Synthesis, characterisation and ROP catalytic evaluation of Cu(II) complexes bearing 2,2′-diphenylglycine-derived moieties

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Abstract: The treatment of CuX_2 (X = Cl, Br) with an equimolar amount of 2-2′-diphenylglycine (DpgH) in EtOH at reflux afforded, after work up, the complexes $[CuCl(Dpg)(EtOH)]_2$ (**1**) and $[(CuBr_2)_2(Dpg)_2Cu(EtOH)_4]$ (**2**), respectively. The compounds were obtained microanalytically pure in low to moderate yield (13 and 27%, respectively) and were fully characterised. Synthetic attempts towards Cu-alkoxide species led to the isolation of the heterobimetallic species $[(CuCl_2)(Dpg)Li(THF)]\cdot THF$ (**3**·THF). Finally, complex **4**, bearing an imine ligand derived from the decarboxylation of DpgH, was serendipitously obtained from the synthesis of **3**. These complexes were found to be inactive in the homo- and co-ring opening polymerization (ROP) of cyclic esters (ε -caprolactone *rac*-lactide) and epoxides (propylene oxide and cyclohexene oxide). Compounds **1** and **2** were shown to be non-toxic (against cancerous cell lines HCT116 and HT-29).

Keywords: Copper; diphenylglycine; crystal structures; cytotoxicity.

1. Introduction

During the past two decades, increasing attention has been dedicated to polyesters, as being both biodegradable and biocompatible, this class of polymer has potential as a sustainable alternative to polyolefins [1]. Currently, polyesters are employed in various fields, spanning from the food and packaging industries to medicinal and pharmaceutical applications [1, 2]. In this scenario, homo- and copolymers of ε-caprolactone (ε-CL) and *rac*-lactide (*r*-LA) are of particular interest [3].

These materials are mainly obtained by ring opening polymerization (ROP) promoted by metal-based catalysts [4]. In particular, the industrial production of PCL and PLA relies on the use of a tin(II)-based catalyst, namely tin(octanoate) [5]. In spite of its cost-effectiveness and efficiency, this process is affected by the toxicity of the metal employed, given that tin can leach into the final material thereby compromising its biocompatibility. Hence, the development of catalysts for ROP of cyclic esters based on non-toxic metals is highly desirable. In this context, copper represents and ideal candidate. In fact, this metal is both relatively inexpensive and abundant, and moreover, it is found in all living organisms. Metal complexes of Cu with different ligands have been successfully employed in the ROP of ε-CL [6] and *r*-LA [7] as well as in the copolymerization of epoxides and CO_2 (CHO) [8]. Herein, we report the synthesis and characterisation of [$CuCl_2$] and [$CuBr_2$] complexes with 2,2′-diphenylglycine (DpgH). The catalytic activity of these new copper systems for the ROP of cyclic esters and epoxides is investigated; their biological evaluation is also discussed.

2. Experimental

2.1 General

All manipulations were carried out under an atmosphere of dry nitrogen using Schlenk and cannula techniques or in a conventional nitrogen-filled glove box. Ethanol was dried over molecular sieves (3 Å). THF and Hexane were dried over sodium/benzophenone. All solvents were distilled and degassed prior to use. $Cu(OEt)_2$ was synthesized according to the reported procedure [9]. All other chemicals were purchased from Sigma Aldrich or TCI UK and used as received. IR spectra (nujol mulls, KBr windows) were recorded on a Nicolet Avatar 360 FT IR spectrometer. Elemental analyses were performed by the elemental analysis service at the London Metropolitan University, the Department of Chemistry & Biochemistry, University of Hull and at Nanjing University of Information Science & Technology.

2.2 X-ray Crystallography

Full sets of X-ray diffraction intensity data were collected in series of ω-scans using a Stoe IPDS2 image plate diffractometer operating with Mo *Kα* radiation at 150(2) *K*. A multi-scan method was applied for the absorption corrections of the collected data [10].

The structures were solved using dual-space methods within SHELXT and full-matrix least squares refinement was carried out within SHELXL-2018 *via* the WinGX program interface [11, 12]. All non-hydrogen positions were located in the direct and difference Fourier maps and refined using anisotropic displacement parameters.

2.3 Synthesis of $[CuCl(Dpg)(EtOH)]_2$ (**1**)

DpgH (0.84 g, 3.70 mmol, 1 equiv.) was added to a solution of $CuCl_2$ (0.50 g, 3.71 mmol, 1 equiv.) in anhydrous ethanol (20 mL). The mixture was refluxed for 4 h and then filtered. On prolonged standing (2 to 3 days) at ambient temperature blue crystals of **1** formed (yield 0.36 g, 13%). $C_{32}H_{36}Cl_2Cu_2O_6$ requires: C 51.73, H 4.89, N 3.77%. Found: C 51.50, H 4.68, N 3.81%. IR (KBr) cm^{-1}: 3442 (w), 3254 (m), 1313 (w), 1664 (s), 1591 (s), 1308 (m), 1200 (s), 1164 (m), 1137 (s),

1090 (m), 1031 (s), 967 (m), 762 (s), 732 (s), 699 (s), 629 (s), 449 (m). MALDI-MS: $^{m}/_{z}$ = 742.934 [M^{+}]. Magnetic moment = 2.5 μ_B.

