Steroids as Chiral Ligands: Different Molecular and Crystal Structures of Copper(II) Complexes of Mono- and Dideprotonated 16β-Salicylideneimino-17β-hydroxy-3-methoxyestra-1,3,5(10)-triene

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The steroidal 16β-salicylideneimino-17β-hydroxy compound **1**, synthesized from the corresponding 16β,17β-amino alcohol, served as a new tridentate chiral ligand for Cu^{2+}-complexation. The X-ray data for **1** and for two dimeric copper complexes **2** and **3** are presented and discussed. Using copper(II) acetate for complexation, dideprotonation of **1** is observed. The neutral complex **2** obtained is characterized by a central planar four-membered copper–oxygen ring. The cycloaliphatic 17β-oxygen anions are bridging atoms; the copper ions are tetracoordinated. Reaction of **1** with copper(II) perchlorate gave only monodeprotonation of the phenolic groups. These oxygen anions are now the bridging atoms; furthermore the two copper ions are bridged by a perchlorate anion. Thus the central four-membered ring is folded (22°), and the copper ions are hexacoordinated (binding of a molecule of water). The crystal lattices of **2** and **3** are also quite different.

Copper complexes with chiral nitrogeneous ligands are of considerable interest for the implementation of stereoselective syntheses[1], but should also prove to be increasingly relevant for modelling copper-containing enzymes[2]. Although easily accessible, vicinal steroid amino alcohols and their derivatives represent stereochemically well-defined ligands on the basis of their relatively rigid structures; up until now, corresponding copper complexes have only been produced in situ in connection with investigations of circular dichroism[3]. As part of a programme addressing chiral steroid ligands of 16-amino-17-hydroxy-3-methoxyestra-1,3,5(10)-trienes of all four configurations, we report here for the first time the synthesis, and molecular and crystal structures of 16β-salicylideneimino-17β-hydroxy-3-methoxyestra-1,3,5(10)-triene (**1**) and corresponding copper complexes **2** and **3** with mono- and dideprotonated ligands **1** (Scheme 1). To the best of our knowledge, X-ray crystallographic structural analyses of chiral ligands with vicinal salicylideneiminic and hydroxy groups, together with their corresponding copper(II) complexes with mono- and dideprotonated ligands, have not previously been described.

Compound **1** is easily accessible from the corresponding amino alcohol[4] and salicylic aldehyde in the form of shiny, yellow crystals. Through the X-ray crystal structure analysis[5] of **1** (Figure 1) one sees a torsion angle of 23° for the 17β-O and 16β-N across the bond C17–C16 (*cis*-configuration of the substituents), while the aromatic ring and chelate ring of the salicylideneimine unit form the expected plane at an angle of 74.5° to the steroid plane. Because this angle can be changed by rotation about the C16–N single bond, **1** should be able to function as a three-dentate ligand in conjunction with metallic ions.

The different deprotonation tendencies of alicyclic and phenolyic hydroxy groups leads one to expect both neutral complexes (doubly deprotonated) and monovalent cationic complexes (singly deprotonated) from bivalent metallic ions such as Cu^{2+}[6]. Using different basic as well as different bridging anions in the form of copper(II) salts[6], an attempt was made to retain both sorts of complexes.

With gentle heating, the combination of **1** with copper(II) acetate monohydrate in THF, with addition of γ-picolin to bind released acid, leads to a deep green solution. Through gas-phase diffusion with petrol ether for several weeks, and the addition of *n*-heptane, black-green, metallic shiny, thermically very stable crystals were obtained from **2**[5]. Compound **2** (Figure 2) proved to be a neutral, dimeric copper(II) complex which contained the dideprotonated ligands. The coordination geometry of both its copper atoms is planar-quadratic. The bridging of both copper atoms is analogous to that in corresponding complexes with nonchiral, single ligands[7]. The central, planar (bending angle 0.2°) four-membered ring of two copper and two alcoholate oxygen atoms has a copper–copper distance of 2.97 Å. Further coordination positions for the copper are the phenolate oxygen and the nitrogen, through which the coordination number of 4 is achieved.

