Supplementary Information

Copper(II)-Flavonolate Complexes of Sterically Hindering 3N Ligands as Enzyme-Substrate Models for Copper(II) Quercetin 2,4-Dioxygenase: Experimental and Computational Study on the Dioxygenation Reactivity

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Experimental

Materials

Pyridine-2-carboxaldehyde, 1-methylimidazole-2-carboxaldehyde, copper(II) perchlorate hexahydrate (Sigma-Aldrich), sodium triacetoxyborohydride, 3-hydroxyflavone (Alfa Aesar), 6-methylpyridine-2-carboxaldehyde, quinoline-2-carboxaldehyde (TCI), ethyl acetate, triethylamine, sodium sulphate (Merck, India), were used as received. Dichloromethane, tetrahydrofuran, acetonitrile (Merck, India), methanol and acetone (Sisco Research Laboratory, Mumbai) were distilled before use. The supporting electrolyte *tetra*-*N*-butylammonium perchlorate (Aldrich) was recrystallized and used.

Synthesis of ligands

The ligands 4-methyl-(1-pyrid-2-ylmethyl)-1,4-diazacycloheptane (**L1**), 4-methyl-(6-methyl(1-pyrid-2-ylmethyl))-1,4-diazacycloheptane (**L2**), 4-methyl-1-(*N*-methylimidazol-2-ylmethyl-1,4-diazacycloheptane (**L3**) and 4-methyl-1-(quinol-2-ylmethyl)-1,4-diazacycloheptane (**L4**) were prepared by using previously reported procedures with slight modifications.[1]

4-Methyl-(1-pyrid-2-yl methyl)-1,4-diazacycloheptane (L1)

This ligand was prepared by adopting the procedure used by one of us elsewhere.[1] To a solution of *N*-methylhomopiperazine (1.14 g, 10 mmol) and pyridine-2-carboxaldehyde (1.07 g, 10 mmol) in CH_2Cl_2 (80 mL), sodium triacetoxyborohydride (4.24 g, 20 mmol) was introduced with stirring. The resultant mixture was stirred for 12 h and combined with a saturated sodium bicarbonate solution, and the stirring was continued for another 20 minutes. Then, the reaction mixture was extracted with ethyl acetate, and the collected ethyl acetate fractions were dried over sodium sulfate, then filtered and dried using a rota evaporator. The product was dissolved in THF (60 mL) and treated with NaH (0.72 g, 30 mmol) to eliminate the traces of pyridyl-2-carbinol and stirred for 90 min. The solvent was then removed by rota evaporation, and the residue was extracted with several portions of n-hexane. The extracts were combined, and the solvent was removed to acquire **L1** as a brown oil, which was utilized to prepare complex **1**. Yield: 1.03 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (m, 1H), 7.22 (m, 1H), 6.97 (m, 2H), 4.65 (s, 2H), 3.70 (s, 4H), 2.68 (m, 4H), 2.46 (d, 3H), 1.75 (m, 2H). Anal. Calcd. For $C_{12}H_{19}N_3$: C, 70.20; H, 9.33; N, 20.47. Found: C, 70.15; H, 9.48; N, 20.37. HR-MS (MeOH) displays a peak at *m/z* 206.1651 [$C_{12}H_{20}N_3^+$] (cal. 206.1652) (**Figure S15**).

4-Methyl-(6-methyl(1-pyrid-2-ylmethyl))-1,4-diazacycloheptane (L2)

The ligand **L2** was isolated by adopting the methodology used for preparing **L1**. It was obtained as a brownish-yellow oil, which was used for preparing the complex **2**. Yield: 1.2 g (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 1H), 7.01 (m, 1H), 6.83 (m, 1H), 4.44 (s, 2H), 3.72 (s, 4H), 2.78 (m, 4H), 2.36 (d, 3H), 1.78 (m, 2H). Anal. Calcd. For $C_{13}H_{21}N_3$: C, 71.19; H, 9.65; N, 19.16. Found: C, 71.50; H, 9.75; N, 19.37.

4-Methyl-1-(*N*-methylimidazol-2-ylmethyl-1,4-diazacycloheptane (L3)

This ligand **L3** was also isolated by adopting the methodology used for preparing **L1**. It was obtained as a brown oil used to prepare the complex **3**. Yield: 1.1 g (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.87 (s, 1H), 4.90 (s, 5H), 4.13 (d, 4H), 2.68 (m, 5H), 2.38 (s, 2H), 1.85 (m, 2H). Anal. Calcd. For $C_{11}H_{20}N_4$: C, 63.43; H, 9.68; N, 26.90. Found: C, 63.50; H, 9.75; N, 26.77. HR-MS (MeOH) displays a peak at *m/z* 209.1770 [$C_{11}H_{20}N_4^+$] (cal. 209.1761) (**Figure S16**).

4-Methyl-1-(quinol-2-ylmethyl)-1,4-diazacycloheptane (L4)

This ligand **L4** was synthesized by adopting the methodology used for preparing **L1**. It was obtained as a dark brown oil, which was used to prepare the complex **4**. Yield: 1.8 g (66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (m, 1H), 7.95 (m,2H), 7.51 (m, 3H), 4.12 (s, 2H), 2.85 (m, 6H), 2.62 (m, 2H), 2.35 (s, 3H), 1.87 (m, 2H). Anal. Calcd. For $C_{16}H_{21}N_3$: C, 75.26; H, 8.29; N, 16.46. Found: C, 75.11; H, 8.30; N, 16.62.

Preparation of Cu(II) complexes

[Cu(L1)(fla)](ClO$_4$) 1. A methanolic solution (5 mL) of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.371 g, 1 mmol) was added to a methanol solution (5 mL) of **L1** (0.205 g, 1 mmol) under stirring at ambient temperature for 1 h. This is followed by adding 3-hydroxyflavone (0.24 g, 1 mmol) suspended in a methanol/dichloromethane solvent combination (10 mL) with stirring. Et_3N (0.1 g, 1 mmol) was then added to the reaction mixture. The stirring was continued for 2 h at ambient temperature. The residue was filtered off and rinsed twice with methanol. All the volatiles were removed under vacuum to yield **1** as a yellowish-green solid. Yield, 0.52 g (64%). ATR (cm^{-1}): ν(C=O), 1541; ν(C=N), 1581. Λ_{max}/nm, in DMF (ε_{max}/dm^3 mol^{-1}): 685 (55), 431 (11,430sh), 415 (10,400sh), 358 (15,570), 341 (19,250), 308 (15,140). Anal. Calcd. For $C_{27}H_{28}N_3ClCuO_7$: C, 53.56; H, 4.66; N, 6.94. Found: C, 53.44; H, 4.60; N, 7.02. HR-MS: (DMF) displays a peak at *m/z* 505.1010 [M – ClO_4]$^+$ (calc.505.1427) (**Figure S17**).

[Cu(L2)(fla)](ClO$_4$) 2. A methanolic solution (5 mL) of Cu(ClO$_4$)$_2$·6H$_2$O (0.371 g, 1 mmol) was introduced to a methanolic solution (5 mL) of **L2** (0.219 g, 1 mmol) and stirred at ambient temperature for 1 h. Then, 3-hydroxyflavone (0.24 g, 1 mmol) suspended in methanol/DCM (10 mL) was added to this, followed by the addition of Et$_3$N (0.1 g, 1 mmol). The stirring of the reaction mixture was continued for 2 h at room temperature, and the residue obtained was filtered off. The residue was rinsed twice with MeOH, and all the volatiles were removed under vacuum to furnish **2** as a bright green crystalline solid. Crystals of **2** suitable for single-crystal X-ray diffraction analysis were acquired by slow evaporation of the saturated solution of **2** in CH$_3$CN/DCM. Yield, 0.58 g (70%). ATR (cm^{-1}): *ν*(C=O), 1533; *ν*(C=N), 1579. Λ_{max}/nm, in DMF (ε_{max}/dm^3 mol^{-1}): 760 (134), 642 (136), 427 (5,980sh), 410 (5,520), 359 (8,900), 343 (10,860), 308 (9,680). Anal. Calcd. For $C_{28}H_{30}N_3ClCuO_7$: C, 54.28; H, 4.88; N, 6.78. Found: C, 54.35; H, 4.78; N, 6.90. HR-MS: (DMF) displays a peak at *m/z* 519.1604 [M – ClO$_4$]$^+$ (calc. 519.1583) (**Figure S18**).

[Cu(L3)(fla)](ClO$_4$) 3. To a methanolic solution (5 mL) of **L3** (0.208 g, 1 mmol) was added, a methanolic solution (5 mL) of Cu(ClO$_4$)$_2$·6H$_2$O (0.371 g, 1 mmol) was charged under stirring at ambient temperature for 1 h. Then 3-hydroxyflavone (0.24 g, 1 mmol) in methanol/DCM (10 mL) was added to it, followed by Et$_3$N (0.1 g, 1 mmol). The reaction mixture was stirred for 2 h at ambient temperature. The residue obtained was filtered off and rinsed twice with methanol. All the volatiles were removed under vacuum to produce **3** as a yellowish-green solid. Yield, 0.42 g (52%). ATR (cm^{-1}): *ν*(C=O), 1540; *ν*(C=N), 1581. Λ_{max}/nm, in DMF (ε_{max}/dm^3 mol^{-1}): 690 (91), 432 (20,130), 413 (17,970), 358 (27,180), 342 (33,63), 306 (26,570). Anal. Calcd. For $C_{26}H_{29}N_4ClCuO_7$: C, 51.32; H, 4.80; N, 9.21. Found: C, 51.44; H, 4.85; N, 9.35.HR-MS: (DMF) displays a peak at *m/z* 540.4908 [M + CH$_3$OH – ClO$_4$]$^+$ (calc.540.1798) (**Figure S19**).

[Cu(L4)(fla)](ClO$_4$) 4. A methanolic solution (5 mL) of Cu(ClO$_4$)$_2$·6H$_2$O (0.371 g, 1 mmol) was introduced to a methanolic solution (5 mL) of **L4** (0.255 g, 1 mmol) and the reaction mixture was stirred at room temperature for 1 h. Then, 3-hydroxyflavone (0.24 g, 1 mmol) suspended in methanol/DCM (10 mL) was added, followed by Et$_3$N (0.1 g, 1 mmol). The reaction mixture was stirred for 2 h at ambient temperature. The residue obtained was filtered off and rinsed twice with methanol. All the volatiles were removed under a vacuum to form **4** as a yellowish-green solid. Yield, 0.41 g (48%). ATR (cm^{-1}): *ν*(C=O), 1538; *ν*(C=N), 1580. λ_{max}/nm, in DMF (ε_{max}/dm^3 mol^{-1}): 690 (45), 431 (8,310), 411 (9,520), 344 (19,760), 309

(15,000). Anal. Calcd. for $C_{31}H_{30}N_3ClCuO_7$: C, 56.79; H, 4.61; N, 6.41. Found: C, 56.85; H, 4.55; N, 6.52. HR-MS: (DMF) displays a peak at *m/z*555.1125 $[M - ClO_4]^+$ (calc.555.1583) (**Figure S20**).

Caution! The compounds of perchlorate salts are potentially explosive. It is advisable to prepare limited quantities of these substances and take suitable precautions during their handling.

Physical Methods

^1H and ^{13}C NMR spectra were recorded (400 and 100 MHz, respectively) on a Bruker Avance DPX 400 MHz spectrometer using $CDCl_3$ as solvent. Chemical shifts for proton and carbon resonances are reported in parts per million (d) relative to tetramethylsilane (d 0.00) and chloroform (d 77.23), respectively. Multiplicities are indicated by singlet (s), doublet (d), triplet (t) and multiplet (m). Electron Paramagnetic Resonance (EPR) spectra for the copper(II) complexes were obtained as polycrystalline samples and frozen solution at LNT using a JEOL Model: JES-FA200 spectrometer. Electronic absorbance spectra were recorded using a 1 cm cuvette on a Varian Cary 300 UV–Visible spectrophotometer. Kinetic measurements were recorded using a 1 cm cuvette on an Agilent diode array spectrometer (Agilent 8453). Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) on glassy carbon electrodes were performed in DMF at 25 °C. The voltammograms were generated using a CH instruments 620C electrochemical analyzer. A three-electrode system was used to study the electrochemical behaviour of the complexes (0.001 M). It comprises a glassy carbon working electrode (A = 0.0707 cm^2), a platinum wire auxiliary electrode and a saturated calomel reference electrode. TBAP (0.1 M) was used as the supporting electrolyte. Solutions were deoxygenated by purging with dinitrogen gas for 15 min prior to the measurement. Microanalyses (C, H and N) were carried out using PR 2400 Series II PerkinElmer equipment. ESI-mass spectra were recorded using a Thermo LC-MS instrument. High-resolution mass analyses were performed using the electron spray ionization (ESI) technique on a Thermo Scientific Exactive plus EMR instrument.GC-MS and GC analysis were performed on an Agilent 5977E GCMSD using HP-5 MS ultrainert (30 m × 250 μm × 0.25 μm) capillary column.

Crystallographic data collection, refinement and structure solution

The crystal and molecular structure of complex **2** was unambiguously determined by a single crystal X-ray structure determination. Intensity data were measured on a Bruker SMART APEX II single crystal X-ray CCD diffractometer at -150 °C using graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å). The structure was solved using direct methods and refined with the SHELX-2014 suite of programs.[2] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms bound to the carbon were placed in geometrically constrained positions and refined with isotropic temperature factors, constrained to the bonded carbon or nitrogen atoms. Crystallographic data are listed in **Table S1**. Crystallographic data for **2** have been deposited with the Cambridge Crystallographic Database; CSD 2189147 contains the supplementary crystallographic data. These files can be obtained free of charge from the CSD or the authors.

Computational details

All the geometries in the present study were optimized at the DFT level using the B3LYP[3-5] method with Grimme's-D3 empirical dispersion corrections[6] in the Gaussian16program.[7] The calculations were done with a mixed basis set (B1) of LanL2DZ for Cu(II) with relativistic effective core potentials. The remaining atoms were optimized using the 6-31G** basis set.[8, 9] All the stationary points are fully characterized via analytical frequency calculations as either minimum (positive eigen values) or transition states (one imaginary eigen value). To obtain reliable energies, the single point calculations were performed on the B3LYP-D3/B1 optimized geometry using LanL2DZ for Cu and the 6-311++G** basis set for the remaining atoms (B2). The solvation effect of DMF was incorporated at the B3LYP-D3/B2 level with single-point calculations using the polarized continuum model (PCM).[10-12] The energetics collected herein are those calculated at the B3LYP-D3/B2//B3LYP-D3/B1 level with solvent corrections and include the free energy corrections obtained from B3LYP-D3/B1 level optimized geometries.