2.4 Synthesis of [$(CuBr_2)_2(Dpg)_2Cu(EtOH)_4$] (**2**)

According to the procedure reported for **1**, complex **2** was synthesized by reacting $CuBr_2$ (0.50 g, 2.23 mmol, 1 equiv.) and DpgH (0.50 g, 2.23 mmol, 1 equiv.) in anhydrous ethanol (20 mL). Green crystals of **2** were obtained on prolonged standing (2 to 3 days) at ambient temperature (yield 0.69 g, 27%). $C_{36}H_{48}Br_4N_2Cu_3O_8$ requires: C 37.66; H 4.18; N 2.44%. Found: C 37.53; H 4.27; N 2.52%. IR (KBr) cm^{-1}: 3424 (w), 3258 (w), 1600 (s), 1495 (m), 1241 (s), 1256 (s), 1196 (s), 1105 (s), 1083 (s), 1043 (s), 955 (s), 878 (s), 819 (s), 764 (s), 734 (s), 706 (s), 639 (s), 455 (m). MALDI-MS: $^{m}/_{z}$ = 1147.535 [M^{+}]. Magnetic moment = 3.0 μ_B.

2.5 Synthesis of [$(CuCl_2)$(Dpg)Li(THF)]·THF (**3**·THF)

DpgH (0.84 g, 3.70 mmol, 1 equiv.) was added to a solution of $CuCl_2$ (0.50 g, 3.71 mmol, 1 equiv.) in anhydrous ethanol (20 mL) and the mixture was refluxed for 4 h. Volatiles were removed under reduced pressure affording a dark green/blue residue which was dissolved in anhydrous THF (20 mL). A solution of LiOEt in THF (7.40 mL, 1M, 7.40 mmol, 2 equiv.) was added dropwise at room temperature and the mixture was then refluxed for 16 h. The mixture was filtered, the mother liquor was concentrated to 5 mL and anhydrous hexane (20 mL) was layered on top of the solution. On prolonged standing (2 to 3 days) at ambient temperature, blue crystals of **3** formed (yield 0.25 g, 13%). $C_{22}H_{28}Cl_2CuLiNO_4$ requires: C 51.62, H 5.51, N 2.74%. Found: C 51.88, H 5.71, N 2.86%. IR (KBr) cm^{-1}: 3625 (w), 1784 (w), 1587 (m), (s), 1305 (s), 1260 (s), 1190 (w), 1086 (s), 1032 (s), 883 (s), 767 (s), 733 (s), 620 (m), 547 (s), 4477(s). Magnetic moment (m) = 1.8 μ_B

2.6 Synthesis of [$CuCl_2$(diphenylmethanimine)$_2$] (**4**)

Complex **4** was serendipitously obtained from the preparation of **3**. Due to the very limited amount of sample, only its structural determination by X-ray analysis could be performed.

2.7 Ring Opening Polymerization (ROP) of cyclic esters and epoxides

Thermal Conditions: Under nitrogen atmosphere, a Schlenk flask was charged with the required amount of a toluene solution of the complex (0.01 M) and, if required, the corresponding amount of a toluene solution of the co-activator. The monomer (4.5 mmol) was then added *via* syringe and the mixtrure was stirred at 130 °C for 24 hours. The monomer conversion was determined by ^{1}H NMR spectroscopy. For the solvent-free runs, the toluene was removed under reduced pressure before adding the monomer. For the co-polymerization tests, both monomers were introduced into the reaction vessel at the same time in equimolar amounts (4.5 mmol).

2.8 Microwave irradiation: Under ambient atmosphere, a 20 mL glass vial was charged with ε-caprolactone (1.5 mL, 13.5 mmol, 100 equiv.) and **1** (0.10 g, 0.13 mmol, 1 equiv.) and the mixture was irradiated in a microwave oven (200 W) for 60 minutes. The monomer conversion was then determined by ^{1}H NMR spectroscopy.

2.9 Cytotoxicity

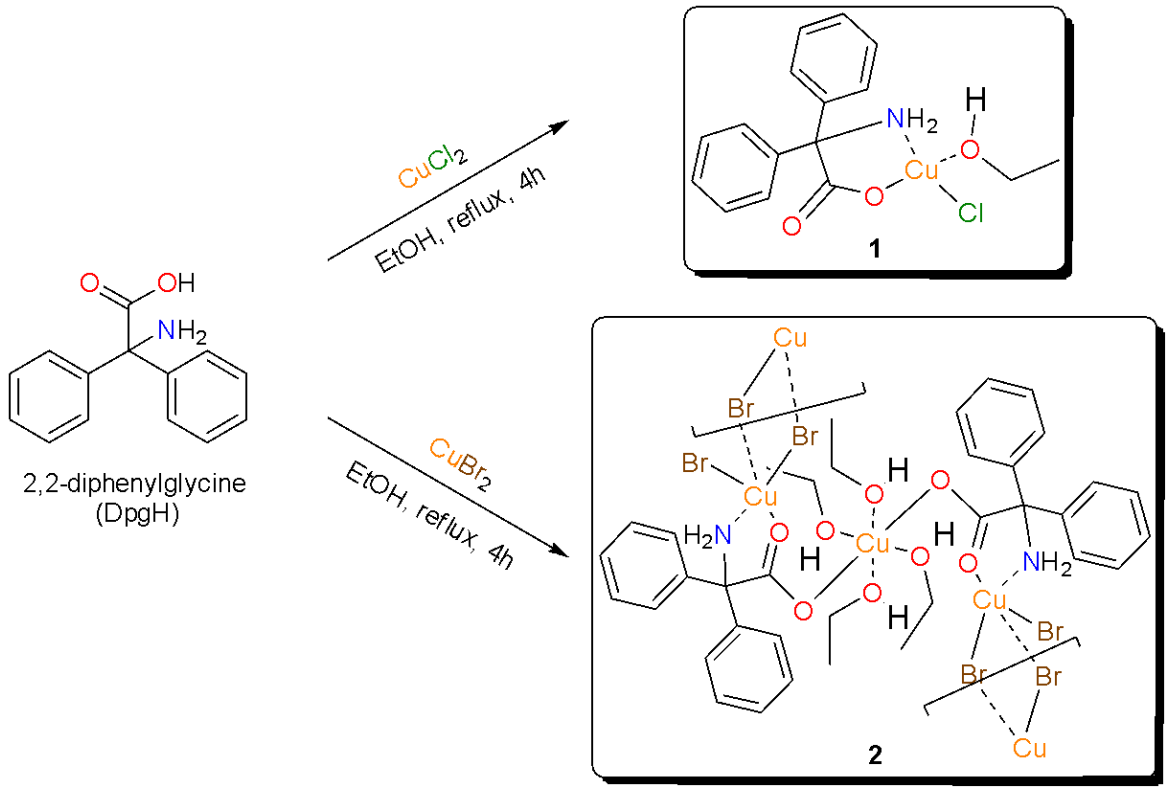
MTS assay was used to calculate the percentage of viable cells in the culture media. This assay depends on the transformation of a tetrazolium salt into formazan in viable cells by mitochondrial dehydrogenase enzyme activity. There is a positive correlation between the amount of formazan and the number of viable cells in the culture media. HCT116 and HT-29 cells were seeded in 96 flat-bottomed microliter tissue culture plates with 20,000 cells per well in 200 μL media of McCoy's and Dulbecco's Modified Eagle's Medium (DMEM). In order to attach the cells to the well base in the microliter plates, the plates were incubated overnight in a 5% CO_2 incubator at 37 °C. After 24 h, the media was removed from the wells and 100 μL of the compound in the media was added. Various concentrations of compounds in the range of 6.25 mM to 6.25 nM were tested. After 24 h of incubation, the contents of the wells were removed using a multipipette, and then 180 μL of sterilized PBS was added followed by the addition of 20 μL of MTS reagent (Promega,

