Copper complexes as biomimetic models of catechol oxidase: mechanistic studies

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X-ray 3D structures and properties of two copper(II) complexes with an asymmetric phenol-based N,O,S-ligand. Influence of the counter ion on the crystal packing[†]

The new asymmetric phenol-based N,O,S-ligand Hpy2th1as (2-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-4-methyl-6-[2-thiophenylmethyl)aminomethyl]phenol) was prepared by the straightforward reductive amination of 3-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-5-methylsalicylaldehyde (= Hpy2ald, Chapter 3) with 2-thiophenylmethylamine. This ligand was designed to bind two copper(II) ions, providing different steric accessibility for each of them, and to mimic the unusual thioether bond in a close proximity to the metal centers, present in the active site of catechol oxidase. The reaction of Hpy2th1as with copper(II) chloride in methanol results in the formation of the complex $[Cu_2(H_2py2th1as)_2Cl_2](CuCl_4)_2$. During the crystallization, the ligand undergoes a protonation of the secondary amine group, which results in the ligand coordination to only one copper(II) ion. Two mononuclear units are further doubly bridged by two chloride anions, and the positive charge is compensated by two tetrachlorocuprate anions, formed during the crystallization. The complex with a very similar structure of the composition $[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4 \cdot 6CH_3OH$ was prepared by reaction of the ligand with copper(II) perchlorate in the presence of the chloride ions. Although the two coordination compounds exhibit virtually identical complex cations, the crystal packings of both molecules are significantly different, apparently induced by the distinct but geometrically related anions, namely tetrachlorocuprate(II) and perchlorate.

[†] This chapter is based on: Koval, I. A., Sgobba, M., Huisman, M., Lüken, M., Saint-Aman, E., Gamez, P., Krebs, B, Reedijk, J., New J. Chem., 2005, submitted for publication

5.1 Introduction

As discussed in Chapters 2-4 of this thesis, phenol-based compartmental ligands of the ‘‘end-off’’ type have often been used for modeling bimetallic biosites,[1-4] in particular catechol oxidase.[5] In Chapter 2 the strategy of the synthesis of dinucleating asymmetric ligands has been discussed,[6] whereas in Chapter 4, the synthesis of the symmetric sulfur-containing phenol-based ligand Hpy2th2s, designed to mimic the presence of a thioether bond in the active site of the enzyme, has been reported.[7] In the present chapter, the two approaches were combined to prepare the asymmetric phenol-based ligand Hpy2th1as, designed to model the two peculiarities of the active site of the enzyme: (i) the asymmetric surrounding of the two metal centers, and (ii) the presence of a sulfur atom in a close proximity to one of them. Similarly to the ligand Hpy3asym, reported in Chapter 2, this ligand contains two dissimilar chelating arms in the 2 and 6 positions of the aromatic ring, designed to provide a different number of donor atoms for the binding of two copper ions. Furthermore, one of these arms contains a thiophene ring, the very weak donor properties of which are expected to prevent its coordination to the metal ions. The reaction scheme of the ligand synthesis is depicted in Figure 5.1. The reaction of the ligand with copper(II) chloride in methanol led to the isolation of the complex $[Cu_2(H_2py2th1as)_2Cl_2](CuCl_4)_2$. Unexpectedly, the secondary amine group of the ligand was found to undergo a protonation during the crystallization, which prevented it from binding to a copper ion. The crystallization of the ligand with copper(II) perchlorate in the presence of chloride anions led to the formation of the complex $[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4{\cdot}6CH_3OH$ with a very similar structure of the complex cation. In this chapter, the single-crystal X-ray structures and solution properties of both complexes are discussed in detail.

5.2 Results and Discussion

5.2.1 Ligand synthesis

The ligand Hpy2th1as (2-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-4-methyl-6-[2-thiophenylmethyl)aminomethyl]phenol) was prepared by the condensation of 3-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-5-methylsalicylaldehyde (Hpy2ald, see Chapter 3) with 2-thiophenylmethylamine, followed by the reduction of the imine formed using sodium borohydride (Figure 5.1). This afforded Hpy2th1as as a light yellow oil in 95% yield.

5.2.2 Synthesis of the coordination compounds

The reaction of Hpy2th1as with copper(II) chloride in a 1:2 ratio resulted in the formation of a green crystalline complex **1** in 49% yield. Single crystals of **1** suitable for X-ray structure determination were obtained by diffusion of diethyl ether into a 0.01 M methanolic solution of the complex. The X-ray analysis revealed that in the complex two copper(II) ions are coordinated by two ligands and are doubly bridged by the chloride anions, resulting in the complex of the formula $[Cu_2(H_2py2th1as)_2Cl_2](CuCl_4)_2$ (Figure 5.2).

In order to avoid the spontaneous formation of the tetrachlorocuprate(II) anions, which would undoubtedly mislead the interpretation of the results of the catecholase activity studies on **1**, and to facilitate the interpretation of the chemical and physical properties of **1**, a complex with a very similar structure, but with perchlorate counter ions, has also been prepared. It has been synthesized by reaction of Hpy2th1as with copper(II) perchlorate in the presence of an external source of chloride ions, which yielded two different reaction products, namely **1** and **2**. Redissolution of both compounds in methanol, followed by the addition of diethyl ether, resulted in the precipitation of **1**, and single crystals of **2** could be obtained upon slow evaporation of the filtrate (see Experimental Section). These crystals were characterized by X-ray crystallography, which showed compound **2** to be structurally closely related to **1** (Figure 5.3), the main differences being the distinct non-coordinated anions and the presence of hydrogen-bonded methanol molecules in the crystal lattice. It should be noted that the best results were achieved, surprisingly, by using hydroxylammonium hydrochloride as a source of Cl^- due to its high solubility in methanol, whereas in case of tetraalkylammonium salts (*e.g.* tetramethyl- and tetraethylammonium chloride), their insoluble perchlorate salts precipitated from the reaction mixture.