Kinetic measurements

Reactivity Studies. Quercetin 2,3-dioxygenase Activity.

The reactions of flavonolate substrate adducts of the complexes [Cu(L)(fla)(ClO_4)] **1**–**4** with O_2 in DMF at the desired temperature were performed in a 10 mm path length UV-vis cell that was held in a Unisoku thermostated cell holder (Osaka, Japan). The temperature of the solutions of the Cu(II)-flavonolate complexes **1**–**4** in DMF (3 mL) was maintained at 80 °C under N_2 for several minutes. Then, the N_2 was replaced with O_2. The time course of the reactions was

followed by monitoring the absorption spectral changes of the band around 430 nm of the flavonol substrate. The kinetic parameters for the catalytic dioxygenation reactions were obtained from $\ln\{(A_t-A_\infty)/(A_0-A_\infty)\}$ vs. time plots (**Table 5**, **Figure 7**, **S10**–**S12**) at a temperature of 80 °C. The O_2 concentrations in DMF were ~50 times higher than those of complexes, and they were calculated based on the partial pressure of DMF.[13, 14]

Identification of Dioxygenated Products

In a typical experiment, 10 mL of deaerated DMF solution of the flavonolate complexes [Cu(L)(fla)](ClO_4) **1**–**4** (1.0×10^{-3} M) was taken in a 50 mL RB flask tightly closed with a rubber septum. The reaction vessel was maintained at 80 °C under N_2 for several minutes. Continuous bubbling of N_2 was made using a balloon with a syringe. Then, the N_2 was replaced with dioxygen to start the reaction. Small samples of the reaction mixture were taken periodically (ca. every 5 min) using a syringe, and the time course of the reaction was followed by monitoring the absorption spectral changes at 430 nm.

Table S1. Structure refinement details for **2**

	2
Sum formula	$(C_{28}H_{30}CuN_3O_3)^+ \cdot (O_4Cl)^-$
Formula weight	619.54
Temperature (K)	123
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	*P*21/*n*
a(Å)	12.8840 (6)
b(Å)	15.2319 (8)
c(Å)	15.1533 (7)
α(°)	90
β(°)	113.908 (2)
γ(°)	90
Volume (Å3)	2718.6 (2)
Z	4
D_x (g.cm^{-3})	1.514
Reflections collected	7230
R indices (all data)	0.0564, wR_2 = 0.1606

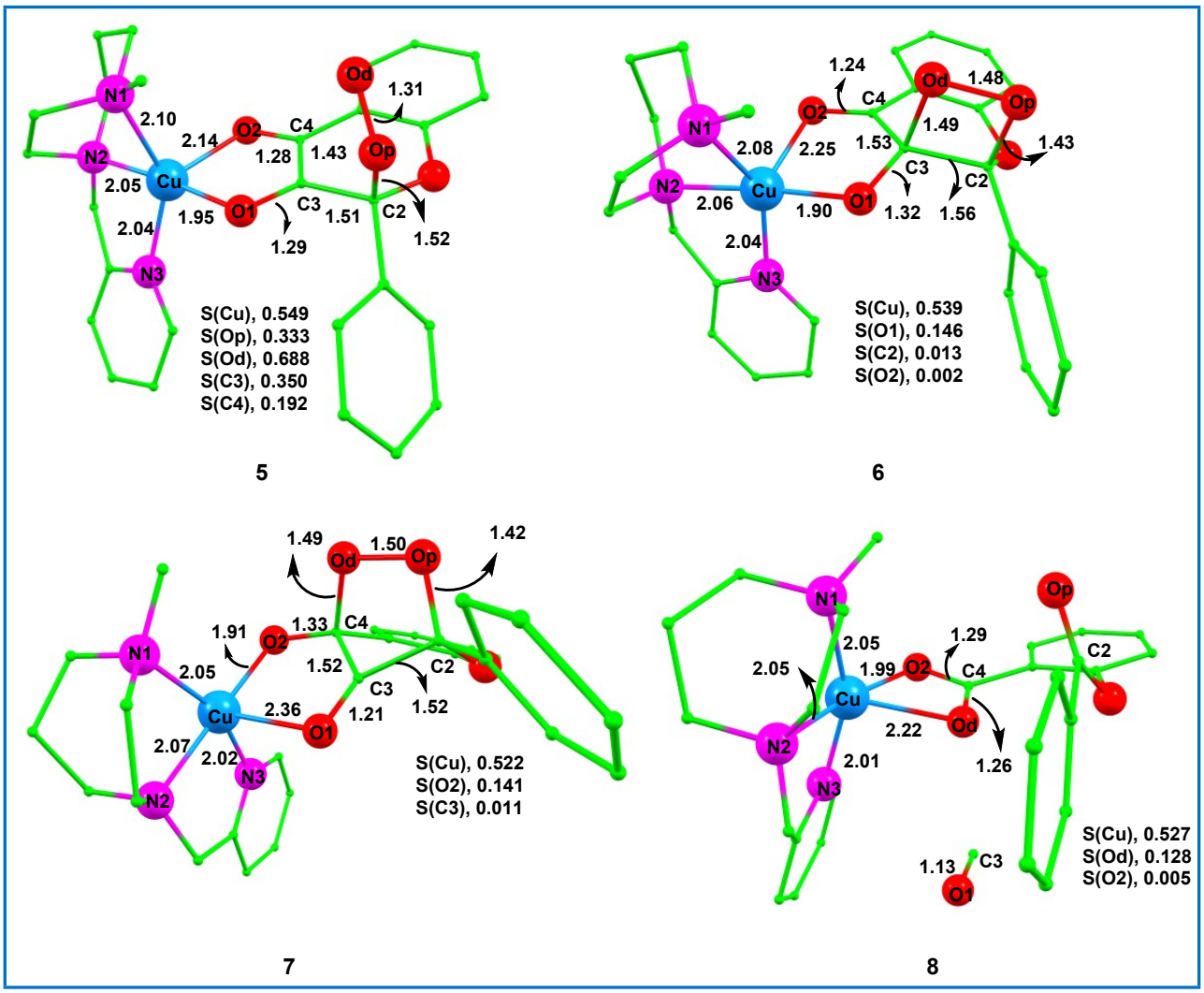


Figure S1. Optimized intermediates (**5**, **6**, **7** and **8**) involved in the $[Cu(L1)(fla)]^{+}$ **1**, mediated oxidative degradation of the flavonol. Key bond lengths (Å), angles (°) and spin densities are shown. H-atoms are omitted for clarity.

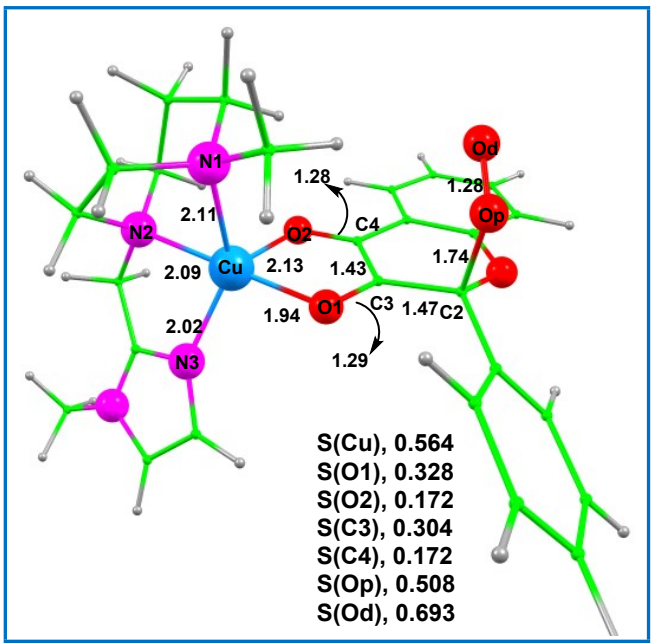


Figure S2. Optimized rate-determining transition state for $[Cu(L3)(fla)]^+$ **3.** Key bond lengths (Å), angles (°) and spin densities are shown.

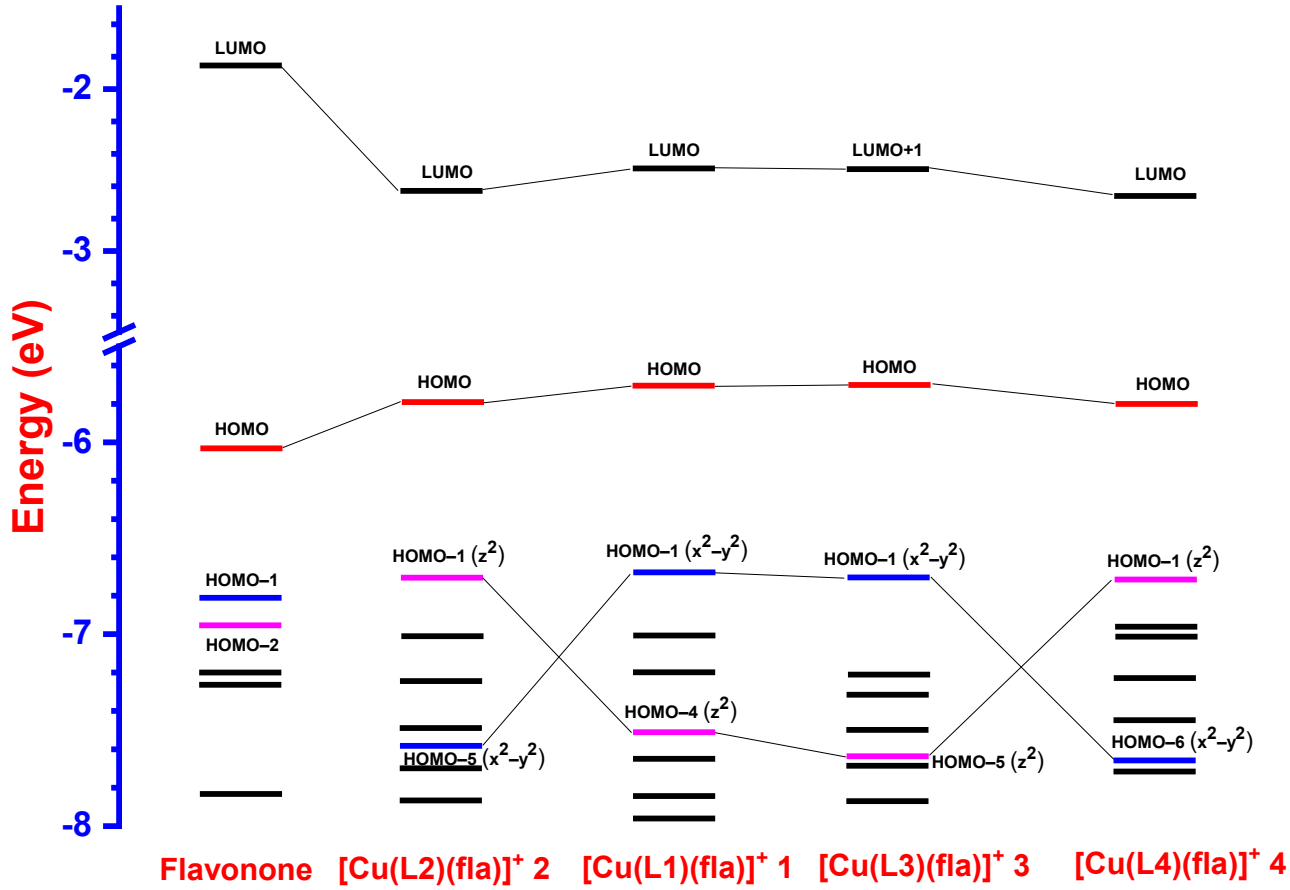


Figure S3. LUMO and HOMO energy profile diagram for the ligand 3-hydroxyflavone and complexes **1**–**4**.

Table S2. Computed bond angles [°] of complexes [Cu(L)(fla)](ClO_4) **1–4**.

