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Journal of Organometallic Chemistry 641 (2002) 71–80

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

Structural and mechanistic studies of the copper(II)-assisted *ortho*-hydroxylation of benzoates by trimethylamine N-oxide

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Received 10 May 2001; accepted 20 August 2001

Dedicated to Professor Rolf Gleiter on the occasion of his 65th birthday

Abstract

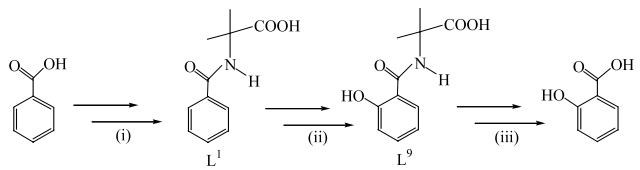
N-benzoyl-2-methylalanine (H_2L^1) is *ortho*-hydroxylated stereoselectively by trimethylamine N-oxide (TMAO) in the presence of copper(II). The experimental structure of $[Cu(L^1)(TMAO)_2]$ suggests that the oxygen transfer agent TMAO transfers the oxygen atom to copper(II), and $(L^1)^{2-}$, coordinated to copper(II) by a carboxylate oxygen and the amide nitrogen donor, is well pre-organized for an oxygen transfer from copper to the *ortho* carbon atom of the benzene ring. Product analyses as a function of reaction time of the copper(II)-mediated *ortho*-hydroxylation reaction with H_2L^1 and various derivatives support the suggestion of a reactive copper-oxo or copper-hydroxo intermediate, stabilized by a five-membered chelate with hard carboxylate and N-amide donors. The analysis also suggests that there is a pre-equilibrium with a Cu:L = 1:1 ratio, and this might involve Cu/L^{2-}/TMAO or dicopper complexes. Depending on the ligand H_2L, complexation with the salicylate product may inhibit the *ortho*-hydroxylation reaction. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: *ortho*-Hydroxylation; Salicylic acid; Selectivity; Reaction mechanism; Chelate ring size

1. Introduction

The hydroxylation of aromatic compounds is a processes of considerable industrial importance [1]. Many simple and efficient reactions, such as the hydroxylation by H_2O_2 via electrophilic (H_2O_2–BF_3 or HF_3) [2] or free radical processes (Fenton's reaction) [3], hydroxylation by $KMnO_4$–H_2SO_4 [4,5] or the addition of $OH^{\bullet}$ [6] by radiolysis, are unselective and lead to product mixtures. In nature there are a number of copper-assisted mono-oxygenases (e.g. phenylalanine monooxygenase, tyrosinase) [7–10], and the industrial production of phenol by pyrolysis of benzoic acid in the Dow–Phenol process is an efficient and selective copper(II)-mediated reaction [11–14]. These processes involve the copper(I/II) and/or copper(II/III) couples, with the aromatic substrate and oxo-, peroxo-, superoxo- or hydroxo-groups coordinated to the metal center.

Recently, an efficient and selective copper(II)-assisted *ortho*-hydroxylation procedure for the conversion of benzoate to salicylate with trimethylamine N-oxide (TMAO) was described (see Scheme 1) [15,16]; the reaction was assumed to proceed via coordination of copper(II) to the carboxylate group, oxidation of this complex by TMAO to produce the reactive species, a copper(III) hydroxo complex, followed by oxygen



Scheme 1. (i) One equivalent benzoyl chloride, one equivalent amino acid; (ii) 1.1 equivalents Cu(II), five equivalents TMAO, CH_3CN (40 ml) or $Cu_2(HL)_4$, five equivalent TMAO, CH_3CN (40 ml); (iii) H_2SO_4 (25%), extraction (ethyl acetate); H_2SO_4 (40%), 6 h at 120 °C extraction (ethyl acetate).

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PII: S0022-328X(01)01291-8

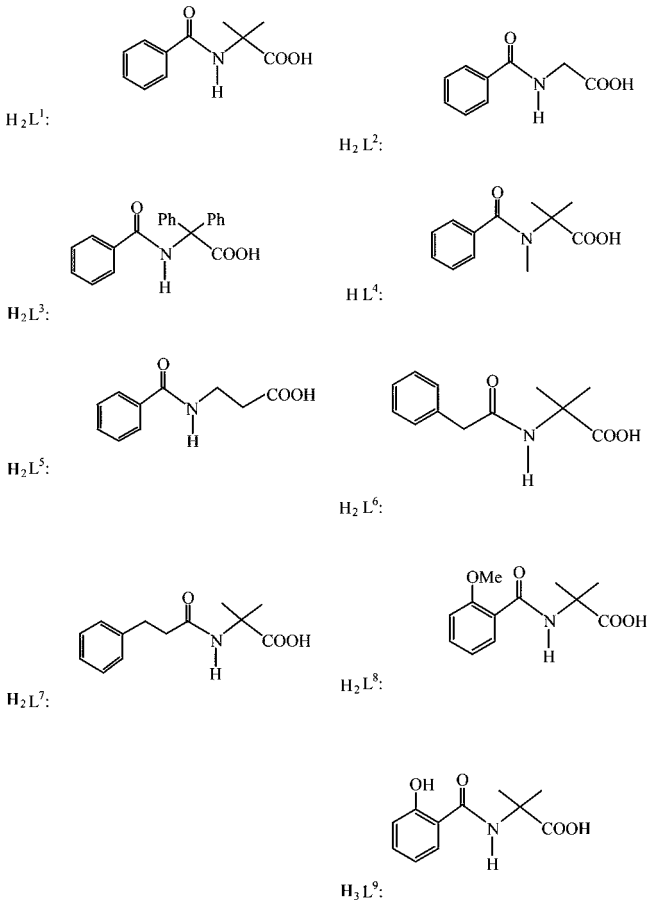


Chart 1.

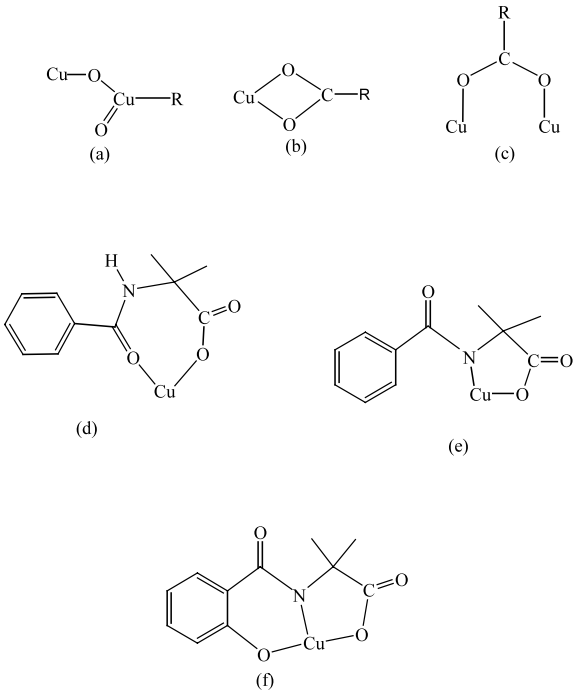


Chart 2.

transfer to the benzoate group [15,16]. This was supported by the determination of the relative reactivities in this process of a number of benzoate derivatives with a substituted benzene ring [15]. With the aim to further analyze the reaction mechanism and to investigate the scope of this reaction, we have prepared a range of amide derivatives (see Chart 1) and studied their copper(II) complexes, and the *ortho*-hydroxylation reactivities of the metal-free ligands and the isolated and characterized copper(II) complexes.