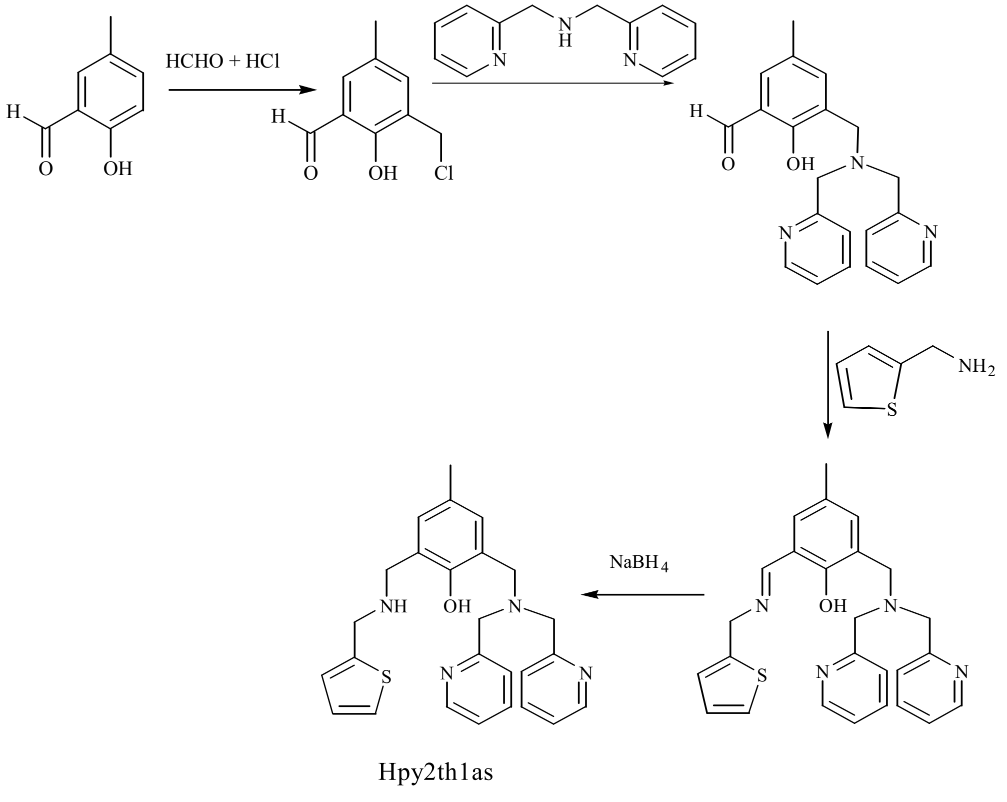

Figure 5.1. The reaction scheme of the synthesis of the ligand Hpy2th1as.

5.2.3 Crystal structure descriptions

[$Cu_2(H_2py2th1as)_2Cl_2$]($CuCl_4$)$_2$ (1)

A representation of the crystal structure of the complex is shown in Figure 5.2. Selected bond lengths and bond angles are reported in Table 5.1.

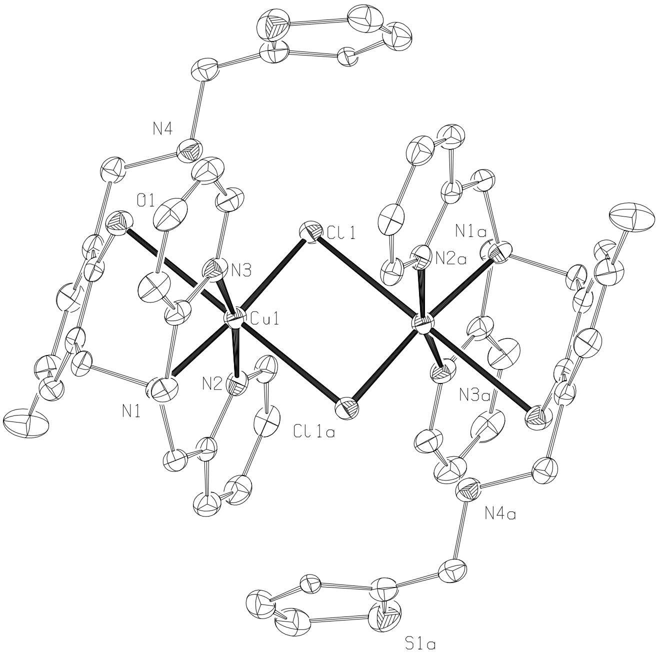

Figure 5.2. ORTEP projection of the complex cation [$Cu_2(H_2py2th1as)_2Cl_2$]$^{4+}$ in **1**. The hydrogen atoms and the non-coordinated tetrachlorocuprate(II) anions are omitted for clarity.

Table 5.1. Selected bond lengths and bond angles for [$Cu_2(H_2py2th1as)_2Cl_2$]($CuCl_4$)$_2$ (**1**)

Bond lengths (Å)			
Cu1…Cu2	3.4387(10)		
Cu1 - N1	2.020(3)	Cu1 - O1	2.784(2)
Cu1 - N2	1.983(2)	Cu1 - Cl1	2.2535(9)
Cu1 - N3	1.996(4)	Cu1 - Cl1a	2.8280(10)

Bond angles (°)			
Cl1 - Cu1 - O1	88.11(6)	Cu1- Cl1 - Cu2	89.32(4)
Cl1 - Cu1 - N1	173.30(8)	O1 - Cu1 - Cl1a	169.31(6)
Cl1 - Cu1 - N2	96.25(8)	N1 - Cu1 - N2	83.51(10)
Cl1 - Cu1 - N3	97.76(8)	N1 - Cu1 - N3	82.43(10)
Cl1 - Cu1 - Cl1a	95.53(4)	N1 - Cu1 - Cl1a	90.63(8)
O1 - Cu1 - N1	85.84(9)	N2 - Cu1 - N3	165.94(11)
O1 - Cu1 - N2	103.68(9)	N2 - Cu1 - Cl1a	85.90(8)
O1 - Cu1 - N3	75.65(9)	N3 - Cu1 - Cl1a	93.90(8)