U.K.). Plates were then returned to the incubator for 4 h. Colour intensity (absorbance) of the treated wells was measured at 490 nm using a Synergy HT microplate reader. The percentages of the cell viability of the treated cells were calculated based on positive and negative control where they represent 100% and 0% viable cells, respectively. IC_{50} values were calculated using GraphPad Prism software.

3. Results and Discussion

3.1 Synthesis and molecular structures

The treatment of anhydrous $CuCl_2$ with an equimolar amount of 2,2′-diphenylglycine (DpgH) in refluxing ethanol for 4 h afforded, after work up, complex **1** as blue crystals in low (13%) isolated yield (Scheme 1).



Scheme 1. Synthesis of complexes **1** and **2**.

The molecular structure of **1** is shown in Figure 1, with selected bond distances and angles given in caption. The asymmetric unit features two independent [CuCl(Dpg)(EtOH)] units (Figure 1, left). Each unique copper centre is bound to a Cl atom, a molecule of ethanol and a Dpg moiety chelating the metal through the one oxygen of the carboxylate and the nitrogen atom of the amino group. Each chloride atom bridges to a second symmetry-equivalent Cu generating two symmetry-unique dimers of the type $[CuCl(Dpg)(EtOH)]_2$ (Figure 1, left). The coordination geometry of each metal centre of the $[Cu_2Cl_2]$ core is square pyramidal (τ_5 values are 0.105 and 0.012 for Cu1 and Cu2 respectively) [13]. In each complex the Cu-Cl_{apix} bond is *ca*. 1.3 times longer than that of Cu-Cl_{plane}; for Cu1 the distance are 2.2373(8) and 2.8239(9) Å respectively, and for Cu2 the values are 2.2347(8) and 2.9400(8). The structure persists at 373 K and there is no evidence that the independent copper centres can become equivalent.

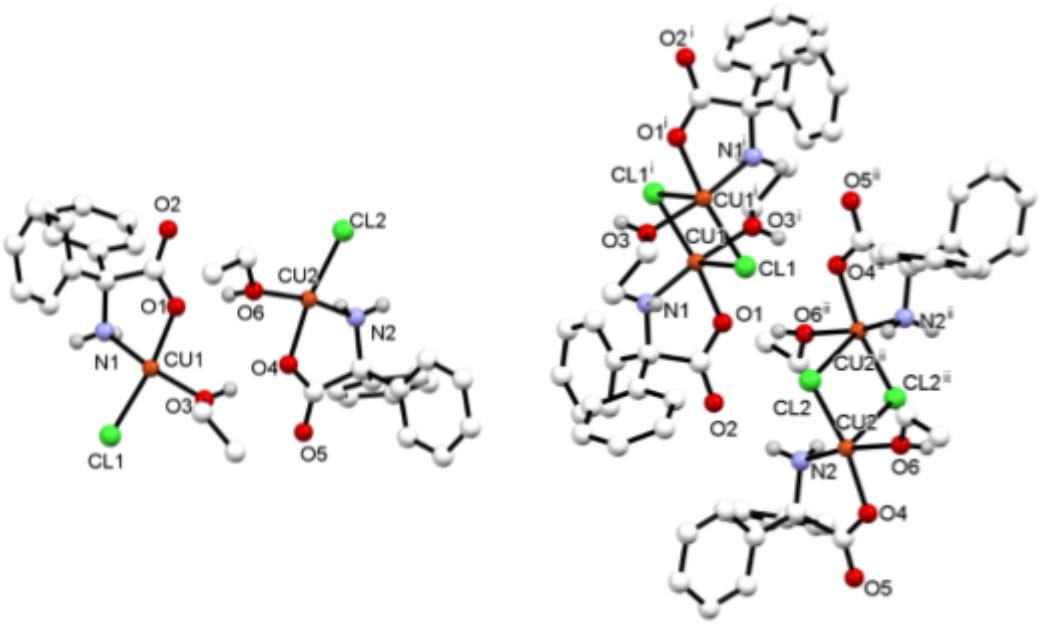


Figure 1. Molecular structure of **1**. (Asymmetric unit shown left) Selected bond lengths (Å) and angles (°): Cu(1)-O(1) 1.9326(19), Cu(1)-O(3) 1.9747(19), Cu(1)-N(1) 1.983(2), Cu(1)-Cl(1) 2.2373(8), C(1)-O(1) 1.305(3); O(1)-Cu(1)-O(3) 91.02(8), O(1)-Cu(1)-N(1) 84.02(9), O(3)-Cu(1)-N(1) 171.28(9), O(1)-Cu(1)-Cl(1) 164.99(7), O(3)-Cu(1)-Cl(1) 91.27(6), N(1)-Cu(1)-Cl(1) 95.37(7). (Symmetry operations used to generate equivalent atoms: i = 1-x, 2-y, 1-z; ii = 2-x, 1-y, 1-z).

