Hydroxylation of N-Heterocycle Ligands Observed in Two Unusual Mixed-Valence Cu^I/Cu^{II} Complexes**

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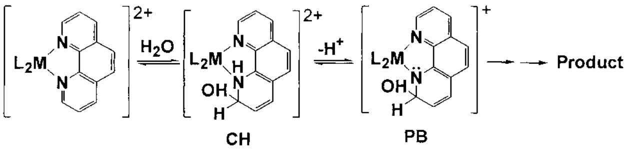
Dedicated to Professor Thomas C. W. Mak
on the occasion of his 65th birthday

The chelate ligands 2,2′-bipyridine (bpy), 1,10-phenanthroline (phen), and their substituted derivatives have played an important role in the development of coordination chemistry,[1, 2] and over the decades a number of so-called anomalies have been reported in reactions of their metal complexes. To rationalize the anomalous properties of complexes such as $[M(bpy)_3]^{n+}$ and $[M(phen)_3]^{n+}$, Gillard borrowed the idea of "covalent hydrates" from the organic literature and proposed an interesting mechanism,[3] the core of which is nucleophilic attack of a hydroxide ion on a coordinated heterocyclic ligand to form a covalent hydrate (**CH**); this may react further by intramolecular shift of OH^- or H_2O onto the metal before the formation of the final products (Scheme 1). The mechanism was questioned[4–8] because of to the lack of structural evidence[6, 7] for the **CH** intermediate.[8] However, if the proposed covalent hydrates of phen and bpy could be isolated as hydroxylated products, they would be novel heterocyclic ligands capable of chelating and bridging ligation for the synthesis of polynuclear metal complexes. Therefore, the hydroxylation of phen and bpy is important both in organic heterocyclic chemistry and as a possible bridge to coordination chemistry.



Scheme 1. Gillard mechanism for the hydroxylation of $[L_2M(phen)]^{2+}$. **PB** = pseudo-base.

We report here on our observation of hydroxylated bpy and phen ligands in the two delocalized mixed-valence Cu^I/Cu^{II} complexes **1** and **2** (Hophen = 2-hydroxy-1,10-phenanthroline, Hobpy = 6-hydroxy-2,2′-bipyridine, tp = terephthalate).

$[Cu_4(obpy)_4(tp)]$ **1**

$[Cu_4(ophen)_4(tp)]$ **2**

Dark brown platelike crystals of **1** and **2** (ca. 50% yield) were obtained by heating $Cu(NO_3)_2$, phen or bpy, respectively, H_2tp, NaOH, and water in the molar ratio 1:1.3:0.25:0.5:1100 at 160 °C for 144 h. Both **1** and **2** are air stable and insoluble in water and most organic solvents. Maintaining the initial pH at >8 is critical to the formation of the products.

The X-ray crystal structures obtained for **1** and **2** (Figure 1) reveal unequivocally that a hydroxy group is attached at the carbon atom adjacent to a nitrogen atom (C–O 1.286(7) – 1.294(7) Å) of the heterocycle ligands. There are two crystallographically independent but chemically very similar copper atoms in **1** and **2**, as both the bond lengths and bond angles for the two metal atoms are very similar. The two metal atoms approach closely with a Cu–Cu separation of 2.415(2) Å in **1** and 2.443(2) Å in **2**. The coordination geometry of each metal atom is roughly a square pyramid composed of a pair of nitrogen atoms (Cu–N 1.950(5) – 2.096(5) Å) from an obpy or ophen ligand, a deprotonated hydroxy group (Cu–O 1.921(5) – 1.943(4) Å) from another obpy or ophen, and the adjacent copper atom at the equatorial positions, and by a tp carboxylate oxygen atom (Cu–O 2.167(5) – 2.302(5) Å) at the apical position. The dinuclear core is somewhat similar to that found in the mixed-valence complex $[Cu_4(tp)_3(4,4'\text{-}bpy)_2]$.[9] The unusually short Cu – Cu distance in combination with the necessity to balance charge indicates that **1** and **2** are delocalized mixed-valence dicopper(I,II) complexes.[9–14] A pair of the dinuclear cores is bridged to form a centrosym-