The two torsion angles from 17β-O and 16β-N across the C17–C16 bond measure 19.8° and 23.2°, and are thus

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Scheme 1. Synthesis of the Cu^{2+} complexes **2** and **3** via double or single deprotonation of **1**

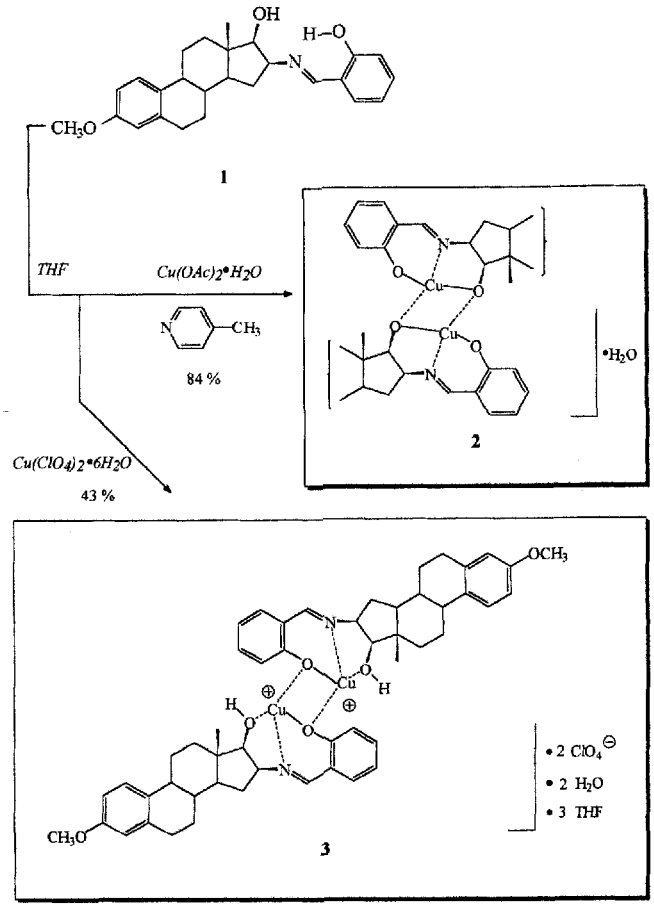
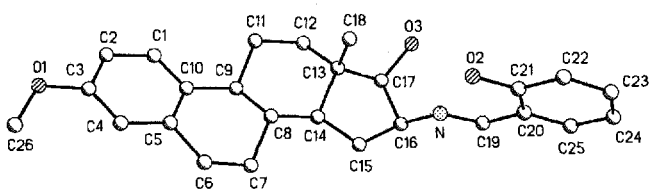


Figure 1. Molecular structure of **1**. Selected distances [Å] and angles [°]: O3–C17 1.372(2), C16–C17 1.577(3), N–C16 1.450(2), N–C19 1.284(2), C19–C20 1.452(3), C20–C21 1.410(3), C21–O2 1.336(2); O3–C17–C16 114.7(2), N–C16–C17 112.0(2), N–C19–C20 120.8(8), C19–C20–C21 120.0(2), C20–C21–O2 120.5(2)



hardly different from the corresponding torsion angle of the ligand. The angles between the D-rings of the steroid molecules and the affiliated copper-containing five-membered rings measure 46.3° and 48.6°. The conspicuous, funnel-shaped molecular structure, where the two steroid molecules together assume an angle of 100°, arises through the central, planar four-membered ring. The aromatic ring and chelate ring of the salicylideneimine are planar, as in the ligand, but assume angles of respectively 46° and 60° to the steroid. The compound crystallizes with one mole of water.

The possibility of monodeprotonation exists only at sufficiently low pH levels. Through the use of a more effective coordinating anion, such as perchlorate[8], the probability of achieving a complex with a monodeprotonated phenolate ligand is increased further. When a THF solution of **1** was mixed with copper(II) perchlorate hexahydrate, a slightly exothermic reaction resulted in an emerald-green solution. Optimal crystallization conditions were achieved through a careful layering with ether, waiting a week and subsequent addition of *n*-heptane: rough, emerald-green sheets were produced which also proved to be quite thermally stable.

This complex (**3**)[5] (Figure 3) is a dimer as well. The central, four-membered ring is in this case folded by 21.7° and consists of two copper atoms and two *phenolate* oxygens[6a] that function as bridges. Thus, a completely different topology is achieved, which is characterized also by the additional bridging of both copper atoms by a perchlorate anion. The second perchlorate anion is disordered. Further ligands for the copper atoms are both the 16-nitrogens and the 17-oxygen atoms, as well as a water molecule in a quasi-axial arrangement on the opposite side of the perchlorate anion. Thus, every copper atom is sixfold coordinated and located in the centre of a distorted octahedron. Two tetrahydrofurane molecules are bound by hydrogen bonds originating at both 17β-hydroxy groups. A further THF molecule is located in the crystal. The distorsion of the four-membered ring provides the conditions to produce an almost linear arrangement of both steroid components, even though the monomer structures of complexes **2** and **3** are otherwise practically the same. In contrast to **2**, **3** possesses C_2-symmetry.

