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Synthesis, Crystal Structure And Catecholase Activity Of [N,N-Bis(3,5-Dimethylpyrazol-1-ylmethyl)-1-Hydroxy-4-Aminobutane] Copper(II) Dichloride

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ABSTRACT: A new tripodal ligand, N,N-Bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-4-aminobutane (bpmhb), has been synthesized. Reaction of (bpmhb) with Copper (II) chloride dihydrate [CuCl₂, 2H₂O] in methanol produced the new complex Cu(bpmhb)Cl₂. The complex crystallizes in the monoclinic system, space group P2₁, the cell dimensions are a = 7.990 Å, b = 14.620 Å, c = 8.590 Å, α = 90°, β = 95.80°, γ = 90°, V = 998.3 Å³ and Z = 2. The single-crystal X-ray structure of the title compound, N,N-Bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-4-aminobutane Copper(II) dichloride shows that the surrounding geometry of the copper (II) ion can be described as being intermediate between a distorted square pyramid and a trigonal bipyramid. The OH group function forms an intramolecular hydrogen bonding with the chloride atom Cl₁. With molecular oxygen as oxidant, this complex catalyzed the conversion of catechol to quinone with a good catalytic activity.

RESUME : Un nouveau ligand, tridenté N,N-Bis(3,5-diméthylpyrazol-1-ylméthyl)-1-hydroxy-4-aminobutane (bpmhb), a été synthétisé. La réaction de (bpmhb) avec le chlorure de cuivre (II) dihydraté, (CuCl₂,2H₂O) dans le méthanol conduit au nouveau complexe Cu(bpmhb)Cl₂. Ce complexe cristallise dans le système monoclinique, groupe spatial P2₁, les paramètres de maille sont : a = 7.990 Å, b = 14.620 Å, c = 8.590 Å, β = 95.80° et Z = 2. L'étude en diffraction de rayons X sur monocristal de ce complexe montre que la coordination du cuivre peut être décrite comme intermédiaire entre une pyramide à base carré

déformée et une bipyramide à bases triangulaires. Le groupement hydroxyle forme une liaison hydrogène intramoléculaire avec l'atome de chlore Cl1. Avec l'oxygène moléculaire comme oxydant, ce complexe catalyse la conversion du catéchol en quinone avec une bonne activité catalytique.

Keywords: Crystal structure, copper complex, tripodal ligand, pyrazole, oxidation, catalysis.

INTRODUCTION:

Notable progress has been made to mimic tyrosinase activity using copper complexes coordinated to multidentate heterocyclic amine ligands [1]. The binding ability and reactivity properties of the synthetic complexes towards small molecules can be readily modulated and compared to the biological systems.

Hemocyanin and tyrosinase have been studied in detail [2-4], tyrosinase is found widely in mammals, plants, bacteria, and fungi. It acts as both a monooxygenase through the hydroxylation of phenols to catechols and as an oxidase via the further oxidation of catechols to quinones. The copper centers of metalloproteins catalyze a variety of substrate oxidation or oxygenation reactions or bind and transport dioxygen [5], leading to extensive efforts by bioinorganic chemists to learn about the structures and mechanism of action of the protein active sites [6]. This approach involves the synthesis and characterization of low molecular weight compounds that can duplicate the protein active sites and mimic their functional attributes [6].

