,6-Bis(aminomethyl)phenol dihydrochloride (7)

A mixture of 11.0 g (0.027 mol) of **6** and 3.0 g (0.059 mol) of hydrazine hydrate in 200 ml of CH_3OH was refluxed for 2.5 h. To the mixture were added 75 ml of H_2O and the CH_3OH was evaporated. Concentrated HCl (100 ml) was added, the solution was refluxed for 2 h, cooled in ice, filtered and the residue was washed with water. The washings and the filtrate were combined and evaporated to dryness. The residue was dissolved in 175 ml of EtOH followed by 75 ml of diethyl ether which resulted in precipitation of a white solid. The solid was dried *in vacuo*; yield 2.79 g (68%). ^{1}H NMR (in D_2O): 4.28 (4H, s), 7.18–7.32 (3H, m).

2,6-Bis[(bis(3,5-dimethylpyrazol-1-ylmethyl)amino)-methyl]phenol (bpamp) (3)

To a stirred solution of 1.0 g (4.44 mmol) of **7** in 20 ml of methanol was added 0.50 g of KOH dissolved in 10 ml of MeOH. The resultant solution was stirred for 0.5 h and filtered into a solution of 1.35 g (8.88 mmol) of 1-(hydroxymethyl)-3,5-dimethylpyrazole [11] dissolved in 30 ml of acetonitrile and stirred for 72 h. The acetonitrile was separated from the water produced, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Thin layer chromatography showed the compound to be of sufficient purity to be used directly in the synthesis of the metal complexes. An analytically pure sample was isolated by dissolving **3** in H_2O/CH_3OH, adding an excess of EDTA and stirring for 2 h. The CH_3OH was evaporated and the solution was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated to give a colorless oil. ^{1}H NMR: 1.99 (12H, s),

2.20 (12H, s), 5.40 (4H, s), 4.90 (8H, s), 5.79 (4H, s), 7.24 (3H, s). MS: *m/e* 584 (M^+).

[Cu_2(bpamp)(Cl)](BF_4)$_2$·H_2O (8)

A solution of 1.60 g (2.70 mmol) of bpamp in 25 ml of methanol was treated with a solution of 1.70 g (5.40 mmol) of $Cu(BF_4)_2 \cdot 6H_2O$ in 50 ml of methanol. The resulting solution was filtered, the solvent was reduced to 25 ml and cooled to −20 °C. Small, green–brown crystals formed which were filtered and washed with methanol to give 0.96 (38%) of **8**. IR (KBr): 3420–3580 (H_2O); 2970, 2930 (Ar); 1010–1140 (BF_4). UV–Vis (CH_3OH; λ_{max} (nm) (ϵ, M^{-1} cm^{-1})): 676 (98), 450 (484), 271 (3370). *Anal.* Calc. for $C_{32}H_{45}B_2ClCu_2F_8N_{10}O_2$: C, 40.98; H, 4.85; N, 14.93. Found: C, 41.28; H, 4.80; N, 14.79%.

[Cu_2(bpamp)(N_3)](BF_4)$_2$·CH_3OH (9)

To a solution of 0.75 g (1.44 mmol) of bpamp in 30 ml of methanol was added a solution of 0.90 g (2.88 mmol) of $Cu(BF_4)_2 \cdot 6H_2O$ in 75 ml of methanol followed by 0.09 g (1.44 mmol) of NaN_3 dissolved in 10 ml of H_2O. The resulting solution was filtered, the solvent was reduced to 25 ml, and cooled to −20 °C. Small green crystals formed which were filtered and washed with cold methanol to give 0.60 g (42%) of **9**. IR (KBr; cm^{-1}); 2077 (N=N=N). UV–vis (CH_3OH; λ_{max} (nm) (ϵ, M^{-1} cm^{-1})): 692 (140), 440 (580), 390 (2850), 266 (3610). *Anal.* Calc for $C_{33}H_{47}B_2Cu_2F_8N_{13}O_2$: C, 41.35; H, 4.95; N, 18.99. Found: C, 41.11; H, 5.03; N, 19.32%.

Results and discussion

Synthesis

Biomimetic approaches to ligand synthesis include the design of organic ligands which enforce various geometrical constraints on metal ions. Compound **1** generates six-membered chelate rings when bound to a metal ion and allows the coppers to maintain a distance of less than 3.1 Å. By comparison, in compound **2** the tertiary nitrogens are connected directly to the aromatic ring and the resultant Cu(II) complexes consist of both five-membered and six-membered chelates resulting in Cu–Cu distances ranging from 3.5 to 3.75 Å. Unlike **1** and **2**, in compound **3** the pyrazole rings are at the end of methylene arms instead of ethylene arms and its complexes will therefore also contain both five and six-membered chelate rings. Complexes of **3** should be intermediate between **1** and **2** in the steric requirements placed on the metal ions.