Bond angles/°	**1**	**2**	**3**	**4**
N1–Cu–N2	78.211	78.705	78.404	78.755
N1–Cu–N3	137.848	125.977	119.479	128.690
N1–Cu–O1	100.177	97.589	97.387	98.427
N1–Cu–O2	102.575	135.809	140.652	130.508
N2– Cu–N3	82.239	80.261	78.222	80.738
N2–Cu–O1	174.576	173.293	170.573	173.640
N2–Cu–O2	102.082	94.665	92.928	94.491
N3–Cu–O1	95.808	106.396	111.109	105.341
N3–Cu–O2	117.935	94.934	95.456	97.472
O1–Cu–O2	83.311	84.074	85.001	82.973
τ	**0.61**	**0.62**	**0.57**	**0.75**
Torsion angles [°]	-11.57	-7.926	11.62	-21.77

Table S3. Computed HOMO and LUMO energies for the complexes **1**–**4**

MOs (eV)	**1**	**2**	**3**	**4**
HOMO	-5.741	-5.799	-5.727	-5.800
HOMO-1	-6.693 (x^2-y^2)	-6.765 (z^2)	-7.041 (x^2-y^2)	-6.785 (z^2)
HOMO-2	-7.036	-7.073	-7.204	-6.943
HOMO-3	-7.203	-7.226	-7.328	-7.069
HOMO-4	-7.519 (z^2)	-7.499	-7.589	-7.227
HOMO-5	-7.631	-7.595 (x^2-y^2)	-7.626 (z^2)	-7.468
HOMO-6	-7.843	-7.699	-7.664	-7.622 (x^2-y^2)
HOMO-7	-7.894	-7.840	-7.887	-7.696

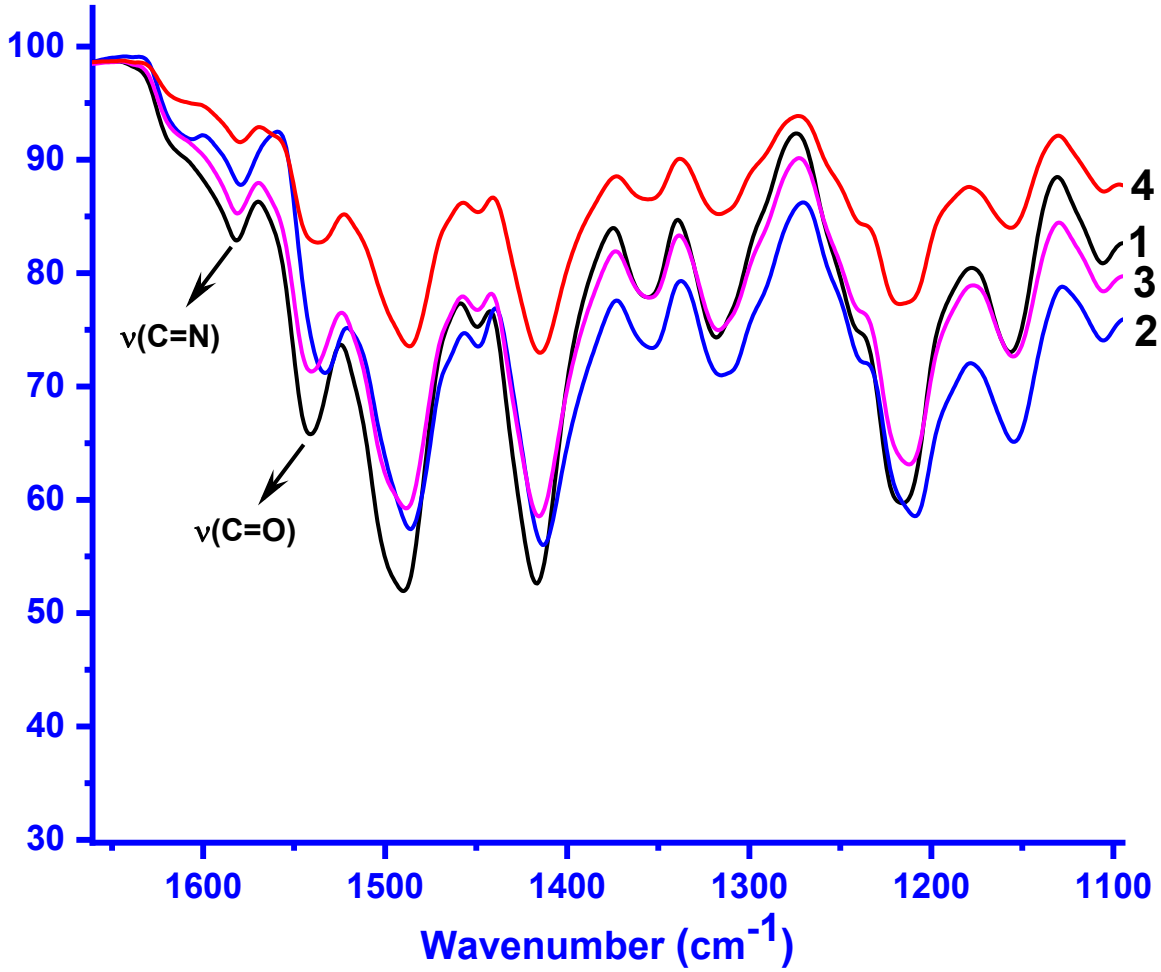


Figure S4. IR spectra of complexes **1**–**4**.

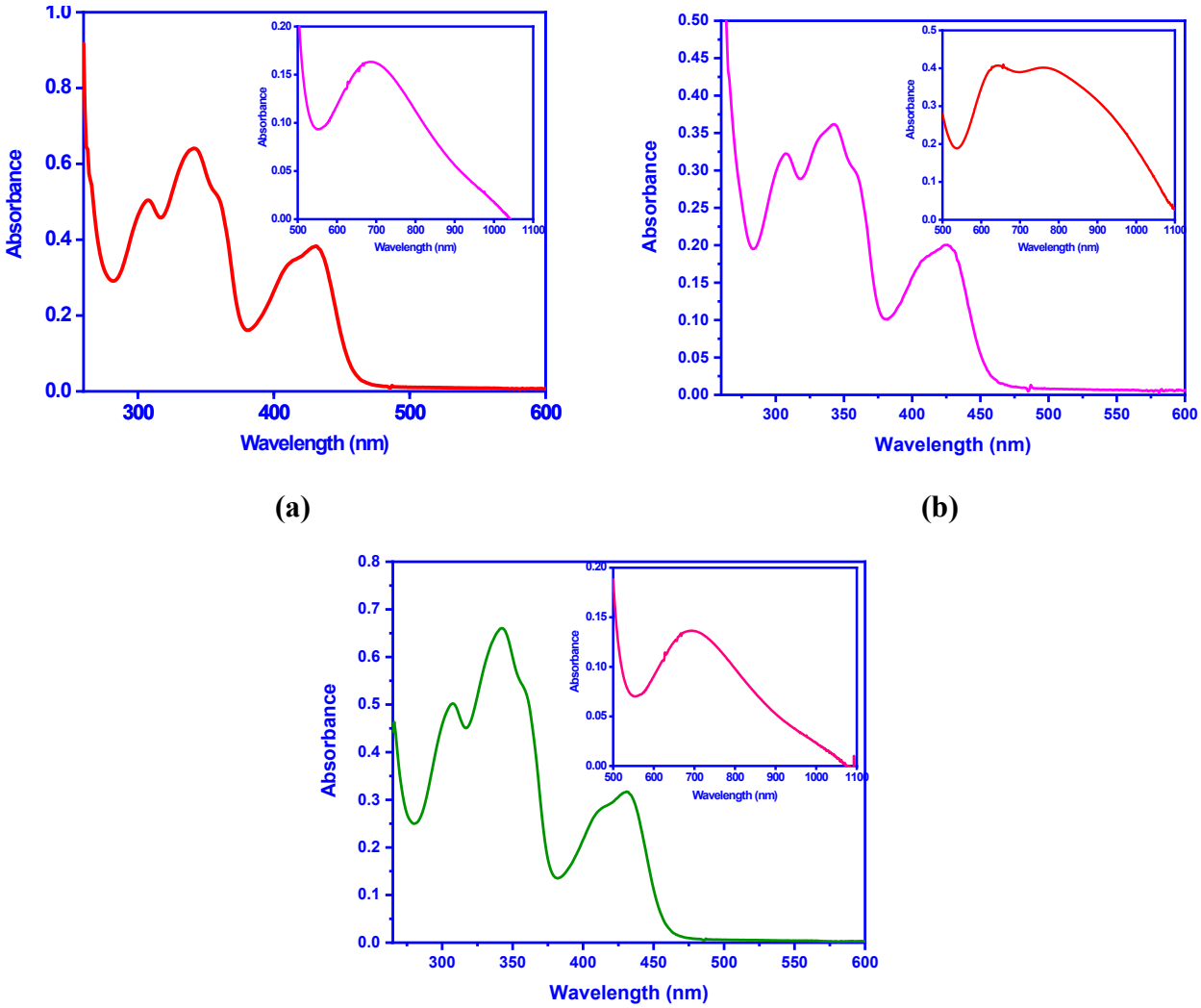


Figure S5. Electronic absorption spectra of [Cu(L1)(fla)](ClO_4) **1** (3.0×10^{-3} M, 3.3×10^{-5} M) (**a**), [Cu(L2)(fla)](ClO_4) **2** (3.0×10^{-3} M, 3.3×10^{-5} M) (**b**) and [Cu(L4)(fla)](ClO_4) **4** (3.0×10^{-3} M, 3.3×10^{-5} M) (**c**) in DMF solution at 25 ºC.

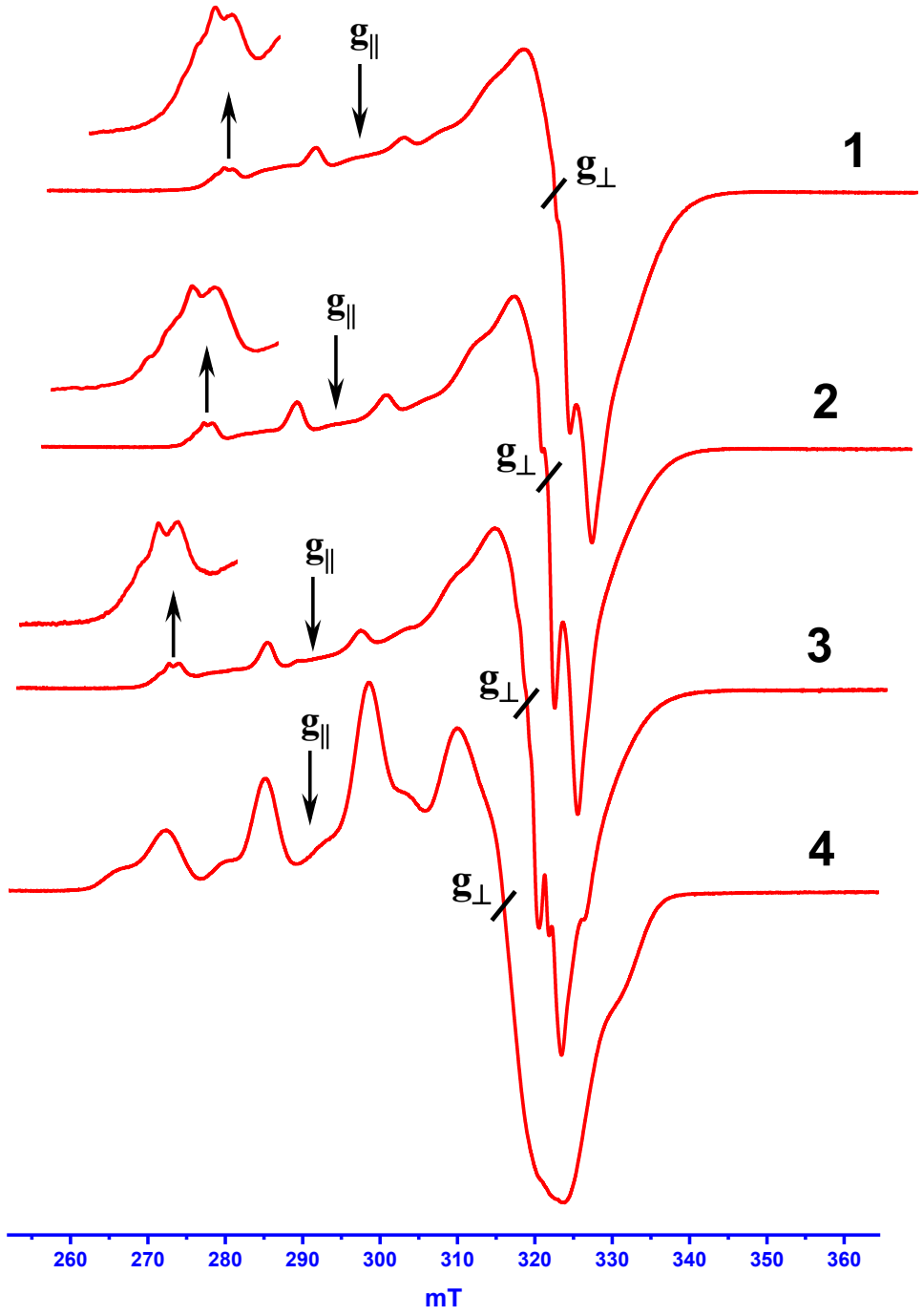


Figure S6. Frozen solution EPR spectra of Cu(II) complexes [Cu(L)(fla)](ClO_4) **1–4** in DMF solution (1 × 10^{-5} M) at 77 K. Microwave frequency: **1**, 9.16; **2**, 9.18; **3**, 9.16; **4**, 9.10 GHz.

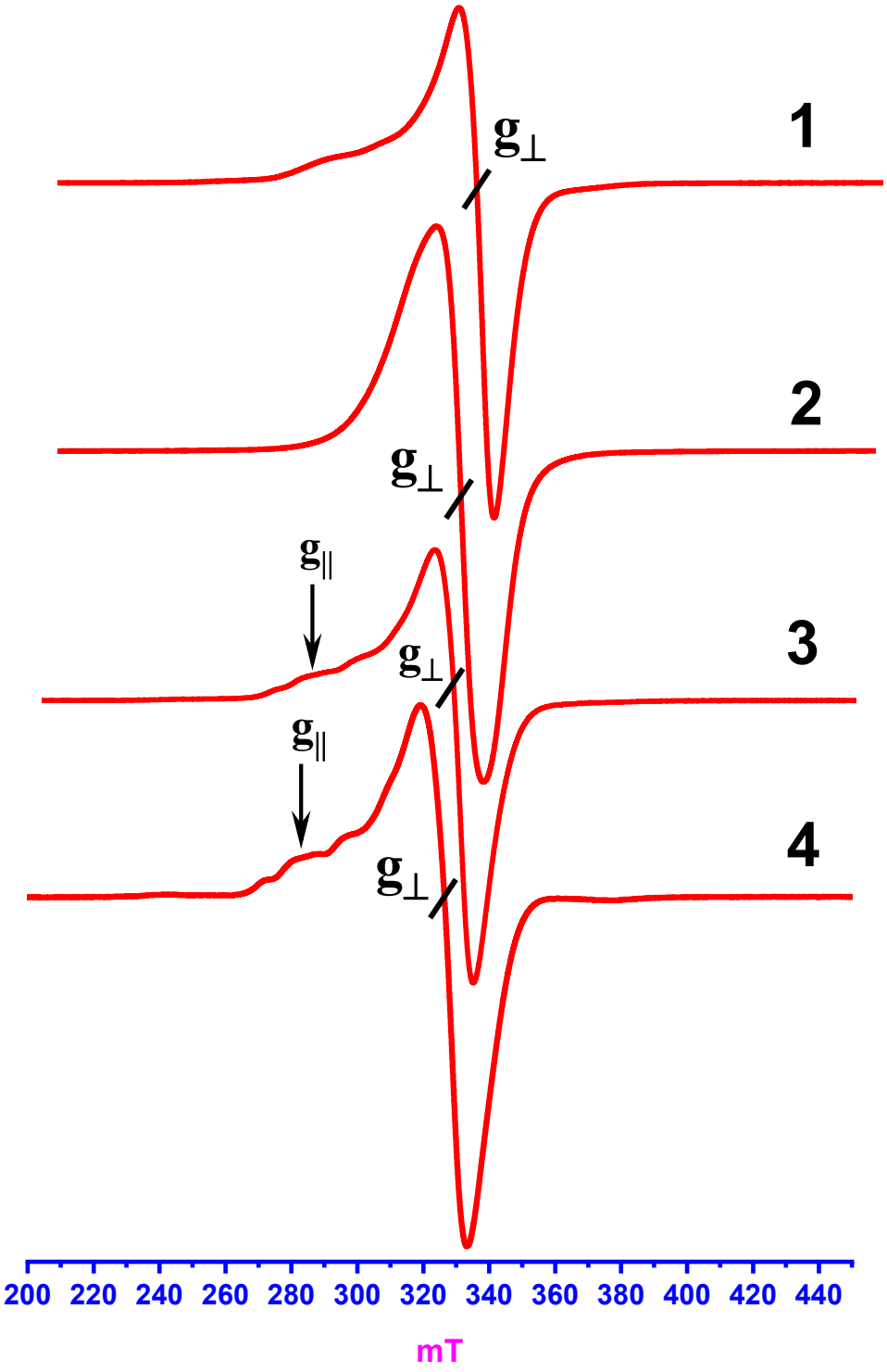


Figure S7. Polycrystalline EPR spectra of copper(II) complexes [Cu(L)(fla)](ClO_4) **1**–**4** at RT. Microwave frequency: 9.45 GHz.

