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Substituted bis(beta-diketones) for molecular squares

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SUBSTITUTED BIS(BETA-DIKETONE) LIGANDS FOR MOLECULAR SQUARES

A Thesis

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Abstract

Our group has been synthesizing porous supramolecular metal-organic molecules using multidentate β-diketones as ligands. For example, *m*-phenylenebis(acetylacetone) (*m*-pbaH$_2$, **1**) and *m*-phenylenebis(dipropionylmethane) (*m*-pbprH$_2$, **2**) were readily converted to the molecular squares Cu$_4$(*m*-pba)$_4$ (**6**) and Cu$_4$(*m*-pbpr)$_4$ (**7**), which bind guests such as 4,4'-bpy and C_{60}.[1] However, **6** and **7** are only soluble in a few solvents, limiting their use in practical applications. It is therefore necessary to derivatize the ligand with different functional groups in order to improve solubility and adjust host-guest properties. Simple alkoxy derivatives should prove useful in testing this idea as they would be relatively chemically inert and should not interfere with reactions in their synthesis. Herein, I report synthesis of the ligands 5-MeO-*m*-pbaH$_2$ (**3**), 5-BuO-*m*-pbaH$_2$ (**4**), and 2-MeO-*m*-pbaH$_2$ (**5**). Ligand **3** was synthesized from 5-methoxy-1,3-benzendimethanol in a two step reaction and reacted with Cu^{2+} to form a complex that is soluble in CH_2Cl_2 and THF. X-ray analysis of this complex confirms that it is a molecular square with the formula Cu$_4$(5-MeO-*m*-pba)$_4$ (square **8**). Ligand **4** was synthesized from dimethyl 5-hydroxyisophthalate in a three step reaction and used for the synthesis of Cu$_4$(5-BuO-*m*-pba)$_4$ (square **9**). Square **9** is soluble in a wide range of solvents including CH_2Cl_2, $CHCl_3$, THF, and several benzene derivatives. Ligand **5** was synthesized from 2-methoxyisophthalic acid in a three step reaction and used for the synthesis of Cu$_4$(2-MeO-*m*-pba)$_4$ (square **10**).

Chapter 1: Introduction

1.1 Literature review

Supramolecular metal-organic molecules have attracted much interest because they may have a variety of applications, such as in gas storage,[2-4] host-guest chemistry,[1, 5-8] and catalysis.[9-12] They are made by reacting multidentate organic linkers with metal ions, resulting in one-dimensional structures such as ladders and ribbons, two-dimensional structures such as squares and triangles (sometimes referred to as metal-organic macrocycles or MOM's) or even three-dimensional polyhedra (sometimes referred to as metal-organic polyhedra or MOP's). A wide variety of organic linkers have been used, such as carboxylates, N-heterocyclic carbenes, pyridine derivatives, β-diketones, etc. The most common method for synthesizing molecular squares is to use a capping ligand to force the metal center to have a 90° binding angle for incoming linear ligands, called bridging ligands. As a result most squares have the metal ions at the corners and the bridging ligands at the edges.

The first molecular square was reported by Fujita, et al. in 1990.[13] This square was synthesized by using $Pd(en)(NO_3)_2$ (en = ethylenediamine) and 4,4'-bipyridine (4,4'-bpy). The ethylenediamine groups acted as a cap so that removal of the nitrate leaving groups would generate a 90° angle for the 4,4'-bpy ligands. Thus the $Pd(en)^{2+}$ units can be viewed as the corners of the square while the 4,4'-bpy units are the edges (see figure 1.1). Because both 4,4'-bpy and en are neutral, the square has an overall +8 charge and is balanced by eight nitrate ions from the starting material. This means that the square is soluble in polar solvents such as water. The square is also able to encapsulate organic molecules, such as 1,3,5-trimethoxybenzene, in aqueous media.

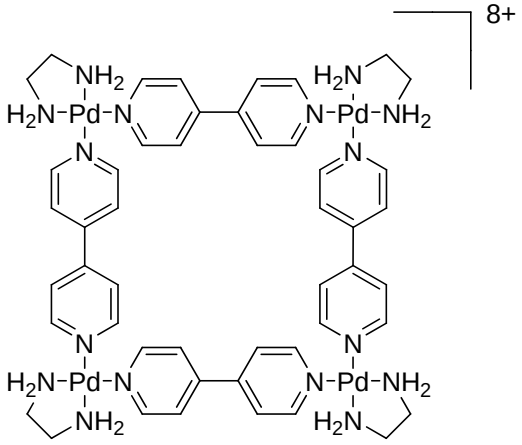


Figure 1.1. Structure of the first reported molecular square.[13]

In 1995 Stang et al. reported several molecular squares that were synthesized using phosphine capped "corners" $Pt(dppp)(OTf)_2$, $Pd(dppp)(OTf)_2$, *cis*-$Pt(PEt)_2(OTf)_2$, and *cis*-$Pd(PEt)_2(OTf)_2$ (dppp = 1,3-bis(diphenylphosphino)propane, OTf^- = triflate) and a variety of linear nitrogen donor ligands (see figure 1.2).[14] Much like the Fujita square, the metal center acts as the corner while the ligands act as the edges and the square is overall positively charged.

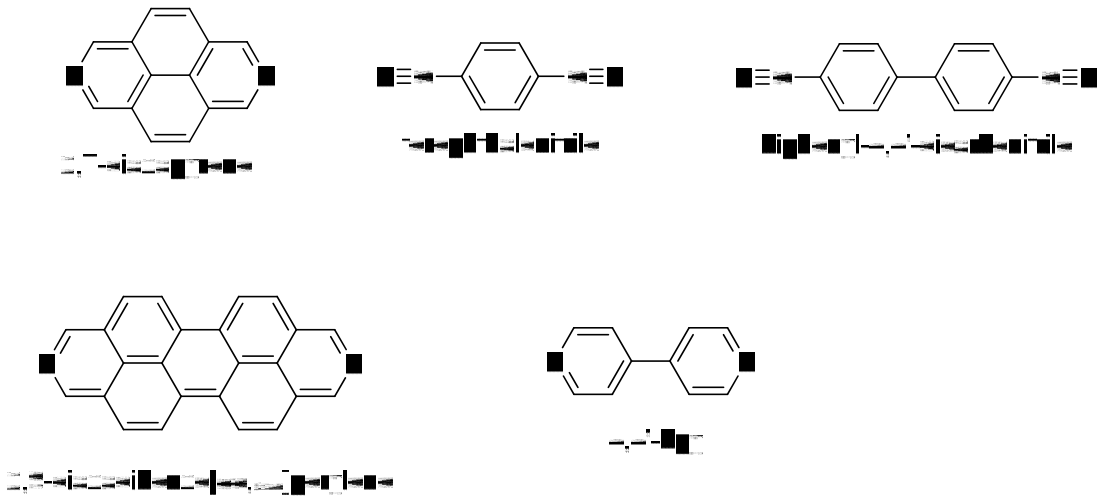


Figure 1.2. Bridging ligands used by Stang et al.[14]

In 1996 Slone et al. reported the first molecular squares to use octahedral metal centers instead of square planar centers.[15] The squares were synthesized by using $Re(CO)_5Cl$ as the capped metal unit and various pyridine derivatives such as pyrazine, 4,4'-bpy or 1,2-bis(4-pyridyl)ethane as the linear building unit. During the reaction, two of the carbonyl ligands are removed to open up sites for the pyridine derivatives to bind to. Since the metal ion is Re(I), the chloride anion provides charge balancing resulting in the first reported neutral squares. Thus the $Re(CO)_3Cl$ units are the corners with the pyridine derivatives as the edges (see figure 1.3). When pyrazine and 4,4'-bpy were used as ligands the resulting squares exhibited luminescent properties, as the result of π–π^* transitions of the ligand and metal-to-ligand charge transfer (MLCT). However, when 1,2-di(pyridin-4-yl)ethane was used as the ligand, the excited state decayed via nonradiative pathways, possibly due to rapid rotation around the ethylene bond.

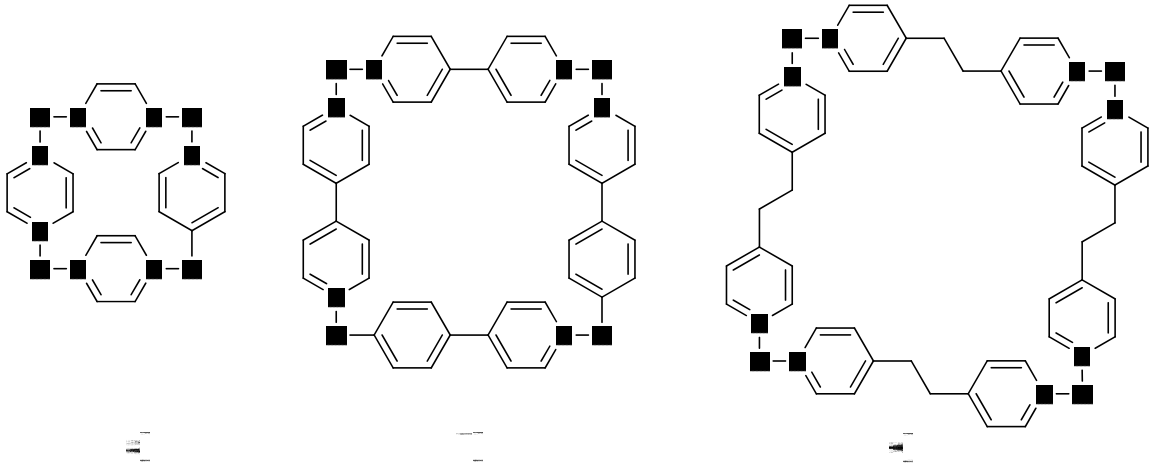


Figure 1.3. Molecular squares synthesized by Slone et al[15], a) L = pyrazine, b) L = 4,4'-bpy, c) L = 1,2-bis(4-pyridyl)ethane. M = $Re(CO)_3Cl$.

The first examples of chiral squares were also reported in 1996 by Olenyuk et al.[16] Olenyuk et al. synthesized the squares using 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), a chiral molecule, as metal capping groups for Pd or Pt(II) centers (see figure 1.4).

In addition to the commonly used linear pyridine derivative bridging ligands, an unusual ionic ligand with a 90° binding angle, bis[4-(4-pyridyl)phenyl]iodonium, was used (see figure 1.4). For squares synthesized with this ligand, two corners are occupied by capped metals while the other two corners are occupied by the iodonium portion of the ligand (see figure 1.5). They also used bis(3-pyridyl)iodonium triflate (see figure 1.4) to synthesize squares with twisted components that exhibited elements of helicity.

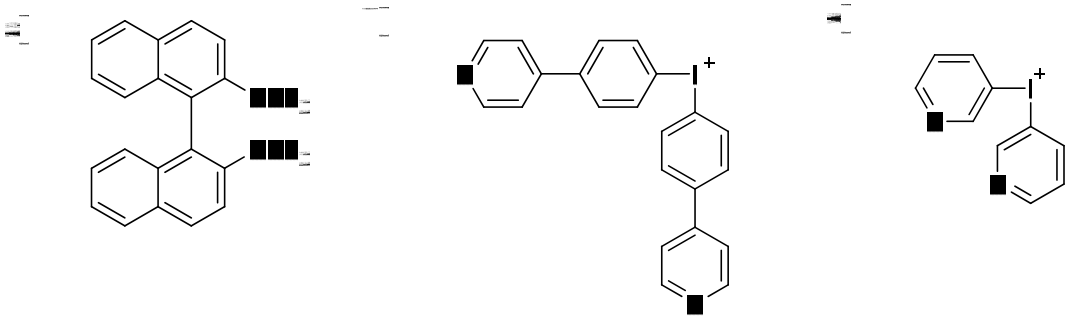


Figure 1.4. Structures of a) BINAP, b) bis[4-(4-pyridyl)phenyl]iodonium, and c) bis(3-pyridyl)iodonium.

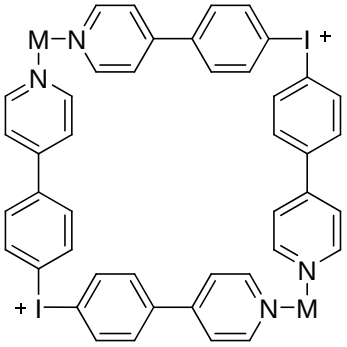


Figure 1.5. Structure of squares synthesized with bis[4-(4-pyridyl)phenyl]iodonium triflate. M = $Pd(BINAP)^{2+}$ or $Pt(BINAP)^{2+}$.

In 1998 Zhang et al. reported a molecular square that was chiral in the solid state.[17] In solution the square shows zero optical rotation, indicating that it is racemic in solution; however, individual crystals contained only one enantiomer. By using octahedral Co(II) with di-2-pyridylamine as the metal capping group and the dianion of tetraacetylethane, a bis(β-diketone), as the bridging ligand (see figure 1.6), they generated chiral metal centers. This square exhibited weak ferromagnetic exchange at temperatures around 65 K.

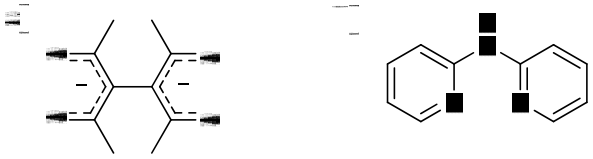


Figure 1.6. Structures of a) tetraacetylethane dianion and b) di-2-pyridylamine.

In 2001 Cotton et al. reported several squares that were synthesized from Mo_2^{4+} units and carboxylate ligands.[18] The two Mo ions were held together using *N*,*N*'-di-*p*-anisylformamidinate ($DAniF^-$) (see figure 1.7). The Mo_2(*cis*-$DAniF)_2$ units were linked together with various carboxylate ligands, such as oxalate, fumarate, 4,4'-biphenyldicarboxylate, acetylenedicarboxylate, tetrafluorophthalate (see figure 1.8), ferrocenedicarboxylate, and carboranedicarboxylate (see figure 1.9). Because the capping group $DAniF^-$ and the carboxylate ligands were anions the resulting squares were neutral.

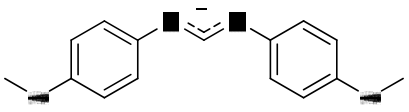


Figure 1.7. Structure of *N*,*N*'-di-*p*-anisylformamidinate.

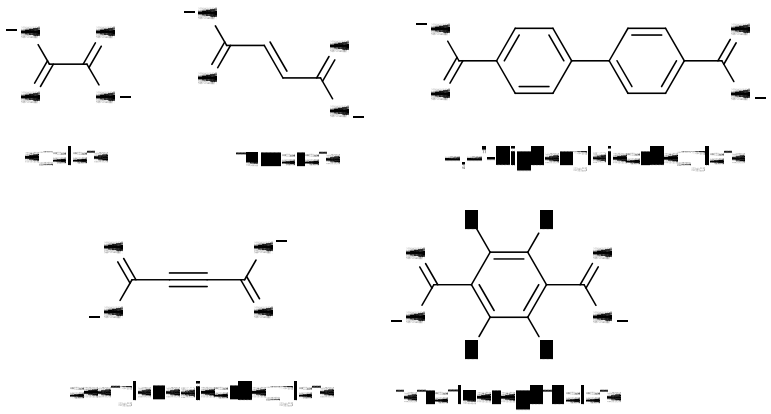


Figure 1.8. Carboxylate ligands used by Cotton et al.[18]

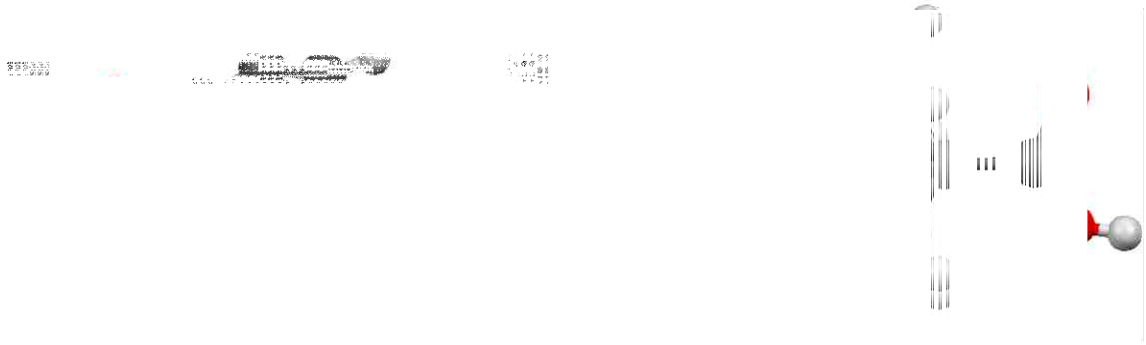


Figure 1.9. X-Ray structure of a) ferrocenedicarboxylate and b) carboranedicarboxylic acid. Figures created with Mercury 2.2 software. Dark Grey = C, Light Pink = B, Light Grey = H, Red = O, Dark Red = Fe.

In 2001 the Hupp group reported a molecular square with metalloporphyrin ligands that had the ability to encapsulate a catalytic species for epoxidation.[12] The Zn(II) porphyrin units (see Figure 1.10) were linked together via $Re(CO)_3Cl$ groups using pyridine functional groups on the porphyrin rings. The Zn(II) centers of the ligands had open coordination sites allowing them to bind to a similar Mn(III) porphyrin as the catalytic species (see Figure 1.10).

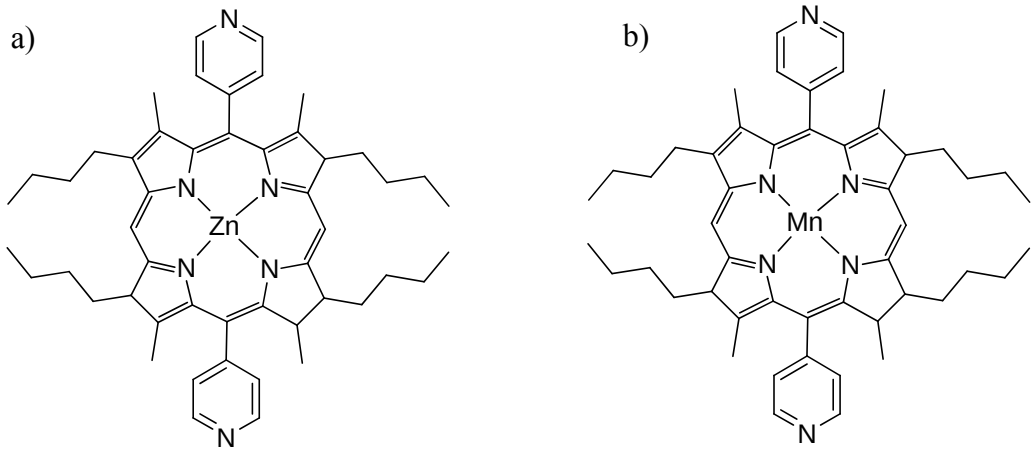


Figure 1.10. Structures of a) Zn(II) porphyrin ligand and b) encapsulated catalytic species.

In 2002 the Lin group reported the synthesis of several related chiral squares.[19] A series of related enantiopure chiral ligands were used in the synthesis to produce a chiral structure (see figure 1.11). Once again, an octahedral capping group was used, $Re(CO)_3Cl$. Like two of the Re(I) squares synthesized by Slone et al.[15], this square also exhibited luminescent properties. The square with L_4 produced the strongest luminescence and the luminescence could be quenched by encapulsating chiral 2-amino-1-propanol as a guest, demonstrating the square's ability to be used as a chiral luminescence sensor.

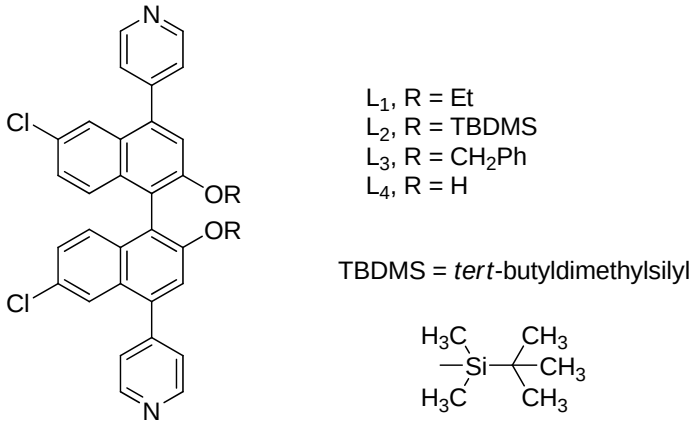


Figure 1.11. Ligands used by the Lin group.[19]

More recently in 2007, a derivative of the square Fujita synthesized in 1990 was synthesized by Uehara et al.[20] Rather than using $Pd(en)(NO_3)_2$, Uehara et al. used $Pd(en^*)(NO_3)_2$, where en* is tetramethylethylenediamine. This square is in equilibrium with the triangular structure $[(en^*)Pd(4,4'\text{-bpy})]_3(NO_3)_6$ (see figure 1.12) and this equilibrium can be adjusted by changing the solvents. In DMSO the square and triangle were in equilibrium, while in H_2O the square was the major species. Several other molecular squares have also been synthesized where the corresponding triangles were isolated.[21, 22] The square is able to encapsulate polyoxometalates (POMs) such as $[W_6O_{19}]^{2-}$ and $[W_{10}O_{32}]^{4-}$ but not larger ones such as $[\alpha\text{-}SiW_{12}O_{40}]^{4-}$ (see Figure 1.13).

