Cu(II) complexes derived from N-carboxymethyl and N-carboxyethyl amino acids as catalysts for asymmetric oxidative coupling of 2-naphthol

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Abstract

The synthesis, characterization and catalytic performance of chiral Cu(II) complexes derived from N-carboxymethylated and N-carboxyethylated amino acids is reported. The ligand precursors are prepared by single step N-alkylation of the sodium salts of the appropriate chiral amino acid with either sodium chloroacetate or sodium 3-chloropropionate in water. The Cu(II) complexes are obtained upon reaction of Cu(CH₃COO)₂ with the aqueous or alcoholic suspension of the suitable ligand under vigorous stirring or ultrasound irradiation at room temperature. The Cu(II) compounds are characterized by EPR, UV-Vis, circular dichroism and ESI-MS. The molecular structures of two of the prepared complexes are also obtained by single-crystal X-ray diffraction analysis. The catalytic activity of the complexes in the asymmetric oxidative coupling of 2-naphthol is described. All compounds exhibit moderate activity, selectivity and enantioselectivity in ethanol/water mixtures, under aerobic conditions and using potassium iodide as additive. The yields of 1,1'-bi-2-naphthol (BINOL) reached 50 % under the optimal conditions, while enantiomeric excesses reached ca. 48 %. The effect of variables such as ligand substituents, solvent, temperature and additives on the catalytic activity is also described. In the absence of a base, the complexes only show catalytic activity in the presence of alkali metal iodide such as KI. Details of the oxidative coupling mechanism are studied using spectroscopic and electrochemical methodologies.

Keywords: amino acid, copper, 2-naphthol, oxidative coupling, asymmetric catalysis
1. Introduction

The synthesis of atropisomeric compounds such as 1,1'-bi-2-naphthol (BINOL) by transition metal catalysed aerobic oxidative homo-coupling under mild conditions remains a challenge [1]. The significant advances that have been recently made regarding the general subject of oxidative coupling of phenolic compounds, namely 2-naphthols, reflect the importance of these synthetic methodologies [2,3].

In light of these recent reports, we continue our effort to develop structurally simple Cu(II) catalysts for the synthesis of BINOLs, under the mildest experimental conditions possible.

In a previous work we described a series of bio-inspired copper complexes derived from N-picolyl-L-amino acids and their catalytic activity in the asymmetric aerobic oxidative coupling of 2-naphthols, in aqueous medium [4]. While the catalytic systems did operate under mild conditions and afforded moderate yields and enantiomeric excesses for BINOL, the formation of by-products such as naphthoquinones was significant (Scheme 1). The phenol oxygenase character [5] of these systems was significant and, despite the many attempts for optimisation, the overall selectivity towards the formation of BINOL was moderate at best. Another detrimental aspect was the requirement for an organic base additive in order to observe catalytic activity. To develop a more selective copper catalyst we the option of changing from a \([\text{Npy, Namine, OCOO}]\) to a \([\text{OCOO, Namine, OCOO}]\) donor atom set.

Preliminary testing of structurally simpler Cu(II) complexes derived from N-carboxymethyl and N-carboxyethyl-L-phenylalanine indicated that these were capable of catalysing the asymmetric oxidative coupling of 2-naphthol under mild conditions. The disadvantage, however, was that an excess of alkali metal iodide additive was necessary for catalytic activity in the absence of base additive. The prospect of using simpler conditions in the synthesis of BINOL prompted the investigation of the catalytic potential of this series of complexes. Therefore, herein we report the preparation of Cu-complexes derived from N-carboxymethyl and/or N-carboxyethyl L-aminoacids (Chart 1) and the evaluation of their catalytic potential in the asymmetric oxidative coupling of 2-naphthol using air and under mild conditions.
Scheme 1. General outline of the procedure of the Cu-(amino acid) complex catalysed aerobic oxidative coupling of 2-naphthol.[4]

Chart 1. Structural formulas of the ligand precursor compounds prepared and the corresponding Cu(II) complexes. The letter (S) represents a solvent molecule such as water.
2. Results and discussion

2.1 Synthesis of the ligand precursor compounds

The ligand precursor compounds were synthesised by N-alkylation of the sodium salt of the appropriate amino acid with either sodium chloroacetate or 3-chloropropionate in water, at 95 °C for 24 h [6,7]. The expected neutral ligand precursors were obtained as white to cream-coloured precipitates after cooling and acidification of the reaction mixture with HCl to ca. pH 2. With the exception of the valine derived compounds, all are insoluble in protic and most aprotic solvents. The insolubility of these compounds was an obstacle for the adequate characterization by solution NMR. This could be solved by converting the compounds to the alkali metal salts in situ with inorganic base such as K$_2$CO$_3$ or KOH in D$_2$O. In contrast, compounds H$_2$2 and H$_2$4 are very soluble in protic solvents. This, in turn, made their isolation as pure products much more difficult, as this involved concentration of the reaction mixture and careful washing of the obtained precipitate. In addition, the ligand precursors were characterised by ESI-MS, using DMSO as sample solvent. The obtained positive and negative mode MS spectra are included in the Supplementary Data (SD). The ligand precursors were also characterised by elemental analysis.

2.2 Synthesis of the Cu(II)-(amino acid) compounds

The copper compounds were prepared in accordance to the method published in a previous report [4]: ligand precursor and Cu(OAc)$_2$ monohydrate (OAc = acetate) were suspended in ethanol or water/ethanol mixture and the resulting suspension was vigorously stirred or subject to ultrasound irradiation till complete dissolution of the metal precursor. A blue precipitate formed in all cases. The blue solid was filtered and the excess Cu(OAc)$_2$ and acetic acid by-products removed by washing with ethanol and acetone. Compounds 6 and 7 were already reported in the literature, but to the best of our knowledge, no reports exist so far regarding their catalytic activity in the asymmetric oxidative coupling of 2-naphthol.[7,8] The obtained copper compounds are water-soluble, but solubility in ethanol is limited. The
characterization of the prepared complexes was carried out by electron paramagnetic resonance (EPR), electrospray ionization mass spectrometry (ESI-MS) and by elemental analysis. Circular dichroism (CD), electronic absorption spectroscopy (UV-Vis) were used to assess the spectroscopic characteristics of the compounds. It was also possible to obtain crystals suitable for single-crystal X-ray diffraction (XRD) of Cu-complexes 7 and 8. Study of the interaction of 8 with potassium halides was also carried out by $^1$H NMR, UV-Vis and CD. The redox properties of all Cu(II) complexes and the effect of potassium iodide on their electrochemical behaviour was studied by cyclic voltammetry (CV).