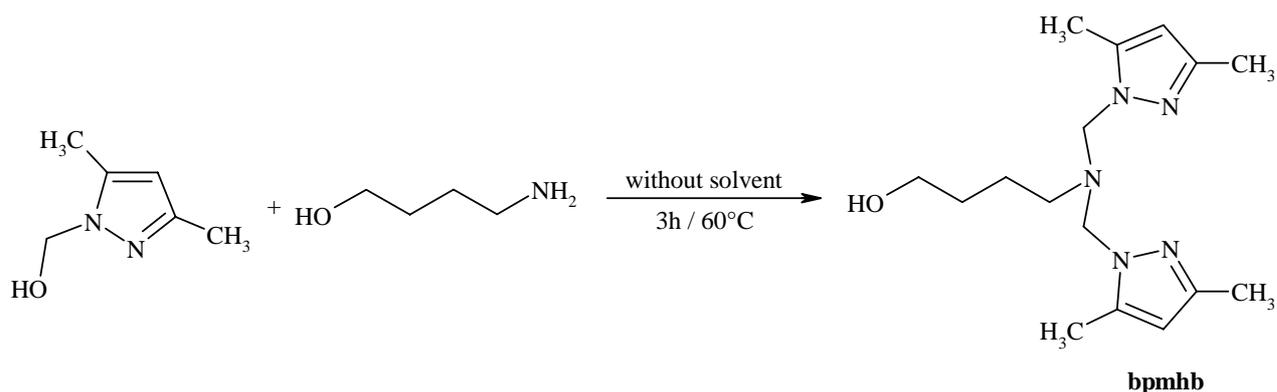
In previous papers we have reported the synthesis and crystal structures of [N,N-Bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-2-amino ethane] copper(II) dinitrate [Cu(bpmhe)(NO₃)₂] (NO₃) [7] and [N,N-Bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-2-amino ethane] copper(II) dichloride [Cu(bpmhe)Cl]₂ · 2[Cl, H₂O] [8].

In this paper we describe the preparation of the new tripodal organic ligand [N,N-Bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-4-aminobutane] (bpmhb) capable of donating three nitrogens (two pyrazoles and one aliphatic) per metal as well as the synthesis, the characterization by X-ray analysis and the catecholase activity of his copper (II) complex Cu(bpmhb) Cl₂.

RESULTS AND DISCUSSION

Synthesis of (bpmhb):

The synthesis of the new tropical nitrogen ligand (bpmhb) was carried out by condensation of 2 equivalents of 1-hydroxymethyl-3,5-dimethylpyrazole and one equivalent of 4-aminobutanol in the absence of solvent for 3 hours at 60°C. The compound was obtained with excellent yield (90%).



Scheme1

Synthesis of Cu(bpmhb)Cl₂:

Suitable crystals of the title complex [N,N-Bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-4-aminobutane] Copper(II) dichloride (Cu(bpmhb)Cl₂) were obtained by treating a solution of (bpmhb) in methanol with a solution of Copper(II) dichloride [CuCl₂, 2H₂O] in methanol at 25°C.

X-ray experiment:

On a bulk synthesised, some crystals were selected and checked for singularity by preliminary oscillation and weissenberg photographs. The best diffractant crystal was used for intensity measurements on a CCD diffractometer (Xcalibur, Oxford Diffraction), it displays the monoclinic system, space group P2₁, with parameters $a = 7.990\text{\AA}$, $b = 14.620\text{\AA}$ and $c = 8.590\text{\AA}$, $\alpha = 90^\circ$, $\beta = 95.80^\circ$ and $\gamma = 90^\circ$.

The recorded frames, with theta max = 25.62° gave a total of 5918 reflections of which 1693 were unique and 1689 observed. All crystallographic and data collection parameters are given in Table 1

Table 1: Crystal and experimental data of Copper(II) complex Cu(bpmhb)Cl₂.

Empirical formula	C ₁₆ H ₂₇ Cl ₂ Cu N ₅ O
Formula weight	439.88
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2 ₁
Unit cell dimensions	a = 7.990 Å α = 90°
	b = 14.620 Å β = 95.80°
	c = 8.590 Å γ = 90°
Volume	998.3 Å ³
Z	2
Density (calculated)	1.463 Mg/m ³
Absorption coefficient	1.376 mm ⁻¹
F(000)	458
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	2.92 to 25.62 °.
Index ranges	-9<=h<=9; -16<=k<=16; -10<=l<=10
Reflections collected	5918
Independent reflections	1693 [R(int) = 0.1130]
Reflections observed (>2σ)	1689
Data Completeness	0.484
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Goodness-of-fit on F ²	1.170
Final R indices [I>2σ(I)]	R ₁ = 0.0914 wR ₂ = 0.2296
R indices (all data)	R ₁ = 0.0916 wR ₂ = 0.2297
Absolute structure parameter	0.0(4)
Largest diff. peak and hole	0.863 and -0.560 e.Å ⁻³