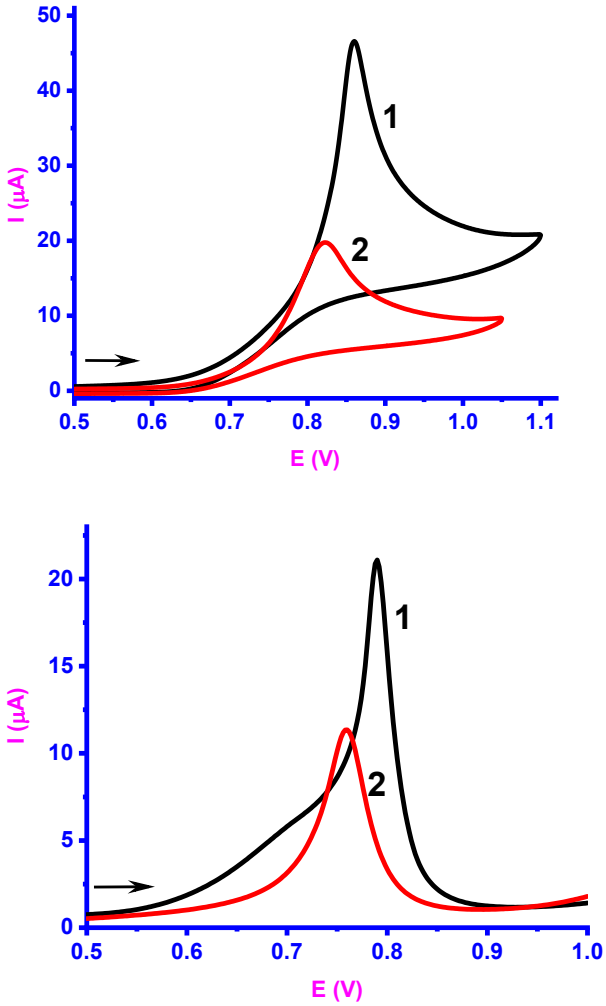


Figure S8. Cyclic voltammogram and DPV of complexes [Cu(L1/L2)(fla)](ClO_4) **1** and **2** (2.0×10^{-3} M) in DMF at 25 ºC. Conditions: supporting electrolyte, 0.1 M TBAP; Scan rate, CV, 50 mVs^{-1} and DPV, 2 mVs^{-1} for all complexes, reference electrode, Calomel electrode; working electrode, Glassy carbon; Counter electrode, platinum wire.

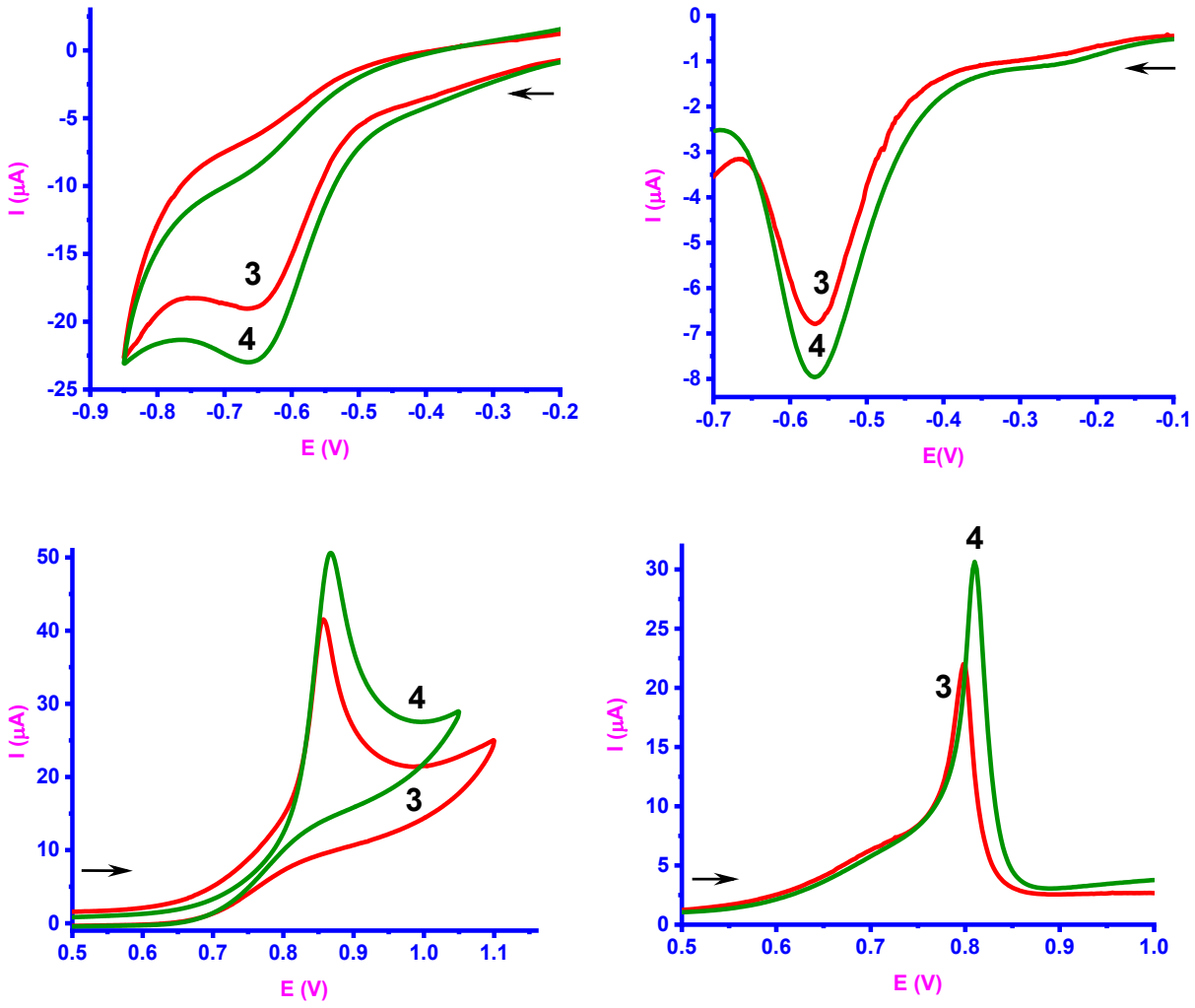
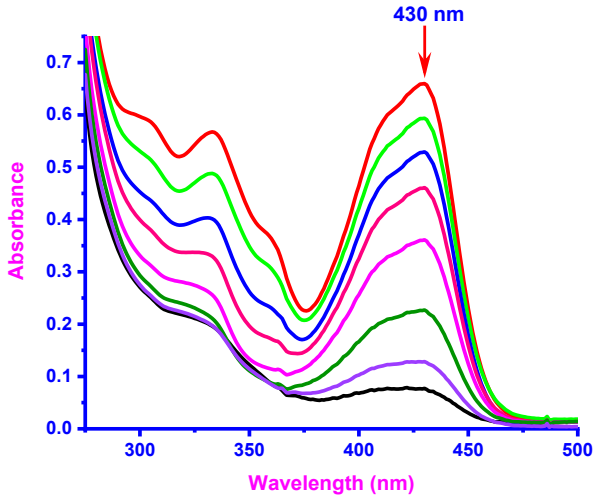
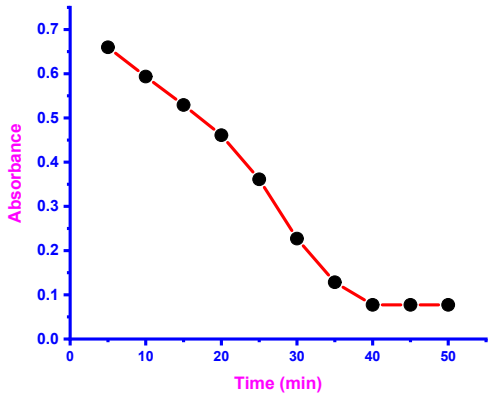


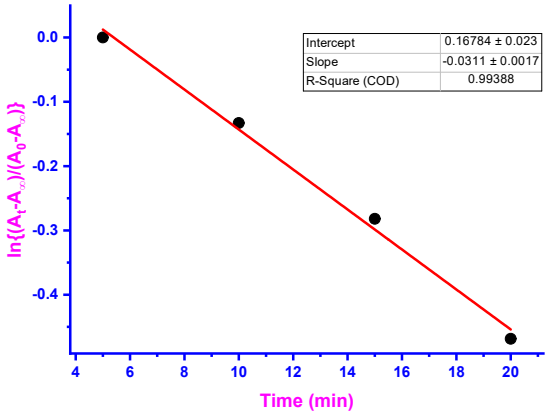
Figure S9. Cyclic voltammogram and DPV of complexes [Cu(L3/L4)(fla)](ClO_4) **3** and **4** (2.0×10^{-3} M) in DMF at 25 ºC. Conditions: supporting electrolyte, 0.1 M TBAP; Scan rate, CV, 50 mVs^{-1} and DPV, 2 mVs^{-1} for all complexes, reference electrode, Calomel electrode; working electrode, Glassy carbon; Counter electrode, platinum wire.



(a)

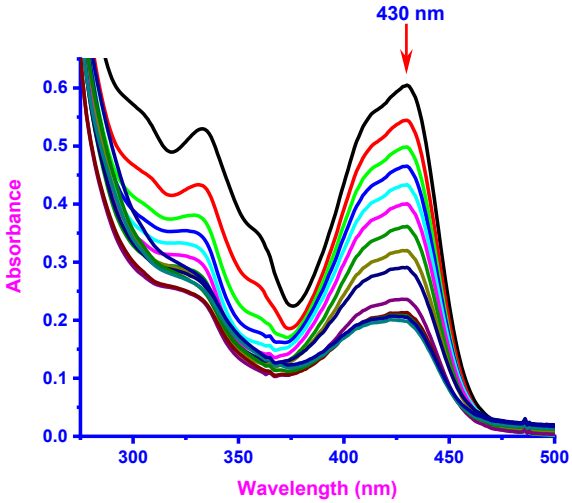


(b)

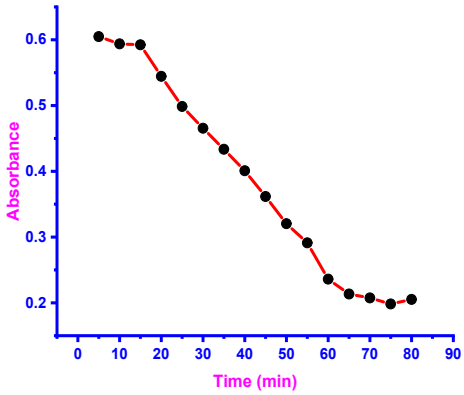


(c)

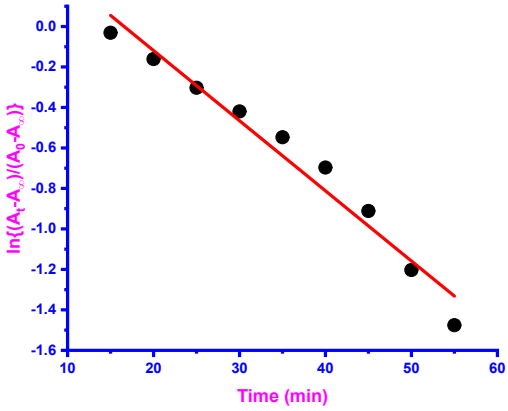
Figure S10. a) UV-Vis spectral changes observed in the presence of O_2 in DMF solution of [Cu(L1)(fla)](ClO_4) **1** (1×10^{-4}M) at 80 ºC, **b)** The time course of absorbance at 430 nm and **c)** Plot of [$\ln\{(A_t-A_\infty)/(A_0-A_\infty)\}$] vs time observed at 430 nm**.**



(a)

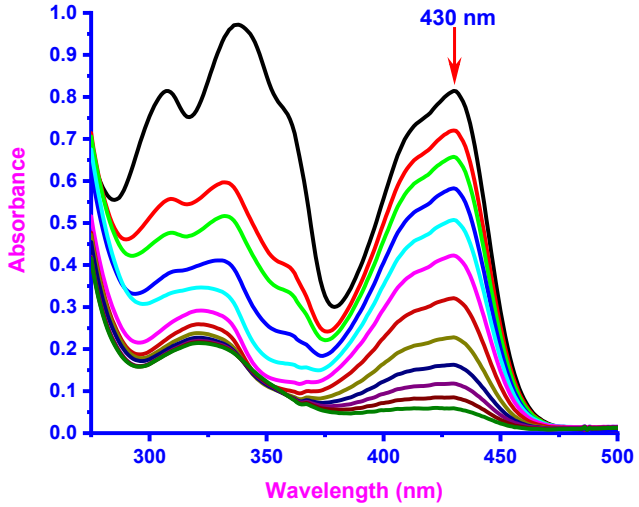


(b)