2. Results and discussion

2.1. Syntheses and properties of the benzoate derivatives and their copper(II) compounds

Ligands H_2L^1 to H_3L^9 were prepared by standard methods, involving the arylation of amino acids with the corresponding acid chlorides (61–81%), see Section 3 [17–20]. Copper(II) compounds of these ligands were obtained by heating the copper salt, usually copper carbonate hydroxide ($CuCO_3 \cdot Cu(OH)_2$) with the ligands in *iso*-propanol–water (7:5) solutions (see Section 3). H_2L^1 to H_2L^8 have carboxylate and amide donor groups (amide-N coordination of HL^4 is blocked by *N*-methyl substitution), H_3L^9 has an additional phenol donor group.

There are various possible stoichiometries and structural motives for copper(II) complexes with these ligands, some of them might be in equilibrium with each other, and the reactive starting material for the *ortho*-hydroxylation process might not be the most abundant compound in solution. Possible structural types are shown in Chart 2: The carboxylate might act as a monodentate (a), a bidentate (b) or a bridging donor group (c); depending on the extra ligands, carboxylate–copper(II) interactions are not very strong and induce only moderate ligand fields; the structural type (c), with $[Cu_2(HL)_4]$ or $[Cu_2(HL)_6]^{2-}$ (two ligands HL^- as monodentates) stoichiometries leads to the well known 'paddle-wheel' structures, which are a required structural feature in the Dow–Phenol process [12,13,21–24]. The amide group might act as a monodentate donor (not shown in Chart 2) or, together with the carboxylate, lead to a chelating structure (d), (e); at higher pH one assumes that the amide is deprotonated and coordinated via the nitrogen atom (e) [25]. With ligands H_2L^1, H_2L^2, H_2L^3, H_2L^6, H_2L^7, H_2L^8 and H_3L^9 this leads to a particularly stable five-membered chelate ring; the phenolate of H_3L^9 may act as an additional donor in any of the arrangements discussed so far, shown in Chart 2 is the structural type with a tridentate carboxylate–N-amide–phenolate donor set (f); in combination with the five-membered chelate ring discussed above, the six-membered ring involving the phenolate group leads to a

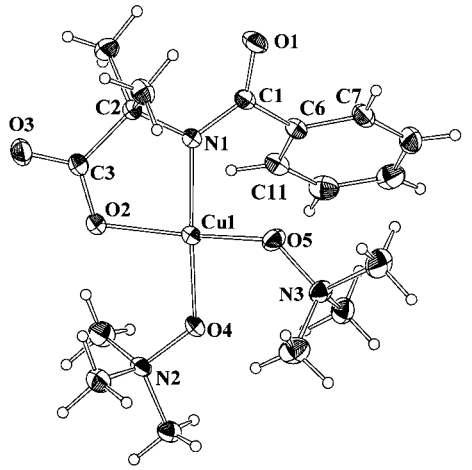


Fig. 1. ORTEP [29] plot of (*N*-benzoyl-2-amino-2-methylpropanoato-*O*-)bis-(trimethylaminoxido)-copper(II).

favorable, relatively unstrained geometry [26]. The amide–carboxylate donor set (e), (f) is relatively hard and, therefore, stabilizes high oxidation states. That is, it might stabilize copper(III) over copper(II) [27,28], and this has been assumed to lead to the active species in the hydroxylation reaction of benzoates with TMAO [15,16].

The stoichiometric and spectroscopic analyses of the copper(II) complexes of H_2L^1–H_3L^9 (see Section 3, $[Cu_2(HL^1)_4]$, $[Cu(L^1)(Me_3NO)_2]$, $[Cu_2(HL^2)_4]$, $[Cu_2(HL^3)_4(C_3H_8O)_2]$, $[Cu(L^4)_2]$, $[Cu_2(HL^5)_4]$, $[Cu_2(HL^6)_4(C_4H_8O_2)]$, $[Cu(HL^7)_4]$, $[Cu_2(L^8)_4]$, $[Cu(HL^9)(H_2O)_{1.5}]$) suggest that the paddle-wheel structures are destroyed when adding TMAO to the copper complexes in dry acetonitrile (the hydroxylation reaction studied here proceeds in dry acetonitrile and H_2L^1, H_2L^3, H_2L^6 and H_2L^8 are soluble in dry acetonitrile), as there is a change of the color (shift of λ_{max} from 682 to 736 nm, H_2L^1; from 698 to 754 nm, H_2L^3; from 683 to 746 nm, H_2L^6; and from 685 to 750 nm, H_2L^8). These color changes and the known lability of copper(II) suggest that the stoichiometry and structure of the complexes in solution are different to those of the solid samples without addition of TMAO.

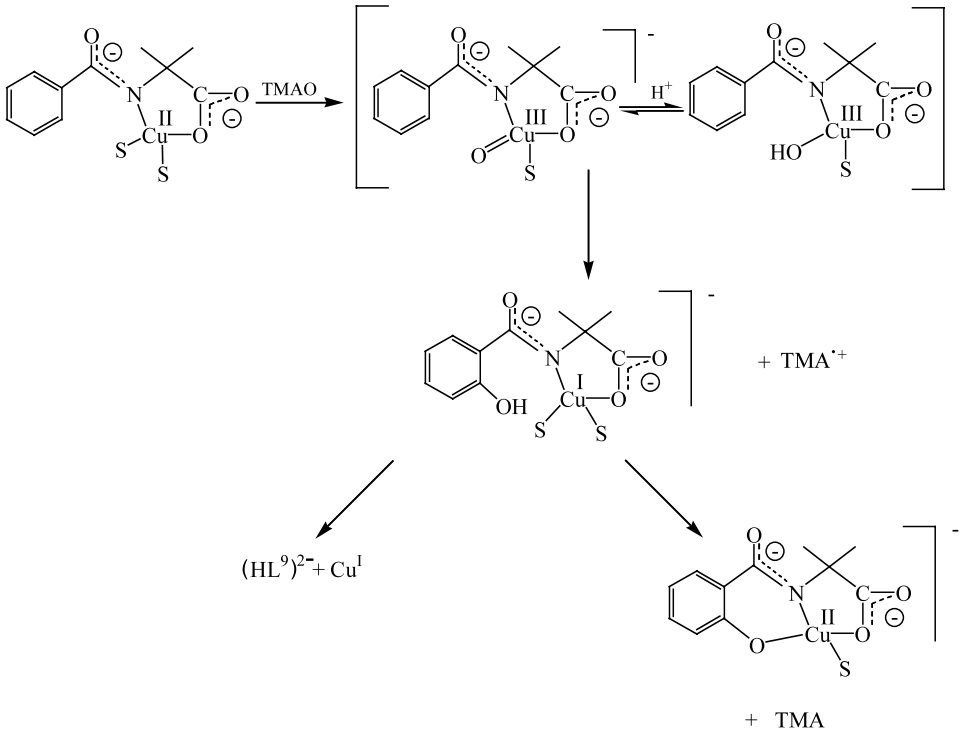
Single crystals for an X-ray structural analysis of $[Cu(L^1)(TMAO)_2]\cdot CH_3CN$ were obtained after addition of five equivalents of TMAO to the copper complex of H_2L^1 (color change of the solution from turquoise to green) in dry acetonitrile at room temperature and crystallization in the refrigerator at −18 °C. Fig. 1 is an ORTEP [29] plot with the atom numbering scheme of $[Cu(L^1)(TMAO)_2]$, relevant structural parameters are given in Table 1. The Cu–O bond distances to the two TMAO donors are significantly different (Cu1–O4 1.928(1) Å, Cu1–O5 1.955(1) Å) and obviously dependent on the donor in *trans* position. The bond distances to the carboxylate and amide groups are in the expected range. There is no other known structure with TMAO coordinated to copper(II); however, there is an experimental structure with TMAO coordinated to rhenium(II) [30]. The N–O bond distances in the copper(II) structure (1.406(2) Å) and the rhenium(II) structure (1.408(1) Å) are close to identical; in the rhenium(II) structure the M–O distances (2.149(1) Å) are much larger than those in the copper(II) structure (1.95 Å). From the copper(II) structure presented here it appears that rotations around the N_{amide}–C_{amide} and the C_{amide}–$C_{benzene}$ bonds (ca. 30° each, see Table 1), and a twist of one of the TMAO oxygen donors into the copper–peptide plane may lead to an ideal arrangement of the oxygen substrate for an *ortho*-hydroxylation of the benzoate group.