A comparison of the molecular structures of **1**, **2**, and **3** shows that the angle between the salicylideneimine unit and the steroid changes from 74.5° in **1** to 46° and 60° in **2** and 33.5° in **3**. The torsion angles of 17β-O and 16β-N across the C17–C16 bond of the complexes are 19.8° and 23.2° (**2**) and 12.6° (**3**). Comparison with the value of 23° for the ligand **1** demonstates the relatively stable preferred conformation of the steroid D-ring.

As shown in Figures 4, 5 and 6, substantial differences are also found between the crystal structures of **1**, **2**, and **3**. For the ligand **1**, an intermolecular hydrogen bond between the 17β-OH group and the phenolic oxygen is determining (O–O distance of 2.776 Å). Through it, the molecules are arranged as polymer strands. The previously mentioned angle between the salicylideneimine component and the steroid component is obviously determined by this chain structure as well.

Two alternating stacking possibilities can be recognized in the saddle structure of the dimer of the crystal structure of complex **2**, whereby dideprotonation here prevents the formation of intermolecular hydrogen bonds.

In the perchlorate complex **3**, a supermolecular arrangement of the flat dimers can be seen. This arrangement arises via the hydrogen bonds between the water and perchlorate molecules which are coordinated on opposite sides of the copper atoms. The distance between the copper atoms of two dimers is 9.15 Å.

These investigations have clearly demonstrated how molecular as well as crystal structures can be significantly

Figure 2. Molecular structure of **2**. Selected distances [Å] and angles [°]: O2B–C17B 1.44(2), C16B–C17B 1.55(2), N1B–C16B 1.38(2), N1B–C18B 1.33(2), N1B–CuB 1.913(10), C18B–C19B 1.42(2), C19B–C24B 1.39(2), C24B–O3B 1.38(2), O3B–CuB 1.864(10), CuB–O2A 1.916(9), CuB–O2B 1.931(10), CuA–CuB 2.974(2); O2B–C17B–C16B 107.0(11), N1B–C16B–C17B 111.7(11), N1B–C18B–C19B 125.0(13), C24B–O3B–CuB 124.8(8), CuB–O2A–CuA 101.6(4), N1B–CuB–O2B 83.7(4)