Although no intramolecular hydrogen bonds are detected, intermolecular N-H···O=C and O-H···O hydrogen bonds are observed between adjacent molecules. These interactions assembly the dimers into a hydrogen-bonded chain that runs along the crystallographic [110] direction (Figure 2).

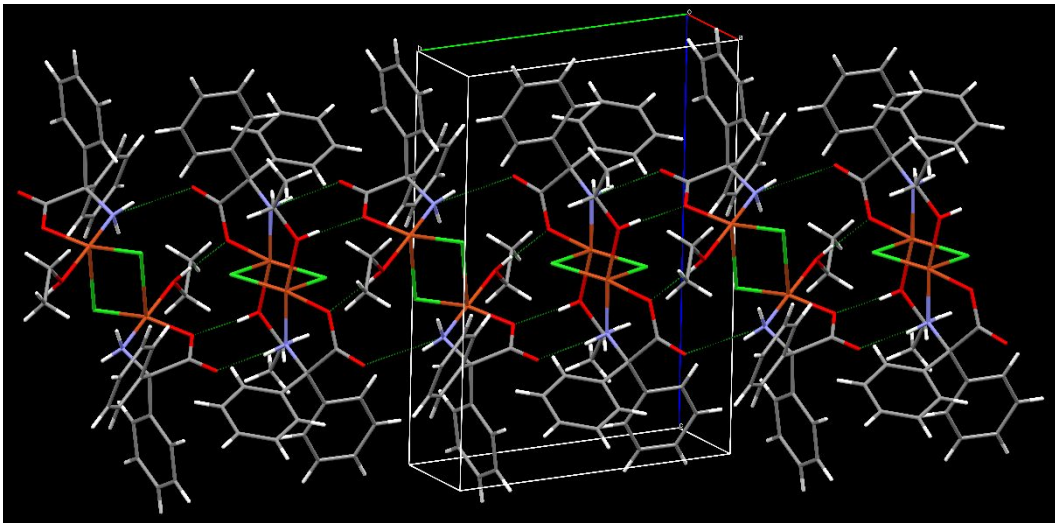


Figure 2. Structure of complex **1** arranged in hydrogen-bounded chains running along the [110] direction.

The IR spectrum of **1** displayed a band at 449 cm^{-1} assigned to the Cu-Cl stretching [14], as well as peaks at 3254, 1664 and 1090 cm^{-1} assigned to the N-H, C=C and C-O stretching bands, respectively [15]. The molecular ion was observed at m/z 742.934 on the MALDI-TOF spectrum; this value is compatible with the molecular mass of $[(CuCl)_2(Dpg)_2(EtOH)_2]$. Finally, the magnetic moment (m) was found to be 2.5 μ_B, which is consistent with the values typically observed for Cu(II) complexes [16].

The reaction of $CuBr_2$ with DpgH under the same conditions employed for **1** afforded, after work-up, the complex $[(CuBr_2)_2(Dpg)_2Cu(EtOH)_4]$ (**2**, Scheme 1). Two unique Cu(II) centres are found in the asymmetric unit of complex **2** (Figure 3, left). One centre, namely Cu(1), is bonded to

two Br atoms and one Dpg moiety chelating the metal by the carbonyl oxygen of the carboxylate group and the nitrogen atom of NH_2. The Cu-Br bond lengths were found to be 2.381(4) and 2.374(5) Å for Br(1) and Br(2), respectively. Br(1) is also bound to an equivalent Cu(1) centre at a much greater distance (3.098(5) Å), forming a centrosymmetric 4-membered ring of the type $[Cu(1)_2Br(1)_2]$, as shown in Figure 3, right.