X-Ray structure Determination:

The crystal structure solution of the title compound was carried out with SHELXS97 [9] using Patterson method. The copper, chlorides and some nitrogen atoms are determined.

The other Non-hydrogen atoms were found by Fourier difference synthesis. The atomic parameters and anisotropic temperature factors were refined using full-matrix least squares methods of SHELXL97 [10]. Hydrogen atoms were positioned via HFIX. The final agreement factor is 0.0914. The molecular viewer used is ORTEP3 [11].

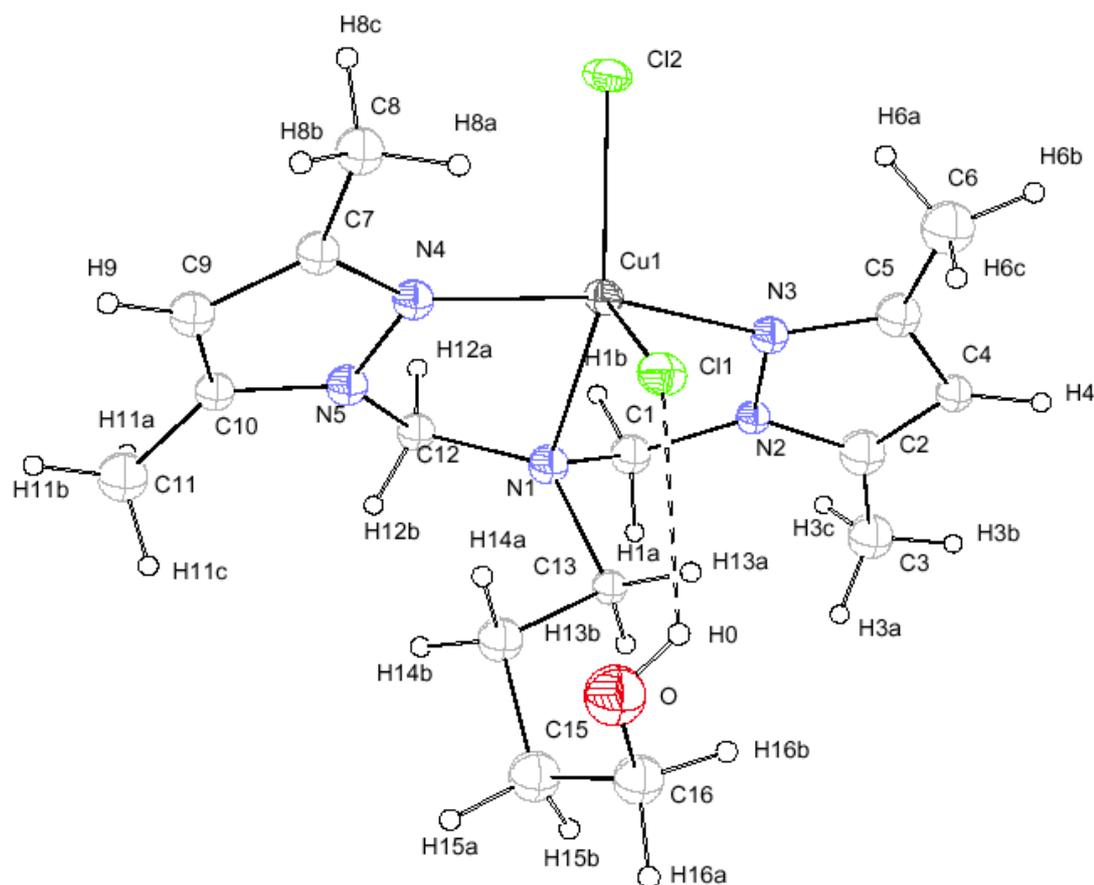


Figure 1: Molecular structure of Cu(bpmhb)Cl₂

The asymmetric unit [Cu(bpmhb)Cl₂] equals the formula unit. Bond distances and selected angles are listed in table 1. An ORTEP drawing of [Cu(bpmhb)Cl₂] and atomic labelling are given in Fig1.