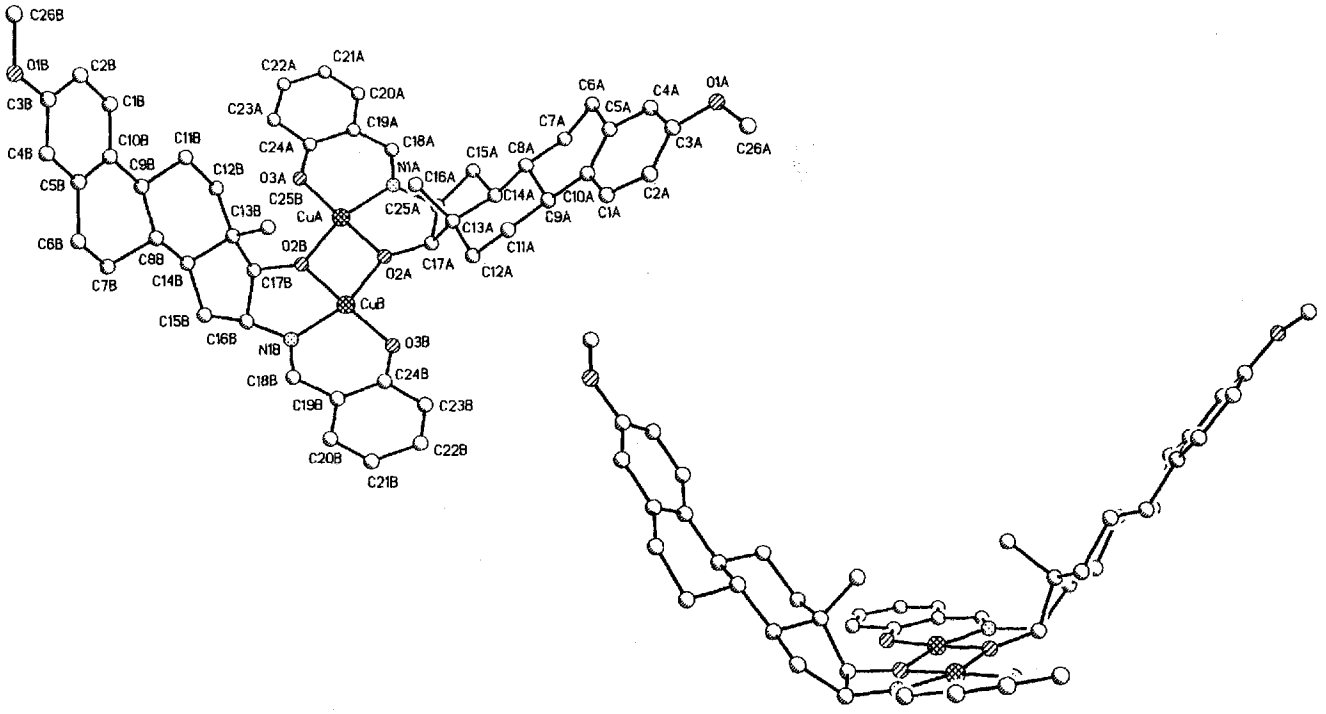
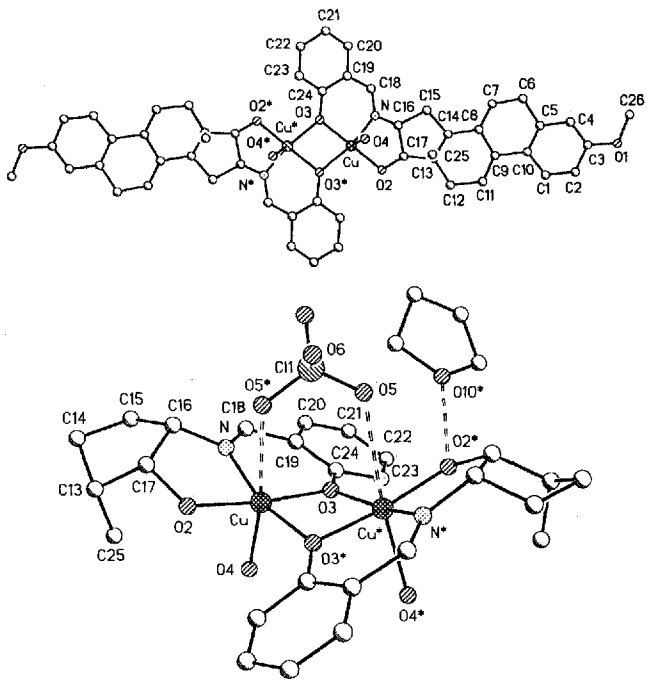
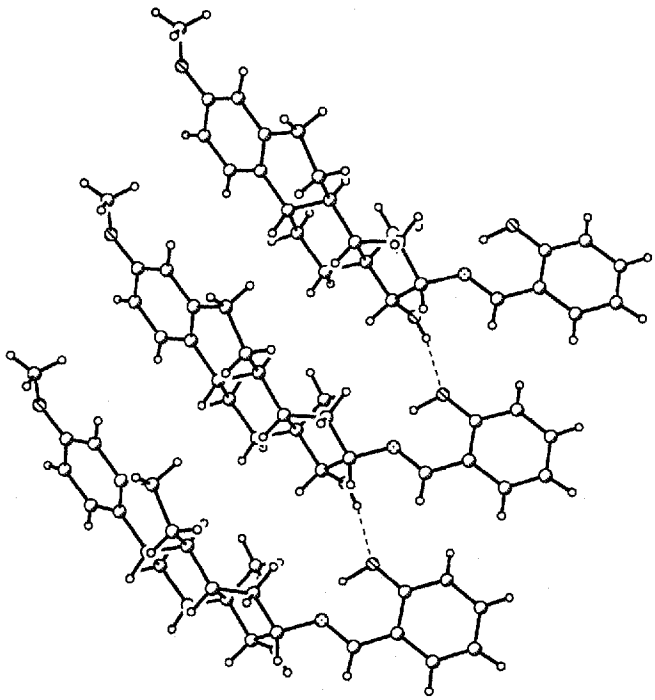