2.3 X-ray Diffraction Studies

The crystal structures of 7 and 8 were established by single crystal XRD. ORTEP drawings of the asymmetric units of the compounds are shown in Fig. 1 and 2, respectively, and in Table SD-1 in the Supplementary Data (SD) are listed selected bond lengths and angles.

Compound 7 crystallized in the space group $P2_1$, monoclinic system, displaying two molecules in the asymmetric unit (Figure 1). Each molecule contains two independent Cu(II) atoms, each coordinated to a [O,N,O] donor set of the ligand, two water molecules and to a O atom of a carbonyl moiety of the adjacent [O,N,O] donor set of the ligand, giving rise to a solid state structure of a coordination polymer (Figure SD-1 in the SD).

In complex 7, both metal centres can be described as mer (meridional) isomers, as the ligand binds in the meridional coordination mode, which probably reflects a better stereochemical position of the ligands. The geometry around the Cu atoms is described as octahedral. This is indicated by the angles shown by the two trans O- (or N-) atoms and the metal centre (ca. 180°), and also by the dihedral angles between the planes of cis-coordinated chelate ligands, which are close to 90° (Table 1). In each metal centre, two sites are filled by water molecules (O1 and O11 (for Cu1) and O6 and O12 (for Cu2), respectively), which bind through intermolecular and intramolecular hydrogen bonds with the carboxyl O-atoms of the [O,N,O] ligands. Some atoms become stereogenic centres upon coordination; chiral atoms N1 (Cu 1) and N2 (Cu 2) take the $R$ configuration, whereas atoms C3 (Cu 1) and C10 (Cu 2) retain the $S$ configuration, which is observed in both molecules present in the unit cell. The bond distances Cu–donor atoms (1.9439–1.9867 Å) are in the range of those seen for N-, O-donor ligands–Cu(II) complexes [9]. The Cu–O$_{\text{water}}$ bond lengths in each Cu centre (Cu1–O11,
2.6862(15), and Cu2–O12, 2.4625(13) Å) have longer distances than those displayed in analogous Cu(II) compounds.[9] A crystal structure similar to that of 7 has been reported by Porter et al. [8], although some differences between that crystal structure and the one reported herein were observed. In fact, even though the monomeric structure is identical in both structures, they crystallized in the same space group (P2_1) but with different unit cells (a = 10.0240(15), b = 7.5434(13), c = 15.151(3) Å, β = 94.815(5) ° for compound 7, and a = 9.840(10), b = 7.260(10), c = 6.630(10), β = 107.12(4) ° for ref. 9, respectively). This is actually due to the existence of a water molecule co-crystallized in the asymmetric unit of 7, which is not present in the crystal described in ref. 9.

The crystal structure of compound 8 is presented in Figure 2. It crystallized in the space group P21 within the monoclinic system, with a molecule in the asymmetric unit. Similarly to 7, the solid state structure of 8 is that of 1D-coordination polymer (Figure SD-2 in the SD). In the asymmetric unit, each molecule contains two independent Cu(II) atoms, where Cu1 is coordinated to a [O,N,O] ligand, one water molecule (O1) and to a O-atom (O10) of a carbonyl moiety of the adjacent [O,N,O] donor set of the ligand, whereas Cu2 is bound to a [O,N,O] donor set, one water molecule (O9) and to the two O atoms of an acetato group of the adjacent [O,N,O] donor set of the ligand (O2 and O5). The geometry displayed at Cu1 is that of a distorted square pyramid (τ = 0.12) [10]. One N- and the two O-atoms (O2 and O3) of the [O,N,O] ligand and one of the O-atoms of the adjacent carboxylato moiety (O10) define the equatorial plane, being the metal atom 0.114(6) Å above this plane. A water molecule (O1) occupies the remaining axial site, with a bond length of 2.299(9) Å. On the other hand, the coordination sphere of Cu2 is that of an octahedron, the positions being occupied by the two oxygen and one N-atoms of the ligand (O6, N2, and O7), one water molecule (O9), and two O-atoms of the acetyl moiety of an adjacent ligand, forming intramolecular and intermolecular hydrogen bonds. For both Cu1 and Cu2, all bond distances are in the range of values reported for related N,O-Cu(II) complexes [8,11]. Also in 8, some atoms become chiral centers upon coordination; in both molecules of the unit cell, chiral atoms N1 (Cu 1) and N2 (Cu 2) have the R configuration, and atoms C2 (Cu 1) and C14 (Cu 2) preserve the S configuration.

The crystal structure of compound 6 has been reported by Nguyen-Huy Dung et al.[7] but, to the best of our knowledge, no reports of the crystal structure of 8 are found in the literature.
2.4 Mass Spectrometry

The ESI-MS spectra (positive and negative mode) of the ligand precursors (in DMSO) and the corresponding Cu(II) complexes (in a 1:1 mixture of EtOH/H₂O) were measured and provided additional structural information. Most of the obtained spectra are included in the Supporting Material (Figures SD-3 to SD-22), as well as the assignment Tables SD-2 and SD-3. For the ligand precursors, the MS spectra are simple and show the expected molecular ion in most cases. As for the Cu(II) complexes, extensive aggregation is observed in varying extents in
all spectra. The oligomeric nature of the complexes is particularly evident in the positive mode MS spectra, from which very limited information could be extracted in some cases. Despite their complexity, the negative mode ESI-MS spectra allowed for some peak assignments. Namely, the negative mode ESI-MS spectrum of 6 (Figure SD-13) is representative of this tendency towards aggregation: While monomeric species are detected, as shown by the peak at m/z= 506 (L=ligand, [(CuL)(HL)]⁻), the remaining major species are assigned to mononegative dinuclear and trinuclear species such as [(CuL)₂(EtOH)]⁻ (m/z= 615), {[(CuL)₂(OH)]·4EtOH·H₂O}⁻ (m/z= 790), [(CuL)₃(EtOH)]⁻ (m/z= 899), [(CuL)₃(EtOH)₂(H₂O)]⁻ (m/z= 964), and [(CuL)₃(HL)]⁻ (m/z= 1076). Another common feature of the negative mode spectra is the signal at m/z=247, which could not be assigned to any formulated fragment, known impurity or polyanionic species.