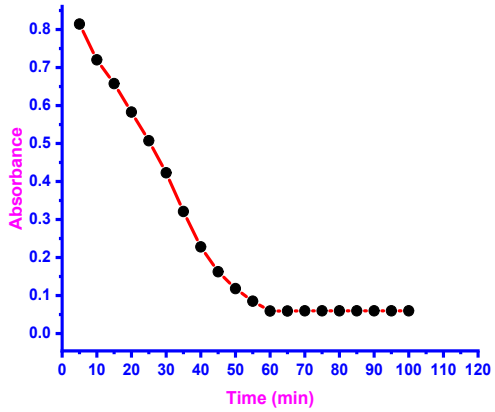


(c)

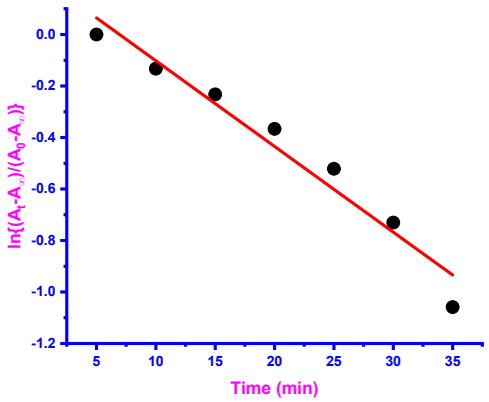
Figure S11. a) UV-Vis spectral changes observed in the presence of O_2 in DMF solution of [Cu(L2)(fla)](ClO_4) **2** (1×10^{-4}M) at 80 ºC, **b)** The time course of absorbance at 430 nm and **c)** Plot of [$\ln\{(A_t-A_\infty)/(A_0-A_\infty)\}$] vs time observed at 430 nm**.**



(c)

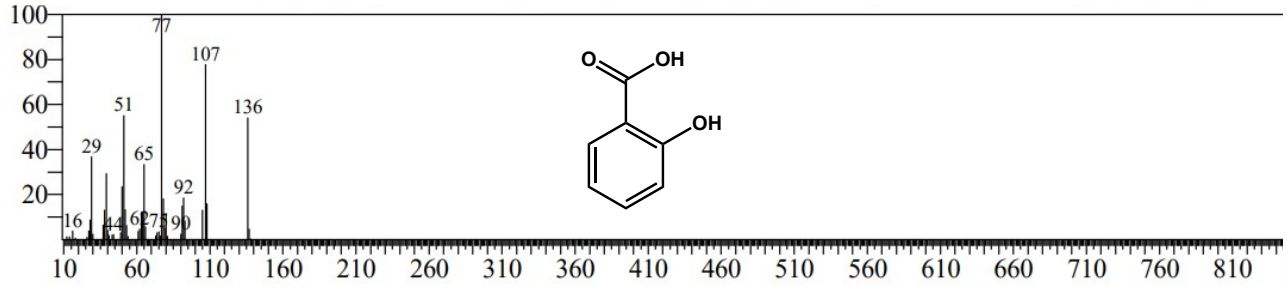


(b)

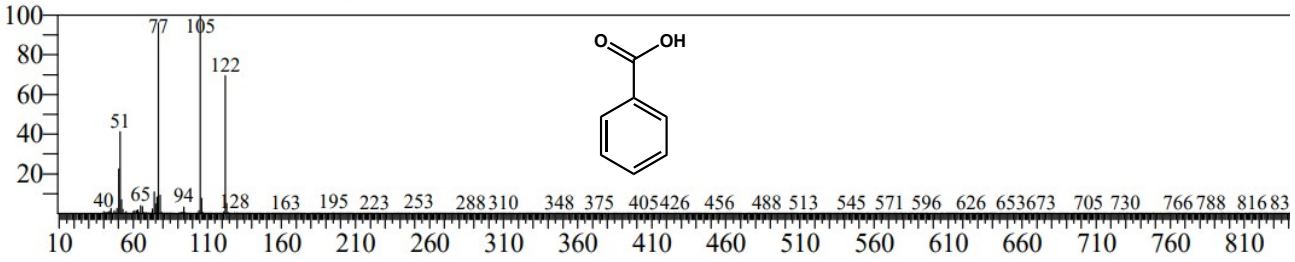


(c)

Figure S12. a) UV-Vis spectral changes observed in the presence of O_2 in DMF solution of [Cu(L4)(fla)](ClO_4) **4** (1×10^{-4}M) at 80 ºC, **b)** The time course of absorbance at 430 nm and **c)** Plot of [$\ln\{(A_t-A_\infty)/(A_0-A_\infty)\}$] vs time observed at 430 nm**.**



(**a**)



(**b**)

Figure S13. GC-MS product analysis of the products of reactions between dioxygen ES model complexes $[Cu(L)(fla)]^+$ **1–4** in DMF at 80 ºC to give rise to (**a**) salicylic acid [*m/z* (neg.): 136 (M − 2H)$^-$], (**b**) benzoic acid [*m/z*: 122 (M)], as ultimate products (**Scheme 2**).

Table S4. GC-MS analysis of the products of reaction between dioxygen and ES model complexes [Cu(L)(fla)](ClO_4) **1–4** (1.0×10^{-3} M) in DMF solution at 80 ºC.

Complex	Yield (%)					Conversion (%)[a]
	o-benzoyl-salicylic acid	Salicylic acid	Benzoic acid	2-Hydroxy-*N*,*N*-dimethyl-benzamide	*N*,*N*-Dimethyl-benzamide	
[Cu(L1)(fla)](ClO_4) **1**	13	33	28	2	12	88
[Cu(L2)(fla)](ClO_4) **2**	32	12	14	-	4	62
[Cu(L3)(fla)](ClO_4) **3**	11	47	32	-	3	93
[Cu(L4)(fla)](ClO_4) **4**	26	8	21	4	-	59

[a]Conversion based on complex concentration

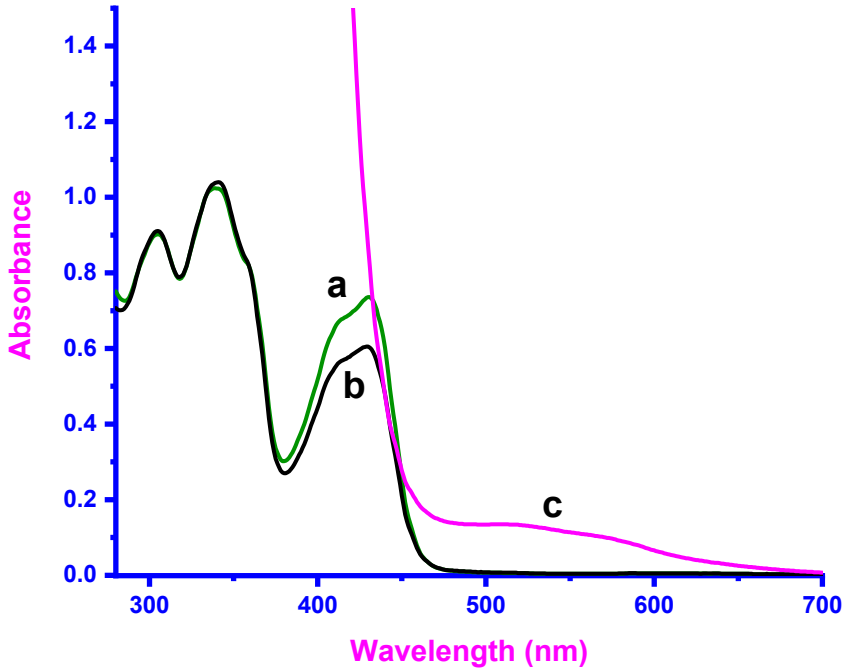


Figure S14. Spectral traces for (**a**) **3** in DMF (1×10^{-4} M) under N_2 at 80 °C, (**b**) **3** in the presence of O_2 and (**c**) **3** treated with O_2 and then NBT^{2+} (1.2×10^{-4} M).

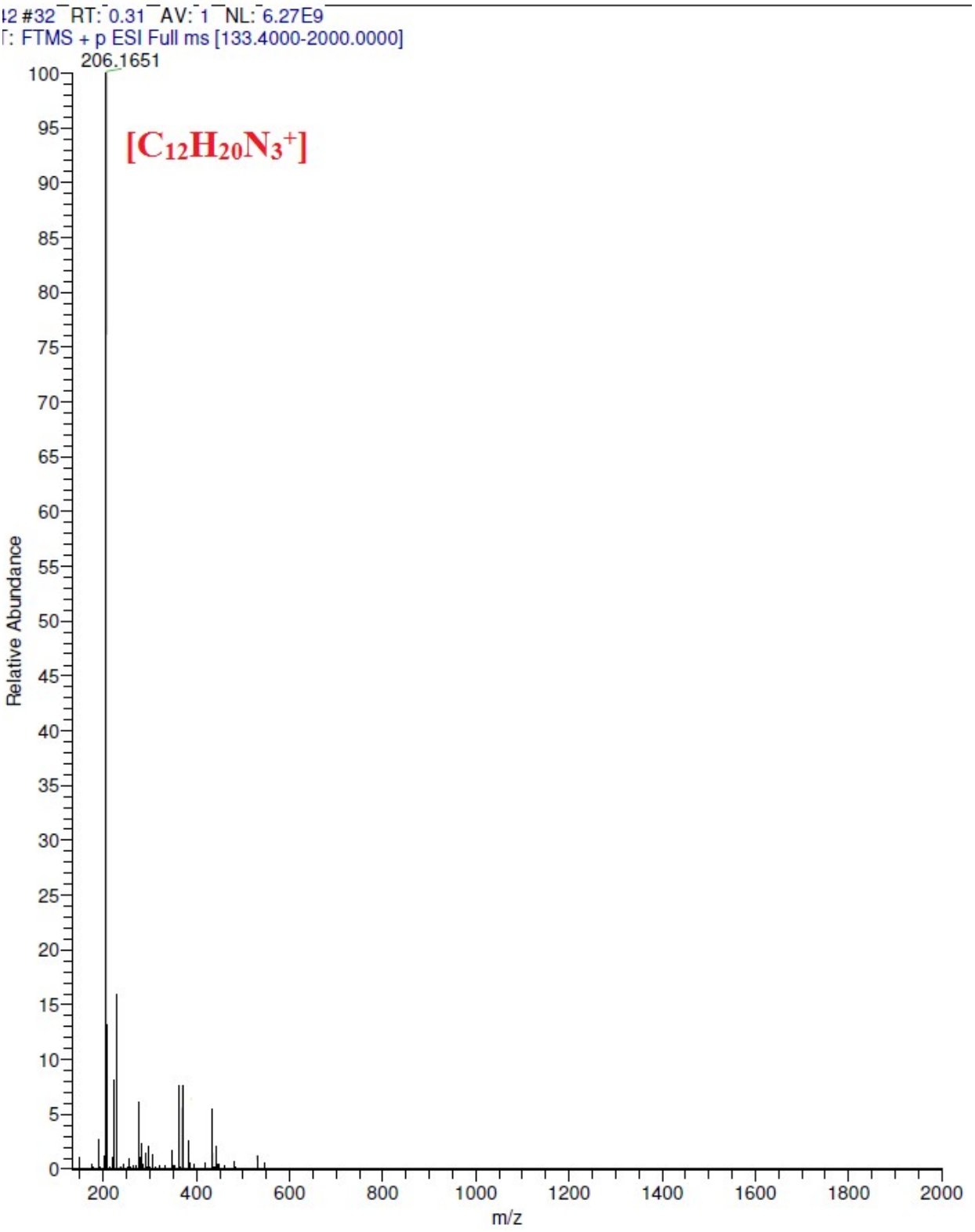


Fig. S15. High Resolution Mass Spectra of **L1** in methanol solution (1×10^{-3} M) at 25 °C.

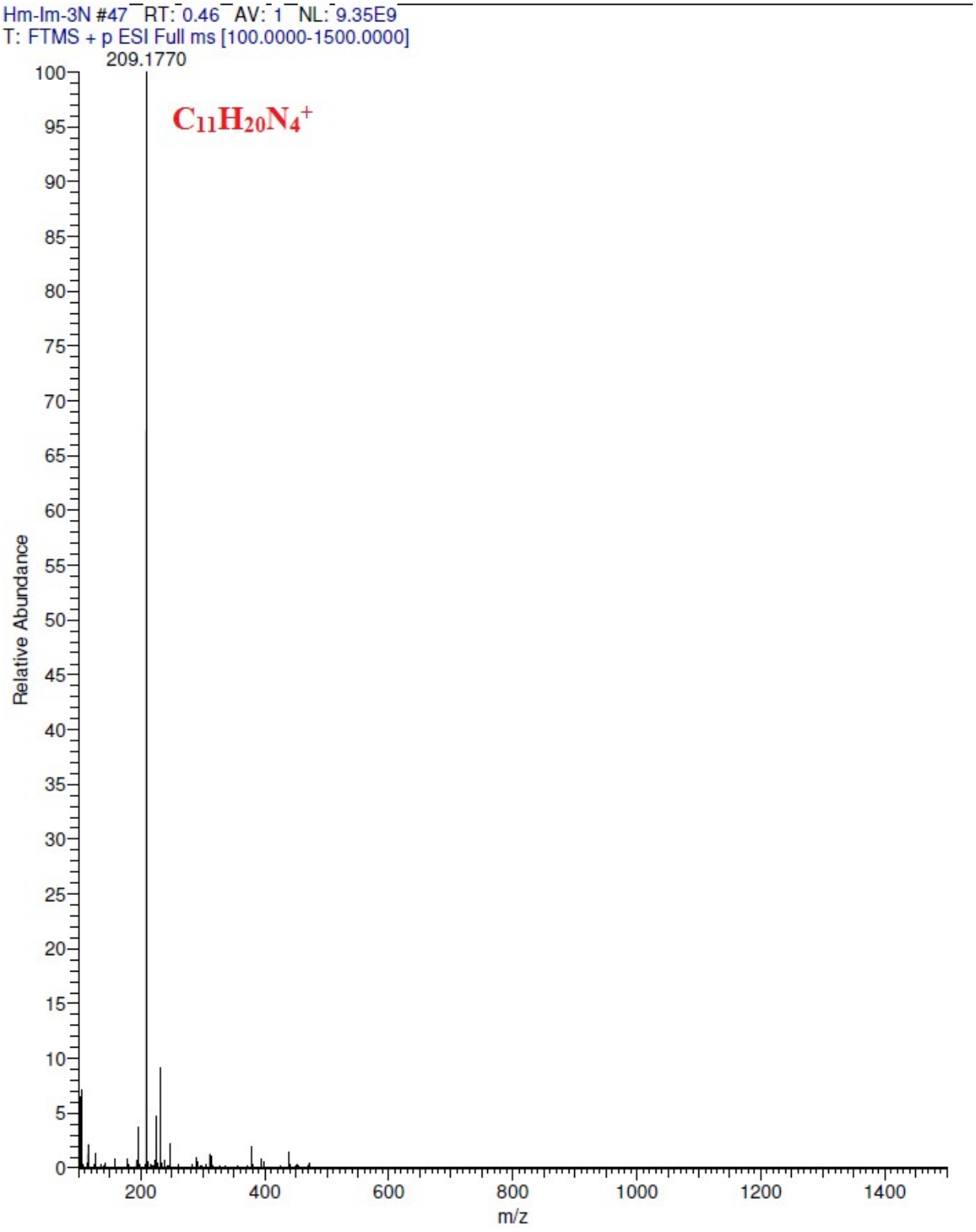


Fig. S16. High Resolution Mass Spectra of **L3** in methanol solution (1×10^{-3} M) at 25 °C.