2.2. The ortho-hydroxylation reaction

Based on earlier studies it appeared that a $Cu^{II}(L^{2-})$ fragment with a bidentate $O_{carboxylate}$–N_{amide} donor set (structural type (e) in Chart 2), i.e. the geometry found for $[Cu(L^1)(TMAO)_2]$ (see Fig. 1) is the complex that, when oxygenated by TMAO, leads to the active hydroxylation intermediate (activation of the hydroxyla-

Table 1
Structural data of (*N*-benzoyl-2-amino-2-methylpropanoato-*O*-)bis-(trimethylaminoxido)-copper(II)

Bond distances (Å)		Valence angles (°)		Torsional angles (°)	
Cu1–N1	1.928(1)	N1–Cu1–O4	160.78(6)	Cu1–N1–C1–C6	31.55(2)
Cu1–O4	1.928(1)	N1–Cu1–O2	83.69(5)	N1–C1–C6–C7	−146.87(2)
Cu1–O2	1.945(1)	O4–Cu1–O2	100.41(5)	N1–C1–C6–C11	38.04(2)
Cu1–O5	1.955(1)	N1–Cu1–O5	91.72(5)		
N1–C1	1.334(2)	O4–Cu1–O5	95.88(5)		
N2–O4	1.406(2)	O2–Cu1–O5	142.82(6)		
N3–O5	1.404(2)	C1–N1–C2	119.9(1)		
O1–C1	1.251(2)	C1–N1–Cu1	125.4(1)		
O3–C3	1.230(2)	C2–N1–Cu1	112.7(1)		
		N1–C1–O1	127.4(6)		
		O1–C1–C6	117.9(1)		
		C6–C1–N1	144.6(1)		



Scheme 2.

tion reaction at elevated temperatures) [15,16]. TMAO is known to act as an oxygen atom transfer reagent, thus possibly producing the putative copper(III) species $[Cu(L)(O)(S)]^-$ (S = solvent; see Scheme 2; note that there is only circumstantial evidence for a copper(III) species, and other intermediates and mechanisms, not discussed here, are possible) [15,16,31]. Oxygen transfer from copper to the adjacent benzoate fragment may lead to the *ortho*-hydroxylated product, coordinated to copper(I) (Scheme 2). This may produce the *ortho*-hydroxylated metal-free ligand $(HL^9)^{2-}$; substitution lability of copper(I)) or its copper(II) complex (via reoxidation of copper(I) by oxygen or $TMA^{\bullet+}$; see $[Cu(HL^9)(H_2O)]\cdot 0.5\ H_2O$, above and in the Experimental section; the structure of this compound is currently under investigation).

ortho-Hydroxylation reactions were performed with the copper(II) complexes ($Cu-H_2L = 1:2$), or the metal-free ligands and a small excess of elemental copper; product analysis was made by HPLC and ^{1}H-NMR spectroscopy (see Section 3). The results are given in Table 2; Fig. 2 shows the time-dependent formation of the *ortho*-hydroxylation product.

Only ligands H_2L^1, H_2L^2 and H_2L^3 are *ortho*-hydroxylated. The fact that L^4 is unreactive supports the importance of the carboxylate–amide-N chelate in the reactive intermediate state. This is further supported by the lack of reactivity with ligand H_2L^5 which would lead to six-membered chelate rings which are less rigid and less stable, i.e., the putative copper(III)-oxo intermediate (see Scheme 2) is only stabilized by five-membered chelate rings with a carboxylate–N-amide donor set, and this is in agreement with the expectations [27,28].

Ligands H_2L^6 and H_2L^7 have a methyl or an ethyl spacer between the amide and the benzene groups. The putative copper(III)-oxo intermediate in these examples is not pre-organized for the *ortho*-hydroxylation process; as expected, therefore, no *ortho*-hydroxylation is observed with these ligands. However, NMR spectra of the extracted products of reactions with H_2L^6 indicate small but significant amounts of benzoic acid formed during the reaction. This must be due to hydroxylation of the α-methylene group and subsequent cleavage of the α-hydroxy amide to benzaldehyde, which is oxidized to benzoate under the reaction conditions. This is

Table 2
Results of the *ortho*-hydroxylation of H_2L^1–H_2L^7 with TMAO (see Section 3 for experimental conditions)

Ligand [a]	% *ortho*-Hydroxylation after 24 h	
	Copper(II) complex	Free ligand and elemental copper
L^1	46.8	98.1
L^2	35.2	49.5
L^3	25.6	56.6
L^4, L^5, L^6, L^7	–	–

[a] See Chart 1.