2.5 EPR spectroscopy

The Cu(II) compounds were examined by low temperature EPR. The solvent used was DMSO so that aggregation of the complexes upon sample freezing is minimised. The recorded 1st derivative of the EPR spectra are presented in Figures SD-23 and SD-24 (See SD section) Table 1 lists the corresponding spin Hamiltonian parameters. The spectra of 6 and 8 exhibit significant broadening and distortion due to the pronounced tendency of these compounds to aggregate. A secondary species may be present in these instances with a z-component g-factor of ca. 2.2, partially overlapping one on the z-component signals of the main species.

Compounds 6 and 7 exhibit very similar z-component spin Hamiltonian parameters. The N-carboxyethyl variants 8 to 10 show high similarity with the N-carboxymethyl compounds in all parameters, with exception of |Aₓ| which is ca. 10×10⁻⁴ cm⁻¹ higher. Using the |Aₓ| vs. gₓ correlation plots and the gₓ/|Aₓ| tetrahedral distortion index reported in the literature [12,13], the gₓ/|Aₓ| representations fall within the range expected for a Cu(II) centre coordinated to a [N,O] donor atom set [14,15]. The gₓ/|Aₓ| index calculated for these compounds is indicative of some distortion of the square-planar or square-pyramidal Cu(II) centers, with the N-carboxymethyl compounds being slightly more distorted than the N-carboxyethyl variants.
### Table 1. Spin Hamiltonian parameters for the prepared Cu(II) compounds. a

| Compound | \( g_x, g_y \) | \(| A_x |, | A_y | \) \( \times 10^4 \text{ cm}^{-1} \) | \( g_z \) | \(| A_z | \) \( \times 10^4 \text{ cm}^{-1} \) | \( g_z / | A_z | \) cm |
|----------|----------------|---------------------------------|----------|-------------------|-----------------|
| 6        | 2.062          | 13.7                            | 2.295    | 169.8             | 135             |
| 7        | 2.061          | 12.6                            | 2.296    | 171.5             | 134             |
| 8        | 2.061          | 13.7                            | 2.287    | 181.5             | 126             |
| 9        | 2.060          | 13.5                            | 2.289    | 181.1             | 126             |
| 10       | 2.059          | 13.4                            | 2.289    | 180.6             | 127             |

a The EPR spectra were measured at 77 K in DMSO.

### 2.6 UV-Vis and CD spectroscopy

The UV-Vis and CD solution spectra for the Cu(II)-compounds were also measured and are depicted in Figures SD-25 to SD-28. Tables SD-4 and SD-5 (see SD section) list the experimental \( \lambda_{\text{max}}, \varepsilon \) and \( \Delta \varepsilon \) values. The electronic absorption spectra of 6 to 10 (Figures SD-25 and SD-26) are quite similar, exhibiting a broad band at \( \text{ca.} \ 700-710 \text{ nm} \). Non-centrosymmetric square-planar or square-pyramidal Cu(II) complexes typically exhibit these partially allowed \( d-d \) transitions in this region [4,16]. There are some differences in \( \varepsilon \) of the \( d-d \) bands between the N-carboxymethyl and N-carboxyethyl compounds, and this is evident in the spectra of 7 and 9. The differences in intensity may be due to the lower symmetry of 9. Below the 400 nm limit are the intra-ligand or charge-transfer transitions; the charge transfer bands in 10 are sufficiently intense and broad to reach the 400-500 nm range, thus explaining the green hue of this complex. The CD spectra of all compounds (Figures SD-27 and SD-28) exhibit optical activity in the 800-600 nm range associated with the \( d-d \) transitions. This is an indication of chirality at the Cu(II) center [17]. The N-carboxymethyl compounds 6 and 7 have similar CD patterns (Figure SD-27), with a single negative band within the 800-600 nm interval. The CD spectrum of the N-carboxyethyl compounds (Figure SD-28) show a more pronounced optical activity of the \( d-d \) transitions. Only the spectrum of 9 bears some similarity with those of the N-carboxymethyl compounds, in particular with 7, but even the \( d-d \) bands appear to be more intense. Compound 10 exhibits an additional band at \( \text{ca.} \ 350 \text{ nm} \), which probably corresponds to charge transfer transitions. The difference in the optical activity of the N-carboxymethyl and the N-carboxyethyl compounds is
clearly seen in Figure SD-29 (See SD section), where 6 shows only one negative band in the 600-800 nm range, while 8 shows a bisignate band within the same range. This suggests that the conformational effect of the chelate ring formed by carboxyalkyl pendant arm has an important influence in the overall chiral-optical properties. It is worth noting that the vicinal and conformational effects are additive in their contribution to the overall optical activity.[17b] For instance, the higher torsion of the carboxyethyl pendant arm in 8, as seen in the crystal structure, may contribute to a more pronounced spatial asymmetric distortion when compared to 6, and consequently to a higher splitting of the d-d levels as well as higher overall optical activity in the 600-800 nm range.

2.7 Cyclic Voltammetry

The redox characteristics of the Cu(II) compounds (6-10) were studied in DMSO using Bu₄NBF₄ as electrolyte. Complexes 8-10 display by cyclic voltammetry one irreversible cathodic wave attributed to Cu(II)→Cu(I) reduction, while 6-7 display two successive cathodic processes (Waves I and Ia, Figure SD-30) at potentials that differ by less than 250 mV (Table 3). The two sequential waves are attributed to the reduction of two slightly different copper centers in agreement with structural differences observed by X-ray analysis in the dinuclear complex 7 (Figure 1). A third irreversible cathodic process is observed at potentials lower than the former ones which is attributed to a ligand based process.