In the design of polypyrazole containing ligands of the type described here, one can envision the synthesis proceeding in one of two ways. The molecule can be built by synthesizing the N_3 arms intact and performing a substitution reaction of this piece with a dihalide. This method has found considerable utility in a number of instances [5]. Alternatively, one can prepare a diamino compound and add the arms through a substitution reaction using 1-(hydroxymethyl)-3,5-dimethylpyrazole [11]. As shown in Fig. 2, we use this second approach in the synthesis of bpamp.

The ligand bpamp was prepared in five steps from the commercially available 2,6-dimethylanisole. Free-radical bromination with *N*-bromosuccinimide and benzoyl peroxide gave compound **4** as a crystalline compound. When **4** was treated with potassium phthalimide in DMF, the nitrogen protected compound **5** was isolated and demethylation of the anisole **5** with refluxing hydriodic acid gave the substituted phenol, **6**. Deprotection of **6** with hydrazine resulted in formation of **7** as the hydrochloride salt. The target compound bpamp, **3**, was prepared using a modification of the procedure of Driessen for the addition of pyrazol-1-methylene units to amines. The condensation of **7** with four equivalents of 1-(hydroxymethyl)-3,5-dimethylpyrazole gave the bpamp ligand **3** from which the copper complexes were directly synthesized. Analytically pure samples of bpamp were obtained by treating an aqueous solution of the copper complex **8** with EDTA followed by extraction with chloroform. The ligand was characterized by ^1H NMR and mass spectrometry.

The Cu(II) complexes were prepared by treating bpamp with $Cu(BF_4)_2 \cdot 6H_2O$ in methanol resulting in a green solution from which complex **8** was isolated. Bpamp was designed to serve as a heptadentate donor to the metal with three nitrogens per copper and a bridging phenoxide oxygen. Additionally, a second bridge would come from either a methanol or water molecule. Mass spectral information (*vide infra*) however, suggests that the second bridge comes from a chloride ion generated from the hydrochloride salt of the ligand which is used in the synthesis of the Cu(II) complexes. The azido derivative **9** was prepared by treating **8** with an aqueous solution of sodium azide from which green crystals were isolated. These complexes were analyzed by fast atom bombardment mass spectrometry, IR spectroscopy and electronic spectroscopy.

Mass spectrometry

Fast atom bombardment mass spectrometry has been shown to be an extremely effective technique for the identification of Cu(II) complexes [13] and was used here to analyze complexes **8** and **9**. In addition, high resolution electron impact mass spectrometry was used to provide additional information about the nature of the Cu(II) complexes.

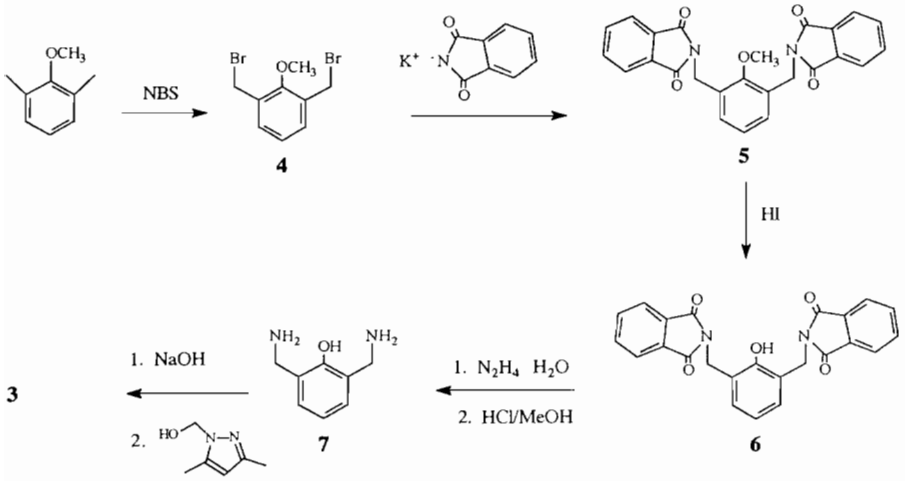

Fig. 2. Synthesis of bpamp ligand.

Exact mass measurements of the peak at 635 in complex **8** showed it to appear at 635.1135 which fits $C_{26}H_{34}N_8OCu_2Cl$ to 0.4 ppm. The presence of chlorine in the complex was unexpected, but certainly must be a byproduct of the ligand synthesis where the hydrochloride salt of **7** is converted to the bpamp ligand **3** in the last step and used without purification to make the copper complex **8**.

The fast atom bombardment mass spectral data for complexes **8** and **9** are shown in Table 1. In FAB-MS, Cu(II) complexes do not produce spectra directly but show ions formed from reduction of both Cu(II) ions to Cu(I) by the addition of two electrons. The base peak for both **8** and **9** occurs at *m/z* 109, a fragment which is the result of the loss of one of the 3,5-dimethylpyrazol-1-ylmethyl arms from the ligand. We have used this peak as being diagnostic for the presence of the pyrazole arms in our ligands.