The Cu(II) ion is coordinated to two pyrazole nitrogens, at 1.942(15) Å and 1.976(15) Å, two chlorine ions at 2.390(4) Å and 2.291(4) Å and an amine nitrogen at 2.190(13) Å. The five-coordinate geometry is quite distorted from either the limiting trigonal bipyramidal or

square pyramidal geometries. Using the so-called structural index parameter $\tau = (\beta - \alpha)/60$ Addison et al [12], where β is the largest angle and α the next in the Cu(II) coordination sphere, gives a value of 0.405 between the values of $\tau = 0.0$ for a regular square pyramid and $\tau = 1.0$ for a regular trigonal bipyramid,

Table 2: Selected angles ($^\circ$), bond distances (\AA) and hydrogen bond for Cu(bpmhb)Cl₂

N ₁ -Cu-N ₃	79.8(7)	N ₃ -Cu-Cl ₁	99.4(6)
N ₁ -Cu-N ₄	81.4(6)	Cl ₂ -Cu-Cl ₁	115.56(17)
N ₁ -Cu-Cl ₂	136.2(4)	Cu-N ₁	2.190 (13)
N ₁ -Cu-Cl ₁	108.1(34)	Cu-N ₃	1.976(15)
N ₃ -Cu-Cl ₂	96.7(6)	Cu-N ₄	1.942(15)
N ₄ -Cu-N ₃	160.5(7)	Cu-Cl ₁	2.390(4)
N ₄ -Cu-Cl ₁	91.1(7)	Cu-Cl ₂	2.291(4)
N ₄ -Cu-Cl ₂	93.4(6)	O...Cl ₁	3.153(19)

The strain imposed on the metal coordination environment by the tripodal ligand is reflected in the chelate angle N₁-Cu-N₃ of only 79.8(7) $^\circ$ and N₁-Cu-N₄ of 81.4(6) $^\circ$ which are similar to those observed in other pyramidal complexes (averaging 79.03(15) $^\circ$ when the ligand is N,N-bis(pyrazol-1-ylmethyl)benzylamine [13].

The Cu-N₁ and Cu-N₃ bond distances (respectively 2.190(13) and 1.976(15)) are similar to those found in other pyramidal complexes CuLCl₂ [13] and [Cu(ddae)Cl₂].C₂H₅OH [14] 2.182(4) and 2.181(4) respectively.

If the function alcohol doesn't participate in the coordination of the copper ion because of the length of the side chain, the hydrogen atom is well arranged to form intramolecular hydrogen bonding with the chloride atom Cl₁, with O to Cl₁ distance of 3.153(19) \AA .

Catalytic activity for the oxidation of catechol:

The catalytic oxidation of catechol has been studied as a model reaction for the catecholase activity of tyrosinase and catechol oxidase [15-18]. It has been shown that rigidity planar mononuclear complexes are not active as catalysts while non-planar complexes will catalyze the oxidation [19]. Since our complexes are non-planar, we anticipated that they would catalyze this reaction. The kinetic studies on the oxidation of catechol were carried out by the method of initial rates by monitoring the increase in the characteristic quinone

absorption band at 390 nm under air as a function of time. The metal complex (0.3 ml of a 1×10^{-3} M methanol solution) and a 2.0 ml solution (1×10^{-1} M methanol solution) of catechol were equilibrated separately to 25 °C and then added together in a spectrophotometric cell at 25 °C. Figure 2 shows the dependence of the reaction rates on the catechol concentration for the oxidation reaction catalyzed by three copper (II) complexes while the activities are shown in table 3.