The complex crystallizes in the space group *P2₁/n*. Similarly to complexes reported earlier with the structurally related ligand Hpy2ald[8] (Chapter 3), the phenol group of the ligand remains protonated and therefore does not act as a bridging ligand connecting two copper ions, instead being only weakly coordinated to one metal center. Furthermore, the secondary amine nitrogen atom N4 is also protonated, resulting in an ammonium moiety which cannot bind to a metal ion. Two mononuclear units are then doubly bridged by two chloride anions, which hold two copper ions at a distance of 3.4387(10) Å. The coordination sphere around the copper ion can be best described as a distorted elongated octahedron with the atoms N1, N2, N3 and Cl1 at the equatorial positions, and the atoms Cl1a and O1 occupying the Jahn-Teller axis. All Cu–N bond lengths are approximately equal, with average Cu–N distances of 2.0 Å. The Cu–Cl1 bond is slightly longer with a value of 2.2535(9) Å. The Cl1a and O1 atoms are located at longer distances of 2.8280(10) Å and 2.784(2) Å and can be best regarded as semi-coordinated to the metal ion. The O1–Cu1–Cl1a angle is 169.31(6)°. The tetrachlorocuprate counter ions, present in the crystal lattice, are hydrogen bonded to two dinuclear units, resulting in a 2D network (Table 5.3).

$[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4 \cdot 6CH_3OH$ (2)

A representation of the crystal structure of complex **2** is shown in Figure 5.3. Selected bond lengths and bond angles are given in Table 5.2.

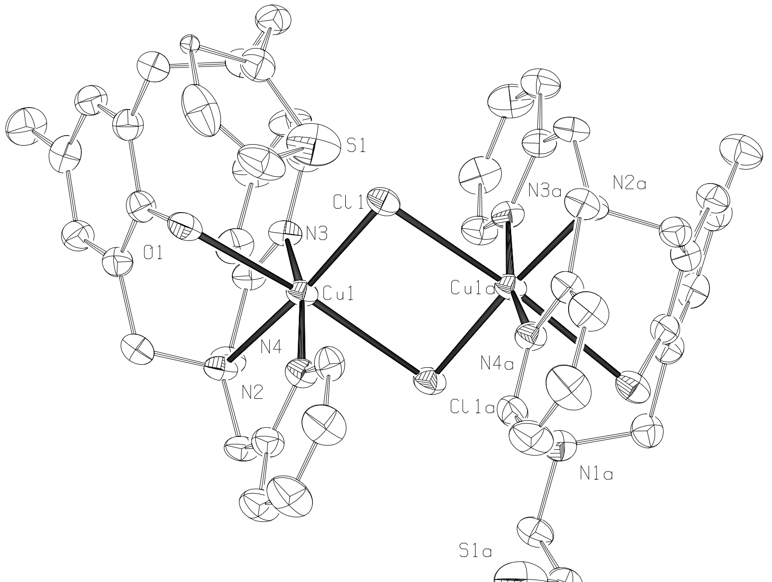

Figure 5.3. ORTEP projection of the complex cation $[Cu_2(H_2py2th1as)_2Cl_2]^{4+}$ in **2**. Hydrogen atoms, non-coordinated perchlorate anions and solvent molecules are omitted for clarity.

Table 5.2. Selected bond lengths and bond angles for $[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4{\cdot}6CH_3OH$ (**2**)

Bond lengths (Å)			
Cu1…Cu1a	3.5252(14)		
Cu1 - Cl1	2.2663(17)	Cu1 - N4	1.982(4)
Cu1 - N2	2.034(4)	Cu1 - Cl1a	2.8579(17)
Cu1 - N3	1.996(4)	Cu1 - O1	2.758(4)

Bond angles (°)			
Cl1 - Cu1 - O1	85.44(10)	Cu1 - Cl1 - Cu1a	86.12(6)
Cl1 - Cu1 - N2	174.76(15)	O1 - Cu1 - Cl1a	168.61(10)
Cl1 - Cu1 - N3	95.77(13)	N2 - Cu1 - N3	83.18(17)
Cl1 - Cu1 - N4	99.14(13)	N2 - Cu1 - N4	82.03(17)
Cl1 - Cu1 - Cl1a	93.85(6)	N2 - Cu1 - Cl1a	91.31(14)
O1 - Cu1 - N2	89.69(16)	N3 - Cu1 - N4	165.08(18)
O1 - Cu1 - N3	100.31(16)	N3 - Cu1 - Cl1a	91.07(14)
O1 - Cu1 - N4	81.56(16)	N4 - Cu1 - Cl1a	87.34(14)

Table 5.3. Hydrogen bond interactions in the complexes **1** and **2**.

	Donor - H....Acceptor	*D – H (Å)*	*H...A (Å)*	*D...A (Å)*	*D - H...A (°)*
$[Cu_2(H_2py2th1as)_2Cl_2](CuCl_4)_2$	O1 - H1...Cl2	0.8402	2.2527	3.035(2)	155.10
	N4 - H4a...Cl4	0.9197	2.2838	3.132(3)	153.09
	N4 - H4b...Cl1	0.9206	2.6649	3.320(3)	128.83
	N4 - H4b...O1	0.9206	2.2483	2.929(3)	130.24
$[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4$ $\cdot 6CH_3OH$	O1 - H1...O10	0.8199	1.8568	2.652(7)	163.06
	N1 - H1a…O11	0.8997	1.8278	2.712(7)	167
	N1 - H1b…Cl1	0.9008	2.5757	3.356(5)	145.38
	N1 - H1b…O1	0.9008	2.3088	2.917(6)	124.71
	O10 - H10…O2	0.8191	2.5113	2.784(8)	100.84
	O11 - H11a…O12	0.8188	2.2674	2.734(9)	116.58
	O12 - H12…O5	0.821	2.506	2.895(10)	110.25
	O12 - H12a…O2	0.821	2.5692	2.973(10)	117.75

The complex crystallizes in the space group *C2/c*. The molecular structure of the complex cation is analogous to the one of **1**. Thus, the copper ion is coordinated by three nitrogen atoms N2, N3 and N4 at an average distance of 2.0 Å and a chloride atom Cl1 at a somewhat longer distance of 2.2663(17) Å, which occupy the equatorial positions of a distorted octahedron. The coordination sphere is completed by O1 and Cl1a which are weakly bound on the Jahn-Teller axis (the Cu1–Cl1a and the Cu1–O1 bond lengths are 2.8579(17) Å and 2.758(4) Å, respectively). The distance between the two doubly bridged copper ions of the two mononuclear units is 3.5252(14) Å, and the O1–Cu1–Cl1a angle is 168.61(10)°. Besides non-coordinated perchlorate anions, six methanol molecules per dimeric unit are present in the crystal lattice, taking part in the formation of an intricate hydrogen bonding network, which is described in Section 5.2.5 (see also Table 5.3).