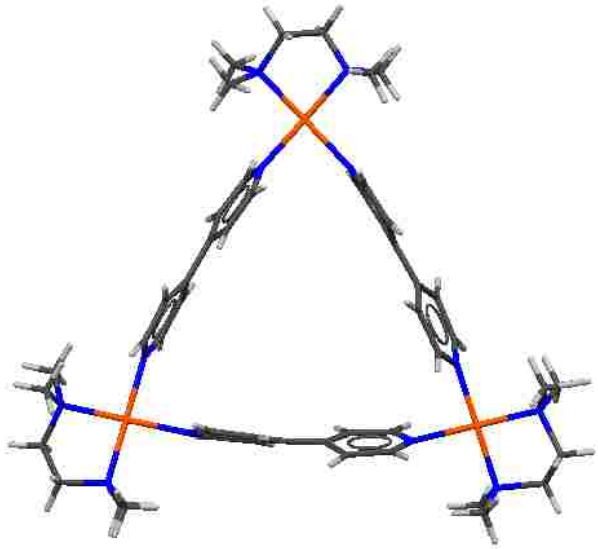


Figure 1.12. Structure of molecular triangle synthesized by Uehara et al.[20] Figure created using Mercury 2.2 software. Orange = Pd, Blue = N, Dark Grey = C, Pink = W, Red = O.

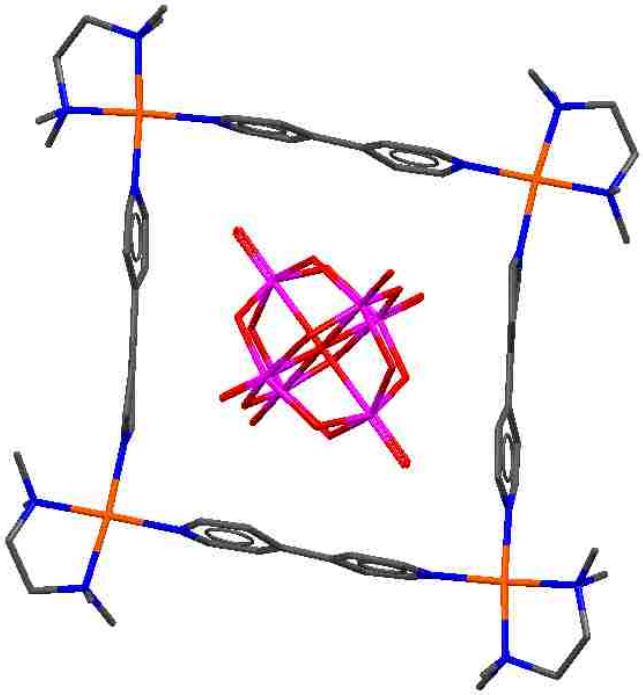


Figure 1.13. Structure of molecular square synthesized by Uehara et al.[20] with encapsulated $[W_6O_{19}]^{2-}$. Figure created using Mercury 2.2 software. Orange = Pd, Blue = N, Dark Grey = C, Pink = W, Red = O.

In 2009 a molecular rectangle was synthesized from nickelocene, 4,4'-bpy, and a bis-N-heterocyclic carbene (NHC) ligand.[23] In this structure the Ni(II) ions were capped by a η^5–cyclopentadienyl (Cp) group and were linked by the NHC ligand and 4,4'-bpy (see figure 1.14). Because the Cp capping group is negatively charged, the rectangle has a +4 charge and is balanced by 4 BF_4^- counter ions.

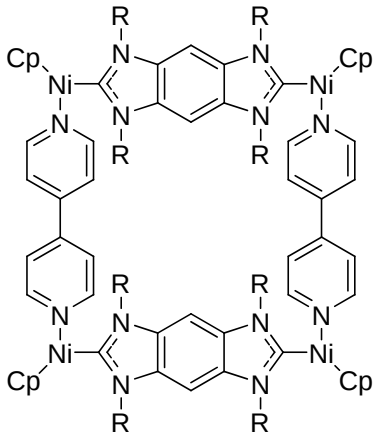


Figure 1.14. Structure of molecular rectangle with NHC ligands.[23]

1.2 Introduction

This thesis deals with the supramolecular complexes of bis(β-diketones). Previous workers in our group have used *m*-pbaH$_2$ (**1**) and *m*-pbprH$_2$ (**2**) (see figure 1.16), and I have studied the new ligands 5-MeO-*m*-pbaH$_2$ (**3**), 5-BuO-*m*-pbaH$_2$ (**4**), and 2-MeO-*m*-pbaH$_2$ (**5**) (see figure 1.15). Ligands **1** and **2** have been used as linkers to connect metal atoms into the molecular squares Cu$_4$(*m*-pba)$_4$ (**6**) and Cu$_4$(*m*-pbpr)$_4$ (**7**) (see figure 1.16).[1] There are two major differences between **6** and **7** and the previous squares. First, the metal atoms occupy the edges and the organic linkers are at the corners. Second, the Cu(II) are coordinatively unsaturated, since the Cu(II) centers are not capped and are in a square planar geometry. This means that the metal ions are free to bind guests, such as 4,4'-bpy (see Figure 1.17). Allowing for guests to interact with the metal center could open pathways for catalysis,[12, 24, 25] improve gas absorption,[26-28] or offer selective separations.[29]

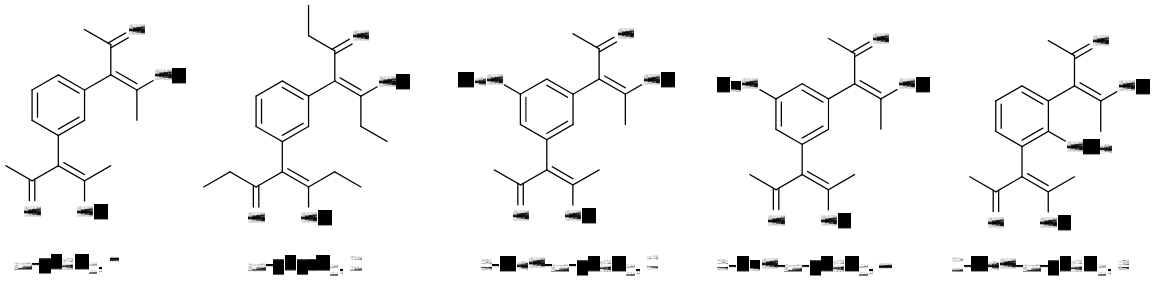


Figure 1.15. Structure of bis(β-diketone) ligands **1**-**5**.

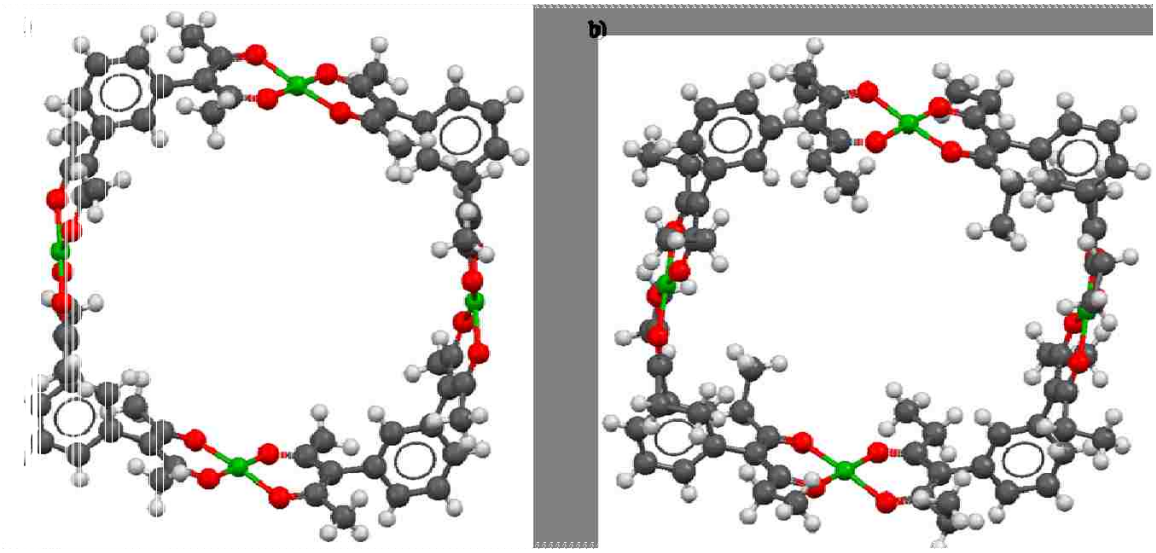


Figure 1.16. X-Ray structures of (a) **6** and (b) **7**. Figure created using Mercury 2.2 software. Green = Cu, Dark Grey = C, Light Grey = H, Red = O.

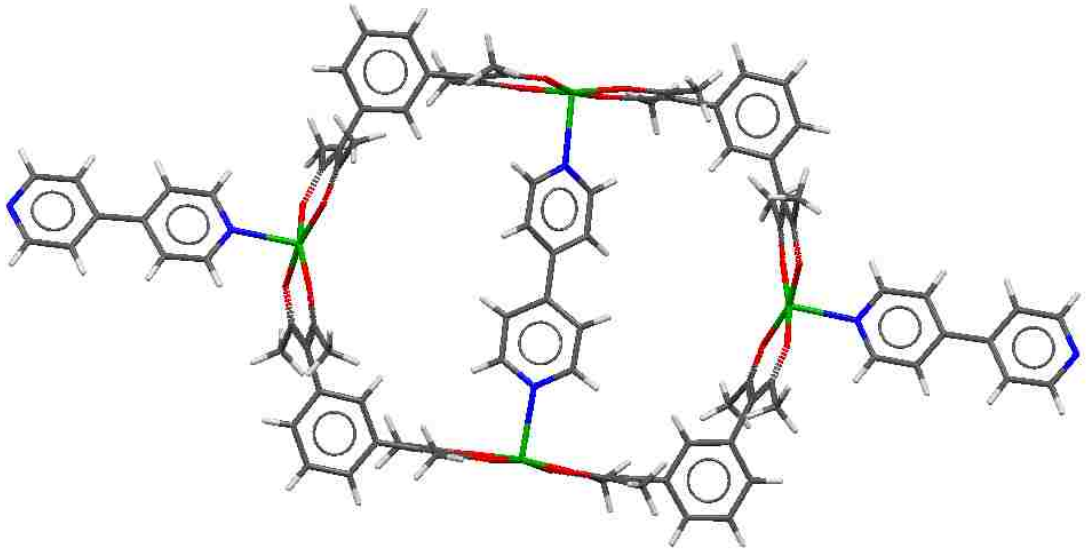


Figure 1.17. X-Ray structure of **6** with 4,4'-bpy guest. Figure created using Mercury 2.2 software. Green = Cu, Blue = N, Dark Grey = C, Light Grey = H, Red = O.

Unfortunately, **6** possessed limited solubility in organic solvents. Pariya synthesized **2** by modifying the β-diketone moieties of **1** in order to improve the solubility; however, **7** showed little improvement in solubility (see Table 1.1). The lack of solubility in a variety of organic solvents limits the ability of **6** and **7** to be used in various applications and also limits testing of some properties. For example, **7** binds C_{60} via π-π interactions (see figure 1.18); however, since C_{60} and the square are not soluble in the same solvents a binding constant could not be determined.

Table 1.1. Solubility of **6** and **7**.

Solvent	6	7
$CHCl_3$	Soluble	Soluble
CH_2Cl_2	Soluble	Soluble
THF	Insoluble	Slightly Soluble

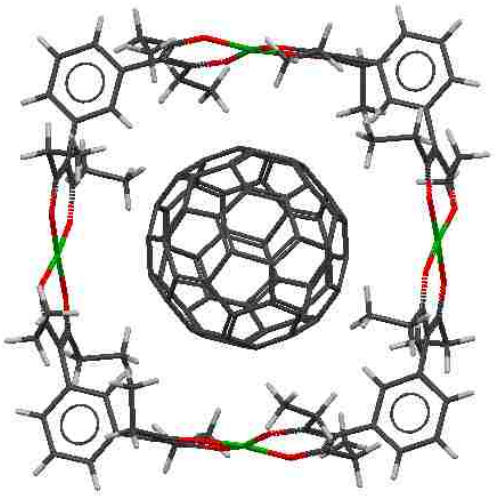


Figure 1.18. X-Ray structure of **7** with C_{60}. Figure created using Mercury 2.2 software. Green = Cu, Dark Grey = C, Light Grey = H, Red = O.

Another possibility for modifying ligand **1** is to add functional groups to the aromatic ring of the ligand. For example, placing a functional group on the 5-position of the ring would lead to a square with functional groups decorating the outside of the square, which could alter the solubility of the square. Another possibility would be to add a functional group to the 2-position of the ring, which would lead to a square with a decorated interior similar to the $M_{12}L_{24}$ "nanoball" synthesized by the Fujita group.[30] Similar to this structure, having functional groups on the inside of the square could adjust host-guest properties or perhaps steric interactions could force the formation of a larger macrocycle such as a pentagon or a hexagon.

In order to test the idea of forming a 5-substituted derivative of **1**, it was decided to start with a methoxy group as it would be unlikely to interfere in the reactions and because a suitable starting material is commercially available. Thus the synthesis of **3**, and Cu_4(5-MeO-*m*-pba)$_4$ (square **8**) was carried out. Based on the encouraging results from **3** and **8** (see chapter 2 for more detail) it was decided to synthesize a derivative of **1** with a longer alkoxy chain. A CHEM 4564 student, Samantha Ingalls, developed a procedure to synthesize **4** as her final project.

Unfortunately, she was unable to complete the project so I decided to attempt it. The long butoxy chain greatly improves the resulting Cu_4(5-BuO-*m*-pba)$_4$ (**9**) square's solubility in non-polar solvents compared to **6**, **7**, and **8** (see chapter 3 for more detail). In order to test the idea of putting functional groups inside the square, it was decided to use the methoxy group once again because of its chemical inertness and it would also provide a good comparison with square **8**. Thus, the synthesis of **5** and Cu_4(2-MeO-*m*-pba)$_4$ (square **10**) was carried out; see chapter 4 for details.

Chapter 2: Ligand 3 and Square 8

2.1 Introduction

The simplest approach to synthesizing a 5-substituted derivative of **1** is to find a suitable precursor with a substituent on the 5 position of the aromatic ring. After searching the literature, such a precursor was found in the form of 5-methoxy-1,3-benzenedimethanol. This diol is fairly expensive (the current Aldrich price is $91.10 for 1 g); however, it proved relatively simple to oxidize to 5-methoxyisophthalaldehyde, which was then converted to **3**. Ligand **3** was then converted into square **8**.

The first step in synthesizing **3** was to oxidize 5-methoxy-1,3-benzenedimethanol to 5-methoxyisophthalaldehyde. To achieve this, a microwave assisted synthesis procedure developed by Lee et al. was used.[31] This procedure offers the advantage of rapid synthesis of aromatic aldehydes from alcohols without the use of solvents or toxic reagents, such as pyridinium chlorochromate (PCC) (see scheme 2.1).

Scheme 2.1. Oxidation of 5-methoxy-1,3-benzenedimethanol.

In order to convert 5-methoxyisophthalaldehyde into **3**, a method developed by Ramirez et al.[32, 33] was used. This method allows for easy synthesis of β-diketones from aromatic aldehyes. The aldehyde was simply mixed with 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene (see figure 2.1) in inert atmosphere with or without solvent.

After the aldehyde was consumed, the mixture was refluxed in MeOH (see scheme 2.2). After the reflux was complete, the solvent was removed and the compound purified via column chromatography.

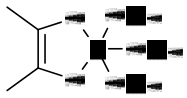
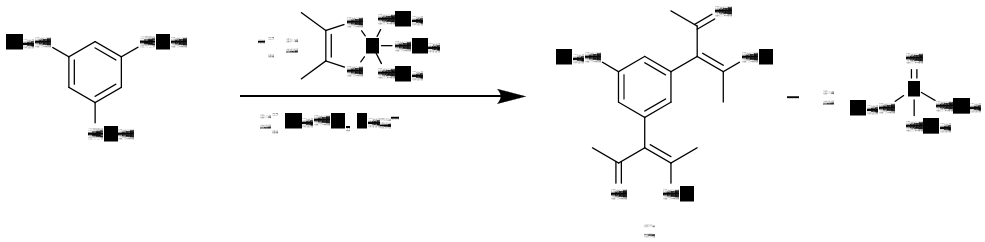


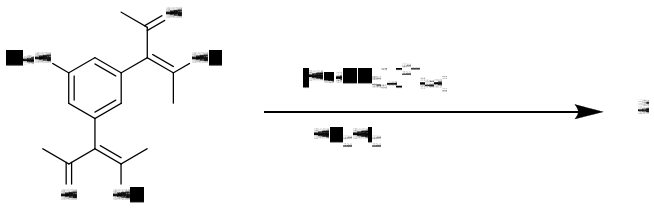
Figure 2.1. Structure of 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene.

Scheme 2.2. Conversion of 5-methoxyisophthalaldehyde to **3**.



To synthesize **8** the same two phase reaction developed for the synthesis of **6** was used.[1] In this reaction Cu^{2+} was dissolved in aqueous ammonia solution and **3** was dissolved in CH_2Cl_2 (see scheme 2.3). The two phase reaction allows for easy separation of **8** and excess Cu^{2+} as **8** was formed in the organic phase. Using NH_3(aq) provides a base to deprotonate **3** and also complexes Cu^{2+} so that it does not precipitate.

Scheme 2.3. Synthesis of **8**.



Since the conversion of 5-methoxyisophthalaldehyde to **3** was successful and **8** did show some improved solubility, it would be beneficial to develop a cheaper synthesis procedure for 5-methoxyisophthalaldehyde. Two attempts have been made at this. The first was the oxidation of 3,5-dimethylanisole and the second was the reduction of dimethyl 5-methoxyisophthalate. The first attempt involved oxidizing 3,5-dimethylanisole directly to 5-methoxyisophthalaldehyde using a patent procedure for the oxidation of 4,4'-oxybis(toluene) to 4,4'-oxybis(benzaldehyde).[34] However, despite repeated attempts and adjusting multiple factors (including metal salt, solvents, temperature, and reaction time), the reaction failed to produce the desired material. The only product recovered was intermediate material with one methyl group converted to aldehyde.

The second attempt was to reduce dimethyl 5-methoxyisophthalate using the reducing agent potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA). Unlike more common reducing agents, such as lithium aluminum hydride (LAH), PDBBA is capable of reducing esters directly to aldehydes rather than to alcohols.[35] Unfortunately, this procedure did not work and all that was recovered was intermediate material with one ester group reduced to aldehyde.

2.2 Experimental Procedures

Reagents were purchased from Aldrich or Acros. NMR spectra were taken on the DPX-250 and the AV-400. Mass spectra were taken with Agilent 6210 (ESI), and Varian Saturn 2200 GC/MS. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. $CDCl_3$ was used as solvent for NMR analysis.

2.2.1 Synthesis of 5-methoxyisophthalaldehyde

First, 502 mg (2.98 mmol) of 5-methoxy-1,3-benzenedimethanol, 2.29 g (12.0 mmol) of *p*-toluenesulfonic acid, and 523 mg (6.15 mmol) of $NaNO_3$ were placed in a microwave reaction vessel and mixed with approximately 2 mL of MeCN. Then the solvent was evaporated and the vessel was placed in the microwave. The microwave unit is controlled via computer and the following program was used: Power set at 850 W, ramp to 100 °C in 10 sec, hold at 100 °C for 20 sec. The mixture was heated for a total of 6 min by using multiple 30 sec intervals with approximately 10 sec of cooling time between intervals.[31] After heating was complete the vessel was allowed to cool down and any built up gas was allowed to vent in the hood. Then the solid was dissolved in CH_2Cl_2 and water and the organic phase separated, dried with sodium sulfate, and excess solvent was removed to yield 470 mg of a yellow solid, which is a 96% yield. Repetition of this procedure has produced yields in the range of 87 to 94%. NMR shows that the product was pure enough to continue to the next step without further purification (See figure A1, p. 56). ^{1}H NMR: δ 10.06 (s, 2H, C*H*O); 7.97 (s, 1H, aromatic C*H*); 7.66 (s, 2H, aromatic C*H*); 3.94 (s, 3H, OCH_3). (94%, 87%,

A purification attempt was made using a literature procedure.[36] First 30 mL of hexane was added to 5-methoxyisophthalaldehyde (orange solid), 170 mg, in a round bottom flask. The hexane was brought to a boil and then the hexane was decanted into a beaker. This procedure was repeated three times. Solid formed in the beaker as the hexane cooled down and the solid was filtered off resulting in 60 mg of yellow solid. NMR spectra of the yellow solid and the orange residue were taken. The spectra of both materials were nearly identical, with the only difference being apparent hexane peaks in the orange residue.

2.2.2. Synthesis of 3

First, 5-methoxyisophthalaldehyde was mixed with 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene (with or without anhydrous CH_2Cl_2 solvent) in the dry box and stirred overnight (see scheme 2.2). Then an NMR sample was taken and if the aldehyde peak at around δ = 10 ppm was gone, the mixture was removed from the dry box and refluxed in MeOH under N_2 for at least 2 h.[1] If the NMR showed aldehyde peak, more 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene was added and the mixture was allowed to stir until NMR showed no sign of aldehyde peak. After refluxing for two hours, an NMR sample was taken to check for presence of the enol peak at $\delta \approx 16$ ppm. If the enol peak was present, then as much solvent was removed as possible and the material was purified by column chromatography using a 1:5 ethyl acetate:hexane solvent mixture.