Figure 3. Molecular structure of **3**. Selected distances [Å] and angles [°]: O2–C17 1.469(7), C16–C17 1.569(9), N–C16 1.490(8), N–C18 1.297(8), C18–C19 1.455(9), C19–C24 1.450(9), C24–O3 1.347(8), O3–Cu 1.943(4), Cu–O2 1.962(4), Cu–Cu*1 2.999(2); O2–C17–C16 111.5(4), N–C16–C17 109.9(5), C16–N–C18 118.9(5), C16–N–Cu 115.6(4), C29–C24–O3 119.8(6), Cu–O3–Cu*1 99.4(2), O3–Cu–O4 87.0(2), O2–Cu–O4 100.3(2)



changed by the deprotonation of a bulky chiral ligand during complex formation. Indications of structural elements

Figure 4. Packing diagram and intermolecular hydrogen bonds of **1**



that are well suited for crystal design[9] have also been obtained through this process.

The investigations are being pursued with the three other configurations of the vicinal amino alcohols.

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Figure 5. Packing diagram and intermolecular hydrogen bonds of **2**

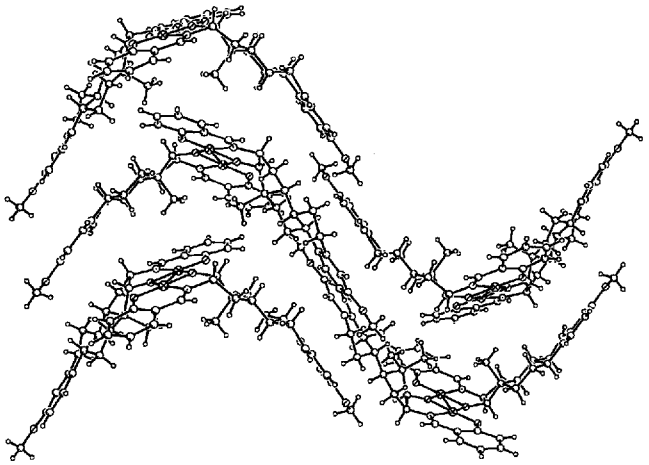
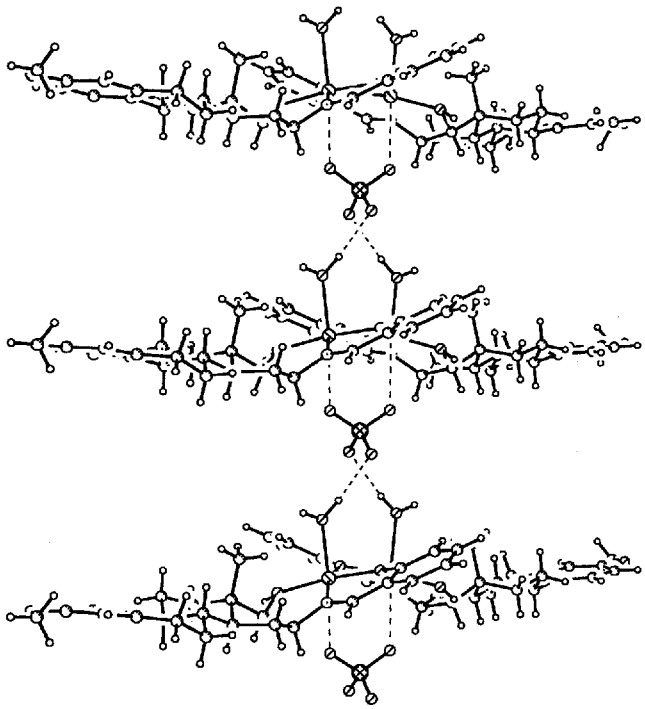


Figure 6. Packing diagram and intermolecular hydrogen bonds of **3**



Experimental

General: Melting points: Boëtius micromelting point apparatus, uncorrected values. – Elementary analyses: CHN-O-Rapid (HERAEUS) or CHNS-932 (LECO). – Mass spectra: AMD Intectra with FAB (3-NBA) or with electron impact ionization at 70 eV. – Optical rotations were measured at room temperature in chloroform with a photoelectronic polarimeter Polamat A (Carl Zeiss Jena) at 546 and 578 nm and extrapolated to 589 nm; *c* in g 100^{-1} ml^{-1}. – UV/Vis: Spectrometer Lambda 19 (Perkin Elmer). – ^1H NMR: 200 MHz Spectrometer AC 200F (Bruker), in chloroform with TMS as internal standard.