5.2.4 Physical Characterization

The diffuse reflectance spectrum of **2** (solid state) is characterized by two peaks at 335 nm and 647 nm, whereas in the solid-state spectrum of **1**, one additional peak at 416 nm with a shoulder at 459 nm can be found (Figure 5.4). The latter peak is most likely caused by the presence of the tetrachlorocuprate anions. Indeed, earlier reports on tetrachlorocuprate complexes describe the presence of an intensive charge transfer band at *ca.* 350-400 nm in the UV-Vis spectra. The peak at 647 nm corresponds to d-d transitions of the Cu^{II} ions, whereas the peak at 335 nm is assigned to the charge transfer band from the chloride ions to the copper centers within the complex cation.

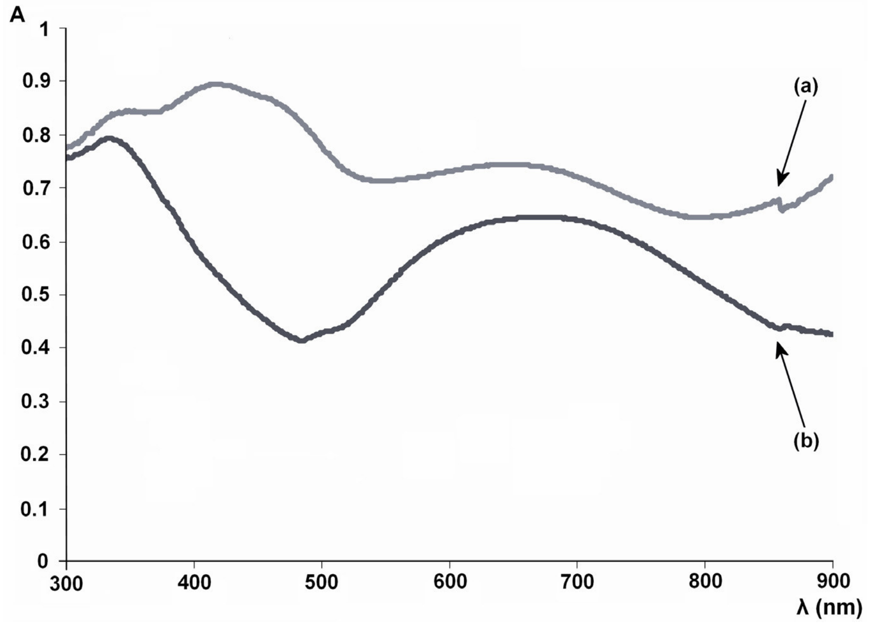

Figure 5.4. Diffuse reflectance ligand field spectra of **1** (a) and **2** (b).

In methanol solution, the UV-Vis spectrum of **2** is characterized by two very weak absorptions at 690 nm ($\varepsilon = 80\ M^{-1}\ cm^{-1}$) and at 480 nm ($\varepsilon = 80\ M^{-1}\ cm^{-1}$). The first one corresponds to the d-d transitions of the Cu^{II} ions, whereas the second is tentatively assigned to the charge transfer band due to the solvation of the metal centers by methanol. The UV-Vis spectrum of **1** in methanol looks very similar, with the d-d absorption at 700 nm ($\varepsilon = 160\ M^{-1}\ cm^{-1}$) and a broad peak at 450 nm with a shoulder at higher wavelength ($\varepsilon = 160\ M^{-1}\ cm^{-1}$), probably originating from the methanol-solvated tetrachlorocuprate(II) ions.

The EPR spectra of both complexes have been recorded in solid state and in methanol glass at 77 K. The solid-state spectrum of **1** is characterized by one very broad isotropic signal centered at $g = 2.14$, whereas the spectrum of **2** exhibits an ill-resolved axial signal with $g_{//} = 2.30$ and $g_{\perp} = 2.06$.

It is very interesting to compare the solution EPR spectra of **1** and **2** (Figure 5.5, left). The spectrum of **2** exhibits an axial character with $g_{//} = 2.25$, $g_{\perp} = 2.02$ and $A_{//} = 183\times10^{-4}\ cm^{-1}$. Three out of the four lines of the $^{63,65}Cu$ hyperfine splitting are easily observed, whereas the fourth one is hidden in the $g_{\perp}$ region. The data obtained clearly indicate the dissociation of the dinuclear unit in solution, producing two mononuclear species.

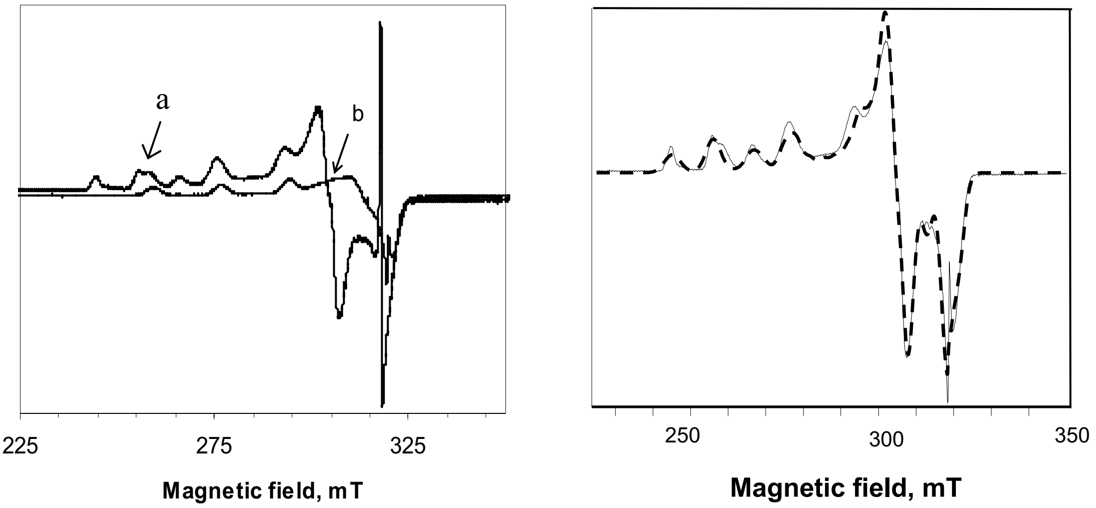

Figure 5.5. Left: frozen methanol EPR spectra of **1** (a) and **2** (b). Right: experimental (frozen methanol glass, solid line) and simulated[9] (dashed line) EPR spectra of **1**. A sharp signal in the spectra corresponds to the reference DPPH (g = 2.0036)