After purification a yellow or white solid was obtained with the highest yield being 34%. NMR analysis confirms identity of the product as the bis(β-diketone) with both β-diketone moieties in the enol form. See figures A2-A3, p. 57-58 for NMR spectra. ^{1}H NMR: δ 16.6 (s, 2H, O*H*); 6.71 (s, 2H, aromatic C*H*); 6.62 (s, 1H, aromatic C*H*), 3.84 (s, 3H, OCH_3), 1.92 (s, 12H, CH_3). ^{13}C NMR δ 190.46 (*C*=O); 160.06 (aromatic *C*-OCH_3); 138.73 (aromatic *C*-(β-diketone)); 126.14 (aromatic *C*H); 115.62 (aromatic *C*H); 114.63 (CH_3(C=O)*C*(C-OH)CH_3); 55.22 (O*C*H_3), 23.92 ((C=O)CH_3). GCMS: *m/z* 304.9 [M+H]. Elemental analysis calcd for $C_{17}H_{20}O_5$ (M_r = 304.34): C 67.09, H 6.62; found: C 66.13, H 6.93.

2.2.3 Synthesis of 8

First, 177 mg (0.710 mmol) of $CuSO_4 \cdot 5H_2O$ was dissolved in water in an Erlenmeyer flask. Then conc. NH_3(aq) was added slowly until a clear, dark blue solution formed.

Then, 207 mg (0.680 mmol) of **3** was dissolved in CH_2Cl_2 and added to the flask. The mixture was stirred for an hour or more forming an olive green organic phase, which was extracted with CH_2Cl_2 and dried with Na_2SO_4. Removal of solvent gave 240 mg of a green solid (crude yield 96%). Since Cu(II) is paramagnetic the complex cannot be analyzed effectively by NMR. Thus, the material was analyzed by ESI-MS, single crystal X-ray diffraction, and elemental analysis. Single crystal X-ray diffraction of the crystals proved that the complex was the desired molecular square (See figure 2.2). ESI-MS also confirms the identity of the complex. See table 2.1 for list of crystallization attempts. See figures A4-A5, p. 59-60 for ESI spectra. Elemental analysis calcd for $C_{68}H_{72}O_{20}Cu_4$ (M_r = 1463.47): C 55.81, H 4.96; found: C 54.54, H 5.61. ESI-MS: 1463.18 [M+H].

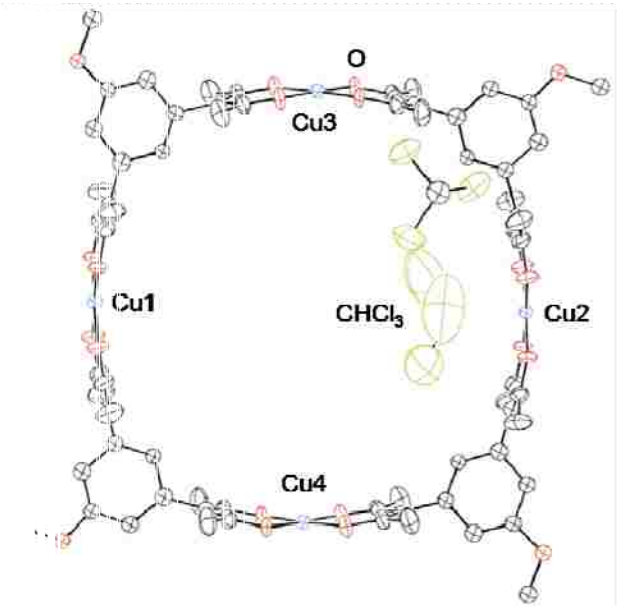


Figure 2.2. X-Ray structure of **8**.

Table 2.1 Crystallization Experiments.

Attempt #	Complex Solvent	Other Solvent	Guest	Observations
1	THF	Et_2O	None	Solvent evaporated after a few days leaving a blue precipitate. Precipitate dissolved in THF for attempts 5 & 6.
2	THF	Toluene	None	No crystals, solid material left
3	THF	C_6H_6	None	No crystals, solid material formed which was dissolved and used for attempt 10
4	THF	C_6H_{14}	None	No crystals, evaporated leaving a precipitate that was dissolved in CH_2Cl_2 for attempt 7.
5	THF	*o*-$C_6H_4Cl_2$	C_{60}	Formed a precipitate, no crystals
6	THF	C_6H_5Cl	C_{60}	Formed a dark green precipitate with no crystals
7	CH_2Cl_2	C_6H_6	None	No crystals, solid material dissolved for attempt 11
8	CH_2Cl_2	C_6H_{14}	None	No crystals, amorphous green solid formed. Dissolved for attempt 9.
9	CH_2Cl_2	Toluene	4,4'-bpy	No crystals
10	THF	Toluene	4,4'-bpy	No crystals, solid dissolved for attempt 14
11	THF	Pentane	None	No crystals, dark blue solid remains
12	CH_2Cl_2	Pentane	None	No crystals, green ppt formed and was dissolved for attempt 13
13	THF	2-Propanol	None	No crystals, blue-green ppt formed
14	CH_2Cl_2	2-Propanol	None	No crystals, light yellow solution became a light yellow ppt
15	CH_2Cl_2	Toluene	4,4'-bpy	No crystals
16	CH_2Cl_2	$CHCl_3$	None	No crystals
17	MeOH	$CHCl_3$	None	Blue crystals formed after 7 days. Crystals analyzed by X-ray diffraction.
18	MeOH	$CHCl_3$	4,4'-bpy	No crystals.
19	MeOH	$CHCl_3$	None	No crystals, solvent evaporated
20	MeOH	$CHCl_3$	4,4'-bpy	No crystals, solvent evaporated
21	MeOH	MeCN	$W_6O_{19}^{2-}$	Blue ppt formed, solvent evaporated
22	THF	$CHCl_3$	4,4'-bpy	Blue crystals formed
23	THF	MeCN	$W_6O_{19}^{2-}$	Blue ppt formed, solvent evaporated
24	THF	$CHCl_3$	None	No crystals, solvent evaporated
25	CH_2Cl_2	$CHCl_3$	4,4'-bpy	Green ppt formed
26	THF	$CHCl_3$	None	Blue crystals formed
27	THF	MeCN	$W_6O_{19}^{2-}$	Blue ppt formed
28	THF	DMSO	$W_6O_{19}^{2-}$	Blue ppt formed

Table 2.1 continued

29	CH_2Cl_2	$CHCl_3$	4,4'-bpy	Green ppt formed
30	MeOH/ CH_2Cl_2	DMSO	$W_6O_{19}^{2-}$	Blue ppt formed
31	MeOH/ CH_2Cl_2	$CHCl_3$	4,4'-bpy	Blue ppt formed
32	MeOH/ CH_2Cl_2	$CHCl_3$	4,4'-bpy	Crystals formed
33	MeOH/ CH_2Cl_2	DMSO	$W_6O_{19}^{2-}$	Crystals formed

For 30 & 31: Square dissolved in minimal amount of CH_2Cl_2 and larger amount of MeOH added.
For 32 & 33: Square suspended in MeOH and CH_2Cl_2 added until clear, blue solution obtained.

2.3 Results and Discussion

2.3.1 X-Ray Crystal Structure

Square **6** crystallizes in the P-1 space group whereas **8** crystallizes in the *I*4/*m* space group. What this means is the only symmetry element in **6** was an inversion center whereas **8** has a C_4 axis and a mirror plane. In other words, the two sides of **8** are mirror images of each other and if rotated the structure would look identical to the structure before rotation. The mirror plane runs through the molecule horizontally (i.e. the mirror plane is the plane of the Cu atoms). The higher symmetry can clearly be seen by comparing the structures of **8** and **6** (see figure 2.3). Because of the lower symmetry of **6** it appears "lopsided" compared to **8**.

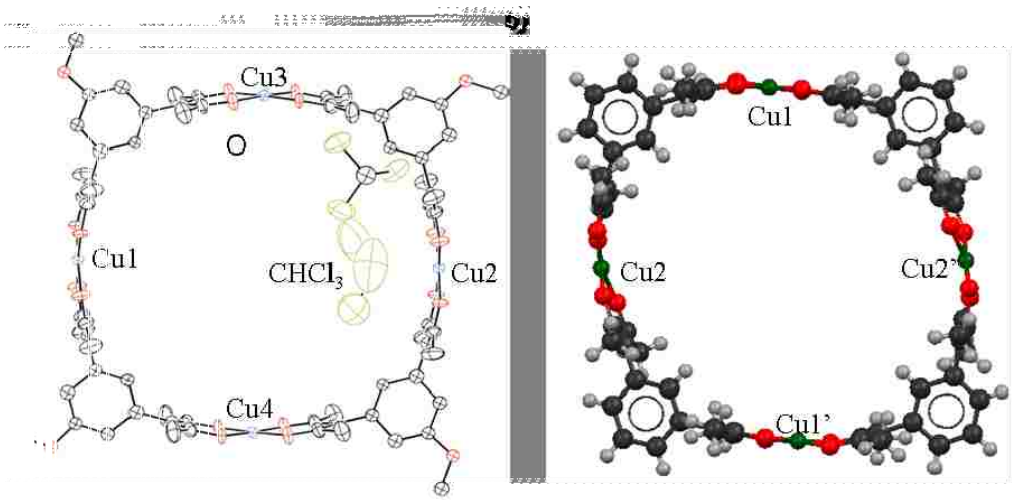


Figure 2.3. Comparison of (a) **8** and (b) **6**.

The Cu···Cu distances in **6** and **8** are summarized in table 2.2. Because of the four-fold symmetry of square **8**, all of the Cu···Cu distances are the same; however, the lower symmetry of **6** results in two different Cu···Cu distances. The Cu···Cu distances of **8** are in between the two Cu···Cu distances of **6**.

Table 2.2. Cu···Cu distance comparison for squares **6** and **8**.

Square **6**		Square **8**	
Copper atoms	Distance	Copper atoms	Distance
Cu1···Cu1'	14.317 Å	Cu1···Cu2	14.325 Å
Cu2···Cu2'	14.647 Å	Cu3···Cu4	14.325 Å

2.3.2. Solubility

Square **8** was soluble in CH_2Cl_2 and THF and it was insoluble in $CHCl_3$, EtOH, MeCN, acetone, and DMSO (see Table 2.3). In CH_2Cl_2 it was an olive green solution much like **6** while it was a blue solution in THF. This color change was probably due to oxygen coordinating to the Cu(II) centers changing their coordination number from 4 to 5.

Originally it was assumed that the **8** was soluble in MeOH, and the crystals used in the first diffraction experiment were grown in a MeOH/$CHCl_3$ mixture. However, the most recently synthesized batch of **8** did not dissolve in MeOH. It could be solubilized in MeOH by adding CH_2Cl_2 dropwise until a clear, blue solution was obtained. This indicates that the material used to determine solubility in MeOH originally was still slightly wet with CH_2Cl_2 and that **8** is insoluble in pure MeOH.

Table 2.3. Solubility Comparison Table.

Solvent	6	7	8
CH_2Cl_2	Soluble	Soluble	Soluble
$CHCl_3$	Soluble	Soluble	Insoluble
THF	Insoluble	Slightly Soluble	Soluble
MeOH	Insoluble	Insoluble	Insoluble, but soluble in MeOH-CH_2Cl_2 mixtures
EtOH	Insoluble	Insoluble	Insoluble
MeCN	Insoluble	Insoluble	Insoluble
Acetone	Insoluble	Insoluble	Insoluble
DMSO	Insoluble	Insoluble	Insoluble

2.3.3 Host-Guest chemistry

Several of the crystallization experiments included guests, C_{60} or 4,4'-bpy; however, these attempts failed to produce crystals instead producing precipitates. The precipitates were not analyzed and in some cases were dissolved for other crystallization experiments. The lack of crystals forming with C_{60} is not that surprising since C_{60} has also failed to produce crystals with **6**. It would seem that since only **7** has produced crystals with C_{60} the ethyl groups on **2** are needed to hold the C_{60} inside the square and prevent it from slipping out, or that they did not crystallize under the conditions tried (see figure 2.4).

For crystallization attempt 22, although crystals formed after X-Ray analysis was performed, it was revealed that the crystals were of **8** with no guest and the data was of equal or lower quality to the previous data. Also, when crystals were grown of **6** with 4,4'-bpy, the experiment was performed at low temperature. Thus the experiment could be performed again but at low temperature and maybe with a higher concentration of 4,4'-bpy. With attempt 26, Dr. Fronczek was unable to get a clean diffraction pattern from the crystals. This indicates that THF/$CHCl_3$ is not a good solvent system for crystallizing **8**. With attempts 32 and 33, Dr. Fronzeck was unable to get anything from the diffraction pattern.

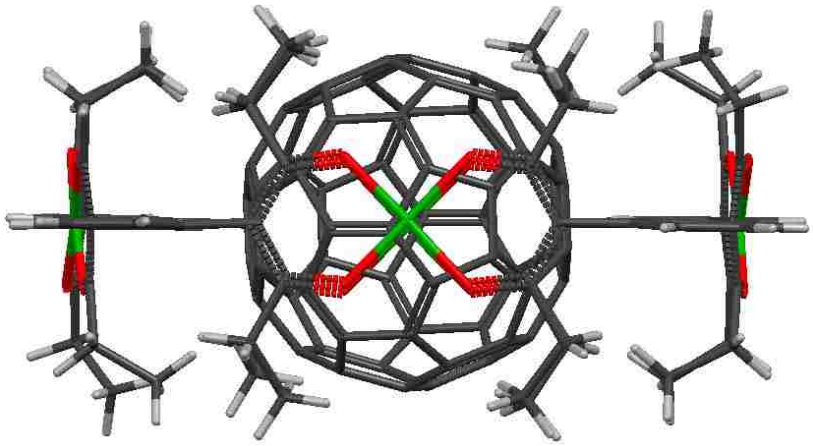


Figure 2.4. Side view of **7** with C_{60} showing how ethyl groups wrap around C_{60}. Figure created using Mercury 2.2.

The polyoxometalate anion $W_6O_{19}^{2-}$ has been encapsulated by a molecular square before.[20] In this square the $W_6O_{19}^{2-}$ neatly fits in the pore (see figure 2.5). The Pd···Pd distances in this square are 11.119 Å and 11.189 Å which is shorter than the Cu···Cu in **8**. Since **8** is bigger than the square synthesized by Uehara et al. it might be able to encapsulate $W_6O_{19}^{2-}$.

However, the square Uehara et al. synthesized is positively charged whereas **8** is neutral, which could lead to weaker interactions between $W_6O_{19}^{2-}$ and **8**. If $W_6O_{19}^{2-}$ were to bind to 8, it is likely that it would bind to the coordinatively unsaturated Cu(II) centers via the four equatorial oxygen atoms. This would give $W_6O_{19}^{2-}$ a different orientation in **8** than in the Uehara et al. square. The attempts at growing crystals resulted in the rapid formation of a blue precipitate (either after a few hours or within a day). However, the solvents used for dissolving the square were THF and MeOH-CH_2Cl_2 so the solution was blue initially.

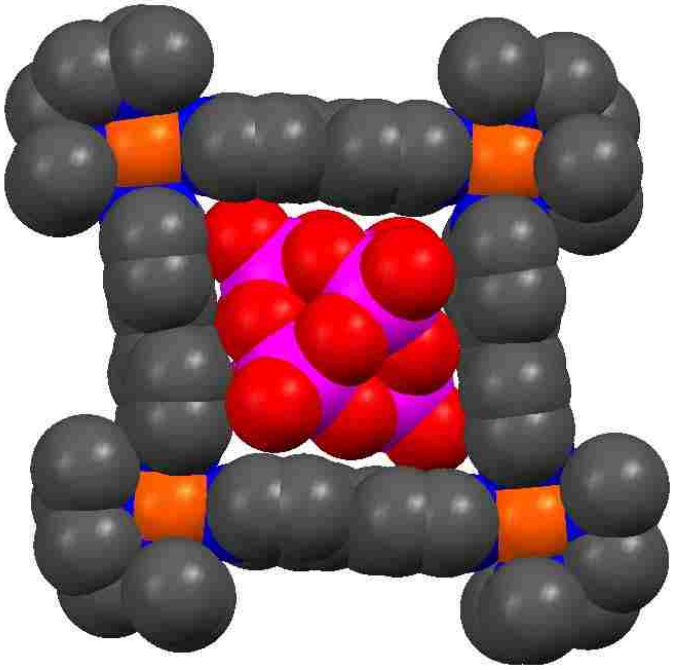


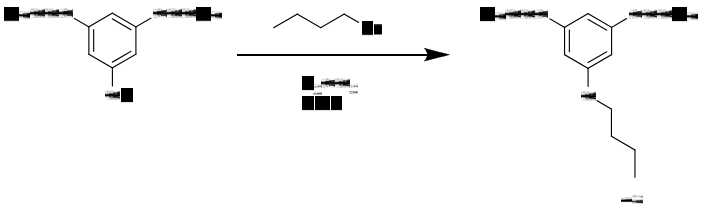
Figure 2.5. Spacefill view of Pd square with $W_6O_{19}^{2-}$ from Uehara et al., Figure created using Mercury 2.2. Orange = Pd, Blue = N, Dark Grey = C, Pink = W, Red = O.

Chapter 3: Synthesis of Ligand 4 and Square 9

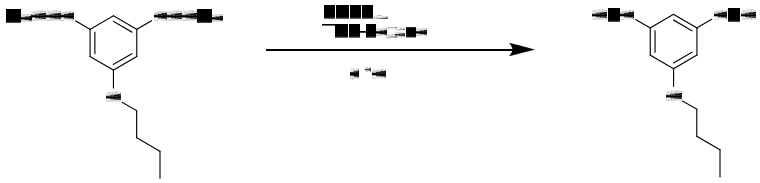
3.1 Introduction

In Chapter 2, I showed that the new molecular square **8** has improved solubility in THF compared to the simpler Cu_4(*m*-pba)$_4$ square we originally synthesized. In order to make the square more soluble in non-polar organic solvents, I decided to try the 5-butoxy derivative 5-BuO-*m*-pbaH_2, **4**. The original synthesis procedure for **4** was developed by a CHEM 4564 student, Samantha Ingalls. In the first step, dimethyl 5-hydroxyisophthalate was converted to dimethyl 5-butoxyisophthalate (**4a**) using a method developed by Valiyaveettil et al. for the conversion of dimethyl 5-hydroxyisophthalate to dimethyl 5-(undecyloxy)isophthalate (see scheme 3.1) .[37] Then the reducing agent PDBBA was used on dimethyl 5-butoxyisophthaltate with the intention of converting it directly to 5-butoxyisophthalaldehyde (see scheme 3.2). Finally, 5-butoxyisophthalaldehyde would be converted to **4** (see scheme 3.3). However, when we attempted this reaction, PDBBA was unable to fully reduce dimethyl 5-butoxyisophthalate to 5-butoxyisophthalaldehyde.

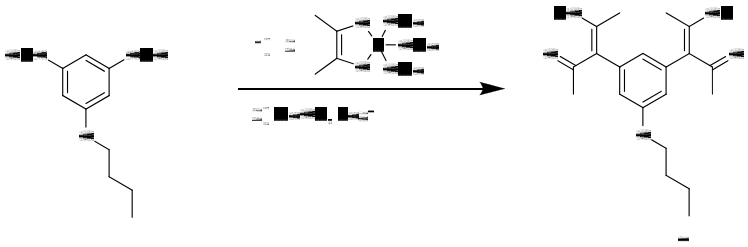
Scheme 3.1. Synthesis of **4a**.



Scheme 3.2. Synthesis of 5-butoxyisophthalaldehyde.

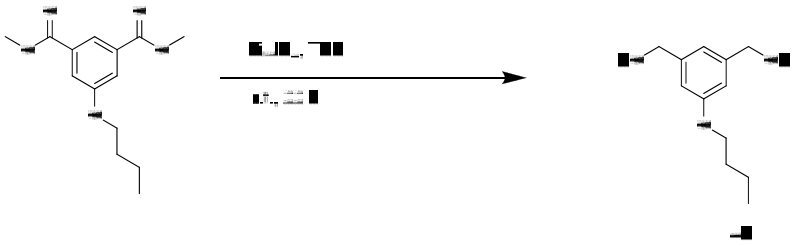


Scheme 3.3. Synthesis of **4**.

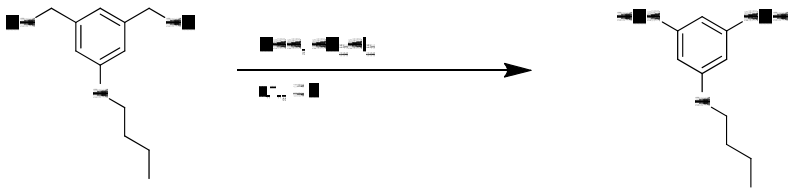


The first step of Ingalls's scheme was successful, but I was unable to get the remaining steps to work; thus, I developed alternate procedures for converting the **4a** into 5-butoxyisophthalaldehyde. First, **4a** was converted to 5-butoxy-1,3-benzenedimethanol (**4b**) using lithium aluminum hydride, or LAH (see scheme 3.4). Then **4b** was oxidized to 5-butoxyisophthalaldehyde using pyridinium chlorochromate, or PCC (see scheme 3.5). Then 5-butoxyisophthalaldehyde was converted to **4**. Finally, **4** was used to synthesize **9**.

Scheme 3.4. Synthesis of **4b**.



Scheme 3.5. Synthesis of 5-butoxyisophthalaldehyde.



3.2 Experimental Procedures

Reagents were purchased from Aldrich or Acros. NMR spectra were taken on the DPX-250 and the AV-400. Mass spectra were taken with Agilent 6210 (ESI), and Varian Saturn 2200 (GC/MS). Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. $CDCl_3$ was used as solvent for NMR analysis.