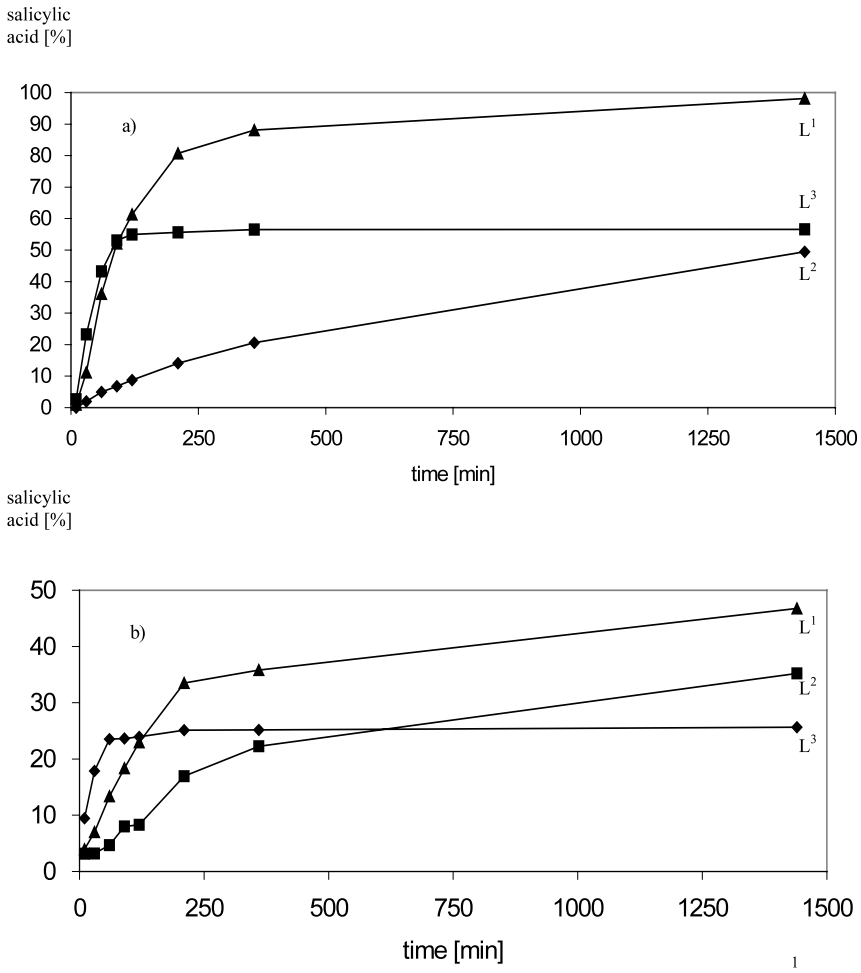


Fig. 2. Conversion of benzoic acid into salicylic acid by reaction of H_2L^1–H_2L^3 with TMAO, followed by cleavage of the amide with H_2SO_4: (a) metal-free ligands, (b) copper(II) complexes of H_2L^1–H_2L^3, for experimental conditions see Section 3.

further support for a reactive copper-oxo intermediate and the necessity for a highly pre-organized geometry with respect to the benzene substrate.

The time-dependent formation of salicylate (see Fig. 2) indicates that the initial rates are, as expected, in general higher in experiments with the copper(II) complexes than in those starting with copper powder and metal-free ligands (air oxidation to the copper(II) compounds). An interesting observation is that, in experiments involving the pre-formed copper(II) compounds, the yield is only half of that observed in experiments with the metal-free ligands and an excess of copper. This indicates that the stoichiometry of the reaction is indeed one copper(II) per ligand H_2L (paddle-wheel $Cu_2(HL)_4$ compounds were used for the reactions with H_2L^1, H_2L^2 and H_2L^3, see Section 3), and this supports the suggested reactive intermediate [Cu(L)(O)(S)], see Scheme 2 and Fig. 1.

Ligand H_2L^3 only leads to ca. 50% *ortho*-hydroxylation product (ca. 25% when the copper(II) complex is used). This must be due to an inhibition by the product formed, i.e., to stable mixed-ligand complexes involving H_2L^3 and its *ortho*-hydroxylation product H_3L^9 (for possible products with H_3L^9, see above and Experimental section). The reactivity of H_2L^1, H_2L^2 and H_2L^3 (see Fig. 2) is as expected on the basis of the substituent influences (Ph > Me > H) and indicates that the reactivity is enhanced by electronic stabilization of the copper-oxo intermediate.

3. Experimental

3.1. Materials

All compounds, including H_2L^2, were purchased from Sigma/Aldrich and used without further purification. The purity ranges were between 97 and 99%.

3.2. Ligand syntheses

3.2.1. N-benzoyl-α-aminoisobutyric acid (H_2L^1) [18]

To 20.63 g (0.20 mol) 2-methylalanine in aqueous solution (100 ml, 2 M NaOH), cooled in an ice bath,

was added 23.20 ml (0.20 mol) BzCl in 100 ml aqueous 2 M NaOH. After 6 h, 40 ml of a 5 M HCl solution was added to obtain the metal-free ligand as a white precipitate, which was collected on a filter, washed with Et_2O, recrystallized from acetone and dried in vacuo. Yield: 31.35 g (75.6%). Anal. Calc. for $C_{11}H_{13}NO_3$ (207.23): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.77; H, 6.26; N, 6.75%. ^{1}H-NMR (300 MHz, d_6-acetone): $\delta = 1.61$ (s, $2CH_3$, 6H); 7.43 (t, ArH_3, ArH_5, 2H, $J = 8$ Hz); 7.50 (t, ArH_4, 1H, $J = 7$ Hz); 7.88 (d, ArH_6, 1H, $J = 7$ Hz). ^{13}C-NMR (300 MHz, d_6-acetone): $\delta = 26.05$ ($2CH_3$); 57.56 (NC); (128.80; 129.71; 132.69; 136.34) (C_{Aromat}); 167.91 (COOH); 176.58 (CO).

3.2.2. N-benzoyl-2-amino-2,2-diphenylacetic acid (H_2L^3) [19]

To 5 g (22 mmol) diphenylglycine, dissolved in 11 ml aqueous 2 M NaOH and 15 ml of water, cooled in an ice bath, was added 3.1 g (22.05 mmol) BzCl and 11 ml 2 M aqueous NaOH. After 1 h, 150 ml of a 1 M HCl solution was added, and the white precipitate was collected on a filter, washed with water and dried in vacuo. Yield: 5.89 g (80.8%). Anal. Calc. for $C_{21}H_{17}NO_3$ (331.37): C, 76.12; H, 5.17; N, 4.23. Found: C, 76.29; H, 5.45; N, 4.29%. ^{1}H-NMR (500 MHz, d_6-Me_2SO): 8.10–7.24 (m, 15H, Phenyl-H). ^{13}C-NMR (500 MHz, d_6-Me_2SO): $\delta = 68.62$ (NC); (126.42; 126.97; 127.43; 127.59; 127.86; 128.01; 128.27; 128.40; 128.53; 128.94; 129.24) (C_{Aromat}); 165.79 (CO); 171.96 (COOH).