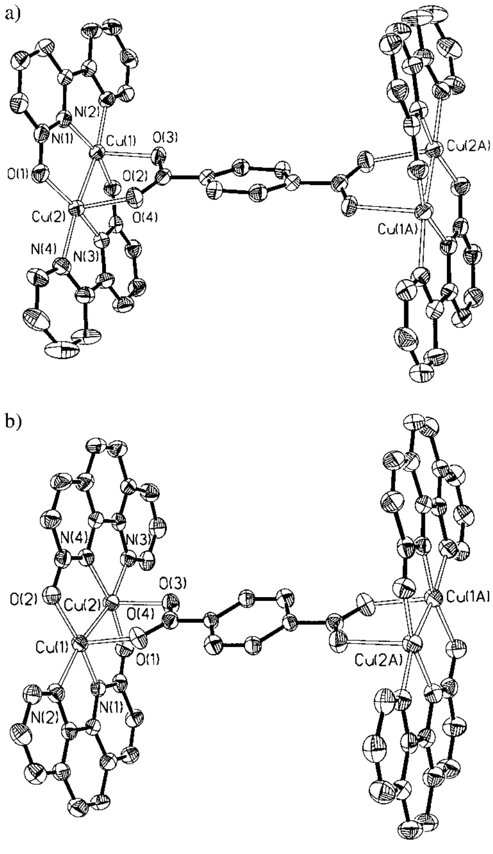


Figure 1. X-ray crystal structures of **1** (a) and **2** (b) with thermal ellipsoids set at 35% probability. Distances of interest are discussed in the text.

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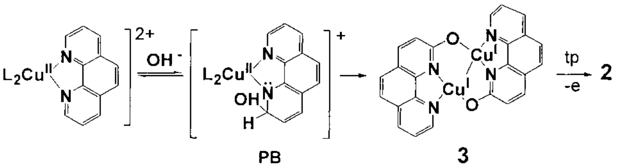
metric neutral tetranuclear $Cu^{I,II}$ complex through a μ_4-tp ligand in **1** and **2** (Figure 2).

As the Gillard mechanism suggests, hydroxylation of bpy and phen leading to Hobpy and Hophen in **1** and **2**, respectively, which was not documented previously, is the result of nucleophilic attack of hydroxide ions. In addition, we found that the formation of **1** and **2** shows significant dependence on pH (higher pH favors the formation of **1** and **2** which also indicates nucleophilic attack by a hydroxide ion on the coordinated bpy or phen during the reaction). Furthermore, our experiments[15] confirm that coordination of bpy and phen to copper ions is critical to their hydroxylation, which is also in agreement with the Gillard mechanism. Therefore, the conversion of bpy or phen ligands into obpy and ophen during the reaction provides the structural evidence for the core of the Gillard mechanism. Based on this mechanism we propose a possible route for the formation of **1** and **2** (Scheme 2). The neutral dimeric Cu^I species $[Cu_2(ophen)_2]$ (**3**) has been isolated as a by-product in the preparation of **2** and has also been structurally characterized.[16] The existence of the Cu^I species suggests that some Cu^{II} ions in intermediate pseudo-base (**PB**) may act as an oxidative agent and assist the elimination of the proton on the carbon atom adjacent to the nitrogen atom. The hydroxy group is thus trapped on the aromatic ring and avoids an intramolecular shift onto the metal center. Finally, one-electron oxidization[14] of the dinuclear Cu^I species, in which the oxidative agent may possibly be the remaining Cu^{II} ions, and coordination of a tp ligand as a bridge result in the formation of tetranuclear **1** and **2** comprising mixed-valence dinuclear cores (Figure 2).



Scheme 2. Proposed mechanism for the formation of **2** and **3**.

Direct evidence for the mixed-valence compounds **1** and **2** also comes from the temperature-dependent magnetic susceptibility of **2**. The magnetic behavior of **2** obeys the Curie–Weiss Law in the temperature range between 2 and 200 K with an effective magnetic moment of 1.73 μ_B per Cu_2 unit at 200 K which is consistent with one unpaired electron per dimer. A small Weiss constant of -3.71 K indicates a weak antiferromagnetic coupling of Cu_2 units either through the μ_4-tp bridge or intermolecular Cu···Cu approaches. An EPR spectrum of **2** ($g = 2.10$) at 40 K shows that the paramagnetism arises from the metal centers.