3.2.1 Synthesis of 4a

First, 4.50 g (21.4 mmol) of dimethyl 5-hydroxyisophthalate, 7.40 g (53.6 mmol) of powdered K_2CO_3, and 3 mL (27.6 mmol) of 1-bromobutane were placed in a round bottom flask. Then, the flask was then flushed with N_2 for about 10 minutes. After flushing was complete, 50 mL of dry DMF was added to the flask via syringe. The flask was then placed in a water bath which was heated to ~90 °C so that the solution in the flask would be ~80 °C with stirring and under nitrogen. After heating for 5.5 hours the heat was turned down and, before the mixture cooled, a sample was taken for TLC analysis. The TLC showed that some reactant was still left so the heat was turned back up for another few hours. A second TLC was performed, which also showed some reactant. The reaction was stopped and the mixture was washed with ethyl acetate and water.

The extracted organic phase was dried with sodium sulfate and solvent was removed under reduced pressure. This yielded a light brown liquid and the flask was placed on the vacuum line for further solvent evaporation. After a few hours, the liquid solidified, and 5.56 g of a tan colored solid was isolated. The material was purified via column chromatography using a 1:4 ethyl acetate:hexane solvent ratio and 3.13 g of a white solid (62% yield) was obtained. GCMS and NMR analysis confirm the identity of the product as dimethyl 5-butoxyisophthalate. See figure A6, p. 61 for NMR spectrum. GCMS: *m/z* 265.9 [M^+]; 235.1 [M-OCH_3]; 179.0 [M-OCH_3, C_4H_9]. ^{1}H NMR: δ 8.25 (s, 1H, aromatic C*H*); 7.74 (s, 2H, aromatic C*H*); 4.04 (t, 2H, $OCH_2CH_2C_2H_5$), 3.94 (s, 3H, CO_2CH_3); 1.79 (quintet, 2H, $OCH_2CH_2CH_2CH_3$); 1.51 (sextet, 2H, $OCH_2CH_2CH_2CH_3$); 1.00 (t, 3H, $O(CH_2)_3CH_3$).

3.2.2 Synthesis of 4b

To reduce **4a** to **4b**, lithium aluminum hydride (LAH) was used according to a procedure developed by Hayama et al. for forming 5-methoxybenzenebis(methanol-α,α-d_2) from dimethyl 5-methoxyisophthalate and lithium aluminum deuteride.[38] Notice: Extra care should be taken when handling LAH as it is extremely reactive and can cause fires if it comes into contact with water. First, about 30 mL of dry THF was added to a three neck round bottom flask with an addition funnel under N_2. Then 5.0 mL (10 mmol) of lithium aluminum hydride (2 M in THF) was added via syringe. Then 1.097 g (4.12 mmol) of dimethyl 5-butoxyisophthalate was dissolved in about 20 mL of dry THF and added to the LAH dropwise. The mixture was allowed to stir for 22 hours. At this point, NMR showed that the ester groups had been consumed, so the mixture was cooled down to 0 °C and 16 mL of 1 M H_2SO_4 was added slowly. Then some deionized water and 100 mL of ethyl acetate were added to the mixture.

The organic layer was separated and washed with 100 mL of saturated NaCl(aq). Then the organic layer was separated again, dried with Na_2SO_4, and solvent was removed *in vacuo* resulting in 690 mg (80% yield) of a light yellow solid. NMR and ESI-MS confirm the identity of the material. The material was used for the next step without purification. See figure A7, p. 62 for NMR spectrum. ^{1}H NMR: δ 6.93 (s, 1H, aromatic C*H*); 6.85 (s, 2H, aromatic C*H*); 4.66 (s, 4H, CH_2OH); 3.98 (t, 2H, OCH_2CH$_2$C$_2$H$_5$); 1.77 (multiplet, 2H, OCH$_2$CH_2CH$_2$CH$_3$); 1.48 (multiplet, 2H, OCH$_2$CH$_2$CH_2CH$_3$); 0.97 (t, 3H, O(CH$_2$)$_3$CH_3). ESI-MS: *m/z* 193.12 [M−OH]. Elemental analysis calcd for $C_{12}H_{18}O_3$ (M_r = 210.27): C 68.54, H 8.63; found: C 67.33, H 8.06.

3.2.3 Synthesis of 5-butoxyisophthalaldehyde

To oxidize **4b** to 5-butoxyisophthalaldehyde, pyridinium chlorochromate (PCC) was used according to a procedure developed by Bennani et al. to convert 5-*tert*-butyl-1,3-benzenedimethanol to 5-*tert*-butylisophthalaldehyde.[39] Notice: Care should be taken when handling PCC as it and its byproducts are toxic. First 1.54 g (7.15 mmol) of PCC and 3 g of Celite were added to a three neck round bottom flask equipped with an addition funnel and N_2 flow. Then about 10 mL of dry CH_2Cl_2 was added to the PCC and the mixture was vigorously stirred. Then 520 mg (2.47 mmol) of 5-butoxy-1,3-benzenedimethanol was dissolved in about 10 mL of dry CH_2Cl_2 and added to the PCC solution dropwise. The mixture was stirred for 3 h and then the material was filtered through a short pad of silica gel using CH_2Cl_2 and ethyl acetate. Then the solvent was removed *in vacuo*, resulting in 420 mg of a yellow liquid (82% yield). NMR, ESI-MS, and elemental analysis confirm the identity of the product which was used for the next step without further purification. See figure A8-A9, p. 63-64 for NMR spectra.

^{1}H NMR: δ 9.97 (s, 2H, C*H*O); 7.86 (s, 1H, aromatic C*H*); 7.56 (s, 2H, aromatic C*H*); 4.00 (t, 2H, OC*H*$_2$CH$_2$C$_2$H$_5$); 1.74 (quintet, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_3$); 1.42 (sextet, 2H, OCH$_2$CH$_2$C*H*$_2$CH$_3$); 0.91 (t, O(CH$_2$)$_3$C*H*$_3$). ^{13}C NMR δ 190.82 (*C*HO); 160.19 (aromatic *C*-OBu); 138.15 (aromatic *C*-CHO); 123.74 (aromatic *C*H); 119.71 (aromatic *C*H); 68.41 (O*C*H$_2$CH$_2$C$_2$H$_5$); 30.84 (OCH$_2$*C*H$_2$CH$_2$CH$_3$), 18.98 (OCH$_2$CH$_2$*C*H$_2$CH$_3$); 13.60 (O(CH$_2$)$_3$*C*H$_3$). ESI-MS: *m/z* 207.10 [M+H]. Elemental analysis calcd for $C_{12}H_{14}O_3$ (M_r = 206.24): C 69.88, H 6.84; found: C 69.80, H 6.66.

The leftover material from the mass spec sample was left to slowly evaporate in air so solid could be obtained for various tests. After several days a large block shaped crystal formed. Since SciFinder and Cambridge Crystallographic Database searches turned up no hits for this compound, the crystal was submitted for X-ray diffraction, see figure 3.1.

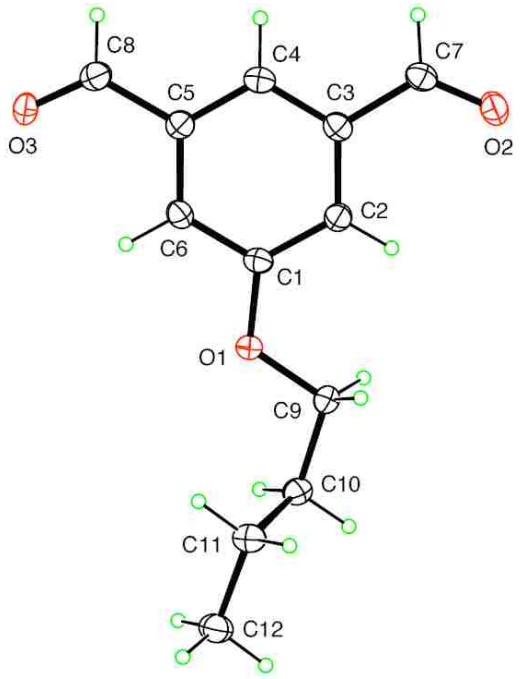


Figure 3.1. X-Ray Structure of 5-Butoxyisophthalaldehyde

3.2.4 Synthesis of Ligand 4

First 420 mg (2.04 mmol) of 5-butoxyisophthalaldehyde was placed in a round bottom flask and put in the dry box. Then 1.01 g (4.81 mmol) of 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene was added and the mixture stirred for 19 h. At this point,the aldehyde groups were consumed (NMR), so the sample was taken out of the dry box and 15 mL of MeOH was added. Then the mixture was refluxed for 2 h under N_2 , which led to the development of enol peaks in the NMR. Then the reflux was stopped and the solvent removed *in vacuo*. The resulting brown liquid was placed in the refrigerator to see if product would precipitate. After several days no product had precipitated so column chromatography using a 1:2 ethyl acetate:hexane solvent mixture was performed. After the fractions were collected and solvent removed, 310 mg of a dark yellow/brown solid (44% yield) was recovered. NMR and GCMS confirmed the identity of the product. Several attempts at taking a ^{13}C NMR were made before a spectrum that had all of the peaks was collected. However, the sample had been sitting in the tube overnight between some of the attempts and a new peak at around δ = 208 ppm appeared. This peak could belong to a ketone, however the β-diketone peaks appear at δ = 190 ppm. Also the peaks for the β-diketone moieties have split compared to the spectrum of **3.** There are now two peaks for the C=O/COH groups and two peaks for the methyl groups. This indicates a change in the rate of tautomerization between keto and enol forms of the β-diketone moieties. See figures A10-A11, p. 65-66 for NMR spectra. ^1H NMR: δ 16.6 (s, 2H, enol O*H*); 6.70 (s, 2H, aromatic C*H*); 6.60 (s, 1H, aromatic C*H*); 3.97 (t, 2H, $OCH_2CH_2C_2H_5$); 1.92 (s, 12H, CH_3); 1.80 (multiplet, 2H, $OCH_2CH_2CH_2CH_3$); 1.53 (multiplet, 2H, $OCH_2CH_2CH_2CH_3$); 1.00 (t, 3H, $O(CH_2)_3CH_3$).

^{13}C NMR δ 190.76 (*C*=O); 190.55 (*C*-OH); 163.86 (aromatic *C*-OBu); 138.62 (aromatic *C*(β-diketone)); 125.90 (aromatic *C*H); 116.15 (aromatic *C*H); 114.70 (CH_3(C=O)*C*(C-OH)CH_3); 67.79 (O*C*$H_2CH_2C_2H_5$), 31.01 (OCH_2*C*$H_2CH_2CH_3$); 26.06 ((C=O)*C*H_3); 23.93 ((C-OH)*C*H_3); 19.07 (OCH_2CH_2*C*H_2CH_3); 13.71 ($O(CH_2)_3$*C*H_3). GCMS: *m/z* 347.0 [M+H].

3.2.5 Synthesis of Square 9

First, 220 mg (8.81 mmol) of $CuSO_4 \cdot 5H_2O$ was placed in an Erlenmeyer flask and dissolved in deionized water. Then NH_3(aq) was added until a clear, dark blue solution was obtained. Then 290 mg (8.37 mmol) of ligand **4** was dissolved in CH_2Cl_2 and added to the Cu solution. The organic phase turned olive green and the mixture was stirred for 2 h. Then the organic phase was separated, dried with Na_2SO_4, and then solvent was removed *in vacuo*, resulting in 380 mg of an olive green solid. The percent yield is higher than 100% so the material probably had some extra solvent or water present. Solubility tests and crystallization attempts have been performed on this material. The details of these experiments are covered in the results and discussion section. Several attempts at growing crystals have been made, the results of which are summarized in table 3.1. Crystals suitable for X-Ray diffraction were grown by dissolving **9** in $CHCl_3$ and layering with 4,4'-bpy in MeOH. The crystal structure is shown in figure 3.2. See figures A12-A13, p. 67-68 for ESI spectra. Elemental analysis calcd for $C_{80}H_{96}Cu_4O_{20}$ (M_r = 1631.79): C 58.88, H 5.93; found: C 57.88, H 6.41. ESI-MS: 1632.49 [M+4H].

Table 3.1. Crystallization Attempts for **9**.

Attempt #	Complex Solvent	Other Solvent	Guest Molecule	Observations
1	Toluene	Hexane	None	No crystals
2	Toluene	Ethyl Ether	None	Green ppt formed after 11 days
3	*o*-$C_6H_4Cl_2$	Hexane	None	No crystals
4	Toluene	Ethyl Acetate	None	No crystals
5	THF	MeOH	None	No crystals
6	THF	Ethyl Acetate	4,4'-bpy	No crystals
7	THF	MeOH	None	No crystals
8	THF	Hexane	None	No crystals
9	Toluene	Hexane	4,4'-bpy	Green ppt formed after 1 day
10	Toluene	Hexane	4,4'-bpy	No crystals, green ppt formed after several days
11	*o*-$C_6H_4Cl_2$	Pentane	None	No crystals
12	C_6H_5Br	Pentane	None	No crystals
13	C_6H_6	Pentane	None	No crystals
14	$CHCl_3$	Pentane	None	No crystals
15	$CHCl_3$	Pentane	None	No crystals
16	$CHCl_3$	MeCN	None	No crystals
17	$CHCl_3$	MeOH	None	No crystals
18	Toluene	MeOH	None	No crystals
19	*o*-$C_6H_4Cl_2$	Ethyl Ether	None	Green ppt formed
20	$CHCl_3$	MeOH	4,4'-bpy	Blue crystals formed

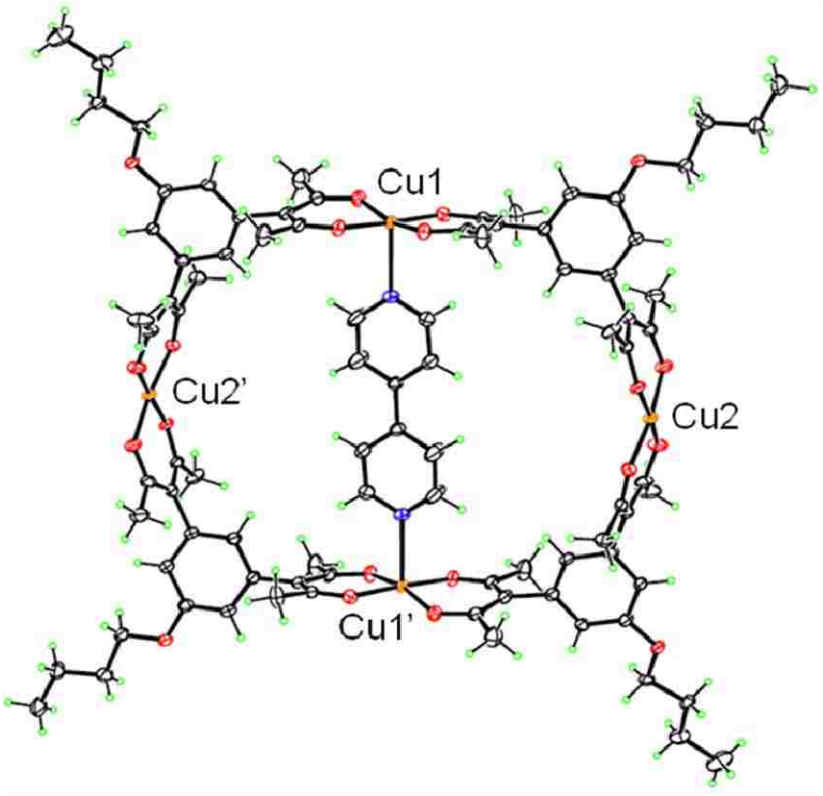


Figure 3.2. X-Ray crystal structure of **9** with 4,4'-bpy guest.

3.2.5 Microwave synthesis of 5-butoxyisophthalaldehyde

First, 690 mg (3.63 mmol) of p-TsOH, and 156 mg (1.75 mmol) of $NaNO_3$ were added to a microwave reaction vessel. Then 190 mg (0.904 mmol) of 5-butoxy-1,3-bezenedimethanol dissolved in MeCN was added to the vessel and the mixture was stirred. Solvent was evaporated and the vessel was placed in the microwave. Program JDS1 was used, Power = 850 W, ramp to 100 °C in 10 sec, hold at 100 °C for 20 sec. After a total of 6 min of heating the vessel was taken out of the microwave, the material was extracted with ethyl acetate, dried with Na_2SO_4, and excess solvent was removed, resulting in 180 mg (96% yield) of an orange solid. NMR confirms the identity of the product; however, the peak for the $OCH_2CH_2C_2H_5$ at 4.09 ppm has a more complicated splitting pattern and higher integration than expected (3.84 compared with 2). It is possible that this peak and an ethyl acetate peak have merged.

Other peaks for ethyl acetate are seen at around 2.00 ppm (singlet) and 1.26 ppm (triplet) (see figure A14, p. 69). ^{1}H NMR: δ 10.1 (s, 2H, C*H*O); 7.95 (s, 1H, aromatic C*H*); 7.65 (s, 2H, aromatic C*H*); 4.09 (multiplet, OC*H*$_2$CH$_2$C$_2$H$_5$); 1.82 (quintet, 2H, OCH$_2$C*H*$_2$CH$_2$CH$_3$); 1.54 (sextet, OCH$_2$CH$_2$C*H*$_2$CH$_3$); 1.00 (t, 3H, O(CH$_2$)$_3$C*H*$_3$).

3.3 Results and Discussion

3.3.1 Oxidation methods for synthesizing 5-butoxyisophthalaldehyde

Two different methods for synthesizing 5-butoxyisophthalaldehyde have been tried, one using PCC and the other using the microwave procedure. The NMR spectrum for the PCC reaction appeared to be slightly cleaner than that for the microwave procedure; however, this may be due in part to the short silica gel pad that was used to separate the aldehyde from the PCC byproducts rather than some effect of the PCC reagent. The microwave procedure offered a seemingly higher yield than the PCC procedure and avoids the use of the toxic chromium reagent. The PCC procedure was done at a gram scale whereas the highest scale the microwave procedure has been performed is around 600 mg (using 5-methoxy-1,3-benzenedimethanol). Although this is mostly because the microwave procedure was originally developed for use with small vials in a domestic microwave oven[31] and most of the experiments performed with it used 5-methoxy-1,3-benzenedimethanol which was in limited supply. The original microwave reactions performed by Lee et al. were done at a scale of around 100 mg and scaling the reaction up to around 600 mg had no negative effect on the yield, and the microwave reaction vessels we use are large enough that a few grams of alcohol could probably be used for reactions without running the risk of building up too much pressure in the microwave vessel.

However, the main purpose of the microwave unit is teaching the organic labs and it is also used by other research groups, so the PCC procedure could still prove useful for times when the microwave is in use by the organic labs or other research groups.

3.3.2 X-Ray structure of 5-butoxyisophthalaldehyde

The crystal structure of 5-butoxyisophthalaldehyde shows some slight disorder at O3. About 7% of the time the oxygen exists at O3' rather than at O3 (see figure 3.3). A search of the Cambridge Structural Database showed that one isophthalaldehyde derivative, 5-isopropyl-2-methylisophthalaldehyde, also has a disordered carbonyl oxygen atom (see figure 3.4). With this derivative, the oxygen is at position O1 90% of the time and it is at O1' 10% of the time. The same search also showed that isophthalaldehyde and several derivatives have the two different arrangements of CHO groups in the crystal (i.e. one syn and one anti with respect to the 5-BuO substituent; see figure 3.5). This shows that syn and anti configurations of the aldehyde groups have about the same stability.

Figure 3.3. Structure of 5-butoxyisophthalaldehyde using CIF file showing disordered oxygen atom. Figure created with Mercury 2.2. Dark Grey = C, Light Grey = H, Red = O.

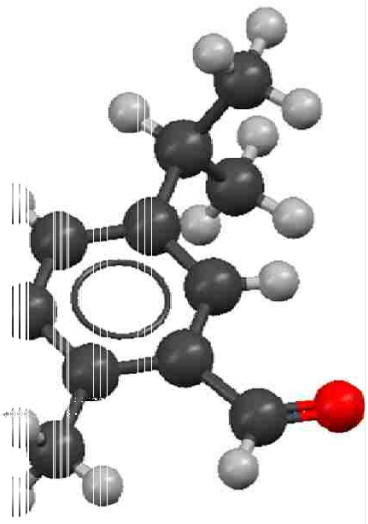


Figure 3.4. X-Ray structure of 5-isopropyl-2-methylisophthalaldehyde. Figure created with Mercury 2.2 software. Dark Grey = C, Light Grey = H, Red = O.