In contrast, complexes 8-10 display just one irreversible cathodic process at a potential in between those observed for complexes 6 and 7 (Table 3) suggesting that the two copper centers are electronically similar (see Fig. SD-31).
Table 3. Cyclic voltammetry data\textsuperscript{a} for Cu(II) complexes obtained in Bu\textsubscript{4}NBF\textsubscript{4}/DMSO

<table>
<thead>
<tr>
<th>Complex</th>
<th>(E_{\text{red}}) (V)</th>
<th>(E_{\text{ox}})</th>
<th>Wave generated by reduction</th>
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<tr>
<td>6</td>
<td>-0.86, -1.10</td>
<td>-2.03</td>
<td>10.2</td>
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<tr>
<td>7</td>
<td>-1.11, -1.21</td>
<td>-2.10</td>
<td>1.00</td>
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<tr>
<td>8</td>
<td>-0.96</td>
<td>1.06</td>
<td>0.04; 0.24(ads)</td>
</tr>
<tr>
<td>9</td>
<td>-0.80</td>
<td>1.13</td>
<td>-0.07; 0.22(ads)</td>
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<tr>
<td>10</td>
<td>-0.98</td>
<td>1.02</td>
<td>-0.04; 0.25(ads)</td>
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\(\text{a}\)Values in V (± 10 mV) \textit{versus} SCE using Fe(C\textsubscript{5}H\textsubscript{5})\textsubscript{2}\textsuperscript{3+/0} (\(E_{\text{ox}}\) =0.44 V) as internal reference.

Upon reduction, all complexes display on the reverse scan a characteristic adsorption (Figure SD-31) attributed to formation of Cu\textsuperscript{0}. The adsorption process is followed in the cases of complexes 6 and 7 and preceded in the case of complexes 8, 9 and 10 by a new anodic wave (A) also generated by reduction. This data is consistent with two distinct processes being promoted by electrochemical reduction, one leading to formation of a new complex (wave A) and the other to reduction to copper metal (adsorption). The electrochemical behavior of the N-carboxymethyl (6, 7) and N-carboxyethyl (8-10) complexes evidences that in addition to different structural characteristics, \textit{i.e.} the six (8-10) \textit{versus} the five (6 and 7) member rings of the ONO ligands and distinct arrangements, the complexes have different electronic properties and behaviors in electron transfer processes.

In order to check whether the electrochemical behaviour and/or the redox properties of the complexes changed in the presence of iodide (known to have a marked effect into the catalytic activity of the complexes) cyclic voltammetry studies were made in the presence of Bu\textsubscript{4}NI, chosen to keep the Bu\textsubscript{4}N\textsuperscript{+} cation in common with the electrolyte. It is worth noting that the redox behaviour of the complexes did not change, neither did the potentials of the cathodic processes, whose values remained within the experimental error (± 10 mV). In the anodic region oxidation of iodide was clearly observed (\(E_{\text{ox}}\) = 0.38 V; \(E_{\frac{1}{2}}\) = 0.58 V). New experiments were then set up and KI added to the solution of complexes 6, 8 and 9, since potassium iodide is the additive used in the catalytic assays. In this case significant changes were observed in the cyclic
voltammograms, *i.e.* in the cathodic region wave I defined better, wave Ia almost disappeared and the potential of wave II (E\text{p}_{\text{red}} = -1.89) shifted ca. 120 mV to higher potential (Figure SD-32). Additionally, the potential and intensity of the cathodically generated waves (adsorption (*)& and anodic (A)) changed as displayed for 6. A shoulder on the left hand side (b) of the adsorption wave denotes formation of a new species not observed in the absence of KI (Figure 3).

**Figure 3.** Cyclic voltammograms of 6 in Bu\text{4}NBF\text{4} / DMSO solution (0.1 M), before (—) and after (---) addition of KI, depicting cathodic generated adsorption (*) and anodic (A) waves.

The electrochemical behavior of complexes 8 and 9 in the presence of KI followed the same trend as 6 showing that KI and Bu\text{4}NI have distinct effects on the redox characteristics of the complexes in solution. In this case, the data obtained by cyclic voltammetry suggests that the potassium cation plays a significant role in the electrochemical processes, thus, in turn, in the catalytic activity (see below).

3. Asymmetric oxidative coupling of 2-naphthol

The catalytic activity of compounds 6 to 10 was assessed in the asymmetric oxidative coupling of 2-naphthol using air (dioxygen) as oxidant. The results are summarized in Table 4.
The first observation is that the enantiomeric excesses depend greatly on the N-carboxyalkyl pendant arm length and less on the amino acid side chain type. For instance, the N-carboxymethyl compounds yield enantiomeric excesses up to 18% (Table 4, entries 1 to 7) whereas under the same conditions the N-carboxyethyl compounds provide enantiomeric excesses above 40% in all cases (Table 4, entries 8 to 21). Another important observation is the variability of the conversions of 2-naphthol and BINOL yields for the same conditions. This is particularly evident for 8 (Table 4, entries 8 to 17), where conversions and yields vary between 44% and 73%. This may be due to differing rates of mass transfer at the air/solvent interface, resulting in differing rates of diffusion of air into the reaction medium. Since the reactions were carried out in vessels with vented screw caps, contact with air was facilitated only by gently stirring the reaction mixture, thus the rate of diffusion of air is difficult to control under these conditions. No injection of air into the reaction mixture was made so that solvent evaporation is minimised, thus also decreasing changes in the solvent composition. Solvent composition indeed revealed to be an important factor and will be addressed in the following section.
Table 4. Asymmetric oxidative coupling of 2-naphthol using the prepared copper complexes as catalysts and air (dioxygen) as oxidant.

<table>
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<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conv. (%)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>Selectivity BINOL (%)</th>
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<sup>a</sup> Reaction conditions: 5 mg of catalyst (ca. 2 mol%), 1 mmol of 2-naphthol, 1 mmol of KI, 4 mL of solvent (EtOH/H<sub>2</sub>O, 1:1). The reaction mixture was stirred for 24 h under air at either 25 or 40 °C. A greater volume of solvent (6 mL) was used in the 72 h runs. <sup>b</sup>Product yields and enantiomeric excesses were determined by chiral HPLC. <sup>c</sup> Reaction run with 1 mmol of Et<sub>3</sub>N.
Despite this, the overall enantiomeric excesses and selectivity towards the formation of the BINOL product at 40 ºC displayed by the N-carboxymethyl and N-carboxyethyl catalysts remained consistent throughout. It was also found that carrying out the reactions at 25 ºC instead of 40 ºC did not yield improvements regarding selectivity and enantiomeric excess, but decreased conversion and yields, despite the longer reaction times. (Table 4, entries 1, 5 and 8).

In face of this, various attempts at optimisation were carried out by studying the effects of the solvent, cation, anion and basic additive effect on overall activity of 8, chosen as a model catalyst.