3.2.3. N-benzoyl-N-methyl-α-amino-2-methylpropionic acid (HL^4) [32]

To 5.1 g (43.53 mmol) *N*-methyl-2-methylalanine, dissolved in 21.8 ml 2 M aqueous NaOH, cooled in an ice bath, was added 6.12 g (43.53 mmol) BzCl and 21.8 ml 2 M NaOH solution. After 2 h, 80 ml 5 M HCl solution was added, and the metal-free ligand was collected as a white precipitate on a filter, washed with Et_2O and dried in vacuo. Yield: 7.0 g (72.69%). Anal. Calc. for $C_{12}H_{15}NO_3$ (221.26): C, 65.14; H, 6.83; N, 6.33. Found: C, 66.10; H, 6.79; N, 6.37%. ^{1}H-NMR (300 MHz, d_3-$CHCl_3$): $\delta = 1.58$ (s, 6H, $2CH_3$); 2.98 (s, 3H, N–CH_3); 7.38–7.50 (m, ArH_3, ArH_5, 2H, $J = 7$ Hz); 7.59 (t, ArH_4, 1H, $J = 7$ Hz); 8.08 (d, ArH_2, ArH_6, 2H, $J = 7$ Hz). ^{13}C-NMR (300 MHz, d_6-acetone): $\delta =$ 24.01 ($2CH_3$); 34.49 (N–CH_3); 61.79 (NC); (128.62; 129.78; 130.97; 139.05) (C_{Aromat}); 172.65 (COOH); 176.28 (CO).

3.2.4. N-benzoyl-β-aminopropionic acid (H_2L^5) [18]

To 35.64 g (0.40 mol) β-aminopropionic acid, dissolved in 200 ml aqueous 2 M NaOH, cooled in an ice bath, was added 56.23 g (0.40 mol) BzCl and 200 ml aqueous 2 M NaOH. After 6 h, 80 ml of a 5 M HCl solution were added, and the metal-free ligand (white precipitate) was collected on a filter, washed with Et_2O and dried in vacuo. Yield: 56.02 g (72.5%). Anal. Calc. for $C_{10}H_{11}NO_3$ (193.20): C, 62.17; H, 5.74; N, 7.25%. Found: C, 62.11; H, 5.72; N, 7.33%. ^{1}H-NMR (300 MHz, d_3-MeCN): $\delta = 2.59$ (t, CH_2–COOH, 2H, $J = 7$ Hz); 3.57 (q, N–CH_2, 3H, $J = 7$ Hz); 7.43 (t, ArH_3, ArH_5, 2H, $J = 6$ Hz); 7.59 (t, ArH_4, 1H, $J = 7$ Hz); 7.76 (d, ArH_6, 1H, $J = 7$ Hz). ^{13}C-NMR (300 MHz, d_6-acetone): $\delta = 34.39$ (CH_2–COOH); 36.45 (NC); (127.94; 129.43; 132.34; 135.48) (C_{Aromat}); 168.22 (COOH); 173.80 (CO).

3.2.5. N-2-phenylacetyl-α-amino-2-methylpropionic acid (H_2L^6)

To 20.63 g (0.20 mol) 2-methylalanine, dissolved in 100 ml aqueous 2 M NaOH solution, cooled in an ice bath, was added 30.92 g (0.20 mol) phenylacetylchloride and 100 ml 2 M NaOH solution. After 2 h, 200 ml of a 5 M HCl solution were added, and the white precipitate of the metal-free ligand was collected on a filter, washed with Et_2O and dried in vacuo. Yield: 29.74 g (67.2%). Anal. Calc. for $C_{12}H_{15}NO_3$ (221.26): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.36; H, 6.72; N, 6.18%. ^{1}H-NMR (300 MHz, d_6-acetone): $\delta = 1.47$ (s, $2CH_3$, 6H); 3.50 (s, CH_2, 2H); 7.32–7.17 (m, ArH_2, ArH_3, ArH_4, ArH_5, ArH_6, 5H). ^{13}C-NMR (300 MHz, d_4-MeOH): $\delta = 25.27$ ($2CH_3$); 43.46 (CH_2); 56.95 (NC); (127.71; 129.43; 130.33; 136.90) (C_{Aromat}); 173.18 (COOH); 177.82 (CO).

3.2.6. N-2-(3-phenylpropionyl)-α-amino-2-methylpropionic acid (H_2L^7)

To 16.64 g (164 mmol) 2-methylalanine, dissolved in 82 ml aqueous 2 M NaOH solution, cooled in an ice bath, was added 27.70 g (164 mmol) 3-phenylpropionic acid chloride and 82 ml aqueous 2 M NaOH solution. After 2 h, 160 ml of a 5 M HCl solution were added, and the white metal-free ligand was collected on a filter, washed with Et_2O and dried in vacuo. Yield: 21.97 g (72.37%). Anal. Calc. for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.39; H, 7.00; N, 5.93%. ^{1}H-NMR (300 MHz, d_6-acetone): $\delta = 1.44$ (s, $2CH_3$, 6H,); 2.46 (t, Ar–CH_2–CH_2–, 2H, $J = 7$ Hz); 2.89 (t, Ar–CH_2–CH_2–, 2H, $J = 7$ Hz); 7.13–7.37 (m, ArH_2, ArH_3, ArH_4, ArH_5, ArH_6, 5H). ^{13}C-NMR (300 MHz, d_4-MeOH): $\delta = 25.34$ ($2CH_3$); 32.73 (Ar–CH_2); 38.68 (CH_2–CO); 56.77 (NC); (127.12; 129.29; 129.40; 142.25) (C_{Aromat}); 174.51 (COOH); 177.97 (CO).

3.2.7. 2-(2-Methoxybenzoyl)-amino-2-methylpropionic acid (H_2L^8) [20]

To 9.00 g (58.59 mmol) α-aminoisobutyric acid methylester hydrochloride, dissolved in 270 ml $CHCl_3$, cooled in an ice bath, was added 13.00 g (128.47 mmol) Et_3N (in 50 ml $CHCl_3$) and 10.00 g (58.62 mmol) *o*-anisoylchloride (in 50 ml $CHCl_3$). After 24 h, the

solution was shaken with 50 ml 1 M HCl, then with 50 ml of $NaHCO_3$ solution. The solvent of the organic phase was evaporated; to crystallize the oily residue 5 ml Et_2O and alkane (40:60) were added. The white precipitate was collected on a filter, washed with Et_2O, and dried in vacuo. Yield: 11.58 g (78.67%). Anal. Calc. for $C_{13}H_{17}NO_4$ (251.28): C, 62.14; H, 6.82; N, 5.57. Found: C, 61.91; H, 6.77; N, 5.54%. ^{1}H-NMR (300 MHz, d_6-acetone): $\delta = 1.55$ (s, $2CH_3$, 6H); 3.67 (s, COO–CH_3, 3H); 4.03 (s, OCH_3, 3H); 7.06 (t, ArH_5, 1H, $J = 8$ Hz); 7.16 (d, ArH_3, 1H, $J = 8$ Hz); 7.50 (t, ArH_4, 1H, $J = 8$ Hz); 8.04 (d, ArH_6, 1H, $J = 8$ Hz). ^{13}C-NMR (300 MHz, d_3-$CHCl_3$): $\delta = 24.74$ ($2CH_3$); 52.31 ($COOCH_3$); 55.76 (OCH_3); 56.33 (NC); (111.15; 121.05; 121.25; 131.93; 132.65; 157.36) (C_{Aromat}); 163.88 ($COOCH_3$); 175.08 (CO).