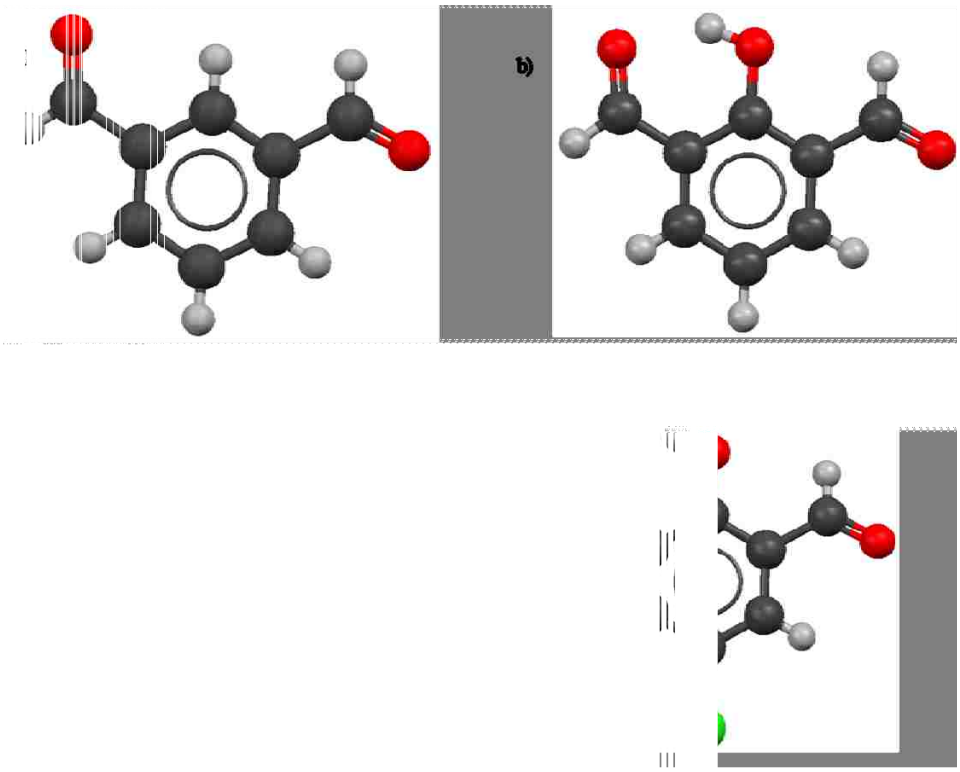


Figure 3.5. X-Ray Structures of a) isophthalaldehyde, b) 2-hydroxyisophthalaldehyde, c) 2,5-dimethylisophthalaldehyde, and d) 5-chloro-2-hydroxyisophthalaldehyde. Figures created with Mercury 2.2 software. Dark Grey = C, Light Grey = H, Red = O, Light Green = Cl.

3.3.3 Solubility of Square 9

Solubility tests were conducted on the metal complex. The material was found to be soluble in CH_2Cl_2, $CHCl_3$, THF, benzene, toluene, chlorobenzene, bromobenzene, and *o*-$C_6H_4Cl_2$. The material is insoluble in MeOH, EtOH, MeCN, hexane, and diethyl ether. For most of the solvents the new square is soluble in it is an olive green solution, but it is blue in THF indicating likely solvent coordination to the Cu centers. Although the material was insoluble in MeOH, it did change color from green to blue after some time had passed. This suggests that some MeOH coordinated to the Cu centers and that maybe it can be solubilized in MeOH like **8**. Table 3.2 compares the solubility of **9** to that of the previous squares.

Based on the speed at which **9** dissolves in some solvents, I would say that it is slightly more soluble in benzene than the other aromatic solvents and slightly more soluble in $CHCl_3$ or CH_2Cl_2 than benzene.

Table 3.2. Square Solubility Comparison Table.

Solvent	6	7	8	9
CH_2Cl_2	Soluble	Soluble	Soluble	Soluble
$CHCl_3$	Soluble	Soluble	Insoluble	Soluble
MeOH	Insoluble	Insoluble	Insoluble*	Insoluble
EtOH	Insoluble	Insoluble	Insoluble	Insoluble
THF	Insoluble	Slightly Soluble	Soluble	Soluble
Ethyl Ether	Insoluble	Insoluble	Not Tested	Insoluble
Benzene	Insoluble	Insoluble	Not Tested	Soluble
Toluene	Insoluble	Insoluble	Not Tested	Soluble
C_6H_5Cl	Insoluble	Insoluble	Not Tested	Soluble
C_6H_5Br	Insoluble	Insoluble	Not Tested	Soluble
o-$C_6H_4Cl_2$	Insoluble	Insoluble	Not Tested	Soluble
MeCN	Insoluble	Insoluble	Insoluble	Insoluble
Hexane	Insoluble	Insoluble	Not Tested	Insoluble

***8** is soluble in MeOH-CH_2Cl_2 mixtures

Some of the material was also tested with 1,2-dichloroethane. At first, the material seemed to be soluble but after some time passed the solution became cloudy. After about a day had passed the solution had turned a light green color and remained cloudy. After the solvent evaporated, CH_2Cl_2 was added to the light green residue left behind. At least some of the residue dissolved into a light green solution. After most of the CH_2Cl_2 evaporated, light green thin, needle shaped crystals formed. However, Dr. Fronczek did not think they were of good enough quality for X-Ray analysis. Because of the solubility of **9** in solvents such as *o*-$C_6H_4Cl_2$, it is possible to determine the binding constant of C_{60} in **9**. Since the interior of **9** and **6** are the same, determining the binding constant of C_{60} in **9** allows for an approximation of the binding constant in **6**.

Likewise the 5-butoxy variant of **2** could be synthesized to estimate the binding constant of C_{60} in **7**. This would allow for comparison to determine how well the ethyl groups on **7** hold C_{60} inside the square.

3.3.4. Crystallization Attempts

Several attempts have been made at crystallizing **9**. So far, none of them have produced crystals. Attempt 9 was placed in the freezer because crystals grown for **6** with 4,4'-bpy were done at low temperature; however, a green ppt formed within one day. Attempt 7 was also placed in the freezer and no crystals or ppt formed after nearly a month in the freezer. Even after taking the material out of the freezer, no ppt or crystals formed after several days. After a little over two weeks with no ppt or crystals formed, attempt 20 was placed in the freezer. The high solubility of **9** makes it more difficult to crystallize than the previous squares. The conformational rotation of the butoxy group may also contribute to difficult crystallization. So far the only crystallization technique attempted has been layering. Using vapor diffusion may prove more effective. In vapor diffusion, **9** would be dissolved in a high boiling solvent (such as toluene or *o*-$C_6H_4Cl_2$) in an open container such as a beaker. This beaker would then be placed in a larger container partially filled with a volatile solvent (such as acetone or diethyl ether) and the larger container would be sealed. The volatile solvent would slowly evaporate and condense in the solution of **9** and hopefully cause crystals to form.

3.3.5. X-Ray Crystal Structure of Host-Guest Complex

Square **9** with 4,4'-bpy guest crystallizes in the P-1 space group much like **6** with 4,4'-bpy. The molecule lies on an inversion center.

The Cu···Cu distances of this new host-guest complex and the previous one are listed in table 3.3. The biggest difference between this new host-guest complex and the previous one is that the 4,4'-bpy does not bind to the outside of the square. This could indicate that 4,4'-bpy first coordinates to the inside of the square. However, this material is still polymeric, with a β-diketone oxygen from one square coordinating to the Cu centers of the adjacent square with a Cu···O distance of 2.491 Å (see figure 3.6). This polymerization could have prevented 4,4'-bpy molecules from coordinated to the outside of the square. As a polymer, this material is unlikely to be soluble, however since the crystals formed after the test tube containing the solution was exposed to low temperatures it could indicate that the material has some limited solubility in $CHCl_3$/MeOH mixtures; although, the crystals formed at the bottom of the test tube and may simply have gone unnoticed for some time.

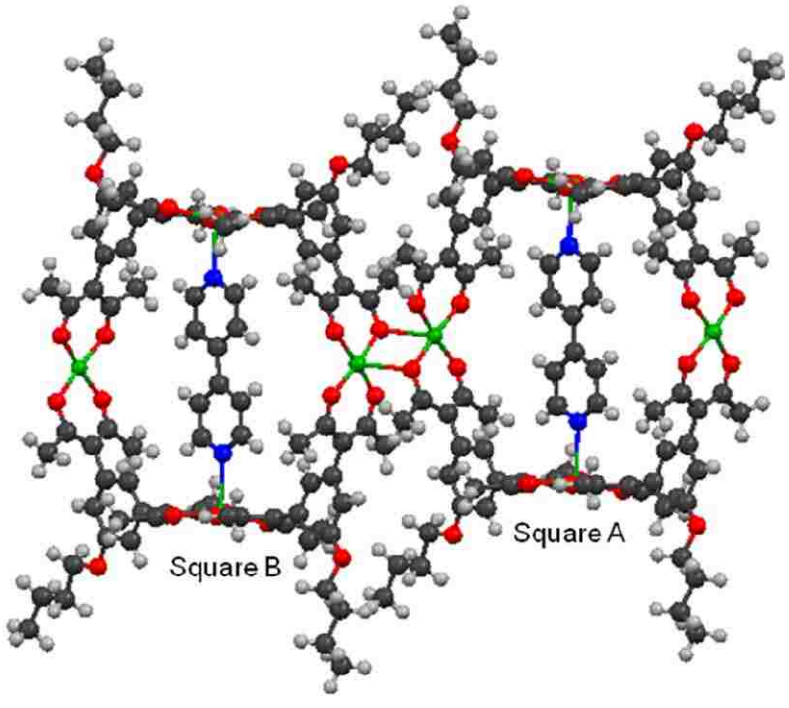


Figure 3.6. X-Ray structure from CIF file showing square polymerization. Figure created with Mercury 2.2.

Table 3.3. Cu···Cu distance comparison for **6** + 4,4'-bpy and **9** + 4,4'-bpy.

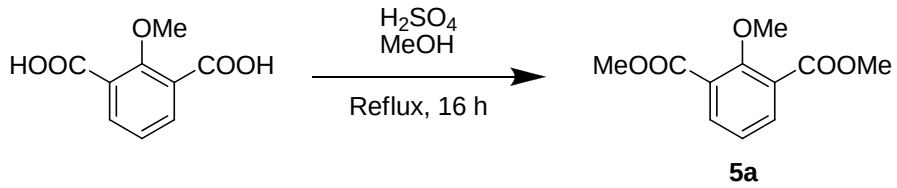
Square **6** + 4,4'-bpy		Square **9** + 4,4'-bpy	
Copper atoms	Distance	Copper atoms	Distance
Cu1···Cu2	11.807 Å	Cu1···Cu1'	11.954 Å
Cu3···Cu4	16.226 Å	Cu3···Cu4	15.985 Å

Chapter 4: Synthesis of Ligand 5 and Square 10

4.1 Introduction

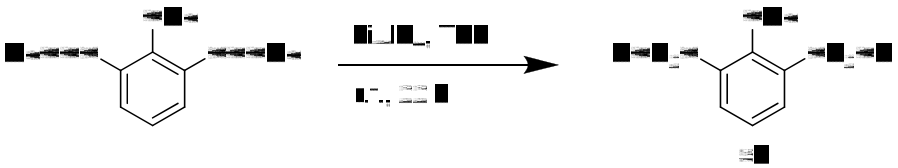
Adding functional groups to the 5-position of the aromatic ring introduces functional groups to the outside of the square. If functional groups were added to the 2-position of the aromatic ring, this would result in a square with a pore decorated by functional groups. This decorated pore could have different host-guest properties than the undecorated pore in the squares mentioned in previous chapters. If the functional group was large enough, it could create a steric interaction that may cause the formation of a larger macrocyle, such as a pentagon. Thus the synthesis of ligand 5 with a methoxy group in the 2-position began. The only available precursor for **5** was 2-methoxyisophthalic acid. First the acid was converted to dimethyl 2-methoxyisophthalate (**5a**) using a procedure used by Zhu et al. to synthesize dimethyl 2-methoxy-5-methylisophthalate from 2-methoxy-5-methylisophthalic acid (see scheme 4.1).[40] Then PDBBA was used in an attempt to convert dimethyl 2-methoxyisophthalate to 2-methoxyisophthalaldehyde. However, like the reaction of PDBBA with **4a** described in chapter 3, this attempt also only produced monoaldehyde intermediate. Thus, **5a** was treated with LAH to convert it to 2-methoxy-1,3-benzenedimethanol, **5b**. Then the microwave procedure was used to oxidize **5b** to 2-methoxyisophthalaldehyde. Finally, 2-methoxyisophthalaldehyde was mixed with 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene to synthesize **5** and this was used to make **10**.

Scheme 4.1. Synthesis of **5a**.



5a

Scheme 4.2. Synthesis of **5b**.



4.2 Experimental Procedures

Reagents were purchased from Aldrich. NMR spectra were taken on the DPX-250 and the AV-400. Mass spectra were taken with Agilent 6210 (ESI), and Varian Saturn 2200 GC/MS. $CDCl_3$ was used as solvent for NMR analysis.

4.2.1 Synthesis of 5a

First, 1.69 g (8.60 mmol) of 85% 2-methoxyisophthalic acid was added (without purification) to a round bottom flask. Then 20 mL of MeOH and 0.5 mL of H_2SO_4 was added and the mixture was refluxed for over 16 hours. When the reaction was complete the mixture was neutralized with NH_4OH and the solvent was removed under reduced pressure. Then the solid was filtered with CH_2Cl_2 and washed with water, brine, and 25 mL of 0.5 M Na_2CO_3. Extraction with CH_2Cl_2 and removal of solvent yielded a light yellow liquid.

NMR analysis of the product shows successful conversion to **5a**; however, discrepancies in the integrations suggest that there may be some starting material remaining, or that impurities originally in the starting material could still be present. The material was purified by column chromatography using a 1:2 ethyl acetate:hexane solvent mixture resulting in 1.15 g of a colorless liquid, which is an 81% yield. This yield has not been reproduced. NMR confirms the identity of the product (see figure A15, p. 70). ^{1}H NMR: δ 7.32 (d, 2H, aromatic C*H*); 7.18 (t, 1H, aromatic C*H*); 3.92 (s, 3H, OCH_3); 3.91 (s, 6H, CO_2CH_3).

4.2.2 Synthesis of 5b

Notice: Extra care should be taken when handling LAH as it is extremely reactive and can cause fires if it comes into contact with water. First, 3.6 mL (7.2 mmol) of LAH (2 M in THF) were added via syringe to a three necked round bottom flask filled with approximately 50 mL of anhydrous THF. Then 527 mg (2.35 mmol) of **5a** were dissolved in approximately 20 mL of anhydrous THF and added to the LAH mixture dropwise. The LAH used had a large amount of white precipitate material, indicating that the LAH had precipitated out of the THF solution. Also I had accidentally performed the reaction at 0 °C. The next day a large amount of white precipitate was observed in the flask. At first I thought that the solvent had evaporated, so I added more anhydrous THF but then notice that there was still plenty of solvent. The stir plate had failed causing the LAH to settle. The flask was moved to a different stir plate and stirring was resumed for 2 h and 25 min. The reaction was tested by TLC and NMR but the analysis was inconclusive. The reaction was stopped by the addition of about 16 mL of 1M H_2SO_4, ethyl acetate, and water at 0 °C. The organic phase was separated and washed with 100 mL of saturated NaCl(aq) and dried with Na_2SO_4.

Then the excess solvent was removed which resulted in 210 mg of a yellow solid (53% yield). NMR and GCMS confirm the material as the desired product which was used without purification. See figure A16, p. 71 for NMR spectrum. GCMS: *m/z* 167.8 [M−H]. ^{1}H NMR: δ 7.33 (d, 2H, aromatic C*H*); 7.15 (t, 1H, aromatic C*H*); 4.75 (s, 4H, CH_2OH); 3.87 (s, 3H, OCH_3).

4.2.3 Synthesis of 2-methoxyisophthalaldehyde

First, 147 mg (0.874 mmol) of **5b**, 669 mg (3.52 mmol) of *p*-TsOH, and 152 mg (1.79 mmol) of $NaNO_3$ were added to a microwave reaction vessel. The solids were mixed with MeCN, then solvent was evaporated and the vessel was placed in the microwave. Program JDS1 was used, Power = 850 W, ramp to 100 °C in 10 sec, hold at 100 °C for 20 sec. After a total of 6 min of heating the vessel was taken out of the microwave, the material was extracted with $CHCl_3$, dried with Na_2SO_4, and excess solvent was removed, resulting in 110 mg (77% yield) of a yellow solid. GCMS confirms the identity of the product. In the NMR spectrum there are several extra peaks. There is a second aldehyde peak, an extra aromatic peak, and two methoxy peaks, which indicate that the material was not completely clean (see figure A17, p. 72). Dr. Crowe suggests that the extra aldehyde and methoxy peaks could be indicative of one of the aldehyde groups in a small amount of the material (ca. 34% as estimated by NMR) oxidizing to an acid group. The material was used in the next step without purification. GCMS: *m/z* 163.9 [M^+]; 165.0 [M+H]. ^{1}H NMR: δ 10.43 (s, 2H, C*H*O); 8.35 (d, 1H, aromatic C*H*); 8.11 (d, 2H, aromatic C*H*); 4.11 (s, 3H, OCH_3).

4.2.4 Synthesis of Ligand 5

First, 110 mg (0.670 mmol) of 2-methoxyisophthalaldehyde were added to a round bottom flask and placed in the dry box. Then 301 mg (1.43 mmol) of 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene were added and the mixture was stirred overnight. The next day NMR analysis showed no aldehyde peak so the flask was taken out of the dry box. The mixture was dissolved in about 30 mL of methanol and refluxed for 2 h and 15 min. NMR analysis showed presence of enol so the reflux was stopped and solvent was removed. Then the material was purified via column chromatography using a 1:1 ethyl acetate:hexane solvent mixture. After purification, 20 mg (10% yield) of a yellow liquid was recovered. NMR confirms identity of product and the presence of ethyl acetate peaks prove that the material was still wet so the yield is not accurate (see figure A18, p. 73). Also the presence of extra aromatic peaks indicates that the material is probably not pure. ^{1}H NMR: δ 16.72 (s, 2H, enol O*H*); 7.86 (d, 1H, aromatic C*H*); 7.74 (d, 2H, aromatic CH); 3.64 (s, 3H, OCH_3); 1.85 (s, 12H, CH_3).

4.2.5 Synthesis of 10

First 23 mg (0.0921 mmol) of $CuSO_4 \cdot 5H_2O$ was added to a beaker and dissolved in water. Then conc. aqueous NH_3 was added until a dark blue solution formed. Then 20 mg (0.0657 mmol) of **5** dissolved in CH_2Cl_2 was added and the mixture was stirred for 1 h. Then the olive green organic phase was extracted, dried with Na_2SO_4, and excess solvent was removed to yield 20 mg of an olive green solid (83% yield). The solid appeared to be wet and **5** was still wet with ethyl acetate when used.

4.3 Results and discussion

4.3.1 Reduction of dimethyl 2-methoxyisophthalate

For the reduction of dimethyl 2-methoxyisophthalate the yield was 53% compared with a yield of 80% for the reduction of dimethyl 5-butoxyisophthalate. There are several possible reasons for the difference in yield: steric interaction created by the 2-methoxy group, the accidental cooling of the reaction, the cloudy LAH solution used, or the limited number of times the reaction has been performed. Any of these factors may have resulted in a lower yield. The literature procedure that was adapted for this reaction used solid LAD suspended in THF, so the cloudy THF solution may not have had that much of an effect on the yield, unless the LAH had partly gone bad. The accidental cooling is probably the biggest contributor to the low yield, and is easily remedied by simply not cooling the reaction next time. If the 2-methoxy group has a negative steric influence on the reaction then it would be harder to improve, though increasing the duration of the reaction could improve the yield some.

4.3.2 Oxidation of 2-methoxy-1,3-benzenedimethanol

The yield of 2-methoxyisophthalaldehyde was lower than the yields obtained for 5-methoxyisophthalaldehyde. While a 77% yield is good for the first try of this reaction, it indicates that some improvement could be possible in the procedure. Lee et al. oxidized many aromatic alcohols to aldehydes, including 1,3-benzenedimethanol and 4-methoxybenzyl alcohol.[31] They used 150 sec for 4-methoxybenzyl alcohol and 60 seconds for 1,3-benzenedimethanol, so I used this as a guideline for determining the time for the reaction of 5-methoxy-1,3-benzenedimethanol. Initially I simply doubled the time used for 4-methoxybenzyl alcohol, but later I found that an extra minute produces better results. Moving the methoxy group to the 2-position would produce different electronic effects than having the methoxy group in the 5-position, so the amount of time needed for the reaction could be different.

For example, Lee et al. converted 4-nitrobenzyl alcohol to 4-nitrobenzaldehyde in 150 seconds, but 2-nitrobenzyl alcohol required twice the time for conversion to 2-nitrobenzaldehyde.[31] This would indicate that a longer reaction time may be needed for the best conversion of 2-methoxy-1,3-benzenedimethanol to 2-methoxyisophthalaldehyde.

4.3.3 Ligand 5 Synthesis

The yields for conversion of aromatic aldehydes to β-diketones using 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene are usually around 50%. The low yield is not that bad as this is the first time this particular reaction has been performed. For example, the first time **3** was synthesized the yield was 23%. The low yield is possibly the result of impurities in the 2-methoxyisophthalaldehyde or errors made during the purification. During the purification some of the crude material was added to the column too fast and resulted in an uneven distribution of material, which could have resulted in poor separation and purification.

4.3.4 Synthesis of 10

An olive green solution formed during the reaction and no precipitate was observed indicating that it formed a metallocycle. This is because a polymer would likely be insoluble and would have precipitated out. The formation of an olive green material also confirms that the methoxy group does not interfere in the formation of a metal complex, which means that other small functional groups (such as hydroxyl, methyl, ethyl, ethoxy, amino) could be tried and they would still likely form the desired material. In CH_2Cl_2, **10** is an olive green color much like our previous squares.

Since **10** was wet and our vacuum pump for the vacuum line was not working, solubility tests were not performed on it as they would have been inaccurate. Also, the fact that the material was still wet means that the yield is not entirely accurate.