Taking into account the information derived from the exact mass measurements, a number of other peaks in the FAB-MS can be readily identified. For complex **8**, the intact cation is found at *m/z* 744 along with an M-35 peak at *m/z* 709 for the loss of Cl. The typical doublets due to the presence of chlorine appear throughout the spectrum. Ligand fragmentations from the complex can also be identified as described in Table 1. In like fashion to a number of Cu(II) complexes derived from similar N_6O ligands, the mass spectral data suggest that the chlorine bridges the two coppers resulting in five-coordinate coppers with two pyrazole nitrogens, one aliphatic nitrogen, a phenoxide oxygen and the bridging chloride bound to each copper.

The FAB-MS of complex **9** does not show a peak for the intact cation, a result which is consistent with results obtained for other Cu(II) systems with bound azide [9, 10]. Instead, the highest mass peak is found at *m/z* 709. However, the presence of the azide bridge is clearly seen in the IR spectrum (*vide infra*). In similar fashion to **8**, both fragmentations of the complex and the ligand can be identified. The similarities of the spectra suggest that the only difference between **8** and **9** is the substitution of the bridging azide for chloride.

TABLE 1. Fast atom bombardment mass spectra for compounds **8** and **9**

Compound	*m/z*	Origin
8	744	$[Cu_2(bpamp)Cl]^+$
	709	$[Cu_2(bpamp)]^+$
	651	$[Cu_2(bpamp)$-pyrazole$)Cl]^+$
	646	$[Cu(bpamp)]^+$
	635	$[Cu_2(bpamp$-CH_2 pyrazole$)Cl]^+$
	542	[635 peak-pyrazole]$^+$
	474	[(bpamp-CH_2 pyrazole)]$^+$
	109 (base)	$[(C_6H_9N_2]^+$
9	709	$[Cu_2(bpamp)]^+$
	646	$[Cu(bpamp)]^+$
	474	$[C_{26}H_{34}N_8O]^+$
	109 (base)	$[C_6H_9N_2]^+$

Spectroscopy

The electronic absorption spectra for complexes **8** and **9** in methanol are similar and are tabulated in Table 2. Both complexes exhibit strong pyrazole to Cu(II) charge-transfer bands between 200–300 nm and d–d transitions at much lower energy (**8**, $\lambda_{max}=676$, $\epsilon=98$; **9**, $\lambda_{max}=692$, $\epsilon=140$). In addition, both **8** and **9** have bands in the region where phenoxide-to-copper charge transfer (CT) bands are expected to occur. For related complexes, these have been shown to typically occur between 400–500 nm [14]. For **8**, this band was found at 450 nm ($\epsilon=484$ M^{-1} cm^{-1}), while for **9** it was observed at 440 nm ($\epsilon=580$ M^{-1} cm^{-1}).

TABLE 2. Electronic spectra for compounds **8** and **9**

Compound	λ (nm)	ε (M^{-1} cm^{-1})	Source
8	676	98	d–d
	450	484	PhO^- to Cu(II)
	271	3370	pyrazole to Cu(II)
9	692	140	d–d
	440	580	PhO^- to Cu(II)
	390	2850	N_3^- to Cu(II)
	266	3610	pyrazole to Cu(II)

In addition to the phenoxide-to-copper charge-transfer band, complex **9** has an absorption at 390 nm. This is in the range of azide-to-Cu(II) LMCT transitions for μ-1,1- and μ-1,3-azido Cu(II) complexes which have been shown to occur between 360–405 nm [14, 15]. By comparison, studies on the azido-met form of *Buscyon* hemocyanin show this absorption to occur at 380 nm [16].

The complexes **8** and **9** also have similar IR spectra, a result which infers that they have similar geometries. Both complexes show BF_4 stretches between 920–1150 cm^{-1} and numerous absorptions attributable to the ligand. Most notable, however, is the strong asymmetric copper-coordinated azide stretch at 2077 cm^{-1} found for complex **9**. In dinuclear Cu(II) systems, N_3^- has been shown to coordinate in either μ-1,1 or μ-1,3 fashion depending on the nature of the ligand set. The range for these modes of binding has been shown to be between 2060–2080 cm^{-1} for μ-1,1 cases [14, 15e, 17], while N_3^- μ-1,3 bridged Cu(II) systems exhibit their asymmetric band between 2020–2040 cm^{-1} [7, 15a, 15d, 17e]. Therefore, the result found for **9** is consistent with the azide bridge coordinating in a μ-1,1 fashion. The bpamp ligand must be flexible enough to allow the two coppers to get close enough together to form the μ-1,1 linkage as opposed to the longer μ-1,3 bridge.

Conclusions

We have prepared the novel dinucleating ligand bpamp which coordinates to Cu(II) as an N_6O donor and generates dinuclear complexes. The Cu(II) complexes **8** and **9** were studied by fast atom bombardment mass spectrometry, electronic spectroscopy and IR spectroscopy. The results of these analyses are consistent with five-coordinate Cu(II) complexes each bound to three nitrogen atoms, an endogenous phenolate oxygen and an exogenous bridge [17d]. The spectroscopic data indicates that for **9**, the azide bridges the coppers in a μ-1,1 fashion. Additional structural information will be uncovered from subsequent X-ray crystallographic data.

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