The spectrum of **1** displays two sets of axial signals, suggesting the presence of two mononuclear Cu^{II} species in solution: one originating from the dissociation of the dinuclear core, and another originating from the tetrachlorocuprate counter ions. The spectrum has been satisfactory simulated[9] (Figure 5.5, right), considering two non-interacting mononuclear species X and Y, with the following simulating parameters: for X, g_x=2.06, g_y=2.10, g_z=2.25 and $A_z = 191\times10^{-4}\ cm^{-1}$; for Y, g_x=2.03, g_y=2.12, g_z=2.45, and $A_z = 126\times10^{-4}\ cm^{-1}$. The parameters for the latter species in fact are very close to the values reported for elongated rhombic octahedral CuO_6 chromophores,[10] which suggest that the tetrachlorocuprate anions are methanolysed in solution, likely forming $[Cu(CH_3OH)_6]^{2+}$ species. The simulating parameters for species X, on the other hand, are close to those experimentally obtained for compound **2**, confirming that they correspond to the mononuclear $[Cu(H_2py2th1as)Cl]^{2+}$ cation.

The electrochemical behavior of both complexes was investigated in methanolic solutions, with tetra-*n*-butylammonium perchlorate (TBAP) as supporting electrolyte (0.1 M). The potentials were referred to a standard Ag/AgCl + 3M KCl reference electrode. The CV curve for both complex **1** (Figure 5.6 (a)) and **2** (Figure 5.6 (b)) is characterized by a quasi-reversible electrochemical signal at $E_{1/2}$ = -0.10 V. However, an additionnal reversible system is seen on the CV curve of **1** at $E_{1/2}$ = 0.39 V. The RDE voltammetry curve for **1** (Figure 5.6 (a)) shows unambiguously that both systems involve the same number of electrons. Comparison of the electrochemical behavior of **1** and **2** allows to assign the electron transfer at -0.10 V to the complexed Cu^{II}/Cu^{I} redox couple, whereas the additionnal reversible system for **1**, at +0.39 V, corresponds to the methanol-solvated tetrachlorocuprate Cu^{II}/Cu^{I} redox couple. It can be noted that extending the scan below –0.6 V leads to the deposition of Cu^0 onto the electrode surface.

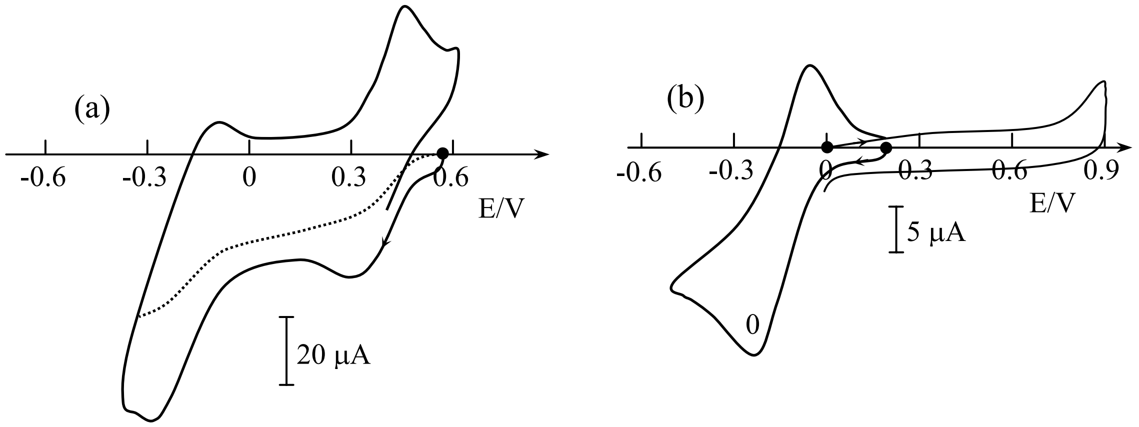

Figure 5.6. (a): Electrochemical curves recorded in a 0.66 mM solution of **1** in MeOH + TBAP 0.1 M on a C disc (∅ = 3 mm); solid line: CV curve, v = 0.1 V s^{-1}; dotted line: RDE curve, N = 600 rpm; V *vs.* standard Ag/AgCl + 3M KCl reference electrode. (b): CV curve of **2** in 0.12 mM in MeOH + NBu_4PF_6 0.1 M, 0.1 V s^{-1}, V *vs.* standard Ag/AgCl + 3M KCl reference electrode.