4.4 Conclusions

In conclusion, our group's previous squares (**6** and **7**) had limited solubility in organic solvents. I synthesized squares **8** and **9** using modified ligands **3** and **4**. Ligand **3** has a methoxy group in the 5-position of the aromatic ring of the ligand and **4** has a butoxy group. Square **8** is soluble in CH_2Cl_2, THF, and CH_2Cl_2-MeOH mixtures, proving that groups in the 5-position of **1** can alter the solubility of the resulting square. Square **9** is soluble in CH_2Cl_2, $CHCl_3$, THF, benzene, toluene, chlorobenzene, bromobenzene, and *o*-dichlorobenzne. The work in this chapter shows that ligand **1** can also be modified at the 2-position of the aromatic ring. This would introduce functional groups to the inside of the square and adjust the host-guest properties or possibly force the ligand to form larger macrocycle. To this end, ligand **5** with a 2-methoxy group was synthesized and used to form metal complex **10**. Although **10** has not been fully characterized, the current work suggests that small functional groups can be placed in the 2-position and would not interfere with the formation of the β-diketone or the metal complex, and that the metal complex is likely a metallocycle. More work is required on **10**, but the introduction of a methoxy group into the pore of the square could increase the polarity of the pore and alter the types of guests that can be encapsulated. Also hydrogen bonding interactions could occur between a guest and the oxygen atom of the methoxy group.

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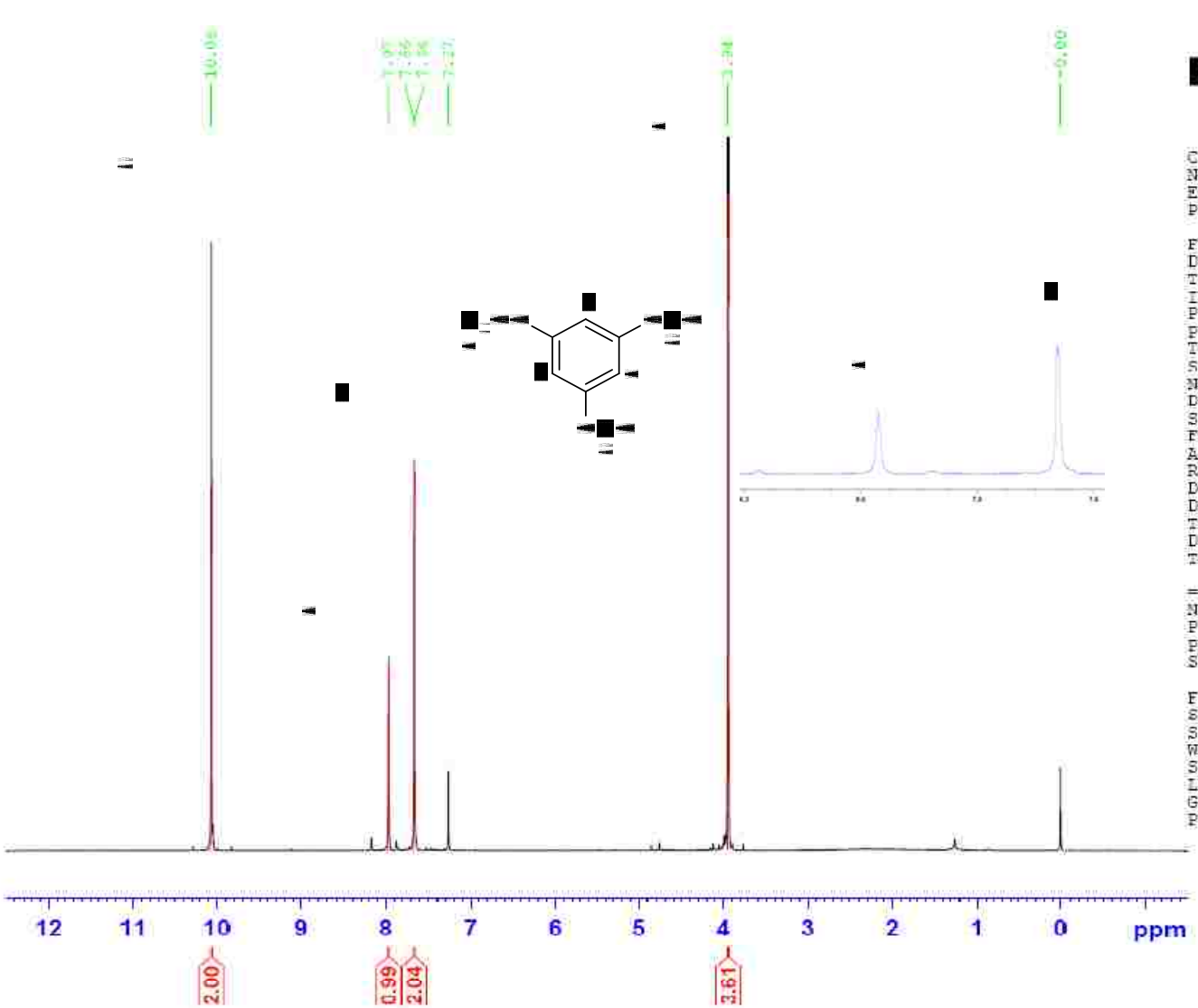


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Figure A1. NMR spectrum of 5-methoxyisophthalaldehyde.

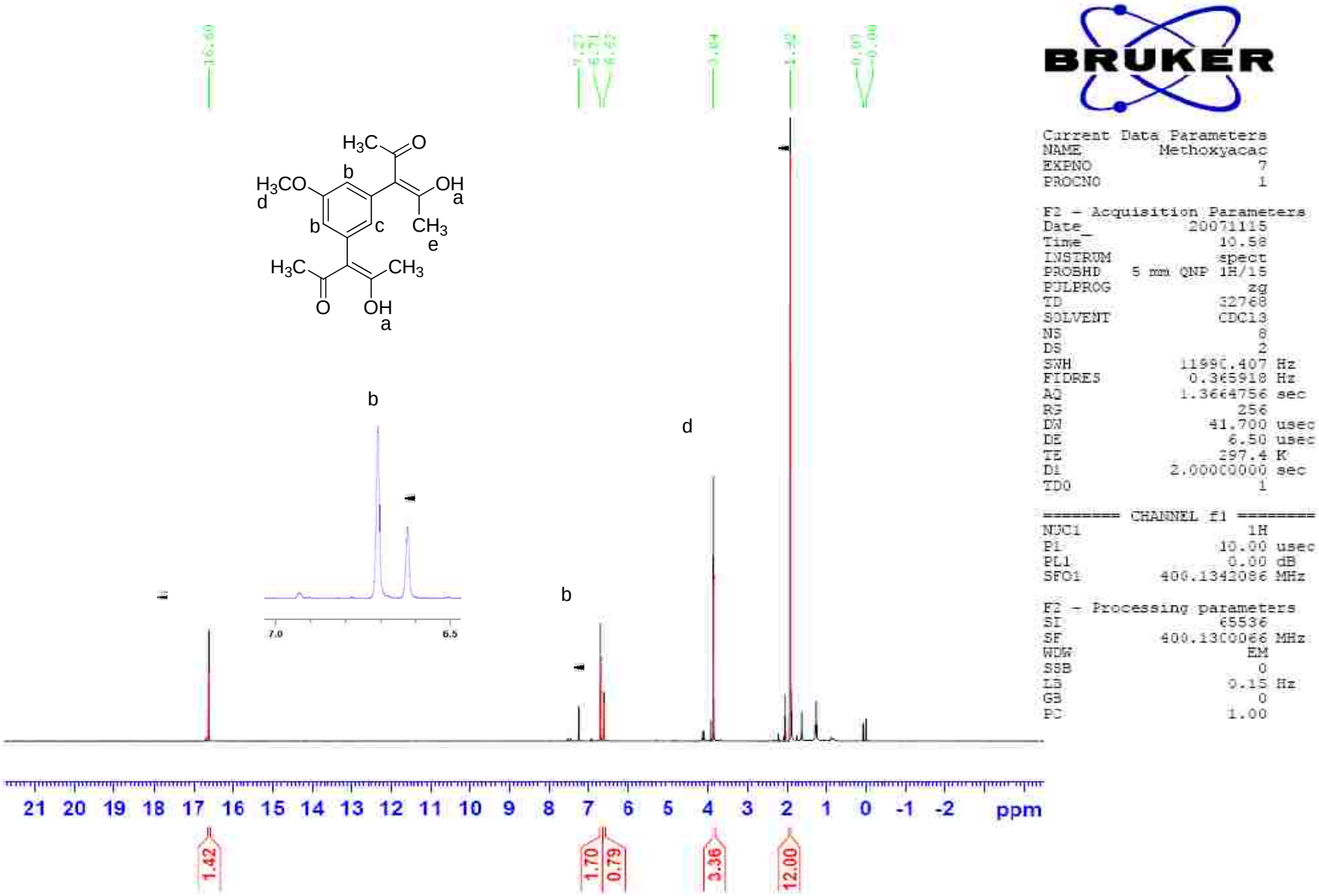

Figure A2. [1]H NMR spectrum of Ligand **3**.

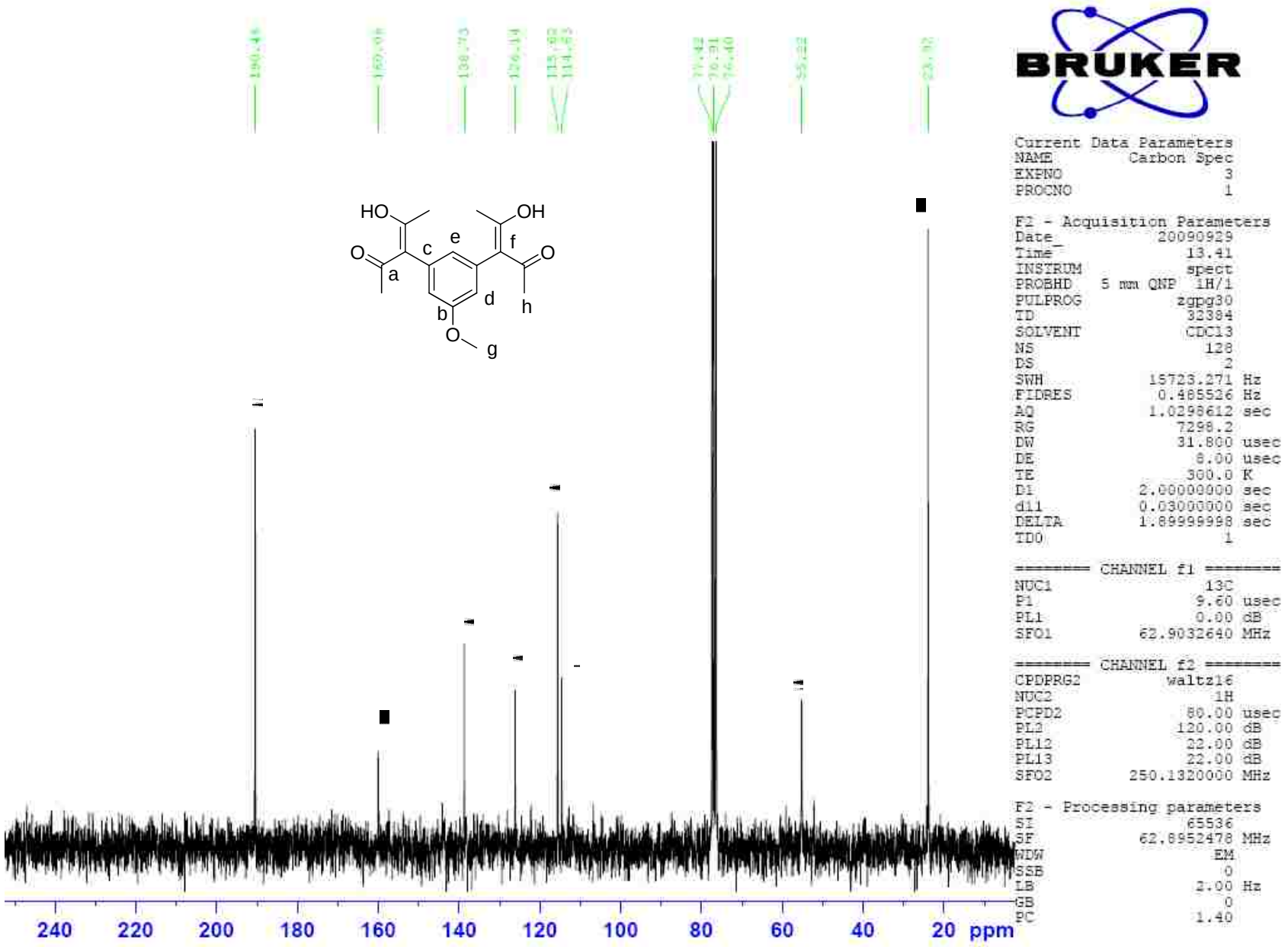

Figure A3. ^{13}C NMR spectrum of Ligand **3**.

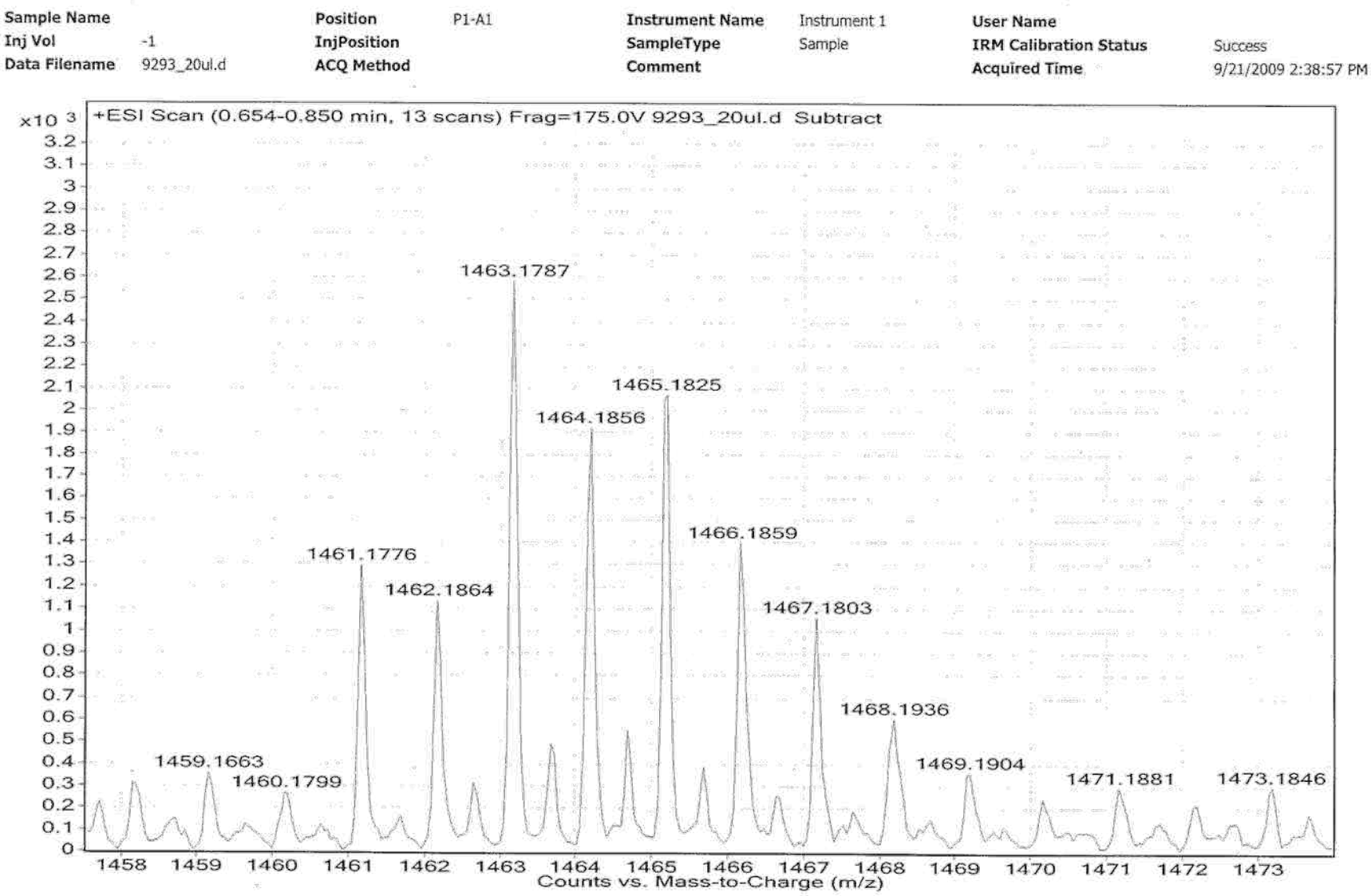

Figure A4. Portion of ESI-MS spectrum of **8**, Cu_4(5-MeO-*m*-pba)$_4$.

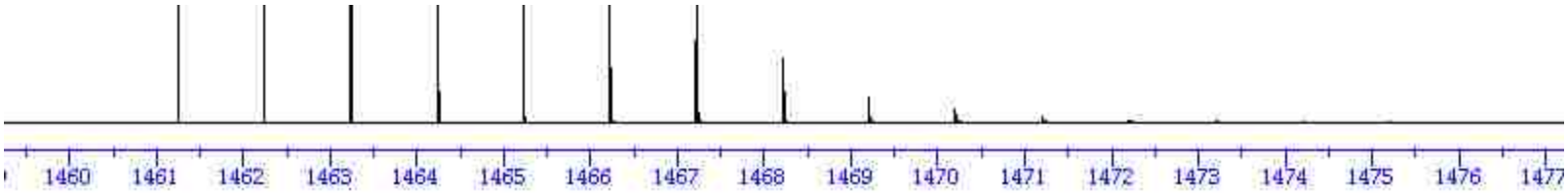

Figure A5. Calculated [M+H] MS spectrum of **8**, Molecular formula: $[C_{68}H_{73}O_{20}Cu_4]^+$, Calculated using: http://www.chemcalc.org/.

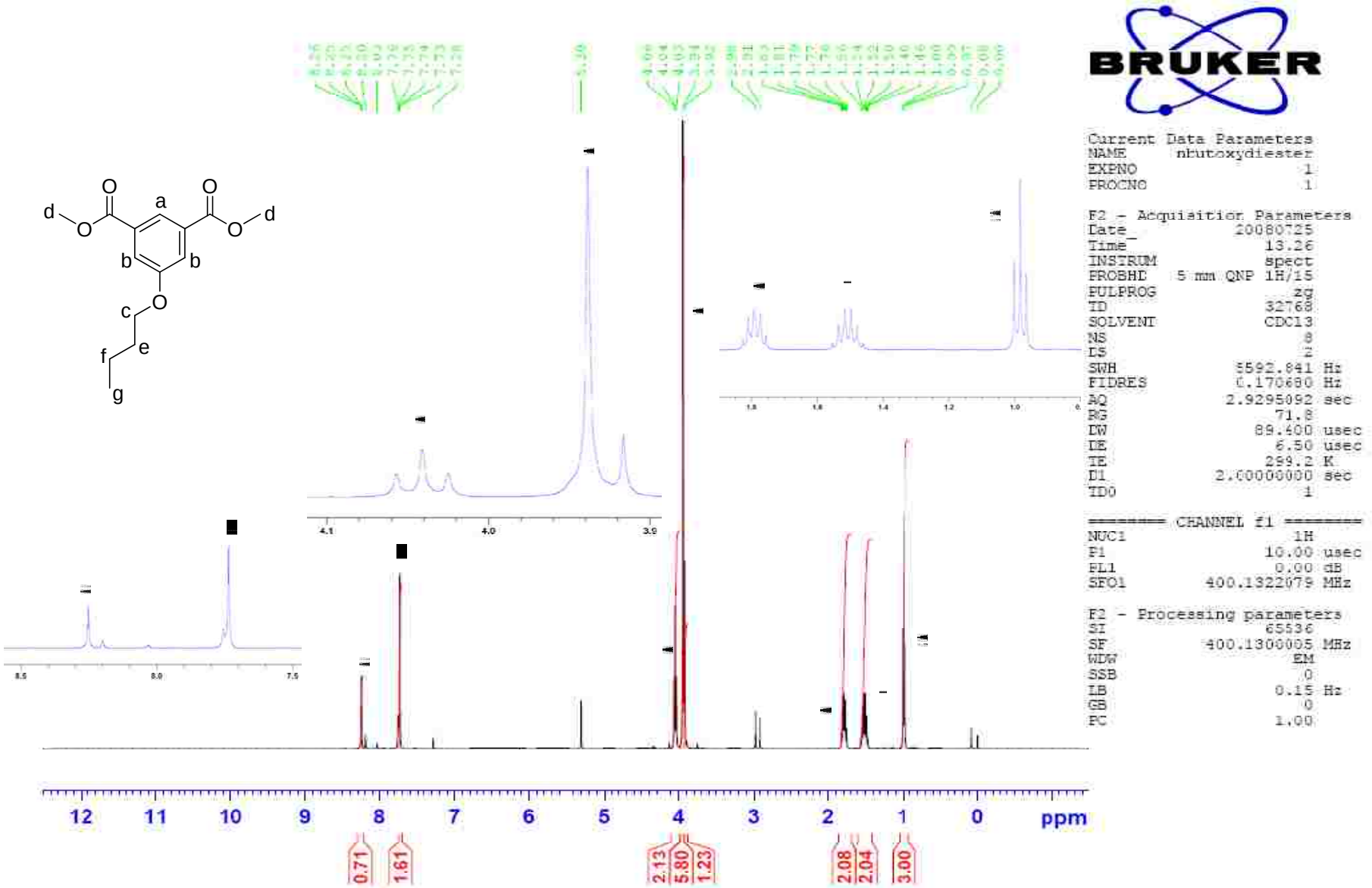

Figure A6. NMR spectrum of **4a**.