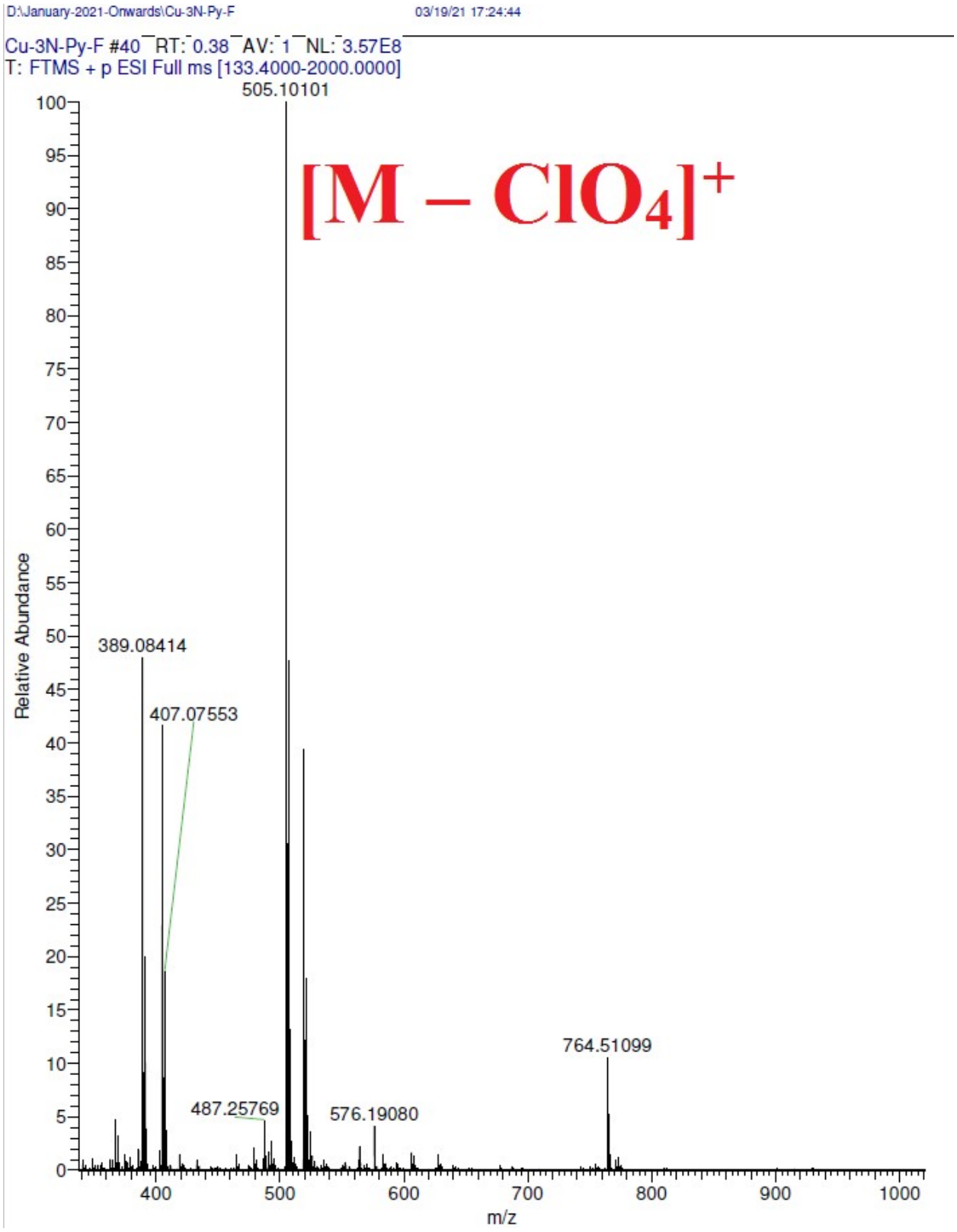


Figure S17. High Resolution Mass Spectra of [Cu(L1)(fla)](ClO_4) **1** in DMF solution (1 ×10^{-3} M) and at 25 °C.

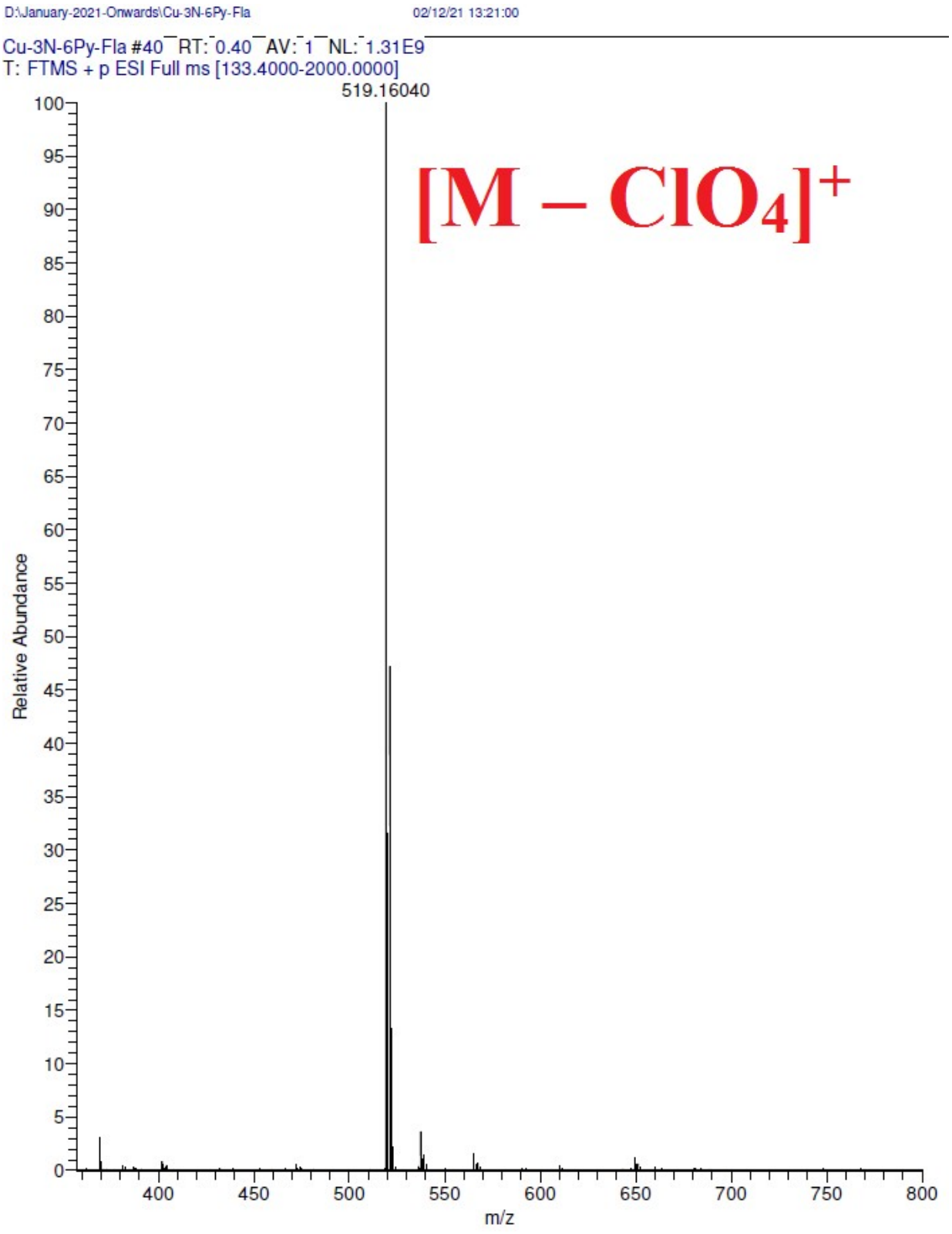


Figure S18. High Resolution Mass Spectra of [Cu(L2)(fla)](ClO_4) **2** in DMF solution (1 ×10^{-3} M) and at 25 °C.

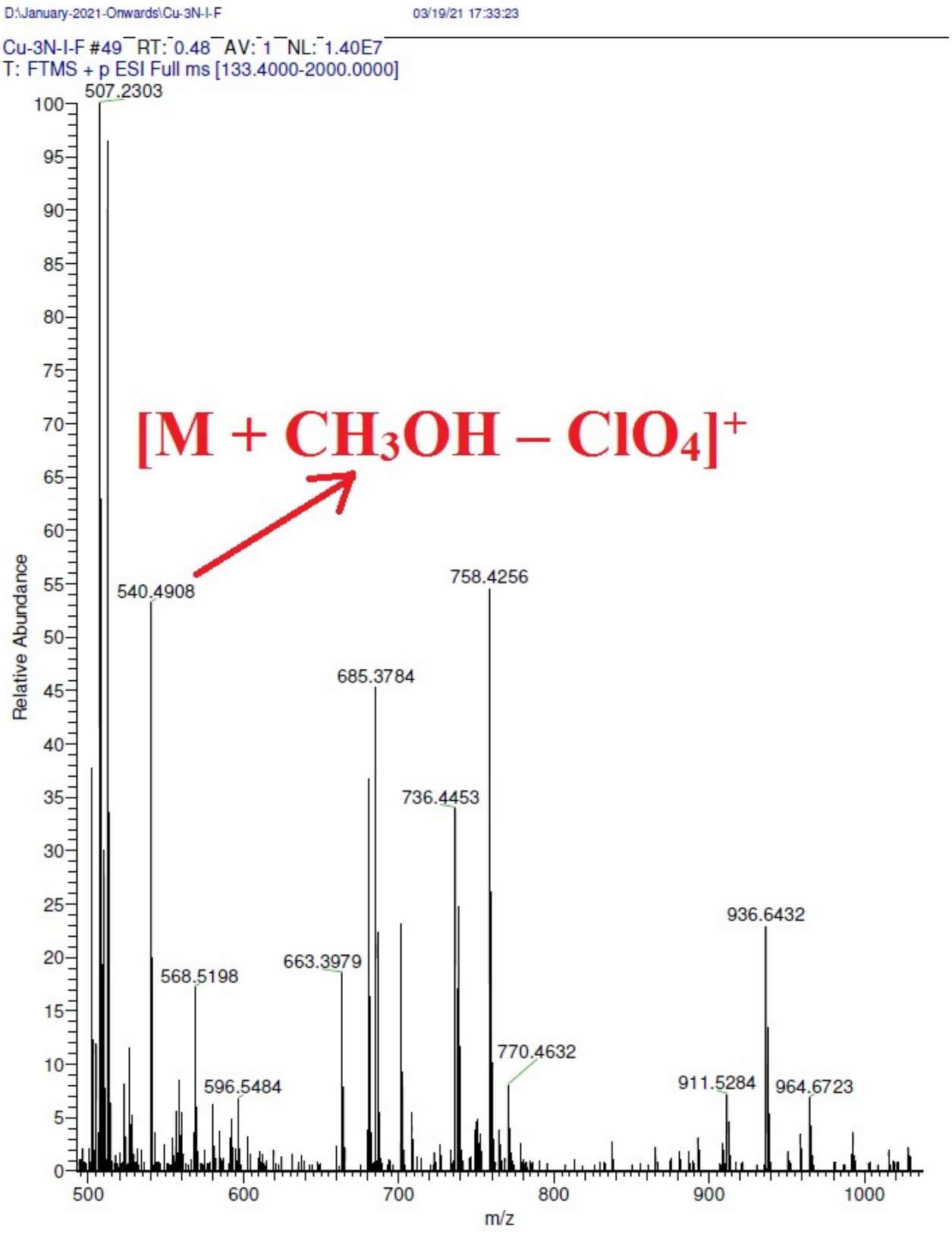


Figure S19. High Resolution Mass Spectra of [Cu(L3)(fla)](ClO_4) **3** in DMF solution (1 ×10^{-3} M) and at 25 °C.