3.2.8. 2-(2-Hydroxybenzoyl)-amino-2-methylpropionic acid (H_3L^9)

To 10.8 g (42.98 mmol) *N*-2-methoxybenzoyl-α-aminoisobutyric acid methylester, dissolved in 70 ml MeOH (ice bath), were added 77 ml aqueous 1 M NaOH solution. After 24 h, 150 ml 1 M HCl were added. The white precipitate was collected on a filter, washed with water and dried in vacuo. Yield: 9.1 g (89.22%). Anal. Calc. for $C_{12}H_{15}NO_4$ (237.26): C, 60.75; H, 6.37; N, 5.90. Found: C, 60.80; H, 6.32; N, 6.01%. ^{1}H-NMR (300 MHz, d_6-acetone): $\delta = 1.64$ (s, $2CH_3$, 6H); 4.03 (s, $ArOCH_3$, 3H); 7.06 (t, ArH_5, 1H, $J = 8$ Hz); 7.17 (d, ArH_3, 1H, $J = 8$ Hz); 7.50 (t, ArH_4, 1H, $J = 8$ Hz); 8.07 (d, ArH_6, 1H, $J = 8$ Hz). ^{13}C-NMR (300 MHz, d_6-acetone): $\delta = 25.83$ ($2CH_3$); 57.23 (OCH_3); 57.71 (NC); (113.48; 122.34; 123.43; 133.04; 134.38; 159.35) (C_{Aromat}); 165.32 (COOH); 176.74 (CO).

To 5 g (25.28 mmol) 2-(2-methoxybenzoyl)-amino-2-methylpropionic acid (see above), dissolved in 500 ml dry dichlormethane under an Ar atmosphere, were added 12.67 g (50.56 mmol) BBr_3 (as an 1 M CH_2Cl_2 solution) within 1 h at a temperature of −78 °C. After 3 h, the mixture was poured on ice and extracted three times with 200 ml of a $CHCl_3$–EtOAc mixture (8:2). The organic phase was extracted with 100 ml of a $NaHCO_3$ solution, and to the water phase was added 200 ml of 5 M aqueous HCl. The resulting white precipitate was collected on a filter, washed with ice water and dried in vacuo. Yield: 2.86 g (60.85%). Anal. Calc. for $C_{11}H_{13}NO_4$ (223.23): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.02; H, 5.82; N, 6.28%. ^{1}H-NMR (300 MHz, d_6-acetone): $\delta = 1.62$ (s, CH_3, 6H); 6.87 (m, ArH_5, ArH_3, 2H, $J = 8$ Hz); 7.40 (t, ArH_4, 1H, $J = 8$ Hz); 7.82 (d, ArH_6, 1H, $J = 8$ Hz). ^{13}C-NMR (300 MHz, d_6-acetone): $\delta = 25.95$ ($2CH_3$); 57.71 (NC); (116.14; 119.16; 119.87; 128.67; 135.52; 163.11) (C_{Aromat}); 171.39 (COOH); 176.13 (CO).

3.3. Syntheses of the copper(II) compounds

3.3.1. $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4]$ ($Cu_2HL^1_4$)

To 6.5 g (31.37 mmol) C_6H_5–CO–NH–$C(CH_3)_2$–COOH, dissolved 600 ml H_2O–*iso*-propanol (5:7), was added 1.66 g (7.51 mmol) $[(CuCO_3)(Cu(OH)_2)]$. The mixture was heated for 24 h at a temperature of 70 °C. After 24 h, the turquoise green precipitate was collected on a filter, washed with Et_2O and dried in vacuo. Yield: 3.3 g (91.7%). Anal. Calc. for $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4]$ ($C_{44}H_{48}Cu_2N_4O_{12}$) (951.98): C, 55.51; H, 5.08; N, 5.89. Found: C, 55.78; H, 5.17; N, 5.87%. IR (KBr, cm^{-1}): ν(N–H) 3396 (s), ν(C–H, aromate) 3062 and 3030 (w), ν(C–H, methyl groups) 2984 and 2936 (s), ν(C=O, amide I) 1620 (s), ν(C=C) 1620 (m), $\nu_{asym.}$(C=O, COO^-) 1578 (s), δ (N–H, amide II) 1514 (s), $\nu_{sym.}$(C=O, COO^-) 1414 (s), δ (C − H, monosubstitution of the aromate) 714 and 692.

3.3.2. $[Cu(\mu_1\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_5)(Me_3NO)_2]$ ($CuL^1(Me_3NO)_2$)

To 0.10 g (0.11 mmol) $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4]$, dissolved in 20 ml MeCN, was added 0.1577 g (2.10 mmol) Me_3NO. The mixture was kept in the refrigerator to crystallize. Yield: 0.0796 g (90.00%). Anal. Calc. for $[Cu(\mu_1\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_5)(Me_3NO)_2]$ ($C_{17}H_{31}CuN_3O_5$) (421.00): C, 48.50; H, 7.42; N, 9.98. Found: C, 47.70; H, 7.05; N, 10.48%. IR (KBr, cm^{-1}): ν(N–H) 3372 (s), ν(C–H, aromate) 3052 (w), ν(C–H, methyl groups) 2968 (w), ν(C=O, amide I) 1632 (s), ν(C=C) 1600 (m), $\nu_{asym.}$(C=O, COO^-) 1552(s), δ (N–H, amide II) 1510 (s), $\nu_{sym.}$(C=O, COO^-) 1390 (s), δ (C–H, monosubstitution of the aromate) 762 and 694.

3.3.3. $[Cu_2(\mu_2\text{-}O_2C\text{–}CH_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4]$ ($Cu_2HL^2_4$)

To 3 g (16.74 mmol) C_6H_5–CO–NH–CH_2–COOH, dissolved 100 ml H_2O–*iso*-propanol (5:7), was added 0.85 g (3.84 mmol) $[(CuCO_3)(Cu(OH)_2)]$. The mixture was heated for 48 h at a temperature of 67 °C. Then the solution was filtrated and the filtrate was evaporated to give a turquoise blue powder. To remove unreacted hippuric acid the precipitate is redissolved in acetone, filtered again and dried in vacuo. Yield: 2.5 g (90.58%). Anal. Calc. for $[Cu_2(\mu_2\text{-}O_2C\text{–}CH_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4]$ ($C_{36}H_{32}Cu_2N_4O_{12}$) (839.76): C, 51.49; H, 3.84; N, 6.67. Found: C, 51.32; H, 3.97; N, 6.60%. IR (KBr, cm^{-1}): ν(N–H) 3408 (s), ν(C–H, aromate) 3056 and 3026 (w), ν(C–H, methylene group) 2976 and 2936 (s), ν(C=O, amide I) 1620 (s), ν(C=C) 1620 (m), $\nu_{asym.}$(C=O, COO^-) 1578(s), δ (N–H, amide II) 1542 (s), $\nu_{sym.}$(C=O, COO^-) 1398 (s), δ (C–H, monosubstitution of the aromate) 736 and 692.

