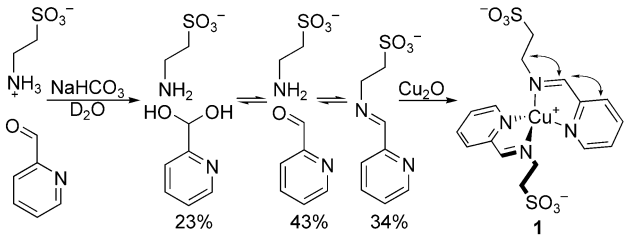
Template Synthesis

Mutual Stabilization between Imine Ligands and Copper(I) Ions in Aqueous Solution**

*Jonathan R. Nitschke**

Dedicated to Professor T. Don Tilley on the occasion of his 50th birthday



Scheme 1. The synthesis of **1**. Double-headed arrows indicate observed NOE interactions.

Imine donors are known to stabilize Cu^{I} ions in environments that would otherwise favor disproportionation to Cu^{II} and Cu^{0}, such as aqueous solution. Herein, it is shown that the converse is likewise true, that Cu^{I} ions are capable of stabilizing and templating the formation of appropriate imine ligands from pyridine-2-carboxaldehyde and sulfonated amines in aqueous solution. This stabilization is mutual and cooperative, since neither Cu^{I} ions nor imines are ordinarily stable in water.

Selective exchange of the amine components of the imine ligands has also been demonstrated, thus representing an advance within the field of directed ligand/component assembly around metal centers.[1–3] This branch of dynamic self-assembly[4,5] is based upon ligand rearrangement reactions (changes in ligand conformation and supramolecular architecture induced by transmetalation,[6] redox processes,[7] or the presence of guest species[8]).

The self-assembly reaction which generates these Cu^{I}–imine complexes proceeds readily in the presence of a dynamic combinatorial library of potential ligand components.[5,9] The best ligand for the chelation of a Cu^{I} ion is formed exclusively, which results in the elimination of its components from the library. This causes a partial "collapse" of the library by eliminating all the other members that had integrated into these components.

The reaction of taurine (2-aminoethanesulfonic acid, 0.14 mmol) with pyridine-2-carboxaldehyde (0.14 mmol) and sodium bicarbonate (0.07 mmol) in deuterium oxide (0.5 mL) yields a product mixture whose ^{1}H NMR spectrum corresponds to the mixture of compounds shown in Scheme 1. The addition of copper(I) oxide (0.035 mmol) to this mixture under anaerobic conditions produces a dark red/brown solution as the copper(I) oxide dissolves over the course of several hours in an ultrasound bath. The ^{1}H and ^{13}C NMR spectra of this product demonstrate that it is diamagnetic and that the mixture of four components initially present has collapsed down to give a single product: the copper(I)–bis(dimine) **1**.

The quantitative formation of an imine ligand was verified by the observation of NOE difference peaks between the imine proton and the pyridine and methylene protons (Scheme 1). The diastereotopic methylene groups α to the imine nitrogen atom exhibit a single proton resonance in water or methanol at room temperature, which is indicative of rapid racemization around the Cu^{I} stereocenter. This signal decoalesces in [D_4]methanol at 233 K and gives rise to two broad resonances that reach a maximum separation of 121 Hz at 183 K. This process corresponds to a $\Delta G^{\ddagger} = 46\ kJ\,mol^{-1}$ at 233 K,[10] a value slightly lower than those observed for Cu^{I}–bis(2-iminopyridine) complexes in chlorinated solvents.[11] Electrostatic repulsion between the sulfonate groups may account for this lower barrier to racemization.

Complex **1** represents a novel example of imine self-assembly around a copper(I) template. The self-assembly of bidentate imine ligands having no negatively charged atom directly bound to the metal center is also noteworthy. With the exception of a tetracopper-grid structure synthesized in acetonitrile from 3,6-pyridazinedicarboxaldehyde and 1,3-diaminopropane,[2] previous examples of metal-templated imine synthesis have involved the formation of a site with three or more metal-binding atoms and/or metal-bound anions to stabilize the resulting complex through chelate and electrostatic effects.[3,12] The preference of the Cu^{I} center for a tetra-imine ligand may eliminate the need for additional stabilizing factors, so preventing the imines from hydrolyzing even in an aqueous environment.

A solution of **1** reacts with atmospheric oxygen to give a pale green product, the NMR spectra of which show broad features, indicative of the presence of Cu^{II} ions. Complex **1** is stable to the presence of oxygen on a time scale of weeks in the solid state.