1: 16β-Amino-17β-hydroxy-3-methoxyestra-1,3,5(10)-triene[4] (904.2 mg; 3 mmol) was dissolved in 40 ml of absolute methanol and mixed while stirring at room temperature with 3.3 mmol (403 mg, 346 µl) of freshly distilled salicylic aldehyde. After approximately 3 hours, the solution was concentrated to 50% of its initial volume and placed in a freezer. After filtration, washing with methanol and drying, 1.3 g (97%) of fine, lemon-yellow crystals were obtained (^1H NMR: practically homogeneous). Recrystallization followed by dissolution in roughly 30 ml of boiling ethyl acetate and subsequent addition of 15 ml of boiling heptane yielded 1.0 g (75%) of rough, shiny yellow needles; m.p.: 221–224°C. – $[\alpha]_D$ (chloroform) = +48° (*c* = 0.938). – ^1H NMR: δ = 0.97 (s, 3H, 18-H_3), 3.71 (d, ^3J = 8.6 Hz, 1H, 17-H), 3.78 (s, 3H, OCH_3), 3.91 (m, 1H, 16-H), 6.62–7.37 (m, 7H, aromatic H), 8.33 (s, 1H, =CH), 13.00 (s, 1H, NH). – $C_{26}H_{31}NO_3$ (405.6 g mol^{-1}): calcd. C 76.99, H 7.71, N 3.47; found C 77.01, H 7.71, N 3.75.

2: 17β-Hydroxy-3-methoxy-16β-[(*E*)-salicylideneimino]-estra-1,3,5(10)-triene (**1**) (202.8 mg, 0.5 mmol) was mixed with 7 ml THF, subsequently combined while stirring with 0.5 mmol (99.8 mg) copper(II) acetate hydrate, and warmed to approximately 45°C. γ-Picoline (70 µl) was added to this homogenous, dark emerald-green solution and it was left at room temperature for 2–3 weeks in a petroleum ether chamber (gas-phase diffusion, petroleum ether replaced several times). For the completion of the crystallization, heptane was directly added towards the end of this period: 200 mg (84%) rough, black-green needles; lightly soluble in chlorohydrocarbons, THF, pyridine; hardly soluble in DMSO, acetone, or ethyl acetate, and practically insoluble in methanol, acetonitrile, and ether – m.p.: 238–244°C (decompn.) – $[\alpha]_D$ (pyridine) = +260 (*c* = 0.11). – IR (KBr): ν [cm^{-1}] = 2930 (m, CH), 1625 (s, C=N), 1604 (s), 1533 (m) and 1499 (m, aromatics), no OH or NH. – UV/Vis (chloroform): λ_{max} (lg ε) = 278 (4.3561), 372 (4.1418) and 602 nm (2.4465). MS-FAB: *m/z* (%): 933 (70.5) [($M^+ - H_2O$) – 1], 467 (100) [(CuL – 2) – 1, L = **1**] $C_{52}H_{58}Cu_2N_2O_6 \cdot H_2O$ (952.1 g mol^{-1}).

3: Compound **1** (202.8 mg; 0.5 mmol) was dissolved in 10 ml THF and subsequently mixed with 0.5 mmol (183.5 mg) of copper(II) perchlorate hexahydrate while stirring. The initially yellow solution then became an intense, emerald-green colour during a mildly exothermic reaction. Optimal crystallization conditions were realized by means of a liquid–liquid diffusion gradient through cautious layering with ether and one week later through the addition of a further 1.5 ml of heptane: 170 mg (43%) rough, emerald-green sheets; as opposed to **2**, only partially to barely soluble in chlorohydrocarbons. – m.p. 233–237°C (decompn.). – $[\alpha]_D$ (pyridine) = +360° to +260° (temporally dependent on deprotonation, *c* = 0.54). – IR (KBr): ν [cm^{-1}] = 3432 and 3158 (m, br, OH), 2930 (m, CH), 1620 (s, C=N), 1607 (s, sh), 1533 (m) and 1500 (s, aromatics), 1147, 1121, and 1108 (s, perchlorate); (Nujol): 3374 and 3158 (w–m, OH). – UV/Vis (chloroform): λ_{max} (lg ε) = 276 (4.6220), 377 (4.1259) and 669 nm (2.6067); (acetonitrile): 226 (4.3039), 274 (3.9505), 373 (3.5552). – MS-FAB: *m/z* (%): 935 (100) [($M^+ - 2\ H_2O - 2\ ClO_4 - 3$ THF) + 1], 467 (100) [CuL – 2, L = **1**], Scan-Electrospray-MS: 406 (100) [L + 1]. $C_{52}H_{60}Cl_2Cu_2N_2O_{14} \cdot 2\ H_2O \cdot 3\ C_4H_8O$ (1387.4 g mol^{-1}).