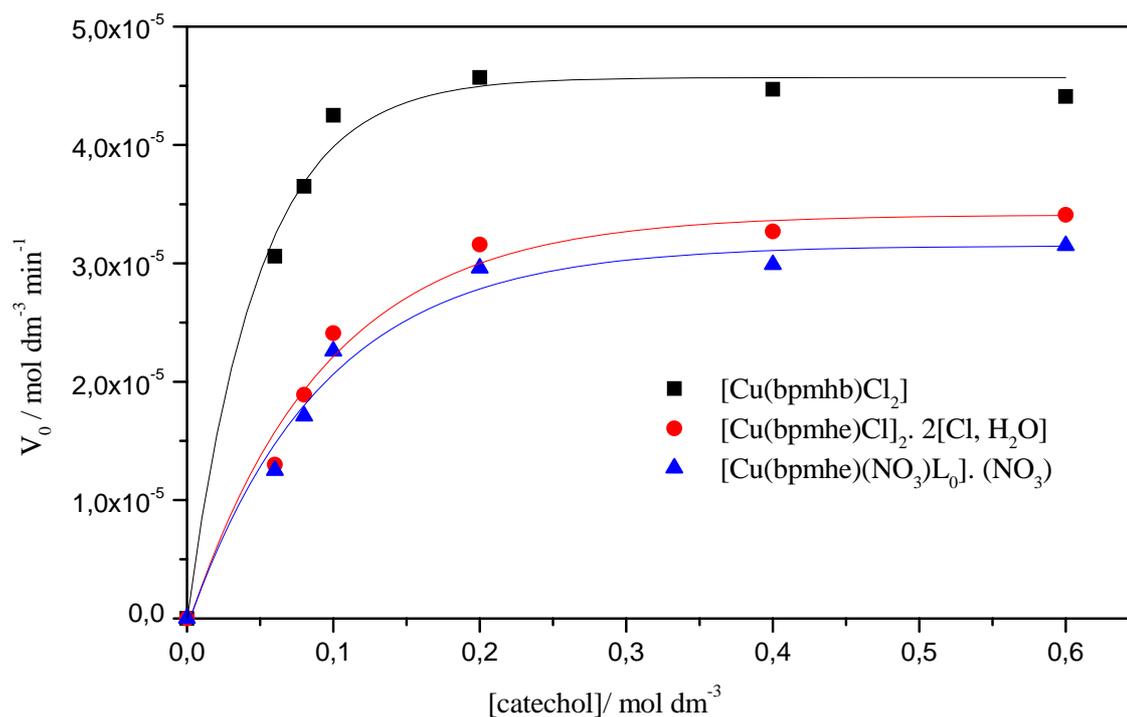


Figure 2: Dependence of the initial rate of the quinone production on the concentration of substrate, catechol, at constant concentration of catalyse (1×10^{-4} M) in methanol.

Table 3. Kinetic data for the oxidation of catechol by copper complexes

Complex	Activity ($\mu\text{mol substrate/mg catalyst per min}$)	Turnover (min^{-1})	K_M (mol/l)	V_{max} (mol/l/min)
$[\text{Cu}(\text{bpmhe})\text{Cl}]_2 \cdot 2[\text{Cl}, \text{H}_2\text{O}]$	24.38	16.10	0.084	$2.74 \cdot 10^{-5}$
$[\text{Cu}(\text{bpmhe})(\text{NO}_3)\text{L}_0] \cdot (\text{NO}_3)$	27.48	15.40	0.073	$2.62 \cdot 10^{-5}$
$[\text{Cu}(\text{bpmhb})\text{Cl}_2]$	56.97	25.04	0.047	$4.25 \cdot 10^{-5}$