Complex **1** is stable in solution in the absence of oxygen. Its thermodynamic stability is demonstrated by the reaction shown in Scheme 2. The conproportionation of copper(II) chloride (0.03 mmol) and copper powder (0.03 mmol) in the presence of taurine (0.12 mmol), pyridine-2-carboxaldehyde (0.12 mmol), and sodium hydrogencarbonate (0.12 mmol) in deuterium oxide (1 mL) yields **1**, which is shown to be identical by NMR spectroscopic analysis to samples prepared from copper(I) oxide. The interaction of the products arising from the equilibria shown on the left of Scheme 2 gives rise to a new equilibrium, which lies entirely to the right under the

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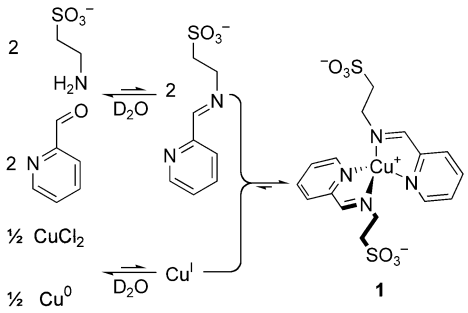
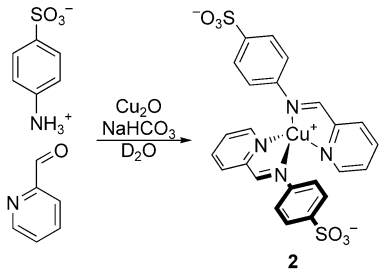


Scheme 2. The mutual stabilization of imine ligands and Cu^{I} ions during the generation of **1**.

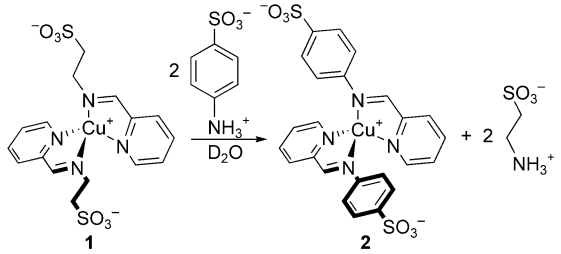
experimental conditions employed, as evidenced by the quantitative formation of **1**. This equilibrium represents a mutual selection of the correct ligand by and for the metal in the correct oxidation state, that is, the cooperative stabilization of two species that are not stable in the absence of each other.

The generality of this reaction is demonstrated by the synthesis of **2**, prepared by using the same procedure as **1**, except that sulfanilic acid (4-aminobenzenesulfonic acid) was used in place of taurine. This synthesis is shown in Eq. (1).



(1)

The addition of sulfanilic acid (0.14 mmol) to a solution of **1** (0.07 mmol) in deuterium oxide (0.5 mL) also gives a near-quantitative yield of **2** [Eq. (2)]. This ligand/component

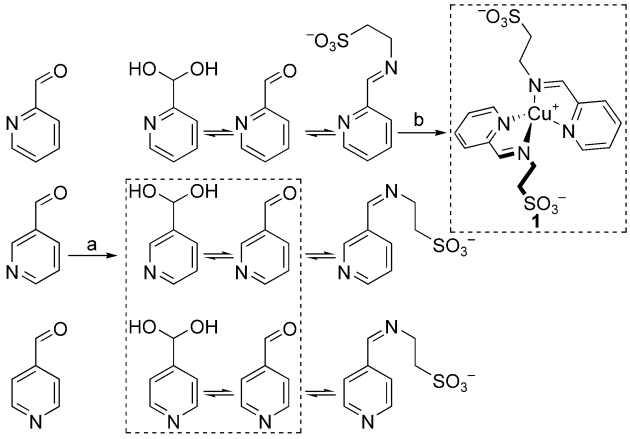


(2)

exchange occurs with a selectivity conservatively estimated as greater than 95%, based on ^{1}H NMR integration: only about 2% of the taurine initially incorporated into **1** is not released. The exchange occurs within seconds of the addition at room temperature.

The driving force behind this ligand/component exchange may be understood in terms of the difference in pK_a values: the NH_3^+ group of taurine is substantially less acidic (pK_a = 9.1)[13] than that of sulfanilic acid (pK_a = 3.2).[14] This favors the displacement of the protonated form of the weaker acid (taurine) from **1** and the incorporation of the deprotonated form of the stronger acid (sulfanilic acid) during the formation of **2**. The more extensively conjugated π system of the ligands in **2** should also stabilize it with respect to **1**, as well as providing lower-energy π* orbitals that would have an enhanced ability to stabilize the electron-rich Cu^{I} center through back-donation.

In addition to the selection of amines, the system is capable of selecting pyridine-2-carboxaldehyde from a library of its isomers based on the ability to form a bidentate imine ligand (Scheme 3). The mixture of the three pyridinecarbox-



Scheme 3. The Cu^{I}-mediated selection of pyridine-2-carboxaldehyde from a library of its isomers. a) Taurine, sodium bicarbonate, deuterium oxide; b) copper(I) oxide. The compounds remaining after the addition of copper(I) oxide are outlined.

aldehydes and taurine (0.12 mmol of each) with sodium bicarbonate (0.06 mmol) in deuterium oxide (1 mL) gives a complex ^{1}H NMR spectrum, which shows resonances attributed to the aldehydes, their gem-diol hydrates, and their taurine-derived imines, all of which undergo dynamic interconversion. This situation corresponds to a dynamic combinatorial library of ten members (including free taurine). NMR specroscopic analysis shows that addition of copper(I) oxide (0.03 mmol) to this mixture, followed by stirring overnight, gives a product mixture in which all of the components of the library derived from taurine and pyridine-2-carboxaldehyde (six out of ten initial members) have been removed by complexation. The product mixture has thus collapsed into **1** and the subset of aldehydes outlined in Scheme 3. This selection works equally well with a library containing sodium 2-formylbenzenesulfonate and 3,4-dihydroxybenzaldehyde as non-incorporated aldehydes in place of pyridine-3-carboxaldehyde and pyridine-4-carboxaldehyde, which suggests there is a certain generality.