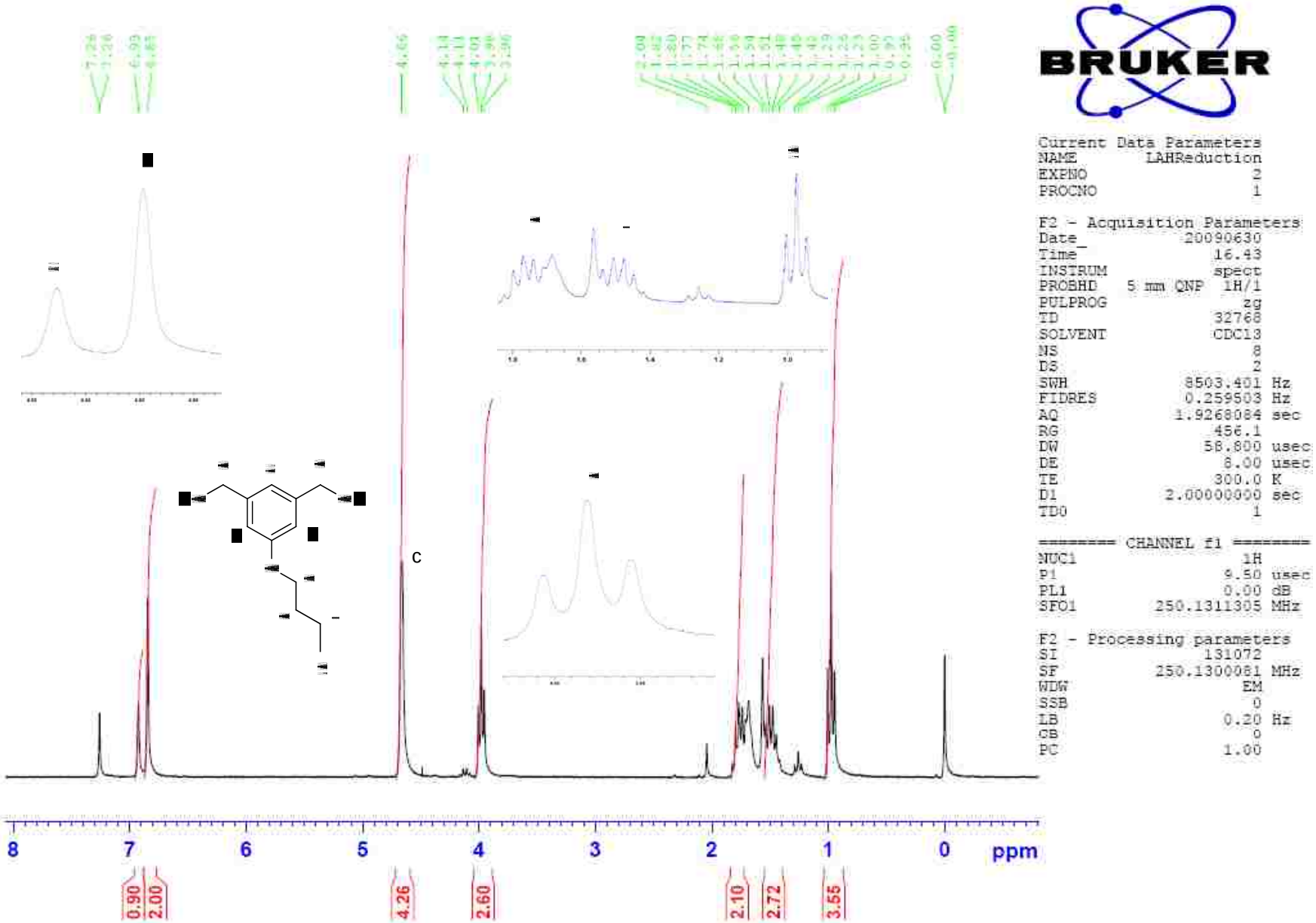

Figure A7. NMR Spectrum of **4b**.

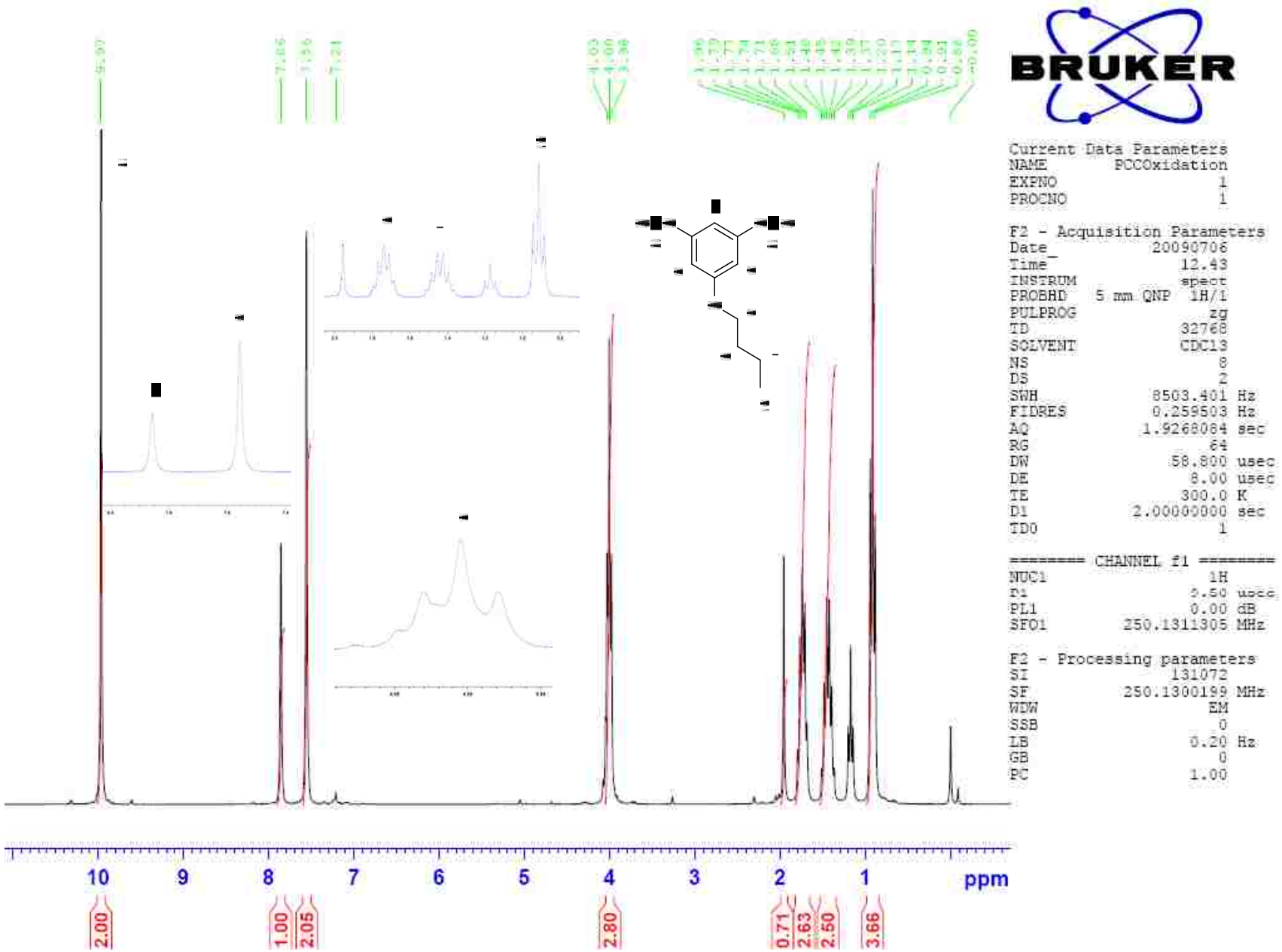

Figure A8. ^{1}H NMR Spectrum of 5-butoxyisophthalaldehyde.

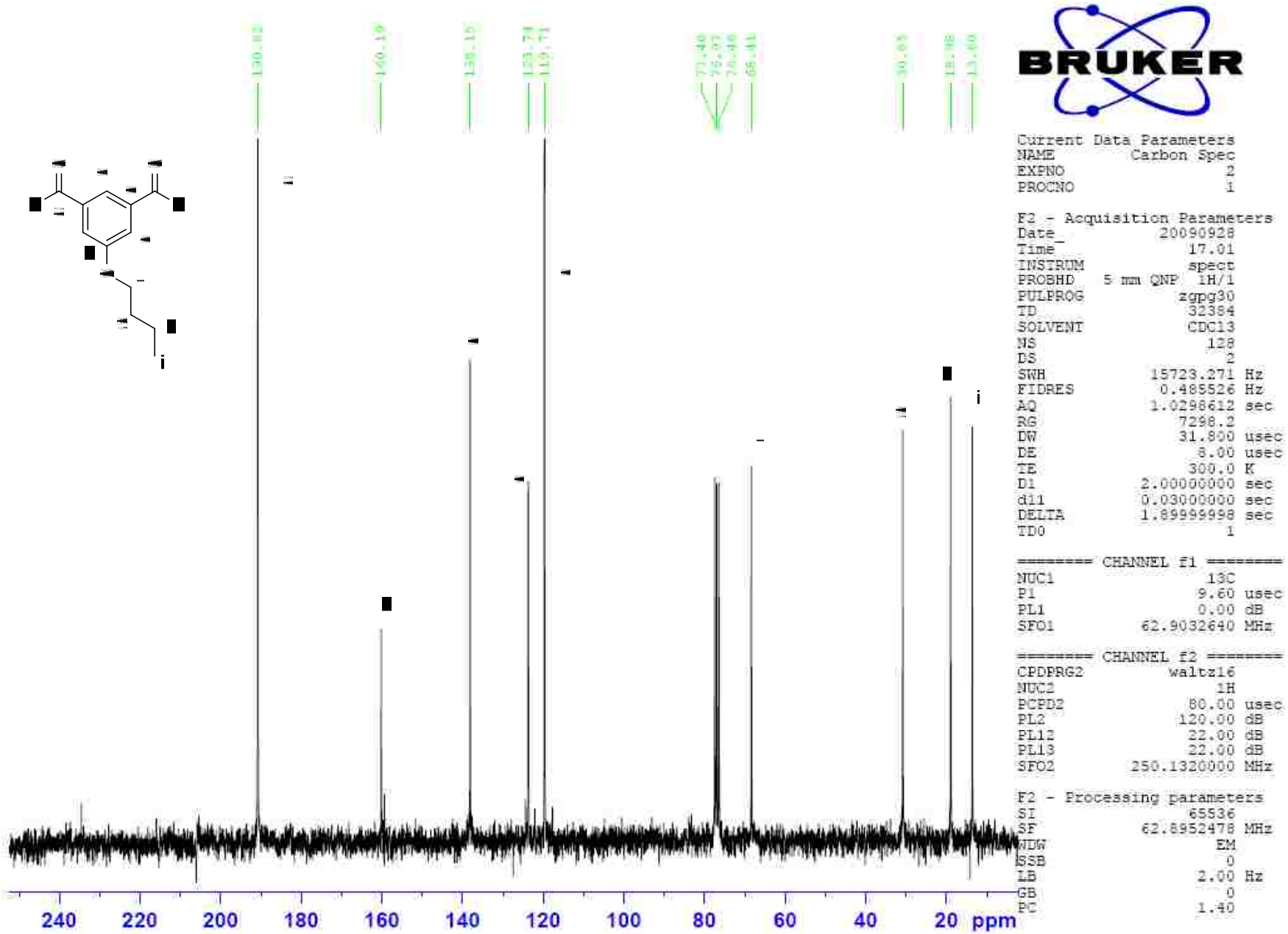

Figure A9. ^{13}C NMR spectrum of 5-butoxyisophthalaldehyde.

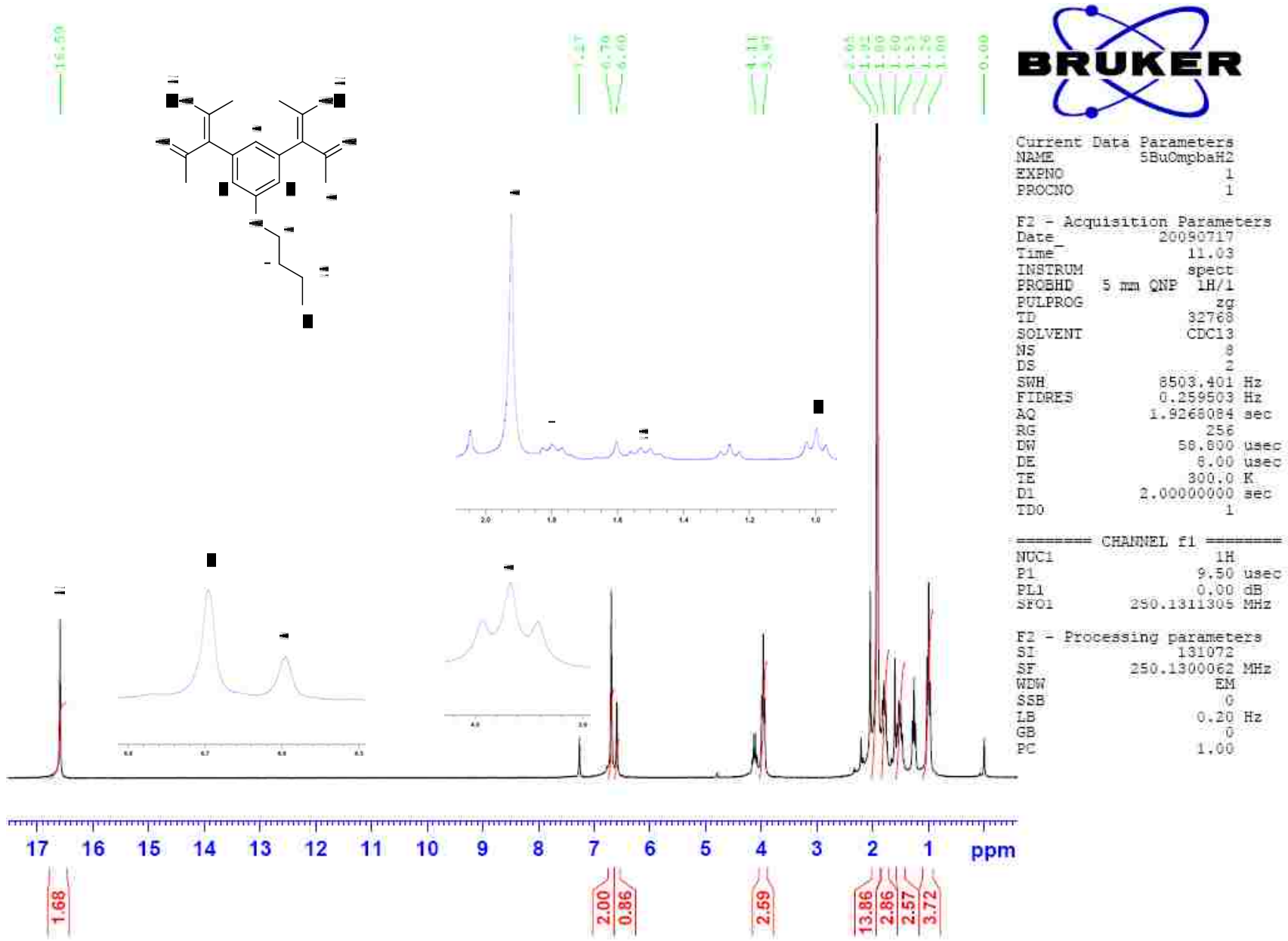

Figure A10. ^{1}H NMR spectrum of Ligand **4**.

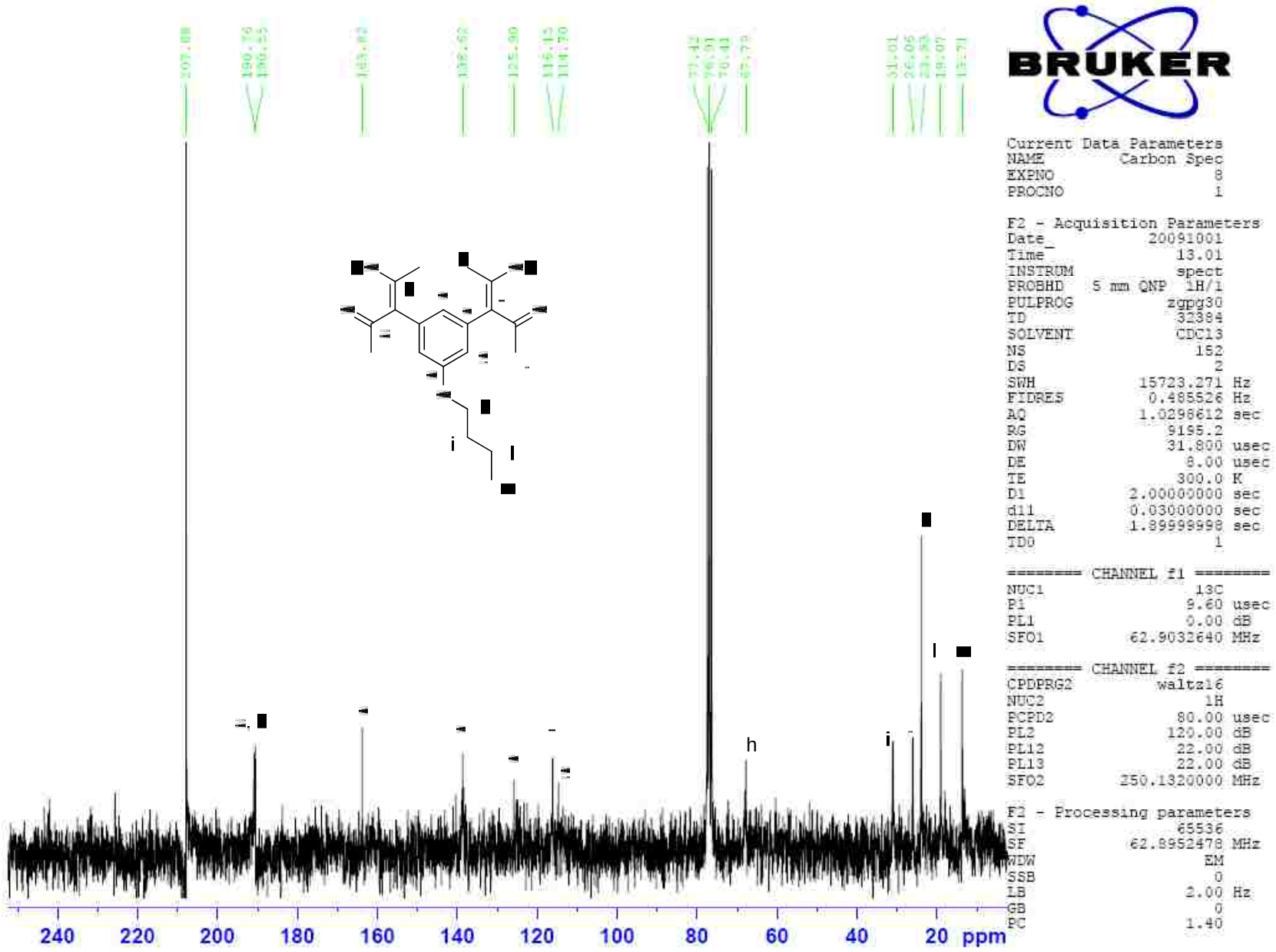

Figure A11. ^{13}C NMR spectrum of Ligand **4**.

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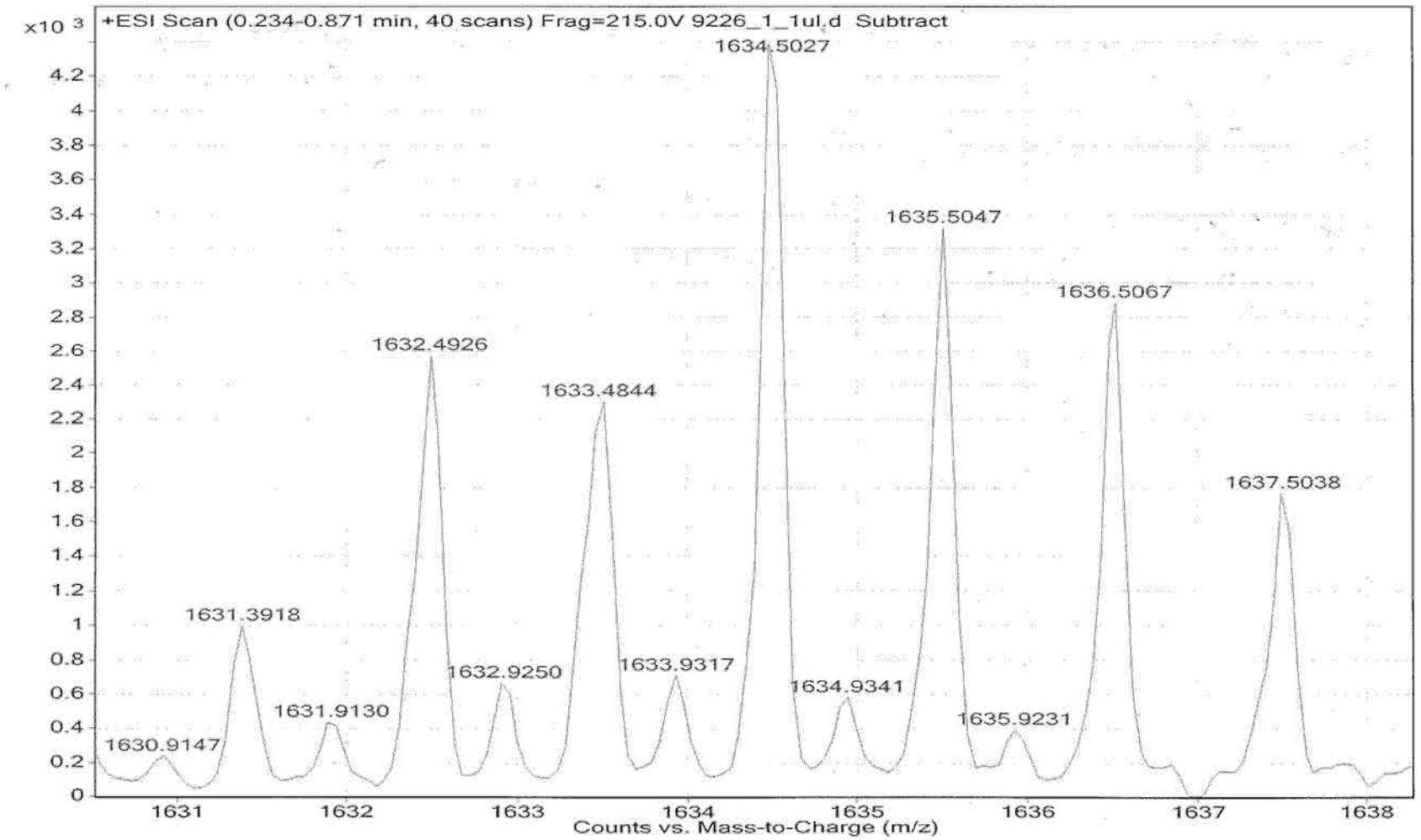

Figure A12. Portion of ESI-MS spectrum of **9**, Cu_4(5-BuO-*m*-pba)$_4$.