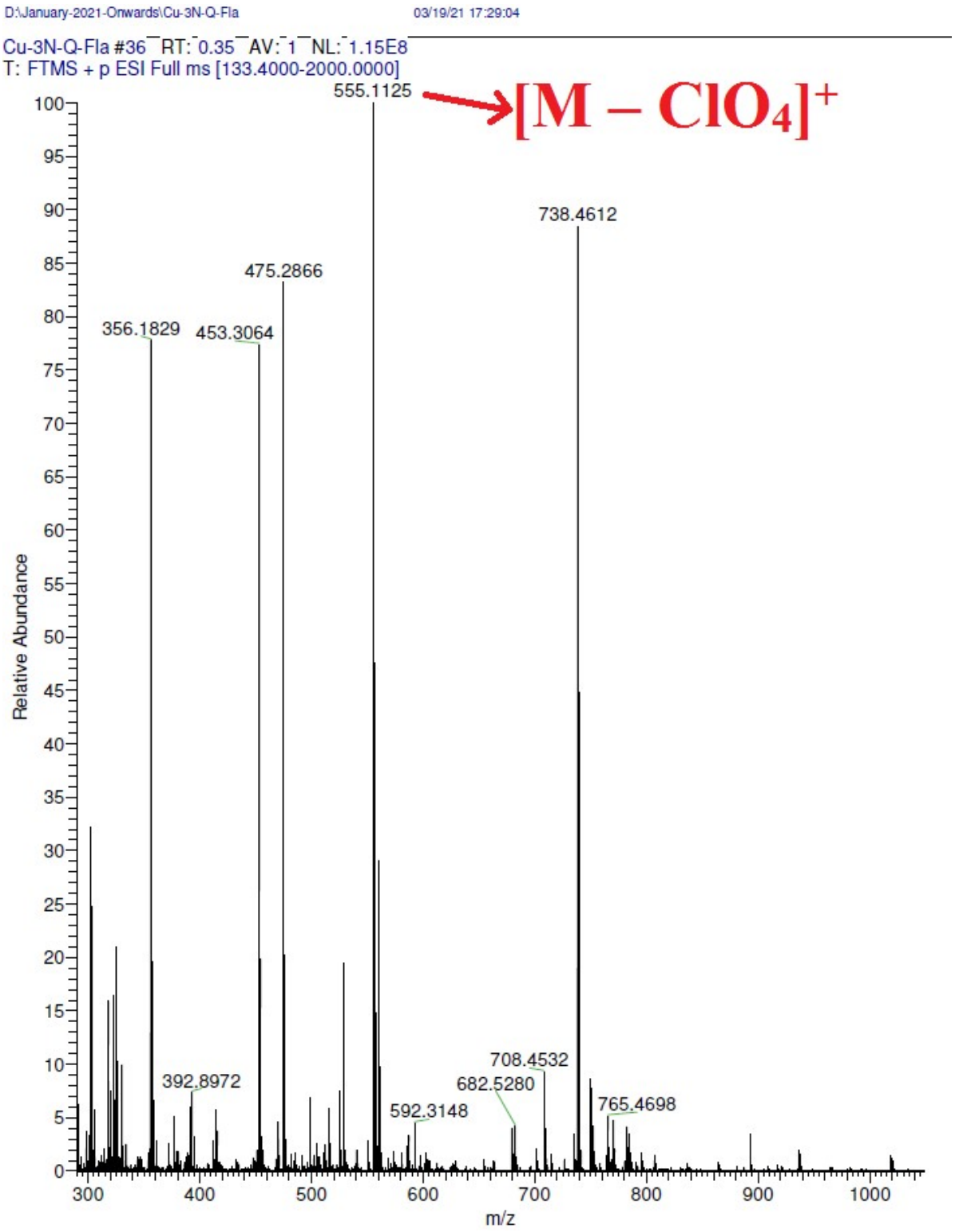


Figure S20. High Resolution Mass Spectra of [Cu(L4)(fla)](ClO_4) **4** in DMF solution (1 ×10^{-3} M) and at 25 °C.

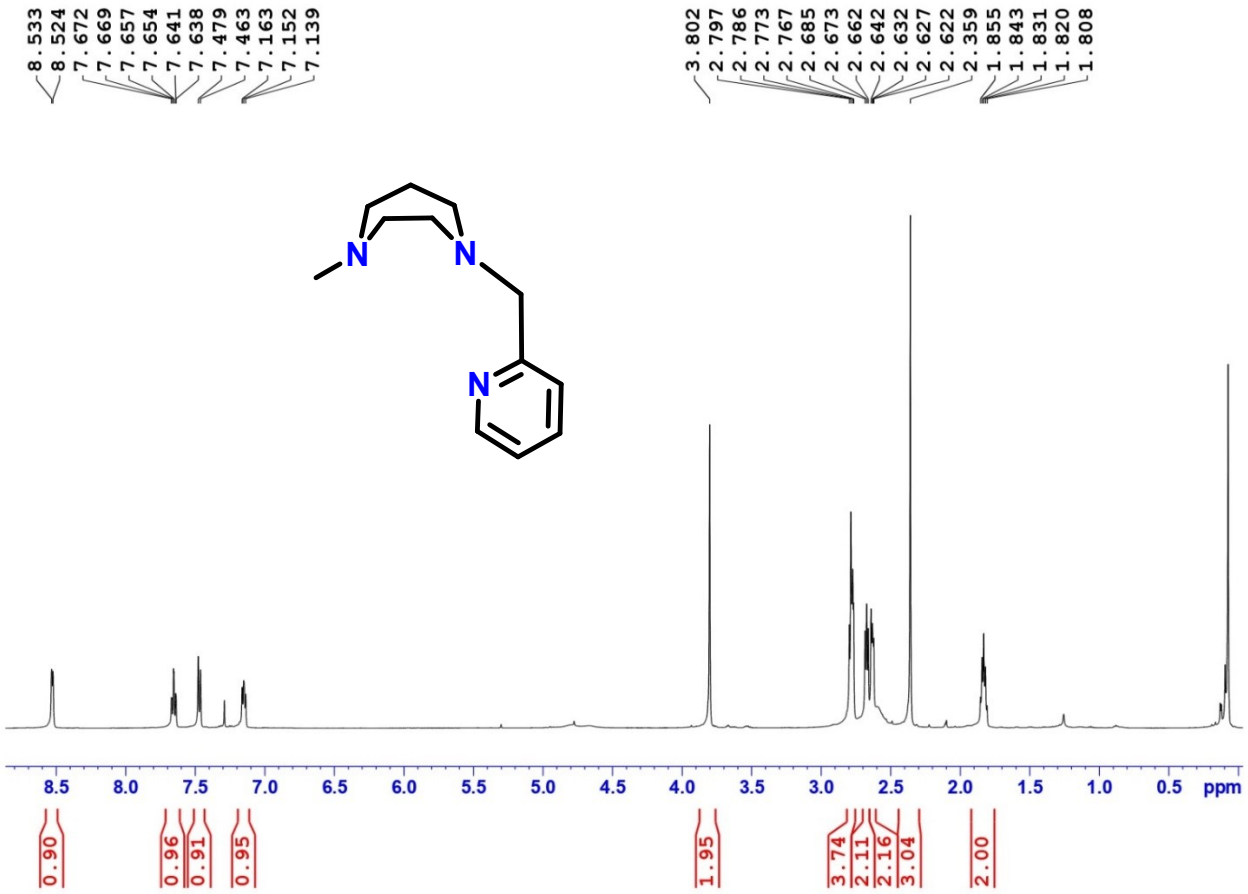


Figure S21. ^{1}H NMR spectra for the ligand **L1**.

Cartesian Coordinates

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Multiplicity= 4
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Enthalpy 0K = 0.515263
Enthalpy 298 K = 0.549084
Free Energy 298 K = 0.446421

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Enthalpy 298 K = 0.547338
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H	-4.246937000	4.336067000	-1.247917000
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H	0.529532000	2.714993000	-0.224692000
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Multiplicity= 4
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Enthalpy 298 K = 0.547633
Free Energy 298 K = 0.452804

Cu	1.471048000	-0.085574000	0.203209000
O	-0.290363000	0.612650000	0.663597000
O	0.328729000	-1.690742000	-0.645295000
O	-3.544620000	-0.341487000	-0.475678000
N	2.098306000	-0.772949000	2.075670000
N	3.381793000	-0.700651000	-0.238463000
N	1.914429000	1.402405000	-1.129219000
C	1.171360000	-0.335528000	3.143162000
H	1.536327000	-0.643259000	4.131491000
H	0.189943000	-0.768548000	2.953549000
H	1.066870000	0.749841000	3.106025000
C	2.131055000	-2.265569000	1.994354000
H	1.173111000	-2.575787000	1.569983000
H	2.213575000	-2.677373000	3.009625000
C	3.449676000	-0.175596000	2.223778000
H	3.309466000	0.838918000	2.601430000
H	4.035932000	-0.722681000	2.972607000
C	4.196666000	-0.105139000	0.856255000
H	4.361157000	0.941832000	0.593249000
H	5.178033000	-0.592475000	0.902212000
C	3.292934000	-2.797508000	1.150295000
H	4.237248000	-2.673669000	1.690527000
H	3.158899000	-3.877714000	1.036822000
C	3.409550000	-2.195971000	-0.252061000
H	2.570676000	-2.513376000	-0.875614000
H	4.347431000	-2.533744000	-0.713859000
C	3.719611000	-0.143445000	-1.571375000
H	3.314049000	-0.833519000	-2.319168000
H	4.805947000	-0.099639000	-1.719539000
C	3.073327000	1.210739000	-1.787206000
C	3.579721000	2.176128000	-2.652747000

H	4.519921000	2.009962000	-3.168233000
C	2.850045000	3.351963000	-2.844092000
H	3.222388000	4.119415000	-3.515284000
C	1.643932000	3.532704000	-2.164687000
H	1.054091000	4.433342000	-2.291735000
C	1.206987000	2.529696000	-1.304004000
C	-1.221832000	-0.152910000	0.200490000
C	-0.900532000	-1.360934000	-0.497165000
C	-2.005999000	-2.151267000	-1.008519000
C	-3.303219000	-1.604925000	-0.970789000
C	-4.391801000	-2.297431000	-1.491703000
H	-5.375461000	-1.843715000	-1.446463000
C	-4.186521000	-3.557657000	-2.050544000
H	-5.033759000	-4.105321000	-2.451086000
C	-2.903171000	-4.124413000	-2.094204000
H	-2.759326000	-5.107570000	-2.529852000
C	-1.821762000	-3.423250000	-1.580730000
H	-0.816489000	-3.829767000	-1.608142000
C	-2.664079000	0.198480000	0.456967000
C	-2.918529000	1.675125000	0.612331000
C	-2.509472000	2.323780000	1.784096000
H	-2.067571000	1.748076000	2.589313000
C	-2.686242000	3.699843000	1.913349000
H	-2.379972000	4.198614000	2.827879000
C	-3.268151000	4.433387000	0.875520000
H	-3.411807000	5.504526000	0.981358000
C	-3.675831000	3.785359000	-0.291950000
H	-4.138127000	4.349695000	-1.096142000
C	-3.501943000	2.406786000	-0.427011000
H	-3.824553000	1.897155000	-1.327840000
H	0.286524000	2.595420000	-0.732049000
O	-2.116723000	-0.956659000	2.503858000
O	-3.100931000	-0.474176000	1.784657000

6

Charge= +1
Multiplicity= 2
SCF Energy (B3LYP-D3) = -1782.16558685
Enthalpy 0K = 0.518328
Enthalpy 298 K = 0.549671
Free Energy 298 K = 0.455800

Cu	1.455275000	-0.108086000	0.226172000

O	-0.245017000	0.478485000	0.851436000
O	0.215215000	-1.834078000	-0.529617000
O	-3.539517000	-0.268531000	-0.326877000
N	2.306901000	-0.823252000	1.988872000
N	3.344226000	-0.600568000	-0.447900000
N	1.606932000	1.352005000	-1.190854000
C	1.480037000	-0.476864000	3.168562000
H	1.997634000	-0.746618000	4.098104000
H	0.527658000	-1.002194000	3.103248000
H	1.261066000	0.591013000	3.151456000
C	2.444172000	-2.305472000	1.865184000
H	1.469895000	-2.683835000	1.546035000
H	2.670892000	-2.728734000	2.853516000
C	3.619625000	-0.126304000	2.011445000
H	3.441477000	0.868087000	2.424795000
H	4.317068000	-0.638529000	2.685974000
C	4.221594000	0.024062000	0.579067000
H	4.288366000	1.085623000	0.331318000
H	5.234114000	-0.393306000	0.518107000
C	3.541331000	-2.730100000	0.884867000
H	4.527051000	-2.547787000	1.325214000
H	3.475075000	-3.814649000	0.753574000
C	3.465220000	-2.089922000	-0.503139000
H	2.586827000	-2.451252000	-1.044235000
H	4.365608000	-2.359915000	-1.072014000
C	3.519817000	0.002602000	-1.792802000
H	3.133054000	-0.717427000	-2.522189000
H	4.581136000	0.159428000	-2.022905000
C	2.722950000	1.284755000	-1.939825000
C	3.054795000	2.301370000	-2.830766000
H	3.962864000	2.237796000	-3.421380000
C	2.192755000	3.395191000	-2.947577000
H	2.428559000	4.200741000	-3.635897000
C	1.033264000	3.445226000	-2.171856000
H	0.343405000	4.278992000	-2.236960000
C	0.773101000	2.399297000	-1.290599000
C	-1.232337000	-0.390454000	0.717889000
C	-0.965497000	-1.520001000	-0.286195000
C	-2.116269000	-2.178730000	-0.863891000
C	-3.369280000	-1.526769000	-0.831672000
C	-4.483325000	-2.119833000	-1.427357000
H	-5.431866000	-1.596052000	-1.394548000
C	-4.350629000	-3.360463000	-2.042662000
H	-5.222959000	-3.822361000	-2.494930000

C	-3.111250000	-4.022234000	-2.086360000
H	-3.027644000	-4.990128000	-2.568601000
C	-2.002922000	-3.427523000	-1.508819000
H	-1.029293000	-3.905941000	-1.525925000
C	-2.692157000	0.173275000	0.712564000
C	-2.800602000	1.666443000	0.814700000
C	-2.624421000	2.286865000	2.054690000
H	-2.501335000	1.673369000	2.940007000
C	-2.616224000	3.679182000	2.140551000
H	-2.492838000	4.158513000	3.106932000
C	-2.769469000	4.454975000	0.989100000
H	-2.765077000	5.538696000	1.058920000
C	-2.941284000	3.834558000	-0.251541000
H	-3.079119000	4.434251000	-1.146726000
C	-2.958702000	2.441949000	-0.340767000
H	-3.108371000	1.954768000	-1.298597000
H	-0.097893000	2.364380000	-0.642758000
O	-1.598070000	-1.113902000	1.972840000
O	-2.966423000	-0.537000000	1.930208000

TS3

Charge= +1
Multiplicity= 2
SCF Energy (B3LYP-D3) = -1782.13880935
Enthalpy 0K = 0.517186
Enthalpy 298 K = 0.548007
Free Energy 298 K = 0.456365