The three complexes catalyze the oxidation of catechol to quinone but at different rates. The complexes $[\text{Cu}(\text{bp1mae})\text{Cl}]_2 \cdot 2[\text{Cl}, \text{H}_2\text{O}]$ [8] and $[\text{Cu}(\text{bp1mae})(\text{NO}_3)\text{L}_0] \cdot (\text{NO}_3)$ [7] in which the OH participate to the complexation of the copper shows similar Turnover (min^{-1}) (of 16.1 and 15.40 respectively), but the $[\text{Cu}(\text{bpmhb})\text{Cl}_2]$ complex in which the function alcohol doesn't participate in the coordinaton of the copper ion because of the length of the side chain, shows significant catalytic activity.

CONCLUSION:

We report the synthesis of a new tridentate ligand, bpmhb, with a functional hydroxy group and its copper dichloride complex. The geometry of the Copper (II) ion can be described as being intermediate between a distorted square pyramid and a trigonal bipyramid. The OH group well arranged to form an intramolecular hydrogen bonding with the chloride atom Cl_1 .

In summary, the tree complexes catalyze the oxidation of catechol to quinone but at different rates. These results show that variation in the arm lengths does drastically affect the catalytic properties of the resultant copper complex. Work is in progress to ascertain the relationship between the structures of the complexes and their reactivity.

EXPERIMENTAL:

General:

The melting point was measured on a BUCHI 510 apparatus and is uncorrected. Proton NMR spectra of the compound bpmhb dissolved in CDCl_3 , was obtained with an AC 200 MHz Bruker spectrometer. Infrared spectra were recorded in KBr pellets using a Perkin-Elmer 1310 infrared spectrophotometer. UV-Visible spectra were followed by JAS.CO 7800. The crystal structure data was collected on CrysAlis CCD diffractometer at 173°K

Synthesis of [bpmhb]:

A mixture of 1-hydroxymethyl 3,5-dimethylpyrazole (2gr, 16 mmol) and 4-amino-1-butanol (0.72gr, 8 mmol) placed In a tree necked round bottom flask equipped with a condenser was heated for 3 hours at 60°C with Marie bath. The reaction mixture was extracted with dichloromethane and washed with water to eliminate the residual butanolamine. The solvent of the dried organic solution was eliminated under reduced pressure to give a white solid.

Yield: 90% (2.2gr)

Melting point: 72-74°C (CH₂Cl₂).

¹H-NMR (200 MHz, CDCl₃) δ: 5.76 (s, 2H, Hpz); 4.83(s, 4H, N-CH₂-N); 3.48(t, 2H, CH₂OH); 2.59 (t, 2H, CH₂-CH₂N); 2.15 (s,12H, CH₃); 1.43(m,4H, HOCH₂CH₂CH₂). IR (KBr, cm⁻¹): 3260, 2920, 2830, 1560, 1460, 1420, 1370, 1300, 1240, 1180, 1140, 1110, 1060, 1030, 980, 850, 800, 760, 700.

Synthesis of [Cu(bpmhb)Cl₂]:

The Copper (II) complex was prepared by the addition of a solution of tridentate ligand bpmhb (0.305gr; 1mmol) in methanol (3 mL) to a solution of the Copper(II) dichloride[CuCl₂, 2H₂O] (0.1704gr; 1mmol) in methanol (3 mL). The resulting solution was filtered and allowed to stand at 25°C. Green crystals formed after a few days, which were filtered and washed with small amounts of cold methanol and dried in air (118.8mg); melting point: 180-182°C (methanol); IR (KBr, cm⁻¹): 3480, 3320, 3080, 2900, 2740, 2720, 1610, 1550, 1440, 1390, 1290, 1260, 1150, 1110, 1080, 1060, 980, 870, 810. UV-Vis (CH₃OH; λ_{max}, nm (ε, M⁻¹ cm⁻¹)): 205(10500); 232.5(8906); 250(8437); 737.5(44).

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