3.1 Solvent effect

Given the limited solubility of the complexes in ethanol, a 1:1 ethanol/water mixture was used as solvent in order to facilitate the dissolution of the catalyst. Considering our previous studies with chiral N-picolyl-L-amino acid Cu(II) catalysts [4], we anticipated that the activity of the present catalysts may also depend on the presence of water. Therefore, it was necessary to ascertain the optimal ethanol/water ratio for maximal BINOL yield and enantiomeric excess. Table SD-6 lists the results obtained with varying ethanol/water ratios.

It was observed that the enantiomeric excess decreases significantly upon increasing the water content of the reaction medium (Figure 4). Conversely, selectivity towards the formation of BINOL increases to a maximum of 74% if the reaction is carried out in water. No clear trend could be observed relating the content of water with conversion and yield. Again, the differing diffusion rates of air into the reaction mixture could explain the fluctuating conversions. The negative impact of water on enantioselectivity could be due to increased disruption of key aromatic π-π and/or cation-π interactions in the asymmetric transition state. Taking into account this trend, optimal enantioselectivity could be obtained in 100% ethanol, but selectivity would then decrease since the BINOL product can also be subject to further oxidative coupling or oxygenation, as we have observed in previous studies [4]. The low solubility of BINOL in water may account for the increasing selectivity, as the product precipitates out of the reaction medium, thus no longer being available for additional oxidation reactions. In face of the above, the optimal trade-off between enantioselectivity and product selectivity was obtained with ethanol/water mixtures with a water content ranging from 50 to 75 %.
Very slight differences in performance were observed when ethanol was replaced with either methanol or isopropanol. With methanol, a more polar reaction medium is obtained and selectivity towards BINOL was slightly higher when compared to the isopropanol/water reaction medium (Table SD-7).

![Graph showing trends in BINOL yields, enantiomeric excesses and selectivity](image)

**Figure 4.** Observed trends in BINOL yields, enantiomeric excesses and selectivity afforded by 8 with increasing water content of the solvent.

### 3.2 Anion effect

In contrast with what was observed in our previous studies with chiral N-picolyl-L-amino acid Cu(II) catalysts, all of the Cu(II)-complexes described herein require KI to exhibit optimal catalytic performance without added base. The electrode potential of the Cu(II)/Cu(I) couple is responsive to the presence of halides coordinated to the copper centre, with the redox couple half-cell potential shifting to more positive potentials with the coordination of heavier halides [18].

With the Cu(II)-(N-picolyl-L-amino acid) complexes, the [N,N,O] donor atom set allowed of the Cu(II)/Cu(I) redox couple to remain at a sufficiently positive electrode potential to induce spontaneous electron transfer from the 2-naphthol substrate without the assistance of KI, whereas the more basic N-carboxylalkyl-L-amino acid ligands may be shifting the electrode potential of the redox couple to increasingly negative potentials, thus making the aforementioned
electron transfer more difficult [19]. Nevertheless, the effect of halides other than iodide on the oxidative behaviour of 6 and 8 was evaluated and the results are listed in Table SD-8.

Among the potassium halides tested, only KI is capable of enabling catalytic activity in the absence of a basic additive. There is some low catalytic activity when KCl or KBr are chosen as additives. Interestingly, when KCl is used with catalytic amounts of Et3N, the overall results are comparable to those obtained with KI alone. This indicates that other potassium halides may be used additives in place of KI, provided that a basic additive is also present.

The amount of KI used in the absence of base is also important. The catalytic performance of 8 decreased sharply when only 0.1 mmol (10 mol%) of KI was used instead of 1 mmol. Part of this activity is regained when 10 mol% of Et3N is also employed, but the overall performance is lower than that obtained when only 1 mmol of KI is used. The possible reasons for the differences in catalytic activity and its dependence on the alkali metal iodide additive are addressed in the following sections.

### 3.3 Cation effect

Not only the anion of the salt additives exerted a determinant effect on the catalytic performance of 8, it was found that the cation also appears to play a relevant role in the catalytic process (Table SD-9). It was observed that considerable catalytic activity is obtained only when alkali metal iodides are used as additives. Little to no coupling products were obtained when tetraalkylammonium iodides were used as additives, with tetrabutylammonium iodide affording the lowest conversions and BINOL yields. This provides a clearer picture of the role of the alkali metal halide additive, in particular of the cation, suggesting that cation-π interactions are also crucial to the catalytic transition state. Overall, the results suggest a synergistic effect of both the cation and anion in the modulation of the catalyst activity.

It is worth noting that there is no clear difference in catalyst performance when using Li, Na, K and Cs iodides, due to the aforementioned variability of substrate conversions and product yields.
3.4 Effect of basic additive

Considering the inactivity of 6 and 8 in the presence of KCl alone and the results obtained with added base, the effect of the basic additive was also evaluated. The possibility of these catalysts exhibiting activity in the absence of iodide salts with only catalytic amounts of Et₃N was also tested. The obtained results are listed in Table SD-10. It was observed that when Et₃N was used in catalytic amounts (1 mol%) with 1 mmol of KI, conversions and yields were increased, while maintaining overall enantiomeric excess and selectivity. Increasing the amount of Et₃N (10 to 100 mol%) did have a negative effect on selectivity, likely due to the increased prevalence of over-oxidation reactions. It was also found that 8 still exhibited catalytic activity when using 1 mol% of Et₃N and KI, or in the absence of KI, although the conversion and yield was significantly lower, with a slightly lower product selectivity and enantiomeric excess. The use of catalytic amounts of morfoline afforded similar results. However, a large excess of this base exerted a negative effect on catalyst performance, which may be due to the coordinating character of morfoline. Using 1 mol% of 2,4,6-collidine did not yield any apparent improvement over the use of Et₃N or morfoline. This confirms that oxidative coupling with 8 as catalyst is possible with only catalytic amounts of the tested organic bases, although optimal catalytic performance is only obtained when an excess alkali metal halide, preferably iodide, is additionally employed.