3.3.4. $[Cu_2(\mu_2\text{-}O_2C\text{–}C(C_6H_5)_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4\text{-}(C_3H_8O)_2]$ $(Cu_2HL^3_4)(C_3H_8O)_2$

To 1.16 g (3.50 mmol) *N*-benzoyl-2-amino-2,2-diphenylacetic acid, dissolved in 150 ml H_2O–*iso*-propanol (5:7), was added 0.1935 g (0.89 mmol) $[(CuCO_3)(Cu(OH)_2)]$. The mixture was heated for 48 h at a temperature of 75 °C. Then the green solution was filtered and the solvent was evaporated. The green powder was filtered, washed with water and dried in vacuo. Yield: 1.10 g (80.12%). Anal. Calc. for $[Cu_2(\mu_2\text{-}O_2C\text{–}C(C_6H_5)_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4(C_3H_8O)_2]$ ($C_{90}H_{80}Cu_2N_4O_{14}$) (1568.74): C, 68.91; H, 5.14; N, 3.57. Found: C, 69.09; H, 5.36; N, 3.71%. IR (KBr, cm^{-1}): ν(N–H) 3408 (s), ν(C–H, aromate) 3056 and 3026 (w), ν(C–H, methyl groups) 2976 and 2936 (s), ν(C=O, amide I) 1620 (s), ν(C=C) 1620 (m), $\nu_{asym.}$(C=O, COO^-) 1578 (s), δ (N–H, amide II) 1542 (s), $\nu_{sym.}$(C=O, COO^-) 1398 (s), δ (C–H, monosubstitution of the aromate) 736 and 692.

3.3.5. $[Cu(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}N\text{–}CH_3\text{–}CO\text{–}C_6H_5)_2]$ (CuL^4_2)

To 1.6 g (7.23 mmol) *N*-benzoyl-*N*-methyl-α-amino-2-methylpropionic acid, dissolved in 50 ml H_2O–*iso*-propanol (5:7), was added 0.3997 g (1.81 mmol) $[(CuCO_3)(Cu(OH)_2)]$. The mixture was heated for 48 h at a temperature of 65 °C. Then the solvent was evaporated and the residue was solved in 50 ml dioxane. The solution was filtered and Et_2O was added to precipitate the product. After filtration it was dried in vacuo. Yield: 1.0 g (56.82%). Anal. Calc. for $[Cu(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}N\text{–}CH_3\text{–}CO\text{–}C_6H_5)_2(H_2O)_{0.5}]$ ($C_{24}H_{29}CuN_2O_{6.5}$) (513.05): C, 56.18; H, 5.69; N, 5.46. Found: C, 56.19; H, 5.87; N, 4.93%. IR (KBr, cm^{-1}): ν(N–H) 3408 (s), ν(C–H, aromate) 3063 and 3026 (w), ν(C–H, methyl groups) 2978 and 2924 (w), $\nu_{asym.}$(C=O, COO^-) 1778(s), ν(C=O, amide I) 1648 (s), ν(C=C) 1620 (m), $\nu_{sym.}$(C=O, COO^-) 1412 (s), δ (C–H, monosubstitution of the aromate) 724 and 698.

3.3.6. $[Cu_2(\mu_2\text{-}O_2C\text{–}(CH_2)_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4]$ $(Cu_2HL^5_4)$

To 5.94 g (30.75 mmol) *N*-benzoyl-β-amino-propanoic acid, dissolved in 50 ml water with 1.23 g (30.75 mmol) NaOH, was added 2.45 g (15.35 mmol) $CuSO_4$ in 50 ml water. The mixture was heated for 12 h at 50 °C to complete the reaction. The turquoise green precipitate was filtered and washed with EtOH and EtO_2 and dried in vacuo. Yield: 4.65 g (93.00%). Anal. Calc. for $[Cu_2(\mu_2\text{-}O_2C\text{–}(CH_2)_2\text{–}NH\text{–}CO\text{–}C_6H_5)_4]$ ($C_{40}H_{40}Cu_2N_4O_{12}$) (895.87): C, 53.63; H, 4.50; N, 6.25. Found: C, 53.26; H, 4.36; N, 6.19%. IR (KBr, cm^{-1}): ν(N–H) 3316 (s), ν(C–H, aromate) 3064 and 3026 (w), ν(C–H, methylene groups) 2944 and 2924 (w), ν(C=O, amide I) 1634 (s), $\nu_{asym.}$(C=O, COO^-) 1588(s), ν(C=C) 1620 (m), δ (N–H, amide II) 1540 (s), $\nu_{sym.}$(C=O, COO^-) 1412 (s), δ (C–H, monosubstitution of the aromate) 716 and 694.

3.3.7. $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}CH_2\text{–}C_6H_5)_4(C_4H_8O_2)]$ $(Cu_2HL^6_4(C_4H_8O_2))$

To 5 g (22.60 mmol) *N*-2-phenylacetyl-α-amino-2-methylpropionic acid, dissolved in 200 ml *iso*-propanol–H_2O (7:5), was added 1 g (4.52 mmol) $[(CuCO_3)(Cu(OH)_2)]$. The mixture was heated for 48 h at 65 °C, then filtered, and the filtrate was evaporated to obtain a blue powder, which was washed with dioxane and dried in vacuo. Yield: 2.42 g (53.19%). Anal. Calc. for $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}CH_2\text{–}C_6H_5)_4\text{-}(C_4H_8O_2)]$ ($C_{52}H_{64}Cu_2N_4O_{14}$) (1096.19): C, 56.98; H, 5.89; N, 5.11. Found: C, 56.99; H, 5.84; N 5.12%. IR (KBr, cm^{-1}): ν(N–H) 3420 (s), ν(C–H, aromate) 3072 (w), ν(C–H, methyl groups) 2976 and 2930 (w), ν(C=O, amide I) 1644 (s), ν(C=C) 1628 (m), $\nu_{asym.}$(C=O, COO^-) 1558 (s), δ (N–H, amide II) 1558 (s), $\nu_{sym.}$(C=O, COO^-) 1412 (s), ν(C–O–C, dioxane) 1282 (w), δ (C–H, monosubstitution of the aromate) 734 and 694.

3.3.8. $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}CH_2\text{–}CH_2\text{–}C_6H_5)_4]$ $(Cu_2HL^7_4)$

To 5 g (21.25 mmol) *N*-3-phenylpropionyl-α-amino-2-methylpropionic acid, dissolved in 200 ml *iso*-propanol–H_2O (7:5), was added 940 mg (4.25 mmol) $Cu(OH)_2$. The mixture was heated for 48 h at 65 °C. The solution was then filtered, and the filtrate was evaporated to obtain a blue powder, which was washed with acetone and dried in vacuo. Yield: 2.90 g (64.02%). Anal. Calc. for $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}CH_2\text{–}CH_2\text{–}C_6H_5)_4]$ ($C_{52}H_{64}Cu_2N_4O_{12}$) (1064.19): C, 58.69; H, 6.06; N, 5.26. Found: C, 58.56; H, 6.04; N, 5.29%. IR (KBr, cm^{-1}): ν(N–H) 3398 (s), ν(C–H, aromate) 3060 (w), ν(C–H, methyl and methylene groups) 2978 and 2934 (w), ν(C=O, amide I) 1622 (s), ν(C=C) 1622 (m), $\nu_{asym.}$(C=O, COO^-) 1540(s), δ (N–H, amide II) 1520 (s), $\nu_{sym.}$(C=O, COO^-) 1412 (s), δ (C–H, monosubstitution of the aromate) 754 and 704.