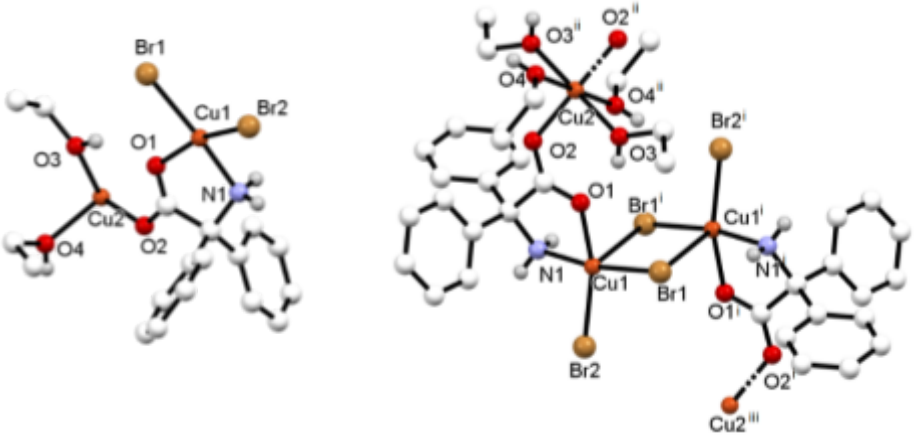


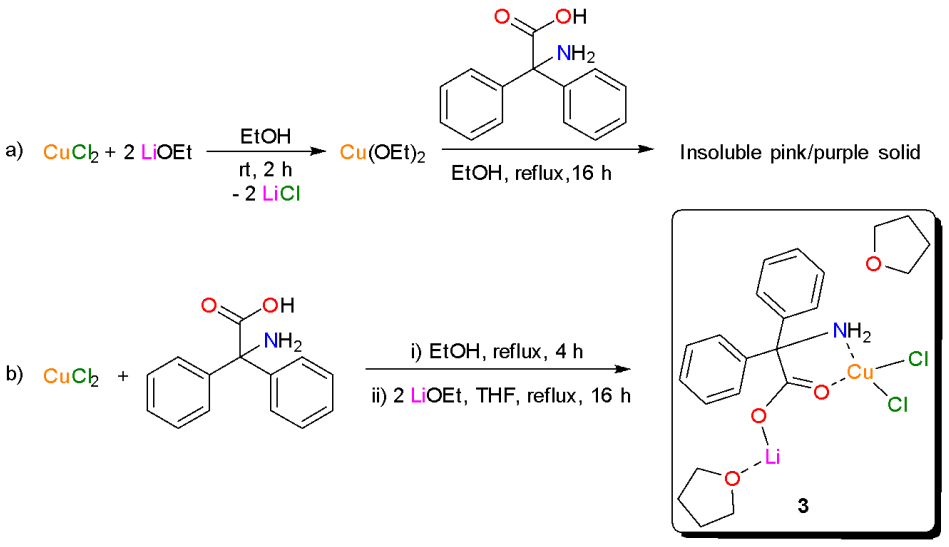
Figure 3. Left: asymmetric unit of complex **2**. Selected bond lengths (Å) and angles (°): Cu(1)-Br(1) 2.3809(4), Cu(1)-Br(2) 2.3736(5), Cu(1)-O(1) 1.9743(17), Cu(1)-N(1) 2.0048(19), Cu(2)-O(2) 1.9710(15), Cu(2)-O(4) 2.136(2), O(1)-C(1) 1.259(3); O(1)-Cu(1)-N(1) 80.65(7), O(1)-Cu(1)-Br(2) 162.78(5), N(1)-Cu(1)-Br(2) 91.08(5), O(1)-Cu(1)-Br(1) 90.33(5), N(1)-Cu(1)-Br(1) 170.00(5). Left: Expanded asimmetric unit of complex **2**; Cu(2) lies on a centre of inversion. (Symmetry operations used to generate equivalent atoms: i = 1-x, -y, 1-z; ii = 2-x, 1-y, 1-z; iii = -1+x, -1+y, z).

Similarly to complex **1**, Cu(1) is 5-coordinate with a square pyramidal geometry in which the apical bond is larger than those found on the square plane. The other unique copper centre, namely Cu(2), is found on either sides of the $[(Cu(1)_2Br_2)(Dpg)]_2$ unit. In this case, the metal is bound to the rest of the structure by means of the carboxylate oxygen of the Dpg unit and it is coordinated by 4 molecules of ethanol. Similar to **1**, the structure of **2** is arranged in chains running along the [110]

direction. Nevertheless, the chains are formed by both chelating Dpg units and bridging Br atoms, rather than by hydrogen bonds.

The IR spectrum of **2** was find to be almost superimposable to that of its Cl-analogue. In fact, bands accountable for the Cu-Br, C=C and N-H stretched were observed at 455, 1600 and 3258 cm^{-1}, respectively. The molecular ion was observed by MALDI-TOF spectrometry at $^{m}/_{z}$ 1147.535. This values is compatible with the $[(CuBr_2)_2(Dpg)_2Cu(EtOH)_4]$ unit. Finally, the magnetic moment of **2** was found to be 3.0 μ_B, which is consistent with previously reported Cu-based complexes [16].

Furthermore, synthetic attempts towards well-defined Cu-alkoxide species were carried out (Scheme 2). Firstly, $Cu(OEt)_2$ was isolated in good yield by reacting $CuCl_2$ and LiOEt in ethanol.



Scheme 2. Synthetic attempts towards Cu-alkoxide species.

Further treatment of this species with DpgH, under the same reaction conditions employed for the synthesis of **1** and **2**, resulted in the formation of a pink/purple solid which was insoluble in common organic solvents, including DMSO (Scheme 2a). In a second attempt, the reaction of $CuCl_2$ with DpgH in refluxing ethanol was followed be the removal of the volatiles and further treatment of the remaining solid with two equivalents of LiOEt in refluxing THF (Scheme 2b). By layering hexane on the resulting solution, blue crystals suitable for X-ray diffraction were obtained

on standing at room temperature for 3 days. The compound was identified as [($CuCl_2$)(Dpg)Li(THF)]·THF (**3**·THF), whose molecular structure is reported in Figure 4, with selected bond distances and angles given in caption. The asymmetric unit (Figure 4, left) shows a [$CuCl_2$] group chelated by a Dpg moiety by the carbonyl oxygen and the nitrogen of the amino group. The Cu-O and Cu-N bond lengths (1.986(3) and 1.993(4) Å, respectively) were found to be comparable to that observed in **1** and **2**. The Dpg carboxylate oxygen bounds a lithium ion with a bond length of 1.908(8) Å, consistent with the values observed in other Li-carboxylate structures [17]. The expanded view of the asymmetric unit shows the coordination environment of both metal centres (Figure 4, right).