4. Elucidation of mechanistic aspects

The mechanism for the oxidative coupling of 2-naphthol using the Cu(II) catalysts described in this work is expected to be similar to that proposed earlier in our previous report [4]. The proposed mechanism consists of the following steps: i) base-assisted binding of 2-naphthol to the Cu(II) centre, with the proton acceptor being the ligand itself or a basic additive; ii) one-electron transfer from the coordinated 2-naphtholate to the Cu(II) centre, generating a Cu(I)-bonded naphthyloxyl radical species; iii) homo-coupling of the Cu(I)-bonded naphthyloxyl radical species to yield a Cu(I)-BINOLate species; iv) product dissociation and protonation; v) oxidation of the Cu(I) species with atmospheric O₂ and regeneration of the Cu(II) catalytic species. Taking into consideration the catalytic results obtained so far with this system, catalytic activity is observed when one of the following conditions is fulfilled: i) an excess of alkali metal iodide is used as additive; ii) a catalytic amount of an organic base is used as additive.
The role of the basic additive consists in assisting in the binding of the substrate to the metal complex, although it was noted earlier that the overall catalytic activity was much lower when only base was used compared to the activity obtained when using only KI as additive. It was found that, when using a basic additive, catalytic activity was enhanced also when KCl was used as additive. However, little catalytic activity was obtained when 1 mmol of KCl was used alone. These observations point to the possible role of the alkali metal halides in the catalytic cycle. It is known that halides have the effect of shifting the electrode potential of the Cu(II)/Cu(I) redox couple to more positive values, and heavier halides exert a stronger effect [18]. Destabilisation of the Cu(II) oxidation state should occur upon coordination of a halide anion, thus translating into an enhanced oxidative character of the Cu(II) complex. When an alkali metal iodide is used, this enhancement is such that the assistance of a base is no longer necessary for the reaction to take place to a significant extent. Combination of KI with base accelerates the reaction further, but may have a negative impact on the overall selectivity.

One noteworthy aspect of the present complexes is the apparent ionochromism exhibited when in the presence of KI in solution, where the initially blue aqueous solutions obtained after dissolution of the complexes turned green upon addition of KI. This indicates that a direct interaction between the iodide anion and the complex is taking place [20]. To obtain further clues regarding the effect of these additives on the catalytic activity of the complexes, UV-Vis and CD spectra of 6 and 8 were measured in the presence of KCl, KBr and KI.

It was observed that an additional absorption band appears in the 300-400 nm range (ca. 360 nm) in the UV-Vis spectra of both 6 and 8, when KI is present. No apparent change is observed with KCl or KBr (Figure SD-33 for 6 and 5 for 8). The changes in the visible absorption spectra observed with KI can be attributed to the halide ligand exchange and/or binding in the apical positions of the square-planar or square-pyramidal Cu(II) centre. The difference in energy between Cu(II)-halide absorption bands could be due the differences in the HOMO-LUMO gap, with the weaker ligand field-effect of iodide contributing to a smaller gap. The HOMO-LUMO gaps for the transitions associated to the Cu(II)-chloride, Cu(II)-bromide bonds may be wider due to the stronger ligand field effects of chloride and bromide, thus the respective higher energy absorption bands fall below the 300 nm limit and are masked by the intra-ligand transitions. Also of note is the fact that that this new absorption band obtained with KI does not appear in the 300-400 nm range of the CD spectra of 6 and 8 (Figures SD-34 for 6
and SD-35 for 8). Some changes in the 400-500 nm range do occur with all potassium salt additives: there is an increase of optical activity for 6 and a decrease for 8 in this range, but the bands associated with the d-d transitions remain essentially unchanged. Overall, and considering the catalytic results obtained with different salt additives, this minor change to the CD spectra of 6 and 8 can be attributed in part to the interaction of the Cu(II) centre with the halide anion. While the halide can coordinate directly to the metal centre, the nature of the interaction of the alkali metal cation (e.g. K⁺) with the complex remains unclear.

**Figure 5.** Isotropic electronic absorption spectra of 8 (2.2 mM), 8 (1.5 mM) with KCl, 8 (1.5 mM) with KBr and 8 (1.7 mM) with KI, recorded at room temperature in EtOH/H₂O 1:1, using 10 mm optical path quartz cells.

Another concern was the possible oxidation of the I⁻ by the Cu(II) complex. This was evaluated by monitoring the NMR paramagnetic shifts in the spectra of a sample containing compound 8 and excess of KI using the Evans method (Figure 6) [21]. No variation of the MeOH and tBuOH methyl group shifts was observed after 24 h at 40 °C in a tightly stoppered NMR tube. No purging of air or inert atmosphere was made in this case. It can be argued,
however, that the presence of air in the test tube may mask any reduction of the Cu(II) complex by re-oxidation of the Cu(I) species that might form. To test this possibility, another experiment was made using an NMR tube under a N₂ atmosphere.

The methyl group chemical shifts of tBuOH in the 1.2-1.4 ppm range were considered to calculate the paramagnetic shifts. The obtained paramagnetic shifts for the samples without and with KI were 54.4 Hz and 51.9 Hz, respectively. The paramagnetic shift obtained for the test run under N₂ was also 51.9 Hz. The magnetic moments were calculated for the square-planar and square-pyramidal species [Cu(4)(H₂O)] (M_w = 316 g/mol) and [Cu(4)(H₂O)₂] (M_w = 334 g/mol), which may exist in aqueous solution, given the solution EPR data and crystal structure obtained for 8 (Table SD-11).

While the magnetic moments obtained for the samples with KI were slightly smaller, all values are slightly above the magnetic moments for paramagnetic species with one unpaired electron (1.71 µB) [21g]. This, in conjunction with the data obtained by cyclic voltammetry, indicates that oxidation of I⁻ by the Cu(II) complex at 40 °C is unlikely to occur.
Figure 6. 300 MHz $^1$H NMR spectra of (A) 8 (4.8 mg, 31.3 mM) in 0.5 mL of MeOH/D$_2$O/$\text{tBuOH},$ (B) 8 (4.7 mg, 30.6 mM) in the presence of an excess of KI (0.45 M) in 0.5 mL of MeOH/D$_2$O/$\text{tBuOH}$ (1:1:0.2) under air and (C) (4.7 mg, 30.6 mM) in the presence of an excess of KI (0.45 M) in 0.5 mL of MeOH/D$_2$O/$\text{tBuOH}$ (1:1:0.2) under a N$_2$ atmosphere. All samples were measured after 24 h at 40 °C in sealed NMR tubes. The (■) denotes the sample MeOH methyl group shift, (*) denotes the reference MeOH methyl group shift, the (●) denotes the sample $^3$BuOH methyl group shift and (+) denotes the reference $^3$BuOH methyl group shift.

To further our understanding of the causes behind the significant differences in reactivity observed with salt and basic additives, theoretical calculations of the spin density distribution were carried out with a model Cu(II)(iminoacetate) complex in the presence of 2-naphthol and iodide.