The development of this aqueous Cu^{I} chemistry should thus enable an extension of the wealth of copper(I) self-assembly chemistry[15] into the aqueous domain, where an interface with biology may be possible. Future work will focus on the investigation of Cu^{I}-templated self-assembly as a means to link copper centers to specific amino groups in biomolecules (such as peptides and nucleic acids). The use of

ligand component exchange to program the self-assembly of larger structures containing multiple copper centers will likewise be developed.

Experimental Section

All manipulations were carried out under argon or nitrogen atmospheres using degassed solvents.

$Na^+\mathbf{1}^-$: Pyridine-2-carboxaldehyde (1.08 g, 10.1 mmol), taurine (1.27 g, 10.1 mmol), copper(I) oxide (0.362 g, 2.53 mmol), and sodium bicarbonate (0.425 g, 5.06 mmol) were added to a 100-mL Schlenk flask. The flask was sealed, a magnetic stirring-bar added, and the atmosphere was deoxygenated by three evacuation/argon fill cycles. Water (50 mL) was then added, which caused gas evolution and the development of a dark-red/brown color. Once gas evolution had ceased the flask was sealed and the reaction was allowed to stir for 8 h at 22 °C. Volatiles were then removed under dynamic vacuum until approximately 5 mL of material remained, which was then triturated with methanol (10 mL) and *tert*-butanol (40 mL). A precipitated brown, microcrystalline solid was then allowed to settle, and the supernatant was removed with a cannula filter. The product (2.50 g, 96 %) was then dried under dynamic vacuum for 4 h. ^{1}H NMR (400 MHz, 300 K, D_2O, referenced to *t*BuOH at 1.24 ppm as the internal standard; peak assignments are consistent with COSY and NOESY spectra): $\delta = 8.73$ (s, 2H, imine), 8.51 (d, $J = 5.8$ Hz, 2H, 6-pyridyl), 8.07 (t, $J = 10.2$ Hz, 2H, 4-pyridyl), 7.87 (d, $J = 10.2$ Hz, 2H, 3-pyridyl), 7.64 (m, 2H, 5-pyridyl), 4.21 (t, $J = 8.5$ Hz, 4H, NCH_2CH_2S), 3.14 ppm (t, $J = 8.5$ Hz, 4H, NCH_2CH_2S); ^{13}C NMR (75.48 MHz, 300 K, D_2O, referenced to *t*BuOH at 30.3 ppm as the internal standard): $\delta = 162.7$, 150.4, 149.2, 138.3, 128.3, 127.0, 54.6, 51.2 ppm; ESI-MS: *m*/*z* 489.0 [$\mathbf{1}^-$], 213.3 [(metal-free imine ligand of $\mathbf{1}$)$^-$]. Elemental analysis (%) calcd for $C_{16}H_{18}CuN_2NaO_6S_2{\cdot}2\,(CH_3OH)$: C 37.46, H 4.54, N 9.70; found: C 37.33, H 4.53, N 9.79.

Complex **2** may be synthesized in an identical fashion in 92 % yield using sulfanilic acid in place of taurine. Characterization data for $Na^+\mathbf{2}^-$: ^{1}H NMR (400 MHz, 300 K, D_2O, referenced to *t*BuOH at 1.24 ppm as the internal standard): $\delta = 8.92$ (s, 2H, imine), 8.15 (d, $J =$ 3.9 Hz, 2H, 6-pyridyl), 8.00 (t, $J = 7.7$ Hz, 2H, 4-pyridyl), 7.91 (d, $J =$ 7.7 Hz, 2H, 3-pyridyl), 7.48 (m, 6H, 5-pyridyl, 2,6-sulfanil), 7.16 ppm (d, $J = 7.3$ Hz, 4H, 3,5-sulfanil); ^{13}C NMR (75.48 MHz, 300 K, D_2O, referenced to *t*BuOH at 30.3 ppm as the internal standard): $\delta = 160.7$, 150.7, 149.7, 149.0, 143.3, 139.3, 129.8, 127.9, 129.4, 123.0 ppm; ESI-MS: *m*/*z* 585.0 [$\mathbf{2}^-$], 261.0 [(metal-free imine ligand of $\mathbf{2}$)$^-$]. Elemental analysis (%) calcd for $C_{24}H_{18}CuN_4NaO_6S_2{\cdot}CH_3OH$: C 46.87, H 3.46, N 8.75; found: C 46.66, H 3.32, N 9.01.

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