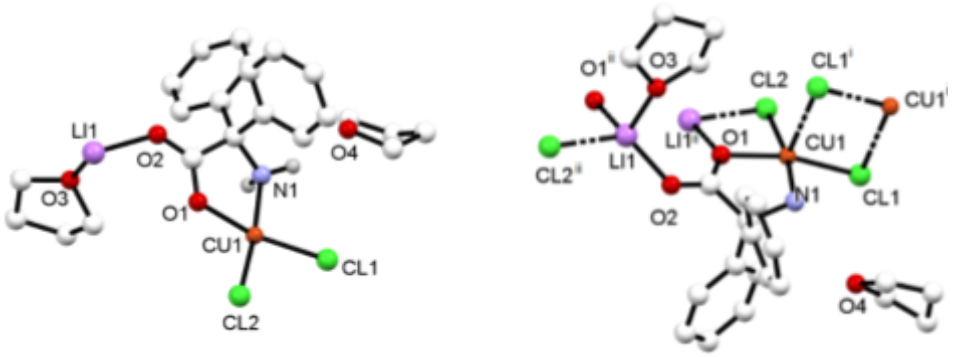


Figure 4. Left: Asymmetric unit of [($CuCl_2$)(Dpg)Li(THF)]·THF (**3**·THF). Selected bond lengths (Å) and angles (°): Cu(1)-Cl(1) 2.2615(13), Cu(1)-Cl(2) 2.2474(14), Cu(1)-O(1) 1.986(3), Cu(1)-N(1) 1.993(4), Li(1)-O(2), Li(1)-O(3) 1.946(8); Cl(1)-Cu(1)-Cl(2) 95.77(5); O(1)-Cu(1)-N(1) 81.22(14), O(1)-Cu(1)-Cl(2) 90.06(10), N(1)-Cu(1)-Cl(1) 92.03(11). Right: expanded asymmetric unit showing the penta-coordinate Cu centre. (Symmetry operations used to generate equivalent atoms: i = 1-x, 1-y, 1-z; ii = 1-x, 2-y, 1-z).

Each copper is penta-coordinate and it is bound to an adjacent unit by a bridging Cl(1) atom. The Li ion is tetra-coordinate and is bound to a Cl(2) and a carbonyl oxygen of the adjacent Dpg unit, as well as to a THF molecule. The structure forms a one-dimensional chain running along *b* (Figure

5). The magnetic moment of the complex was found to be lower than that of **1** and **2** (1.8 μ_B *vs* 2.5 and 3.0), but still in agreement with previously reported data [16].

Interestingly, the samples of complex **3** contained a set of red crystals found to be suitable for X-ray diffraction studies. The compound was characterised as the compound $[CuCl_2(diphenylmethanimine)_2]$ (**4**), whose structure is reported in figure 6 with selected bond lengths and angles given in caption.

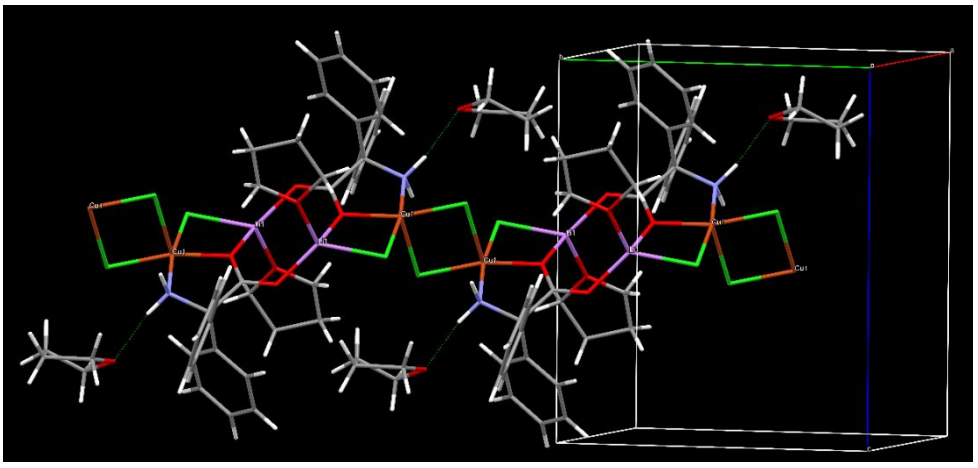


Figure 5. One-dimensional chain running along *b* formed by complex **3**.

The asymmetric unit of **4** contains one half of a copper atom, one bound chloride, and one bound diphenylmethanimine ligand, the latter coordinating to the metal centre by the imine nitrogen; the C1-N1 bond length shows this is a double bond. The inversion centre generates the four coordinate copper species (see figure 6). The copper coordination is unusual as it is a strictly planar arrangement of four ligands with two pairs of angles close to 90 degrees (N(1)-Cu(1)-Cl(1)#1 88.57(6)° and N(1)-Cu(1)-Cl(1) 91.43(6)°. There is no additional ligand above and below this plane, although the Cu1…H1 distance is 2.42(3) Å. The adjacent complexes are held together by hydrogen bonds between H1 and Cl1 (0.84(3) Å N1 - H1, 3.489(2) Å N1 - Cl1_$2, 125(2)° N1 - H1 - Cl1_$2 where $2 is -x, 1-y, 1-z). There are additional C-H…Cl interactions between adjacent complexes. These interactions link the complexes into tapes that project along the

crystallographic *a* direction. There are subsidiary C-H…Cl interactions between these tapes of complexes, see figure 7.

The formation of diphenylmethanimine was thought to occur *via* the decarboxylation of DpgH under the rather forcing reaction conditions employed for the synthesis of **3**. In fact, a similar side reaction was previously observed in the preparation of DpgH-based Schiff bases [18].

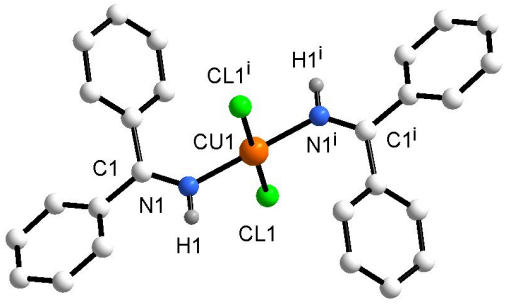


Figure 6. Molecular structure of [$CuCl_2$(diphenylmethanimine)$_2$] (**4**). Selected bond lengths (Å) and angles (°): Cu(1)-Cl(1) 2.2813(6), Cu(1)-N(1) 1.9576(18), N(1)-C(1) 1.286(3); Cl(1)-Cu(1)-N(1)^i 180.0, N(1)-Cu(1)-N(1)^i 180.0. (Symmetry operation used to generate equivalent atoms 1-x, 1-y, 1-z).