Cu	1.456000000	-0.208550000	-0.115559000
O	-0.425874000	-0.833855000	0.451359000
O	0.430645000	1.494240000	-0.781798000
O	-3.374655000	0.843771000	0.636129000
N	1.611691000	-1.358251000	-1.864540000
N	3.391515000	0.188591000	-0.666168000
N	2.227574000	-0.128245000	1.766378000
C	0.471504000	-2.292330000	-2.008572000
H	0.634722000	-2.982290000	-2.846243000
H	-0.426008000	-1.700403000	-2.189953000
H	0.336921000	-2.854910000	-1.083542000
C	1.645706000	-0.423708000	-3.033023000
H	0.794836000	0.248549000	-2.912324000
H	1.507089000	-1.006831000	-3.953602000
C	2.898959000	-2.071298000	-1.657136000

H	2.686832000	-2.931479000	-1.018668000
H	3.282737000	-2.458261000	-2.609429000
C	3.950192000	-1.162766000	-0.948716000
H	4.214058000	-1.604369000	0.014494000
H	4.872873000	-1.071789000	-1.533822000
C	2.952695000	0.362939000	-3.137538000
H	3.764577000	-0.288003000	-3.479146000
H	2.828518000	1.115767000	-3.922024000
C	3.366203000	1.092500000	-1.860199000
H	2.654879000	1.888599000	-1.627278000
H	4.365714000	1.527453000	-1.995594000
C	4.034706000	0.852797000	0.493038000
H	3.783443000	1.917205000	0.431971000
H	5.127407000	0.768897000	0.440728000
C	3.497758000	0.321227000	1.804946000
C	4.219137000	0.349816000	2.994944000
H	5.243528000	0.707190000	3.003210000
C	3.597111000	-0.083162000	4.167779000
H	4.138053000	-0.068398000	5.108582000
C	2.278416000	-0.538037000	4.117726000
H	1.765518000	-0.882170000	5.008564000
C	1.624654000	-0.550566000	2.889529000
C	-1.236749000	0.003492000	0.039566000
C	-0.833948000	1.309075000	-0.595534000
C	-1.748516000	2.437313000	-0.251196000
C	-2.980316000	2.147351000	0.356115000
C	-3.845347000	3.168178000	0.736212000
H	-4.792103000	2.913302000	1.199320000
C	-3.472650000	4.493221000	0.504445000
H	-4.145736000	5.292518000	0.798784000
C	-2.250112000	4.797553000	-0.103693000
H	-1.971959000	5.831233000	-0.280805000
C	-1.390330000	3.766983000	-0.478052000
H	-0.428440000	3.967371000	-0.938196000
C	-2.748504000	-0.167716000	-0.144838000
C	-3.324876000	-1.511674000	0.200781000
C	-3.299562000	-2.533127000	-0.755084000
H	-2.942631000	-2.317213000	-1.756191000
C	-3.765478000	-3.805479000	-0.424302000
H	-3.758547000	-4.593364000	-1.171388000
C	-4.253740000	-4.060739000	0.859013000
H	-4.621211000	-5.050227000	1.113776000
C	-4.279651000	-3.039230000	1.811707000
H	-4.669389000	-3.232473000	2.806480000

C	-3.815064000	-1.764929000	1.486957000
H	-3.845988000	-0.964203000	2.217405000
H	0.604590000	-0.900182000	2.771816000
O	-1.475431000	0.521435000	-1.932779000
O	-2.854303000	0.133870000	-1.533494000

7

Charge= +1
Multiplicity= 2
SCF Energy (B3LYP-D3) = -1782.15407116
Enthalpy 0K = 0.517820
Enthalpy 298 K = 0.549148
Free Energy 298 K = 0.455846

Cu	1.596047000	-0.203744000	-0.461326000
O	-0.426424000	-0.746102000	0.647330000
O	0.436546000	0.805665000	-1.611066000
O	-3.178456000	1.052977000	0.412463000
N	1.780301000	-1.957103000	-1.525297000
N	2.825208000	-1.284227000	0.816832000
N	2.149861000	1.336427000	0.731844000
C	0.800938000	-2.059120000	-2.632941000
H	0.898079000	-3.025020000	-3.144326000
H	0.980224000	-1.242742000	-3.332150000
H	-0.208319000	-1.932476000	-2.245853000
C	3.171254000	-1.964385000	-2.079261000
H	3.316323000	-1.002491000	-2.582478000
H	3.244203000	-2.748187000	-2.845434000
C	1.562914000	-3.012848000	-0.500714000
H	0.483221000	-3.107283000	-0.378763000
H	1.947064000	-3.976176000	-0.858287000
C	2.181637000	-2.623535000	0.878127000
H	1.373250000	-2.555416000	1.605633000
H	2.893033000	-3.379077000	1.231174000
C	4.256578000	-2.209481000	-1.027294000
H	4.240773000	-3.259944000	-0.720724000
H	5.230126000	-2.056760000	-1.503429000
C	4.188157000	-1.313639000	0.211804000
H	4.452961000	-0.280183000	-0.034990000
H	4.910906000	-1.674226000	0.957151000
C	2.813201000	-0.541382000	2.100323000
H	3.657742000	-0.826021000	2.740227000
H	1.890932000	-0.805969000	2.626998000

C	2.785989000	0.954798000	1.856808000
C	3.293117000	1.892075000	2.750827000
H	3.811046000	1.567692000	3.647331000
C	3.112194000	3.249434000	2.472279000
H	3.496367000	4.000217000	3.155560000
C	2.434409000	3.630121000	1.313261000
H	2.270202000	4.674015000	1.071725000
C	1.967672000	2.636846000	0.457122000
C	-1.201345000	-0.128987000	-0.060532000
C	-0.843275000	0.787896000	-1.231707000
C	-1.510927000	2.133287000	-1.005665000
C	-2.653635000	2.186434000	-0.194844000
C	-3.297500000	3.396056000	0.052095000
H	-4.180050000	3.405033000	0.682183000
C	-2.794714000	4.563070000	-0.524895000
H	-3.295437000	5.507302000	-0.334729000
C	-1.666836000	4.522932000	-1.350937000
H	-1.294035000	5.432600000	-1.810438000
C	-1.030617000	3.305135000	-1.590819000
H	-0.161394000	3.238762000	-2.237959000
C	-2.725600000	-0.196144000	-0.119840000
C	-3.383748000	-1.338322000	0.599418000
C	-3.452088000	-2.587554000	-0.028715000
H	-3.108784000	-2.689739000	-1.052820000
C	-3.992612000	-3.677531000	0.652543000
H	-4.058658000	-4.642686000	0.159578000
C	-4.463118000	-3.523501000	1.958815000
H	-4.890044000	-4.371397000	2.485906000
C	-4.393369000	-2.276051000	2.583116000
H	-4.766187000	-2.152234000	3.595239000
C	-3.852009000	-1.181798000	1.908294000
H	-3.802882000	-0.209234000	2.384054000
H	1.424451000	2.843357000	-0.457601000
O	-1.646586000	-0.008410000	-2.210586000
O	-2.956089000	-0.258084000	-1.521642000

TS4

Charge= +1
Multiplicity= 2
SCF Energy (B3LYP-D3) = -1782.11341625
Enthalpy 0K = 0.511964
Enthalpy 298 K = 0.544748
Free Energy 298 K = 0.446748

C	-2.326330000	2.784394000	3.542803000
C	-1.511013000	1.685295000	3.820132000
C	-1.264281000	0.767817000	2.803083000
N	-1.784332000	0.927563000	1.576966000
C	-2.554992000	1.993419000	1.289790000
C	-2.857939000	2.943865000	2.260787000
H	-2.546485000	3.512968000	4.316635000
H	-3.487966000	3.793062000	2.017343000
C	-2.963538000	2.123707000	-0.164545000
H	-3.899392000	2.685330000	-0.271181000
H	-2.177813000	2.691870000	-0.671401000
N	-3.045932000	0.793403000	-0.822758000
C	-4.339773000	0.095145000	-0.545041000
H	-4.781069000	0.529763000	0.354094000
H	-5.031519000	0.282158000	-1.373036000
C	-4.129081000	-1.419168000	-0.310939000
H	-4.094732000	-1.621394000	0.763677000
H	-4.965807000	-1.995748000	-0.727932000
N	-2.836094000	-1.877563000	-0.876323000
C	-2.798215000	-1.749457000	-2.369892000
H	-3.818739000	-1.847670000	-2.763504000
H	-2.213442000	-2.583996000	-2.758791000
C	-2.512567000	-3.252654000	-0.430704000
H	-2.514315000	-3.284051000	0.660247000
H	-3.241016000	-3.972605000	-0.824164000
H	-1.507739000	-3.494701000	-0.772724000
Cu	-1.638429000	-0.434610000	0.064434000
C	1.146241000	0.026210000	-0.447578000
C	0.875841000	-1.489314000	-0.057145000
C	2.997585000	0.290064000	-0.797093000
C	2.086497000	-2.189822000	0.496055000
C	3.335560000	-1.572731000	0.665032000
O	3.545766000	-0.235696000	0.388813000
C	3.173427000	1.776912000	-0.834524000
C	3.004363000	2.421836000	-2.065635000
C	3.454068000	2.521141000	0.318974000
H	2.791062000	1.822839000	-2.944292000
H	3.586878000	2.012603000	1.267094000
C	3.130738000	3.806855000	-2.145994000
C	3.579140000	3.906944000	0.232339000
H	3.015318000	4.305975000	-3.103384000
H	3.810155000	4.484357000	1.122468000
C	3.417136000	4.551001000	-0.997605000

H	3.520265000	5.630220000	-1.062042000
O	0.290885000	0.795074000	-0.778136000
O	-0.215909000	-1.494822000	0.797048000
C	3.012941000	-4.251348000	1.387090000
C	1.946006000	-3.539677000	0.850838000
C	4.247330000	-3.615887000	1.561693000
H	0.980633000	-4.011408000	0.702077000
H	5.088470000	-4.163218000	1.975576000
C	4.411257000	-2.280505000	1.196085000
H	5.361117000	-1.770195000	1.311054000
H	2.890105000	-5.293410000	1.663058000
C	-2.130267000	-0.450617000	-2.823751000
C	-2.751385000	0.847412000	-2.294162000
H	-1.076876000	-0.499555000	-2.529128000
H	-2.145503000	-0.410681000	-3.918269000
H	-3.676451000	1.099730000	-2.828250000
H	-2.037024000	1.655588000	-2.458547000
H	-0.643742000	-0.113989000	2.930814000
H	-1.078521000	1.537037000	4.803044000
O	0.355523000	-2.104784000	-1.169481000
O	2.898811000	-0.418029000	-1.830104000

8

Charge= +1
Multiplicity= 2
SCF Energy (B3LYP-D3) = -1782.30292553
Enthalpy 0K = 0.514974
Enthalpy 298 K = 0.549250
Free Energy 298 K = 0.448731

Cu	1.135717000	-0.621039000	0.917844000
O	0.513899000	-0.598285000	-3.200787000
O	-0.348996000	-1.932477000	1.167238000
O	-3.237740000	0.343041000	-0.888760000
N	0.755031000	0.642611000	2.497889000
N	2.354248000	0.949436000	0.410009000
N	2.264956000	-1.626368000	-0.417290000
C	-0.435963000	0.238629000	3.284488000
H	-0.594883000	0.932251000	4.119683000
H	-0.279370000	-0.771387000	3.665015000
H	-1.314265000	0.245049000	2.641195000
C	1.976407000	0.624080000	3.361714000
H	2.215740000	-0.426460000	3.560431000

H	1.737595000	1.092066000	4.326566000
C	0.545419000	1.960640000	1.833996000
H	-0.495360000	1.985454000	1.515899000
H	0.696414000	2.772525000	2.555712000
C	1.456189000	2.126661000	0.579500000
H	0.816651000	2.172271000	-0.301944000
H	2.042813000	3.051663000	0.622122000
C	3.172094000	1.360590000	2.749441000
H	2.996645000	2.439803000	2.789479000
H	4.044671000	1.179156000	3.384729000
C	3.534623000	0.956452000	1.318539000
H	3.965116000	-0.049965000	1.292055000
H	4.289727000	1.652701000	0.927525000
C	2.743267000	0.673773000	-0.993853000
H	3.612034000	1.271427000	-1.296372000
H	1.899848000	0.954367000	-1.632805000
C	2.990734000	-0.807387000	-1.204185000
C	3.814694000	-1.315464000	-2.203651000
H	4.396435000	-0.642789000	-2.824912000
C	3.860546000	-2.697788000	-2.396924000
H	4.493163000	-3.117764000	-3.172459000
C	3.082075000	-3.532659000	-1.592844000
H	3.084708000	-4.608331000	-1.726545000
C	2.290764000	-2.954733000	-0.604925000
C	-0.017487000	-1.533073000	-2.823526000
C	-1.146179000	-1.295708000	0.368867000
C	-2.570792000	-1.697940000	0.296516000
C	-3.553009000	-0.874224000	-0.290913000
C	-4.881346000	-1.277106000	-0.352689000
H	-5.605712000	-0.612236000	-0.809855000
C	-5.254008000	-2.515597000	0.170913000
H	-6.292213000	-2.827999000	0.117464000
C	-4.300457000	-3.343091000	0.769263000
H	-4.591866000	-4.302851000	1.182945000
C	-2.973246000	-2.929799000	0.834971000
H	-2.218219000	-3.554480000	1.299268000
C	-2.688686000	1.328414000	-0.121742000
C	-1.988087000	2.357128000	-0.931421000
C	-1.742159000	3.607842000	-0.347649000
H	-2.154963000	3.818424000	0.633746000
C	-0.977820000	4.555649000	-1.026497000
H	-0.800220000	5.529639000	-0.580819000
C	-0.446691000	4.251673000	-2.284196000
H	0.150692000	4.989084000	-2.812386000

C	-0.692825000	3.004472000	-2.868077000
H	-0.284780000	2.770926000	-3.846891000
C	-1.469733000	2.059402000	-2.198753000
H	-1.653916000	1.083827000	-2.629155000
H	1.645064000	-3.531352000	0.048990000
O	-0.704493000	-0.319355000	-0.301248000
O	-2.763537000	1.353369000	1.091233000

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