3.3.9. $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_4\text{–}o\text{-}OMe)_4]$ $(Cu_2HL^8_4)$

To 2 g (8.42 mmol) 2-[(2-methoxybenzoyl)]-amino-2-methylpropionic acid, dissolved in 160 ml *iso*-propanol–H_2O (7:5), was added 0.4 g (1.81 mmol) $[(CuCO_3)(Cu(OH)_2)]$. The mixture was heated for 48 h at 60 °C. The turquoise blue suspension was filtered and the filtrate was evaporated to obtain a turquoise green powder, which was washed with water and dried in vacuo. Yield: 1.94 g (69.59%). Anal. Calc. for $[Cu_2(\mu_2\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_4\text{–}o\text{-}OMe)_4]$ ($C_{48}H_{56}Cu_2N_4O_{16}$) (1072.08): C, 53.78; H, 5.27; N, 5.23. Found: C, 53.70; H, 5.41; N, 5.14% — IR (KBr, cm^{-1}): ν(N–H) 3359 (s), ν(C–H, aromate) 3058 (w), ν(C–H, methyl groups) 2974 and 2949 (w), $\nu_{asym.}$(C=O,

COO^-) 1745 (s), ν(C=O, amide I) 1623 (s), ν(C=C) 1600 (m), δ (N–H, amide II) 1545 (s), $\nu_{sym.}$(C=O, COO) 1412 (s), ν(C–O–C, ether) 1245 (m), δ (C–H, 1,2-disubstitution of the aromate) 754 (s).

3.3.10. $[Cu(\mu_1\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_4\text{–}o\text{-}O\text{-}\mu_1)(H_2O)_{1.5}]$ $(CuHL^9\cdot 1.5H_2O)$

To 0.2555 g (0.96 mmol) of the Na-salt of 2-(2-hydroxybenzoyl)-amino-2-methylpropionic acid, dissolved in 20 ml water, were added 0.7086 (1.91 mmol) $[Cu(ClO_4)_2(H_2O)_6]$ (in 20 ml water). The green precipitate was filtered and dried in vacuo. Yield: 0.1979 g (66.52%). Anal. Calc. for $[Cu(\mu_1\text{-}O_2C\text{–}C(CH_3)_2\text{–}NH\text{–}CO\text{–}C_6H_4\text{–}o\text{-}O\text{-}\mu_1)(H_2O)_{1.5}]$ ($C_{11}H_{14}CuNO_{5.5}$) (311.79): C, 42.38; H, 4.53; N, 4.49. Found: C, 41.89; H, 4.22; N, 4.50%. IR (KBr, cm^{-1}): ν(N–H) 3374 (s), ν(C–H, aromate) 3062 (w), ν(C–H, methyl groups) 2984 and 2936 (w), $\nu_{asym.}$(C=O, COO^-) 1745 (s), ν(C=O, amide I) 1608 (s), ν(C=C) 1608 (m), δ (N–H, amide II) 1522 (s), $\nu_{sym.}$(C=O, COO^-) 1406 (s), ν(C–O–C, ether) 1245 (m), δ (C–H, 1,2-disubstitution of the aromate) 754 (s).

3.4. Hydroxylation reactions and analytical procedures

The hydroxylation experiments were performed in 40 ml dry MeCN under an Ar atmosphere. Free ligands (0.4 g) (L^1–L^9) was heated to 75 °C with five equivalents of TMAO per copper and 1.1 equivalents of elemental copper powder. Molecular oxygen was used as the oxidation reagent which was bubbled in the mixture. After 10, 30, 60, 120, 210, 360 and 1440 min a sample of 5 ml was taken out and mixed with 20 ml of 25% H_2SO_4 solution. NaCl (5–7 g) was added to ease the extraction of the organic product. The mixture was extracted three times with 30 ml of EtOAc and the organic layer was evaporated. To cleave the amide, the obtained product was heated up for six hours at 120 °C in 50 ml of 40% H_2SO_4 solution. The benzoic acid and salicylic acid were extracted three times with 30 ml of EtOAc and the organic layer was evaporated. To the organic product mixture was added an internal standard, containing 3-methyl-salicylic acid (250 mg in 250 ml of the MeCN–HCl buffer mixture). To quantify the relation between the benzoic and the salicylic acid the reversed phase HPLC was used with a LiChrosorb-100 5 μm RP8 column (250 × 4 mm, Knauer) at 20 °C, and eluted with a mixture of 10:90 MeCN–buffer solution (CertiPur, citric acid–NaOH–HCl pH 3.0) using a flow rate of 2 ml min^{-1}. A Wellchrom Spectralphotometer (K-2501, Knauer) was used for detection at 250 nm.

Elemental analyses were obtained from the microanalytical laboratory of the chemical institutes of the University of Heidelberg.

Infrared spectra (KBr pellets) were measured with a Perkin–Elmer 16PC FT-IR instrument.

^{1}H-NMR spectra were recorded in a Bruker AS200 (200.13 MHz) or a General Electric QE 300 (300.13 MHz) in different solutions (see Section 3) and referenced to internal Me_4Si.

3.5. X-ray crystallography

Crystallographic data appear in Table 3. Crystal data were collected in a Bruker AXS SMART 1000 diffractometer with a CCD area detector (Mo–K_α radiation, graphite monochromator, $\lambda = 0.71073$ Å) at −83 °C. The reflection intensities were integrated using SAINT and corrected for absorption using SADABS [33,34]. The structures were solved by direct methods and refined by full-matrix least-squares, based on F^2 with all reflections using the SHELXTL programs [35]. Hydrogen atoms were located and refined isotropically.

Table 3
Crystallographic data and structure refinement parametrs for (*N*-benzoyl-2-anino-2-methylpropanoato-*O*-)bis-(trimethylaminoxido)-copper(II)

Chemical formula	$C_{19}H_{32}Br_4CuN_4O_5$
Molecular weight	460.03
Crystal size (mm^3)	$0.30 \times 0.20 \times 0.12$
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	9.4567(6)
b (Å)	8.9514(5)
c (Å)	27.0041(16)
β (°)	95.8940(10)
V ($Å^3$)	2273.8(2)
Z	4
D_{calc} ($g\,cm^{-3}$)	1.344
Absorption coefficient (mm^{-1})	0.996
Reflections collected/unique	30150/7723 [$R_{int} = 0.027$]
Reflections observed	6111
$F(000)$	972
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0373$
R indices (all data)	0.0960
R_1	0.0540
wR_2	0.1055
Goodness-of-fit	1.035
Largest difference peak and hole ($e\,Å^{-3}$)	0.49 and −0.49

4. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 162710 for (*N*-benzoyl-2-anino - 2 - methylpropanoato - *O* -)bis - (trimethylaminoxido)-copper(II). Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements

Financial support by DSM Research, Geleen, The Netherlands is gratefully acknowledged.

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