It should be noted that van der Waals interactions among adjacent Cu_2^{3+} dimers are remarkable in **1** and **2**, as shown in Figure 2. Two Cu_2^{3+} dimers from neighboring molecules form a rectangle in **1** with the longer side of 4.02 Å, and a parallelogram in **2** with the diagonal distance of 3.74 Å and longer side of 4.05 Å. Besides, the adjacent aromatic rings of ophen and obpy stack in a face-to-face fashion with a separation of 3.4–3.8 Å which indicates strong π–π stacking interactions between the aromatic rings. Thus, the stabilization of solids **1** and **2** may result from the intermolecular Cu··· Cu interactions and π–π stacking interaction between aromatic rings.

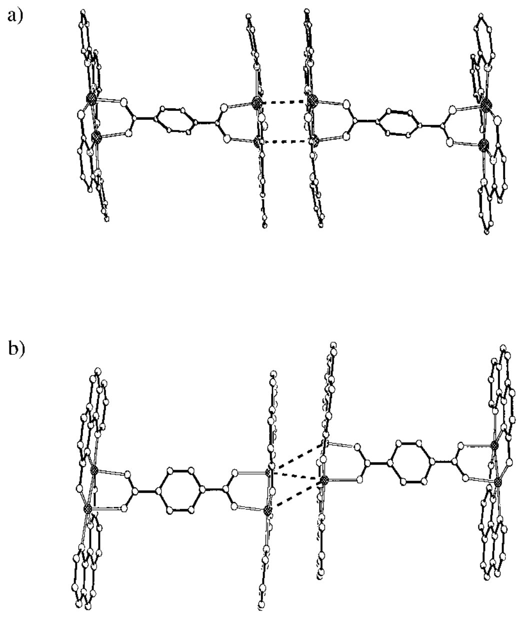


Figure 2. The intermolecular Cu···Cu interactions of adjacent molecules in **1** (a) and **2** (b).

It is also notable that delocalized mixed-valence Cu_2 centers are important in metalloprotein systems because they involve long-distance electron transfer, and the Cu–Cu bond of the Cu_2 core represents the first metal–metal bond in biology.[17] However, up to present there have been only three approaches to stabilize model complexes containing delocalized mixed-valence Cu_2 centers: encapsulation of octaazacryptand macrobicyclic ligands, blocking of ligands, and solid-state entrapment of coordination polymers.[9–14] Thus this work represents a new route to the stable mixed-valence dicopper complexes.

Experimental Section

A mixture of $Cu(NO_3)\cdot 3H_2O$ (0.120 g), phen (0.117 g) or bpy (0.102 g), H_2tp (0.041 g), NaOH (0.02 g), and water (10 mL) in the molar ratio 1:1.3:0.25:0.5:1100 was stirred for 20 min in air, then transferred and sealed in a 23-mL Teflon reactor, which was heated in an oven to 160 °C for 144 h. The oven was cooled to room temperature at a rate of 5 °C h^{-1}. The resulting dark brown platelike crystals of **1** and **2** were filtered, washed, and dried in air (yield 50 %). A minor product was structurally characterized as **3** (yield ca. 3 %).[16]

1: Elemental analysis (%) calcd for $C_{24}H_{16}Cu_2N_4O_4$: C 52.27, H 2.92, N 10.16; found: C 52.16, H 2.88, N 10.03; IR (KBr, cm^{-1}): $\tilde{\nu} = 3433$m, 3070w, 1601s, 1568s, 1492s, 1458s, 1164m, 1013s, 812m, 776s, 746m, 589w; crystal data:[18] triclinic, space group $P\bar{1}$ (no. 2), $M_r = 551.49$, $a = 10.047(8)$, $b = 10.688(7)$, $c = 11.186(7)$ Å, $\alpha = 79.55(1)$, $\beta = 71.76(1)$, $\gamma = 69.94(1)^\circ$, $V = 1065.9(13)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.718$ g cm^{-3}, $\mu = 2.037$ mm^{-1}, $F(000) = 556$; $R = 0.0667$, $R_w = 0.2101$, GOF = 1.003 for 308 parameters, 2655 reflections with $|F_o| = 4\sigma(F_o)$.