5.2.5 Counter-ion influence on the crystal packing of 1 and 2

Despite their obvious similarities, it is interesting to compare the details of the structures of the complex cations in **1** and **2**. Both coordination compounds possess several peculiar features (Figure 5.7). First, in both complexes the thiophenyl substituent is not coordinated to the copper ion, similarly to the complexes with the closely related ligand Hpy2th2s, reported in Chapter 4.[7] Second, the phenol (O1) is not deprotonated and thus does not function as a bridging unit between two copper ions. In **1**, the phenolic proton H1 is hydrogen-bonded to the chloride atom Cl2 of a tetrachlorocuprate(II) anion (the O1···Cl2 distance is 3.036(2) Å). Such discrete chlorocuprate(II) species are known to spontaneously form in solution during the crystallization of copper(II) chloride with neutral amine-based ligands, with the ligand undergoing a protonation.[11] This indeed occurs in the present case, since the secondary amine (N4) bearing the thiophenylmethyl group is protonated and thus not able to coordinate to the copper(II) ion. The resulting ammonium entity is H-bonded to the chloride Cl4 of a tetrachlorocuprate(II) anion (the distance N4···Cl4 is 3.132(3) Å), which is a common characteristic observed in the crystal packing of ammonium halocuprate(II) derivatives,[12,13] and which has been described to be a dominant stabilizing factor. The second ammonium proton, *i.e.* H4B is bonded to the phenolic atom O1, the distance N4···O1 being 2.929(3) Å. As a result, in this network, each dinuclear unit is connected to four neighbors by means of hydrogen bonds, realized between the chloride atoms of the counter-ions and the phenolic and ammonium groups of the complex cation. In addition, the supramolecule is further stabilised via the unusual interactions of the π-clouds of the thiophene rings with the bridging chloride anions (the centroid···Cl distance is 3.64 Å; the angle thiophene plane–centroid–Cl axis is 79.9 º).[14]

On the other hand, in complex **2** the phenol rings and the side-arms holding the thiophene units are positioned differently. Indeed, while the two phenols are *trans* located to each other for **1**, with the *para*-methyl groups pointing in opposite directions (Figure 5.7 (a)), the phenols in **2** can be considered as *cis* located, with the two methyl groups pointing in the same direction (Figure 5.7 (b)). In a similar manner, the thiophenyl moieties are *cis* located as well, preventing the beneficial stabilising π-interactions with the bridging chlorides present in **1**. This significant structural variation is most likely due to the different anions. First, the ratio cation/anion is different for both complexes since the perchlorate ion is monovalent while the tetrachlocuprate ion is divalent. More interestingly, the perchlorate anions are H-bonded to solvent methanol molecules, leading to a completely distinct and intricate hydrogen bonding network, enclosing a large amount of methanol molecules in the crystal lattice (Figure 5.7 (b)). The presence of these solvent entities apparently induces a rotation of the phenol rings through the N1_a–C8_a and C8_a–C2_a axes. Thus, the perchlorate O2 atom is connected to the methanolic proton H10 (the distance O2···O10 is 2.784(8) Å). This methanol is further strongly H-bonded to the proton H1 of the phenol ring (the distance O10···O1 is 2.652(7) Å). The second perchlorate anion is weakly H-bonded to the proton H12A of another methanol molecule (the distance O6···O12 is 3.010(3) Å), and interacts with the sulfur atom S1 of the thiophene (the distance O7···S1 is 3.108(2) Å). Finally, the ammonium proton H1B is connected to the phenolic oxygen atom O1 (the distance N1···O1 is 2.917(6) Å) and the second proton, H1A, is H-bonded to the oxygen atom O11 of a methanol molecule (the distance N1···O11 is 2.712(6) Å). In addition, the methanolic oxygen atom O11 acts as a H donor for a third methanol molecule (the distance O12···O11 is 2.734(5) Å). The resulting [complex–MeOH–ClO$_4^-$] H-bonded network connects all dinuclear units to generate a 3D assembly.

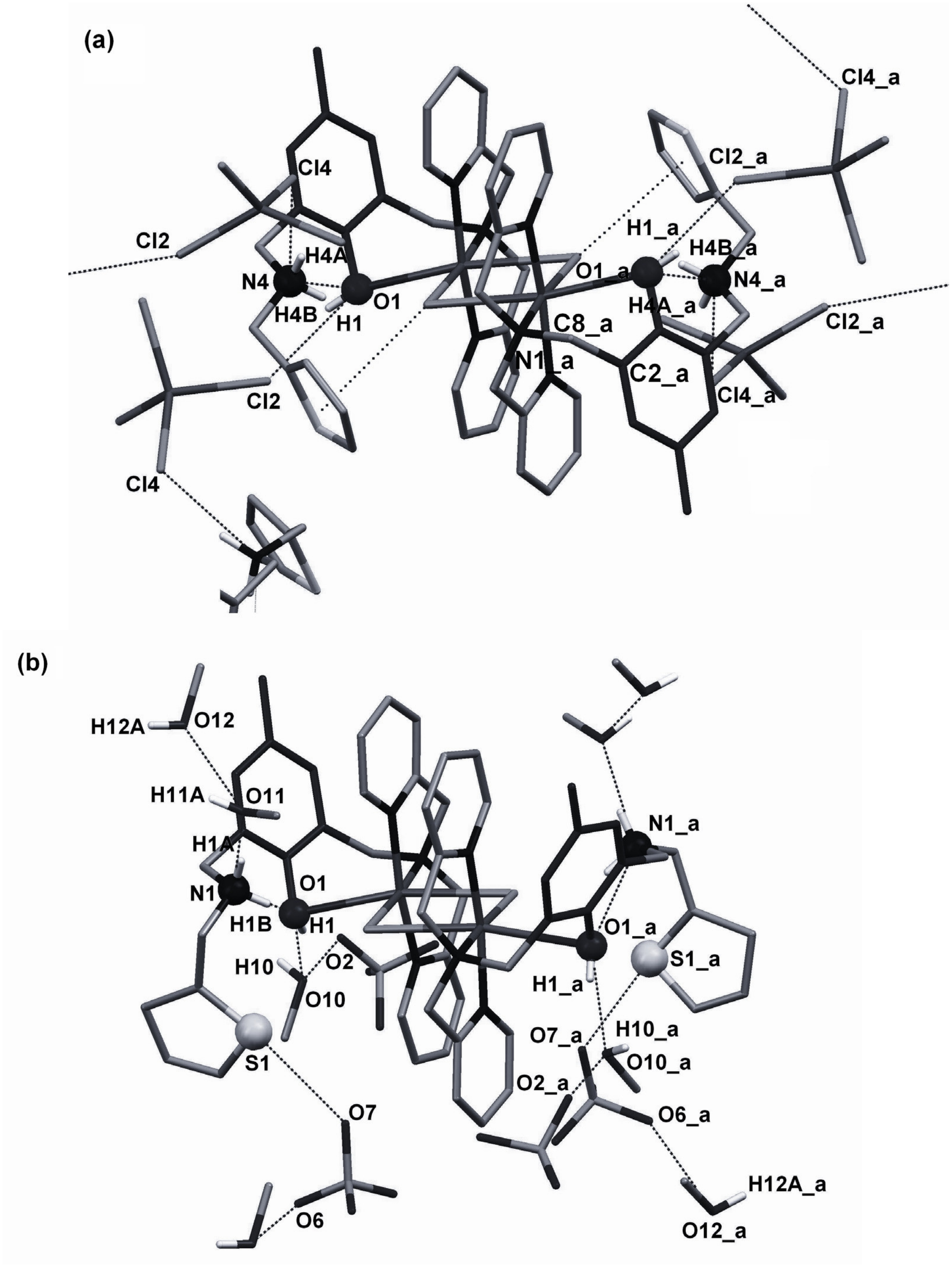

Figure 5.7. Hydrogen-bonding network for complexes **1** (a) and **2** (b).