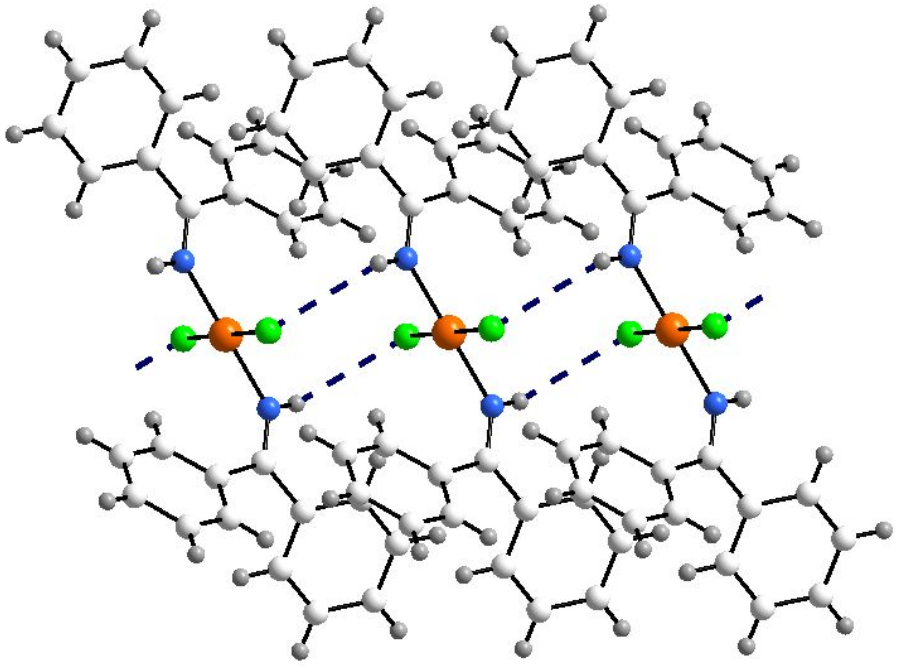


Figure 7: View of the crystal structure of **4** down the *c*-axis. Hydrogen bonds are shown as dashed lines.

3.2 *Ring Opening Polymerisation (ROP) tests*

Complexes **1-3** have been tested as catalysts in the Ring Opening Polymerization (ROP) of cyclic esters and epoxides. Table 1 shows the results obtained for ε-caprolactone (ε-CL) under different reaction conditions. In the absence of an external activator, none of the complexes proved to be active (runs 1-3, 7-9, 13 and 14). No improvement was observed upon using exogenous alcohol (runs 4, 10, 15 and 16). Since metal alkoxides are known to initiate the ROP of lactones [19], we attempted to form Cu-alkoxide species *in situ* by alkoxy/halide exchange in the presence of KO^{t}Bu or AgOAc (runs 5-6 and 11-12). However, also these attempts were unsuccessful. It has to be noted that poor catalytic performances were also exhibited by Cu complexes bearing bis(imino)phenoxide derived ligands previously reported by our group [20].

Table 1. Ring Opening Polymerization (ROP) of ε-CL promoted by complexes **1-3**.

Entry	Complex	Activator	ε-CL:[Cu]:Activator	Conversion[a]
1	**1**	none	250:1:0	none
2		none	100:1:0	none
3[b]		none	100:1:0	traces
4[b]		BnOH	100:1:2	none
5[b]		KO^{t}Bu	100:1:2	traces
6[b]		AgOAc	100:1:2	none
7	**2**	none	250:1:0	none
8		none	100:1:0	none
9[b]		none	100:1:0	none
10[b]		BnOH	100:1:4	none
11[b]		KO^{t}Bu	100:1:4	none
12[b]		AgOAc	100:1:4	none
13	**3**	none	100:1:0	none
14[b]		none	100:1:0	none
15		BnOH	100:1:2	none
16[b]		BnOH	100:1:2	none

Reaction conditions: ε-CL = 4.5 mmol, toluene 2 mL, T = 130 °C, 24 h. [a] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [b] Reaction performed in *solvent-free* conditions.

The complexes were also inactive in the ROP of *rac*-lactide (*r*-LA) and in the ε-CL/*r*-LA co-polymerization. Similarly, no conversion was observed when epoxides, namely propyleneoxide (PO) and cyclohexene oxide (CHO), were employed as monomers.

Finally, complex **1** was tested in the ROP of ε-CL using microwave irradiation instead of conventional heating [21]. Unfortunately, no monomer conversion was observed even after 1 h. Due to this disappointing outcome, no further investigation was performed.

3.3 *Cytotoxicity Studies*

In order to test their potential as anticancer agents, the cytotoxicity of complexes **1** and **2** against cancerous cell lines (HCT116 and HT29) was studied. The IC_{50} values were determined using the cell viability assay, MTS. The MTS graphs for treatment of HCT116 and HT-29 cells with compounds **1** and **2** are shown in figure 8. The IC_{50} values for **1** and **2**, compared to that of cisplatin, are reported in table 2. For both cell lines, the toxicity of complex **1** was found to be higher than that of its Br congener. Interestingly, the opposite trend was observed in our recent investigation involving Re-based complexes [22]. For both cell lines, the IC_{50} values for complex **1** were found to be lower than that of cisplatin, while the opposite was observed for **2**. It must be noted that the IC_{50} value for Cu(II) in HCT116 cell is 1400 μM [23], suggesting we are observing the cytotoxicity from the complexes and not dissociated metal. Overall, both compounds are relatively non-toxic in the concentration range used in PET medical imaging (nM-pM). However, based on the comparison with cisplatin, complex **2** would be an ideal candidate for biological applications given is low cytotoxicity.