2: Elemental analysis (%) calcd for $C_{28}H_{16}Cu_2N_4O$: C 56.09, H 2.69, N 9.34; found: C 55.89, H 2.73, N 9.22. IR (KBr, cm^{-1}): $\tilde{\nu} = 3440$m, 3050w, 1622m, 1563s, 1511s, 1485s, 1459s, 1386s, 1365s, 1142m, 843m, 734m, 653m; EPR: $g = 2.10$; crystal data:[18] monoclinic, space group $P2_1/n$ (no. 14), $M_r =$

599.53, $a = 10.465(8)$, $b = 15.279(8)$, $c = 15.425(12)$ Å, $\beta = 104.60(5)^\circ$, $V = 2387(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.668$ g cm^{-3}, $\mu = 1.827$ mm^{-1}, $F(000) = 1208$, $R = 0.0609$, $R_w = 0.1736$, GOF = 1.006 for 344 parameters, 2606 reflections with $|F_o| = 4\sigma(F_o)$.

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[15] A mixture of phen (0.117 g) or bpy (0.102 g), H_2tp (0.041 g), NaOH (0.02 g), and water (10 mL) in the molar ratio 1.3:0.25:0.5:1100 was sealed in 23-mL Teflon reactor, which was heated in an oven at 160 °C for 144 h. No solid hydroxylated organic product was observed.

[16] Crystal data for **3**: monoclinic, space group $P2_1/n$, $M_r = 517.47$, $a = 10.651(8)$, $b = 6.180(4)$, $c = 15.079(13)$ Å, $\beta = 94.160(10)^\circ$, $V = 989.9(13)$ Å^3, $Z = 2$.

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[18] General crystallographic information: $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). $T = 293$ K. Siemens $R3$m diffractometer, ω scan mode ($4 \leq 2\theta \leq 52^\circ$ for **1** and $4 \leq 2\theta \leq 52^\circ$ for **2**), solved with direct methods (SHELXS-97)[19] and refined with full-matrix least-squares (SHELXL-97).[20] CCDC-170016 and CCDC-170017 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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Diastereoselective Asymmetric Nitro-Aldol Reaction of *α*-Amino Aldehydes under High Pressure without Catalyst**

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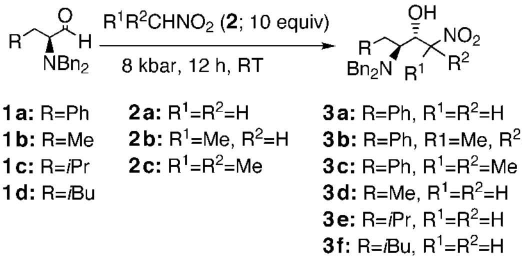
Dedicated to Professor Rolf Huisgen
on the occasion of his 81st birthday

The Henry (nitro-aldol) reaction is one of the most valuable methods for carbon–carbon bond formation and its stereochemical control continues to be a challenge for organic chemists.[1–6] Specifically, an efficient synthesis of medicinally important intermediates such as phenylnorstatine through a diastereoselective catalytic (rare earth-Li-(*R*)-BINOL) asymmetric nitro-aldol reaction of optically active *α*-amino aldehydes with nitromethane has been reported.[4] Tetrabutylammonium fluoride has been also used, albeit with less success.[5] More recently, Corey and Zhang employed a rigid chiral quaternary ammonium salt for this reaction, which leads to a highly stereoselective synthesis of the HIV protease inhibitor amprenavir.[6] More generally, nitro-aldol adducts provide ready access to non-natural 3-amino-2-hydroxy acids and 1,3-diamino-2-hydroxy units, which are substructures of medicinally important compounds.[7, 8] One of us previously demonstrated that the Henry reaction is highly accelerated by pressure.[9] However, to our knowledge, no attempts have ever been made to perform a diastereoselective nitro-aldol reaction without a catalyst.[10] We envisaged that the amino group of optically active *α*-amino aldehydes might act as a base, and that such aldehydes would react with nitromethane under high pressure without a catalyst, thus offering a clean reaction system. Herein, we report the first example of the diastereoselective nitro-aldol reaction without any added catalyst.

N,N-Dibenzyl *α*-amino aldehydes **1** (Scheme 1) were chosen as a model substrate since they bear a free amino group and are relatively stable. The adducts may serve as versatile synthetic intermediates for the synthesis of non-natural



Scheme 1. Reaction of *α*-amino aldehydes **1** with nitroalkanes **2**.

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