5.2.6 Catecholase activity studies

Although the ligand Hpy2th1as has been designed to bind two copper(II) ions, resulting in dinuclear complexes, the structures of **1** and **2** are quite different. The unexpected protonation of the secondary amine group prevents it from coordination to the copper ions; consequently, both complexes are formed by the self-assembly of two mononuclear units, in which a single copper ion is coordinated by a ligand molecule, via the bridging chloride ions. The spectroscopic studies in solution clearly indicated that these dinuclear units fully dissociate into mononuclear species in solution, which in turn makes the complexes in question not very suitable models for the catechol oxidase active site. Unfortunately, the attempts to isolate dinuclear copper(II) complexes with this ligand were unsuccessful.

Nevertheless, the catalytic activity of both complexes towards the oxidation of the model substrate 3,5-di-*tert*-butylcatechol ($DTBCH_2$) has been studied spectrophotometrically in methanolic solution in a dioxygen-saturated atmosphere. Not surprisingly, both complexes do not exhibit catecholase activity, although one equivalent of quinone is produced stoichiometrically upon treating one molar equivalent of **1** with 100 molar equivalents of $DTBCH_2$. This stoichiometric oxidation is obviously caused by the stoichiometric reaction of the methanol-solvated tetrachlorocuprate anions with the substrate.

5.3 Concluding remarks

In summary, a new thiophene-containing phenol-based ligand has been synthesized. Two copper complexes of this N,O,S- ligand have been prepared and fully characterized. Unfortunately, the ligand fails to coordinate two copper(II) ions; instead it binds to only one metal center, generating chloro-bridged dinuclear species. Consequently, the obtained complexes do not bear a large resemblance to the active site of catechol oxidase and do not exhibit catecholase activity. The structural features of both compounds are nevertheless quite interesting. Although the complex cation formulas are identical, the two coordination compounds exhibit significantly different structural arrangements with a distinct ligand conformation, showing the importance of the anion on the crystal packing. The structural difference is obviously due to the counter-ions which are differently charged. Furthermore, the aptitude of the perchlorate anions to form H-bond with less acidic protons, *i.e.* from methanol, contrary to the tetrachlorocuprate(II) ion, which is only capable to act as hydrogen acceptor for more acidic ones, *i.e.* from phenol or ammonium H donors, results in completely distinct supramolecular interactions. For instance, the thiophene ring is involved in uncommon anion-π interactions in **1**, while it acts as H bond acceptor in **2.**

5.4 Experimental Section

5.4.1 Materials and Methods

All starting materials were commercially available and used as purchased. 5-methylsalicylaldehyde was purchased from Fluka, 2-thiophenylmethylamine from Acros, and di-(2-picolyl)amine from Aldrich. 3-chloro-5-methylsalicylaldehyde was prepared according to the procedure described by Lock.[15] The synthesis of 3-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-5-methylsalicylaldehyde is described in Chapter 2.[6] The NMR spectra were recorded on a JEOL FX-200 (200 MHz) FT-NMR spectrometer. The ligand field spectra of the solids (300-2000 cm^{-1}, diffuse reflectance) were taken on a Perkin-Elmer 330 spectrophotometer equipped with a data station. Electrospray mass spectra (ESI-MS) in methanol solutions were recorded on a Thermo Finnigan AQA apparatus. X-band electron paramagnetic resonance (EPR) measurements were performed at 77 K in the solid state or in a frozen methanol solution on a Jeol RE2x electron spin resonance spectrometer, using DPPH ($g = 2.0036$) as a standard. The electrochemical behavior of the complexes was investigated in a 0.1 M solution of tetra-*n*-butylammonium perchlorate (TBAP) in methanol using a EGG 273 potentionstat coupled with a Kipp&Zonen x-y recorder, or an Autolab PGstat10 potentiostat controlled by GPES4 software. The experiments were performed at room temperature in a three-compartment cell. Potentials are referred to a standard Ag/AgCl reference electrode. The working electrode was polished with 1 μm diamond paste prior to each recording.

5.4.2 Ligand synthesis

2-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-4-methyl-6-[2-thiophenylmethyl)aminomethyl] phenol (Hpy2th1as): A solution of 2-thiophenylmethylamine (0.245 g, 2.25 mmol) in 50 ml of dry methanol was slowly added to a solution of 3-[*N,N*-bis(2-pyridylmethyl)aminomethyl]-5-methylsalicylaldehyde (0.75 g, 2.15 mmol) in 250 ml of dry methanol under argon. After the addition was complete, the resulting bright yellow solution was heated for two hours at 50 ºC. The successful formation of the imine derivative was verified by NMR spectroscopy. After cooling to room temperature, a three-fold excess of sodium borohydride (0.244 g, 6.8 mmol) was added and the reaction mixture was refluxed for 2.5 hours. After evaporation of the solvent under reduced pressure, the resulting oil was dissolved in 50 ml of acidified water (pH = 1). The aqueous phase was washed with dichloromethane (2×50 ml) and subsequently basified using a concentrated aqueous solution of ammonia. The aqueous phase was extracted with dichloromethane (2×50 ml). The separated organic phase was dried over sodium sulfate, filtered, and the solvent was evaporated under reduced pressure. Pure ligand Hpy2th1as was obtained as a clear yellow oil. Yield: 0.88 g, 2.0 mmol (95%). ^1H NMR ($CDCl_3$, 200 MHz, ppm): δ = 2.24 (s, 3H, $C\underline{H}_3$), 3.76 (s, 2H, $C\underline{H}_2N$), 3.86 (s, 4H, $C\underline{H}_2$), 3.91 (s, 2H, $C\underline{H}_2NH$), 3.98 (s, 2H, $NHC\underline{H}_2$), 6.83 (s, 1H, 5'-thiophene ring), 6.92 (m, 3H, 3'-thiophene ring, 3'- + 5'-phenol ring), 7.19 (t, 2H, 5'-pyridine rings), 7.35 (d, 2H, 3'-pyridine rings), 7.60 (t, 2H, 4'-pyridine rings), 8.53 (d, 2H, 6'-pyridine rings).