The spin density distribution in the model complexes [Cu(LH)(ONAPH)]$^-$ (I), [Cu(L)(ONAPH)]$^-$ (II) and [Cu(L)(HONAPH)] (III) (L = di(carboxymethyl)amine) calculated using the theoretical (DFT) methods is shown in Figure SD-36 (See SD section). In all complexes, spin density is delocalized between the donor atoms of the ligand L and the copper.
atom. In complex I, the spin density at the copper atom is 0.50 e indicating that the state of Cu is intermediate between CuI and Cu(II). Significant spin density is also revealed at the I– ligand (0.17 e) and the ONAPH– ligand (0.19 e), in particular, at the donor O-atom (0.11 e) and one of the α-C-atoms of the naphtyl moiety (0.09 e). In the anionic complex II, spin density at Cu is noticeably higher (0.58 e) suggesting that the ligand-to-metal electron transfer is less efficient in II than in I. Additionally, only the donor O-atom of the ONAPH– ligand has a noticeable spin density (0.12 e). Since, the formation of the naphthyloxy radical species is crucial for the efficient coupling of 2-naphthol [4], the lower overall spin density at the ONAPH– ligand in II compared to I (0.19 e vs. 0.13 e) may account for the lower reactivity of the Cu(II) catalysts in the presence of an organic base compared to the addition of alkali metal iodide. Finally, in the protonated complex III, the overall spin density at the 2-naphthol ligand is much lower (0.05 e) explaining the inertness of the Cu(II) catalysts in the absence of the additives.

5. Conclusions

A range of water-soluble and structurally simple Cu(II) complexes derived from chiral N-carboxylalkyl amino acids were successfully synthesised and characterised. Solution and solid state characterisation indicates a pronounced tendency of these compounds to aggregate and form oligomeric structures. This is can be observed in the molecular structures obtained by single crystal X-ray diffraction studies, where coordination polymers were obtained for 7 and 8. It was also observed from both the CD and catalytic experiments that the length of the N-carboxyalkyl pendant arm is a key factor in tuning some of the more important properties of the complexes, such as optical activity and overall catalytic activity and/or enantioselectivity. This difference in the CD profiles can be attributed to the possible conformations of the chelate rings, with a combination of a 5- and a 6-membered chelate rings offering a more effective chiral induction than two 5-membered rings, and/or to a more efficient vicinal effect, as the size of the carboxyalkyl pendant arm may contribute to the existence of more rigid structures and stabilize the chiral-at-the metal diastereoisomeric transition state that yields higher selectivities [17].

Regarding the acticity of this series of Cu(II)-(amino acid) complexes in the catalytic oxidative coupling of 2-naphthol using air (dioxygen) as oxidant, it was found that all operate optimally in 1:1 ethanol/ water mixtures, as long as KI is present in excess. The obtained results
show that activity and enantioselectivity depend on the conjunction of several factors: i) ligand structure, ii) type of iodide additive and iii) water content. For instance, The N-carboxymethyl complexes 6 and 7 were significantly less enantioselective than their N-carboxyethyl counterparts 8 and 9. This contrast is attributed to the factors mentioned above in the CD studies. Furthermore, \( \pi-\pi \) and cation-\( \pi \) interactions play an important role in the asymmetric transition state. This was particularly evident in the cases where KI and NaI were replaced by tetraalkylammonium iodides, or when the content of water was increased. The use of an organic base such as Et\(_3\)N is optional, as long as catalytic amounts are used. In addition, this also enabled the use of KCl as inorganic additive, with complex 8 affording comparable results to those obtained with KI under the same conditions. The role of the base is that of assisting in the binding of the substrate to the metal centre. An excess of base leads to lower BINOL yield due to excessive deprotonation of the substrate and its over-oxidation.

The study of the mechanistic aspects revealed that: i) there is an interaction of KI with the Cu(II) complex, as shown by the apparent ionochromism and the cyclic voltammetry data, and that ii) the iodide anion is unlikely to be oxidised by the complexes under the catalytic conditions used. Computational spin density calculations indicate that there is an increased spin distribution in the ortho position of the Cu-bound naphtholate, in contrast to the cases where iodide is absent. These observations are in line with the outline of the catalytic mechanism our group proposed in a previous study [4].

Overall, the series of N-carboxyethyl complexes show promise, given that enantiomeric excesses surpassing 50% were obtained under mild reaction conditions and with structurally simple catalysts. Selectivity towards the formation of BINOL remains at ca. 60% due to the inherent phenol oxygenase-like character of Cu(II), which needs to be suppressed more effectively. The improvement of both the yields and enantiomeric excesses could be achieved by fine-tuning the ligand structure, where bulky and/or chiral 3-halopropionates are used as precursors. It is also worth noting that the catalysts operate in low-toxicity solvent mixtures and mild temperatures, and thus may provide a contribution to the development of efficient methods for the synthesis of enantio-enriched BINOLs with low environmental impact.

The advantage of the catalytic system reported herein over the highly effective and enantioselective copper- and vanadium-based catalysts reported recently in the literature [2,3] lies in the ease of preparation and structural simplicity of the copper complexes, in addition to
the capability of affording enantiomeric excesses of ca. 50 % for BINOL in ethanol/water mixtures. Although there is room for improvement, we are confident that the catalytic systems described in this work present a starting point for the development of a highly enantioselective and effective process for the synthesis of enantiopure BINOLs under mild and low-toxicity conditions.