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[5] Crystal data: CAD4-Diffractometer, Mo-K (λ = 0.71069 Å), ω-

2Θ-Scan, T = 183 K; Solution: Direct Methods (SHELXS-86), Refinement against $|F_o|^2$ (SHELXL-93); when not otherwise mentioned, the hydrogen atoms were included at positions calculated with fixed thermal parameters. – **1**: $C_{26}H_{31}NO_3$, yellow, 0.40 × 0.38 × 0.38 mm^3, M_r = 405.52 g mol^{-1}, triclinic, P1 (No. 1), a = 5.740(1), b = 8.344(2), c = 11.967(2) Å, α = 82.43(3), β = 90.03(3), γ = 69.78(3)°, V = 532.5(2) Å^3, Z = 1, $\rho_{calc.}$ = 1.26 g cm^{-3}, μ = 0.82 cm^{-1}; 3682 reflections collected in ±h, ±k, ±l, measured in the range 2.61° ≤ Θ ≤ 31.97°; 3680 unique reflections, of which 3275 were considered observed ($I > 2\sigma_I$); 395 refined parameters; H-atoms localized from Difference Fourier Synthesis and refined with isotropic displacement parameters, R_1 = 0.041, wR_2 = 0.105, GOOF = 1.66, Flack-parameter 1 (1) absolute configuration could not be determined reliably; max. features of final Difference Fourier Synthesis 0.30 e Å^{-3}. – **2**: $C_{52}H_{55}Cu_2N_2O_6 \cdot H_2O$, green, 0.40 × 0.36 × 0.36 mm^3, M_r = 949.1 g mol^{-1}, orthorhombic, $P2_12_12_1$ (No. 19), a = 12.099(2), b = 13.290(3), c = 30.702(6) Å, V = 4936(1) Å^3, Z = 4, $\rho_{calc.}$ = 1.28 g cm^{-3}, μ = 9.12 cm^{-1}; 6484 unique reflections collected in $-h$, $-k$, $-l$, measured in the range 2.50° ≤ Θ ≤ 28.9°, of which 4320 were considered observed ($I > 2\sigma_I$); 572 refined parameters, R_1 = 0.096, wR_2 = 0.250, GOOF = 1.66, Flack parameter −0.2(3), water molecule is disordered and the reason for the bad crystal structure analysis; max. features of final Difference Fourier Synthesis 1.25 e Å^{-3}. – **3**: $[(C_{52}H_{60}Cu_2N_2O_6)^{2+} \cdot 2\,(ClO_4)^- \cdot 2\,H_2O \cdot 2\,C_4H_8O] \cdot C_4H_8O$, green, 0.40 × 0.38 × 0.36 mm^3, M_r = 1387.34 g mol^{-1}, monoclinic, C2 (No. 5), a = 26.328(5), ρb = 9.153(2), c = 14.730(3), β = 98.95(3)°, V = 3506(1) Å^3, Z = 2, $_{ber}$ = 1.31 g cm^{-3}, μ = 7.51 cm^{-1}; 3763 reflections collected in ±h, ±k, ±l, measured in the range 2.68° ≤ Θ ≤ 27.9°; 3625 unique reflections, of which 3251 were considered observed ($I > 2\sigma_I$); 416 refined paramters, R_1 = 0.058, wR_2 = 0.148, GOOF = 1.03, Flack parameter −0.01(2), uncoordinated ClO_4 group is disordered, the O atoms were isotropically refined, the H-atoms of the water molecule were localized by means of a Difference Fourier Synthesis; max. features of final Difference Fourier Synthesis 0.80 e Å^{-3}. Further details concerning the crystal structure analyses are available on request from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository numbers CSD-405461 (**1**), CSD-405462 (**2**) and CSD-405463 (**3**), the names of the authors, and the journal citation.

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