5.4.3 Syntheses of the coordination compounds

$[Cu_2(H_2py2th1as)_2Cl_2](CuCl_4)_2$ (1): A solution of Hpy2th1as (0.111 g, 0.25 mmol) in 5 ml of methanol was added to 5 ml of a methanolic solution of copper chloride (0.085 g, 0.50 mmol). Diffusion of diethyl ether resulted in the precipitation of the complex as a green powder. Yield: 97 mg (49%). Single crystals were obtained by slow diffusion of diethyl ether into a 0.01 M solution of the complex. Elemental analysis, % found (calc.) for $[Cu_2(H_2py2th1as)Cl_2](CuCl_4)_2$. (=$C_{52}H_{58}Cl_{10}Cu_4N_8O_2S_2$): C, 41.62 (41.64), H, 4.26 (3.90), N, 7.46 (7.47), S, 3.55 (4.28). ESI-MS: m/z 542 ($[Cu(H_2py2th1as)Cl]^+$). IR, cm^{-1}: 2998 (C-H stretching, 1610 ($C{=}N_{arom.}$ and $C{=}C_{arom.}$ stretching).

$[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4{\cdot}6CH_3OH$ (2): Hpy2th1as (0.031 g, 0.08 mmol) and copper perchlorate (0.030 g, 0.08 mmol) were dissolved in methanol (4 ml). 12 mg (0.2 mmol) of $NH_2OH{\cdot}HCl$ were subsequently added. Slow diffusion of diethyl ether into the resulting solution led to the formation of blue and green crystals. These crystals were re-dissolved in methanol and the addition of diethyl ether immediately yielded a green crystalline precipitate of **1**. After rapid filtration, the resulting blue solution was slowly evaporated, producing light blue crystals of **2**. Yield: 12 mg, 0.007 mmol (9%). The complex partially loses non-coordinated solvent molecules, when separated from the mother liquid. Elemental analysis, % found (calc.) for $[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4{\cdot}3CH_3OH$ (= $C_{55}H_{70}Cl_6Cu_2N_8O_{21}S_2$): C, 40.78 (41.73), H, 4.78 (4.46), N, 7.52 (7.08), S, 3.78 (4.05). ESI-MS: m/z 542 ($[Cu(H_2py2th1as)Cl]^+$). IR, cm^{-1}: 3056 (C-H stretching), 1612 ($C{=}C_{arom.}$ and $C{=}N_{arom.}$ stretching), 1098, 1049 (ClO_4^- anions).

5.4.4 X-ray crystallographic measurements

$[Cu_2(H_2py2th1as)_2Cl_2](CuCl_4)_2$ (1): A single crystal of $[Cu_2(H_2py2th1as)_2Cl_2](CuCl_4)_2$ (**1**) was mounted at 100 K on a Bruker AXS SMART 6000 diffractometer, equipped with Cu-Kα radiation (λ = 1.54178 Å). $C_{52}H_{58}Cl_{10}Cu_4N_8O_2S_2$, Fw = 1499.90, a = 12.137(2) Å, b = 11.985(2) Å, c = 20.656(4) Å, β = 96.69(3)°, Z = 2, V = 2984(2) Å^3, $\rho_{calcd.}$ = 1.669 g·cm^{-3}, μ = 6.764 mm^{-1}, absorption correction with SADABS,[16] monoclinic, space group $P2_1/n$ (no. 14), 17214 reflections collected, 5553 independent reflections (R_{int} = 0.0308). The structure was solved by direct methods and refined using the SHELX program package.[17,18] All hydrogen atoms were placed on idealized positions riding on their carrier atoms with isotropic displacement parameters. The final cycle of full-matrix least-squares refinement, including 354 parameters, converted into R_1 = 0.0352 (R_1 = 0.0430 all dat and wR_2 = 0.1172 (wR_2 = 0.1207 all data) with a maximum (minimum) residual electron density of 1.277 (-0.695) e·Å^3.

$[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4 \cdot 6CH_3OH$ (2): A single crystal of $[Cu_2(H_2py2th1as)_2Cl_2](ClO_4)_4 \cdot 6CH_3OH$ (**2**) was mounted at 293 K on a Bruker AXS SMART 6000 diffractometer, equipped with Cu-Kα radiation (λ = 1.54178 Å). $C_{58}H_{82}Cl_6Cu_2N_8O_{24}S_2$, $M = 1679.26$, $a = 19.693(4)$ Å, $b = 13.376(3)$ Å, $c = 27.401(5)$ Å, $\beta = 96.69(3)°$, $Z = 4$, $V = 7169(3)$ Å^3, $\rho_{calcd.} = 1.556$ g·cm^{-3}, $\mu = 4.032$ mm^{-1}, absorption correction with SADABS,[16] monoclinic, space group *C2/c* (no. 15), 20413 reflections collected, 6673 independent reflections ($R_{int} = 0.0520$). The structure was solved by direct methods and refined using the SHELX program package.[17,18] All hydrogen atoms were placed on idealized positions riding on their carrier atoms with isotropic displacement parameters. The carbon C11 of the thiophene ring was defined isotropically. The final cycle of full-matrix least-squares refinement, including 424 parameters, converted into $R_1 = 0.0761$ ($R_1 = 0.1086$ all data) and $wR_2 = 0.2221$ ($wR_2 = 0.2382$ all data) with a maximum (minimum) residual electron density of 1.808 (-0.889) e·Å^3.

5.5 References

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