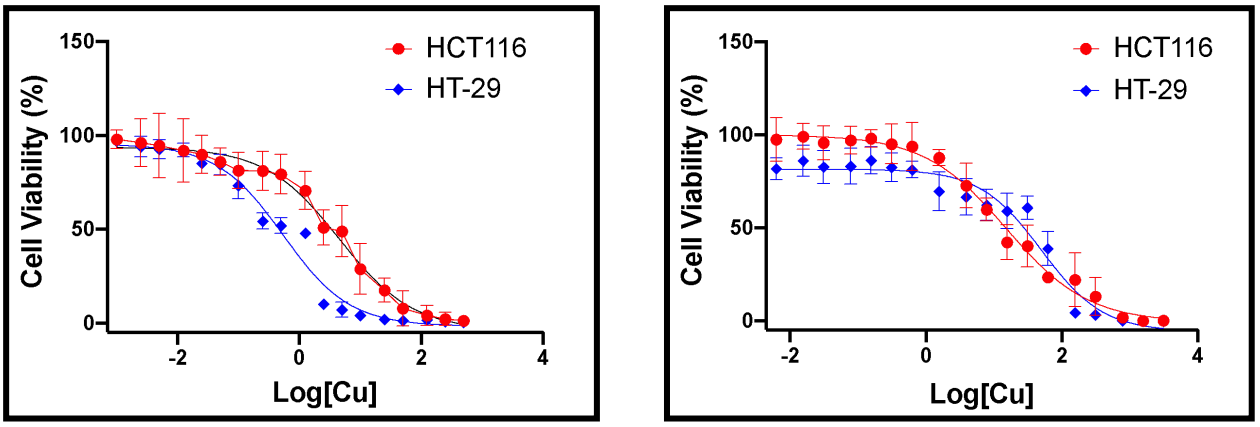


Figure 8. Left: MTS graph for complex **1** against HCT116 and HT-29 cells. Right: MTS graph for complex **2** against HCT116 and HT-29 cells.

Table 2. IC_{50} (μM) for complexes **1**, **2** and cisplatin.

Compound	IC_{50} (μM)
1	4.54 (HCT116); 0.54 (HT-29)
2	15.34 (HCT116), 50.49 (HT-29)
Cisplatin [24]	8.2 (HCT116); 2.7 (HT-29)

4. Conclusions

In conclusion, two novel complexes, **1** and **2**, have been obtained by reacting DpgH with CuX_2 (X = Cl and Br). These species have been fully characterised and their molecular structures thoroughly investigated by X-ray diffraction studies on single crystals. Synthetic attempts towards Cu-alkoxide species led to the isolation of the heterobimetallic Cu/Li species **3**. Finally, complex **4**, bearing an imine ligand derived from the decarboxylation of DpgH, was serendipitously obtained from the synthesis of **3**. Although these complexes resulted to be inactive in the ROP of ε-caprolactone, **1** and **2** displayed interesting cytotoxicity against cancerous cell lines HCT116 and HT-29. Interestingly, both compounds were shown to be relatively non-toxic in the concentration range

used in PET medical imaging. In particular, complex **2** was found to be less toxic than the reference anticancer compound cisplatin.

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Appendix A. Supplementary data

CCDC 2025839-2025842 contain the supplementary crystallographic data for **1**-**4**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

Table 3. Crystallographic data for complexes **1**-**4**.

Compound	**1**	**2**	**3**	**4**
Formula	$C_{32}H_{36}Cl_2Cu_2N_2O_6$	$C_{36}H_{48}Br_4Cu_3N_2O_8$	$C_{22}H_{28}Cl_2CuLiNO_4$	$C_{26}H_{22}Cl_2CuN_2$
Formula weight	742.61	1147.02	511.83	496.89
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic
Space group	P -1	P -1	P -1	P -1
a (Å)	11.2344(11)	9.9696(10)	9.7802(17)	5.2513(8)
b (Å)	11.6365(10)	10.5351(13)	10.2071(17)	9.5848(13)
c (Å)	14.2019(14)	11.6824(10)	13.194(3)	12.2752(18)
α (°)	79.749(7)	91.971(10)	91.386(14)	111.548(11)
β (°)	80.222(8)	99.421(7)	110.259(14)	91.115(12)
γ (°)	65.910(7)	118.183(8)	104.283(13)	99.923(11)
V (Å^3)	1658.1(3)	1058.1(2)	1188.7(4)	563.75(15)
Z	2	1	2	1
Temperature (K)	150(2)	150(2)	150(2)	150(2)
Wavelength, λ (Å)	0.71073	0.71073	0.71073	0.71073

Calculated density ($g.cm^{-3}$)	1.487	1.800	1.430	1.464
Absorption coefficient, μ (mm^{-1})	1.489	5.319	1.171	1.222
Crystal size (mm^3)	0.480 × 0.140 × 0.08	0.300 × 0.200 × 0.185	0.195 × 0.150 × 0.055	0.400 × 0.1060 × 0.040
θ(max) (°)	29.223	29.214	25.680	25.731
Reflections measured	17713	12421	9711	3822
Unique reflections	8827	5698	4497	2031
R_{int}	0.0610	0.0371	0.0858	0.0304
Number of parameters	416	254	273	146
R_1 [$F^2 > 2\sigma(F^2)$]	0.0397	0.0269	0.0462	0.0274
wR_2 (all data)	0.0805	0.0561	0.0904	0.0545
GOOF, S	0.842	0.914	0.765	0.859
Largest difference peak and hole (e $Å^{-3}$)	0.914 and -0.469	0.631 and -0.676	0.698 and -0.471	0.293 and -0.280

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