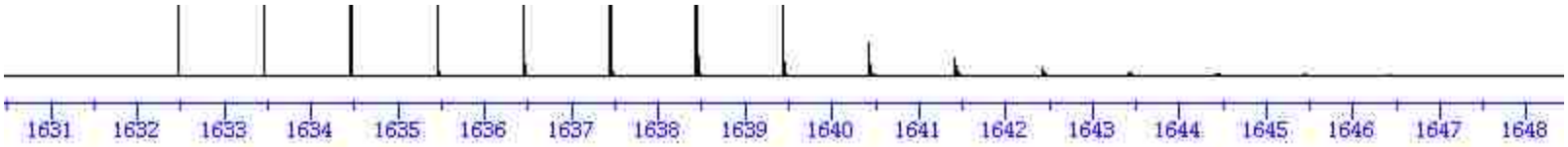

Figure A13. Calculated [M+4H] MS spectrum of **9**, Molecular formula: $[C_{80}H_{100}O_{20}Cu_4]^+$, Calculated using: http://www.chemcalc.org/.

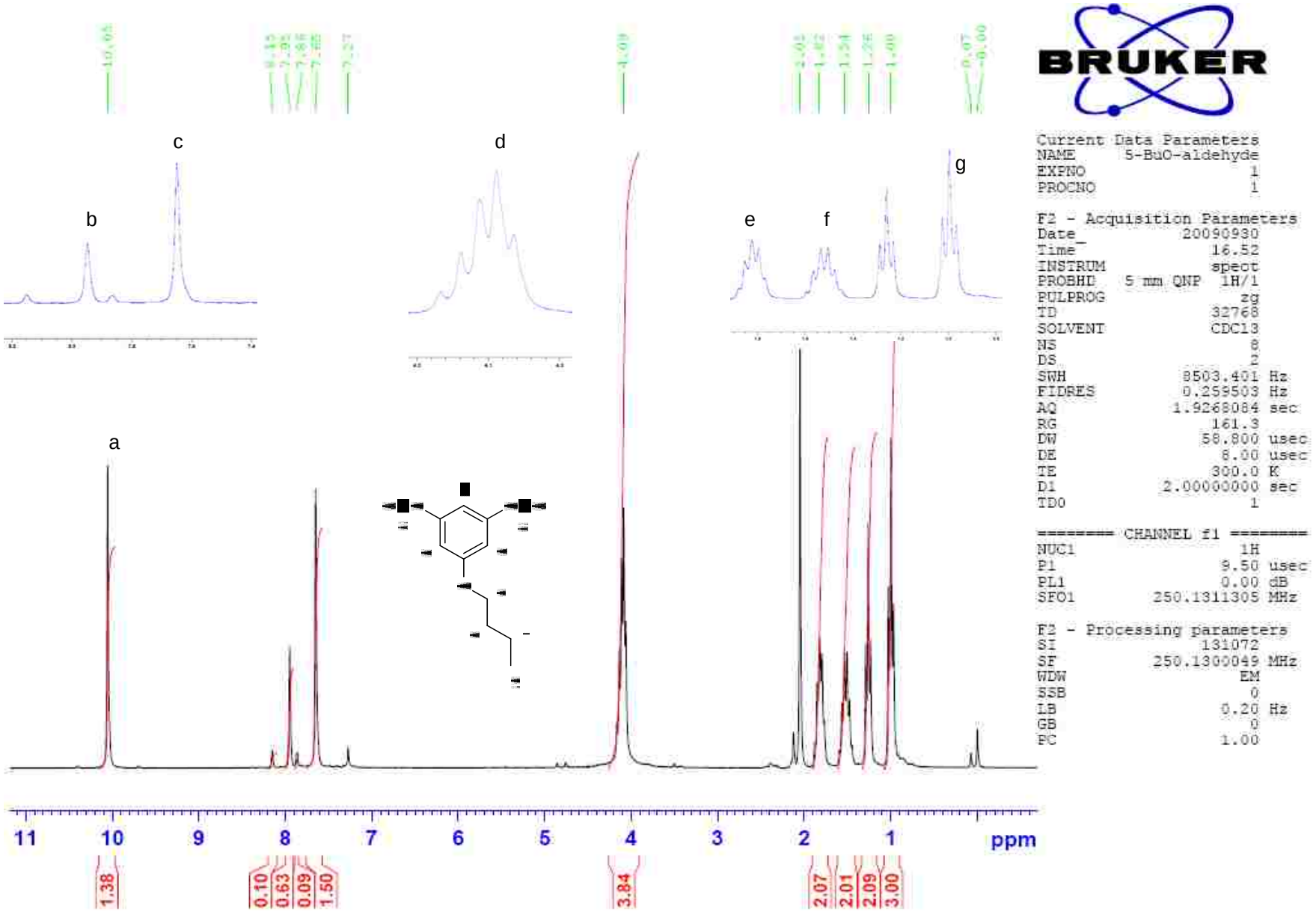

Figure A14. NMR spectrum of 5-butoxyisophthalaldehyde synthesized via microwave procedure.

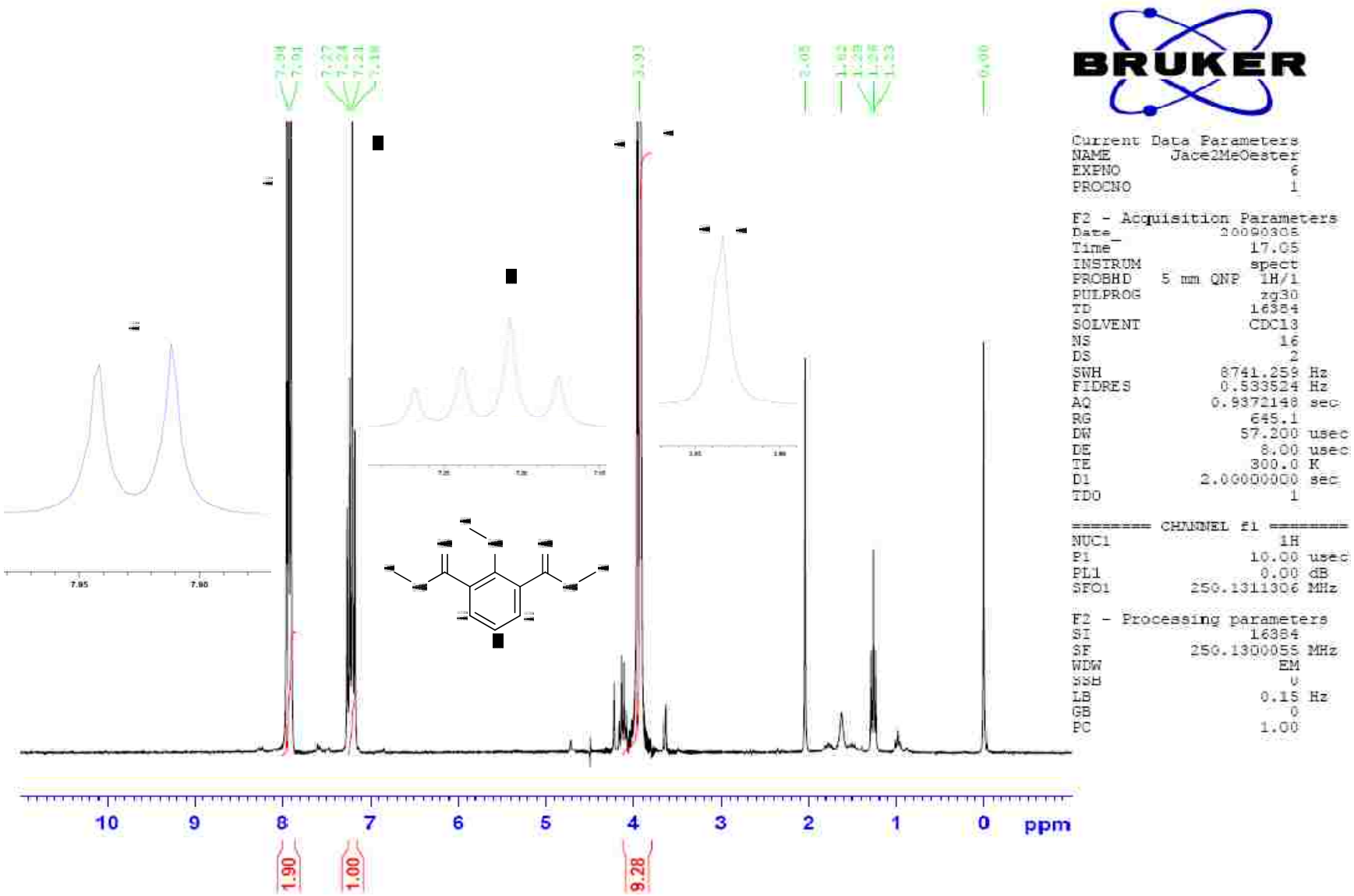

Figure A15. NMR spectrum of **5a**.

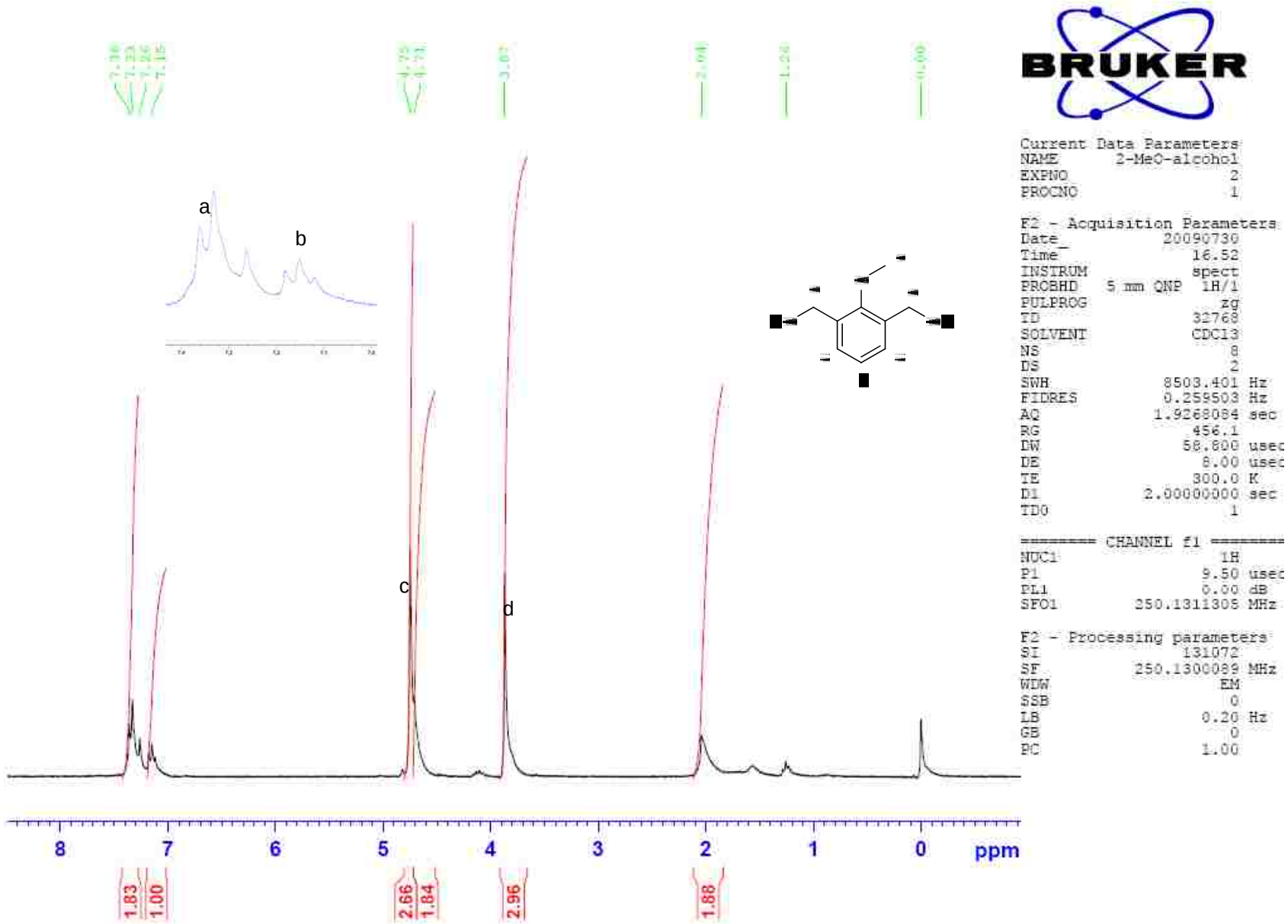

Figure A16. NMR spectrum of **5b**.

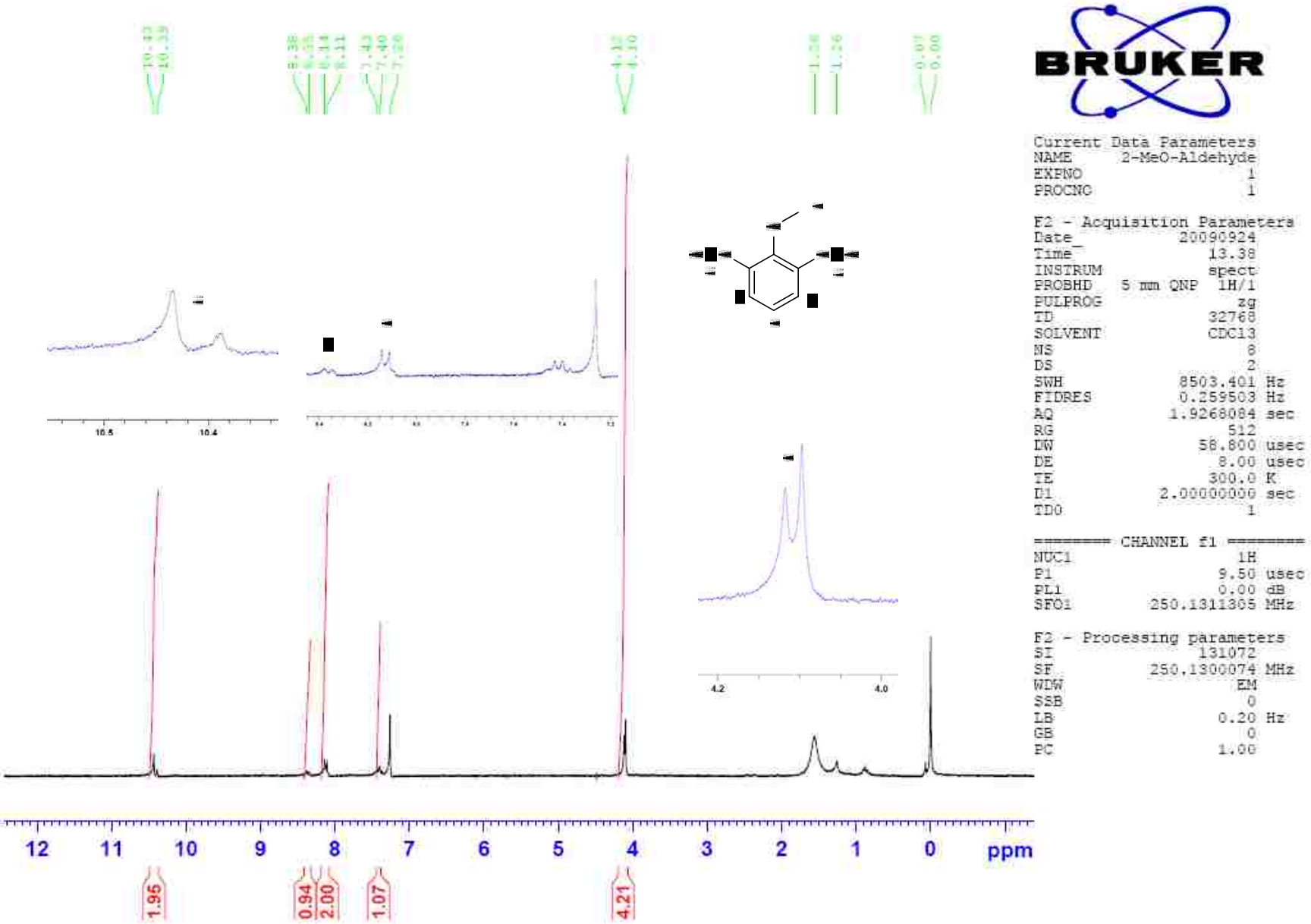

Figure A17. NMR spectrum of 2-methoxyisophthalaldehyde.

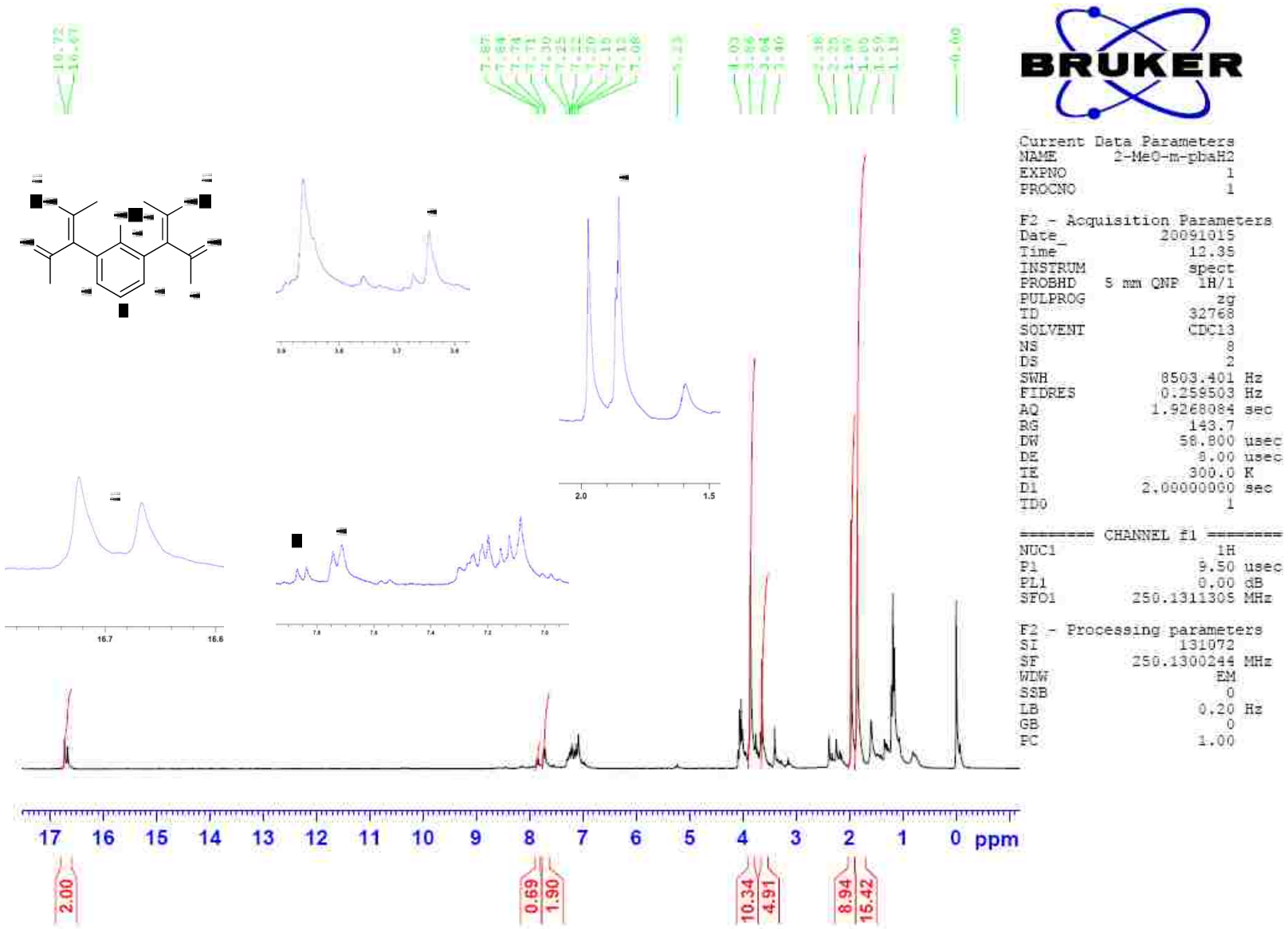

Figure A18. NMR spectrum of Ligand **5**.

Vita

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