6. Experimental Section

6.1 Materials and Equipment

Chiral amino acids L-phenylalanine (L-Phe) and L-Valine (L-Val) were purchased from Alfa Aesar and L-tryptophan (L-Trp) was from Panreac. Chloroacetic acid and 3-chloropropionic acid were from BDH. Metal precursor copper acetate monohydrate was from Panreac. Solvents were from Carlo-Erba, Panreac, Sigma-Aldrich or Fisher. All chemical precursors and solvents were used as received. The UV-Vis spectra were measured on a Shimadzu UV-1603 spectrophotometer and the CD spectra on a Jasco J-720 spectropolarimeter. The NMR spectra (\( ^1H \) and \( ^{13}C \)) were recorded on Bruker Avance+ 400 MHz and 300 MHz Spectrometers. \( ^1H \) and \( ^{13}C \) chemical shifts (\( \delta \)) are expressed in ppm relative to either NaDSS (sodium 4,4-dimethyl-4-silapentane-1-sulfonate), the deuterated solvent residual peak or, for the \( ^{13}C \) spectra, the carbonate peak. The elemental analyses for all compounds were carried out at Laboratório de Análises of Instituto Superior Técnico, using an EA110 CE automatic analyser Instrument. The EPR spectra were measured with a Bruker EMX X-band spectrometer. The sample for the EPR measurement were frozen at 77 K and DPPH radical was used as external reference. Simulation of the measured spectra (1st derivative X-band EPR) was carried out with the computer program developed by Rockenbauer and Korecz [22]. The cyclic voltammetry studies were carried out in a three compartment cell provided with platinum wire electrodes (work and secondary) and a silver wire (reference) electrode, under an N\(_2\) atmosphere. Solutions of Bu\(_4\)NBF\(_4\) in DMSO or MeOH (0.1 M) were used as electrolytes. The cell was interfaced with a VoltaLab PST050 equipment and data acquired using a Pentium(R) Dual-Core computer. The potentials were measured in Volt (± 10 mV) versus SCE at 200 mV/s using (Fe(\( \eta^5 \)-C\(_5\)H\(_5\))\(_2\))\(^{0+/+} \) as internal
reference (DMSO: $E_{\text{red}}^1 = 0.44$ V; MeOH: $E_{\text{red}}^1 = 0.43$ V). The mass spectrometer used is an ion trap equipped with an ESI ion source (Thermo Scientific). The equipment was operated in the ESI negative and positive ion modes. The optimized parameters were as follows: ion spray voltage, $+$ $4/ -5.3$ kV; capillary voltage, $5/-20$ V; tube lens offset, $63/-124$; sheath gas (N2), 20 arbitrary units; capillary temperature 275 °C. Spectra typically correspond to the average of 20-30 scans, and were recorded in the range between 100-2000 Da.

6.2 Synthetic Procedures

The methods for the preparation of all compounds reported herein are included in the Supplementary Data.

6.3 General procedure for the oxidative coupling of 2-naphthol

The solid catalyst (5 mg, ca. 2 mol%), KI (0.01 to 1.0 mmol) and 2-naphthol (1.0 mmol) were dissolved in the appropriate solvent (4 mL for 24 to 48 h runs, 6 mL for longer runs). The resulting solution was stirred at either 25 or 40 °C in a glass vessel with a vented screw cap to maintain a constant contact with air. Control catalytic runs without the catalyst were also carried out.

The analysis of oxidation profiles was done by chiral HPLC, using a Daicel Chiralpak IA column and Borwin software. The detection wavelength used was 254 nm. The eluent was $n$-heptane: 1-propanol (80:20). The flow rate used was 1.0 mL/min. The internal standard (1 mmol of acetophenone) was added to the reaction mixture before analysis by HPLC. In the case precipitate was present, the reaction mixtures were homogenised with an appropriate organic solvent.

6.4 Procedure for the measurement of magnetic moments in solution by NMR

Two NMR tubes were charged with 4.7 and 4.8 mg of 8, respectively. Separately, a stock solution 200 µL of $t$-butyl alcohol, 1 mL of D$_2$O and 1 mL of MeOH prepared. Another stock
solution using the same solvent ratio was prepared including 165 mg of KI. Two reference capillary tubes were prepared using these stock solutions: one reference for the control tube and the reference with the KI stock for the test tube. The control NMR tube containing 4.8 mg of 8, was charged with 0.5 mL of the freshly prepared tBuOH/MeOH/D$_2$O stock solution. The test NMR tube containing 4.7 mg of 8 was charged with 0.5 mL of the freshly prepared tBuOH/MeOH/D$_2$O/KI stock solution. The respective reference capillary tubes were inserted into the NMR sample tubes, which were then tightly stoppered and vigorously stirred till the complex dissolved completely. The tubes were then heated at 40 ºC for 24 h and the samples analysed by $^1$H and $^{13}$C NMR. The magnetic moments were estimated using the method developed by Evans et al. modified for NMR spectrometers with superconducting magnets and applying the appropriate diamagnetic corrections [21].

6.5 X-ray Crystallography
Crystals of compounds 7 and 8 were selected, and mounted on a nylon loop, covered with polyfluoroether oil. Collection of crystallographic data was performed at room temperature, on a Bruker AXS-KAPPA APEX II diffractometer, using graphite monochromated Mo-Kα radiation ($\lambda=0.71073$ Å). Bruker SMART software allowed the determination of cell parameters, which were refined using Bruker SAINT on all observed reflections. The crystal and structure refinement data for compounds 7 and 8 given in Table SD-12. SADABS was applied for absorption correction [23]. Direct methods, programs SIR2014 [24] and SHELXS-97 [25] included in WINGX-Version 2014.1 [26] and SHELXL, were employed for structure solution and refinement [25]. All hydrogen atoms were inserted in idealised positions and allowed to refine riding on the parent carbon atom with C–H distances of 0.93 Å, 0.96 Å, 0.97 Å and 0.98 Å for aromatic, methyl, methylene and methyne H atoms, and with Uiso(H) = 1.2Ueq(C). Even though the crystals of 8 were of poorer quality, and both complexes were refined as a 2-component inversion twin, both refined to a perfect convergence. Graphic diagrams were prepared with ORTEP-III at the 30% probability level, and with Mercury CSD 3.9 [27]. Data was deposited in CCDC under the deposit numbers 1821984 for 7 and 1821985 for 8. Crystal data is listed in Table SD-12.
6.5 Computational Methods

The full geometry optimization of all structures was performed at the Density Functional Theory (DFT) level with the M06 functional [28] using the Gaussian-09 package [29]. No symmetry operations were applied for any of the calculated structures. The relativistic (MDF10) or quasi-relativistic (MWB46) Stuttgart pseudopotentials were used for the copper and iodine atoms, respectively, with the appropriate contracted basis sets (8s7p6d)/[6s5p3d] and (4s5p)/[2s3p] [30]. The basis set for the iodine atom was augmented by a d-function with exponent 0.243. The 6-31+G* basis set was used for other atoms. The nature of the located equilibrium structures was verified by the analytical calculations of the Hessian matrix (no imaginary frequencies).

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Appendix A. Supplementary Data

Conflicts of Interest

There are no conflicts of interest to declare.

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