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A 3-Fold-Symmetric Ligand Based on 2-Hydroxypyridine: Regulation of Ligand Binding by Hydrogen Bonding

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Supporting Information

ABSTRACT: A tripodal ligand based on 2-hydroxypyridine is presented. Cu−Cl adducts of H_3thpa with Cu^I and Cu^{II} provide complexes featuring highly directed, intramolecular hydrogen-bonding interactions. An upper limit for the hydrogen-bonding free energy to Cu^I−Cl was estimated at ∼18 kcal/mol.

Noncovalent interactions are ubiquitous in biological systems and are used to augment reactivity in many metalloenzymes through a combination of hydrogen-bonding (H-bonding), steric, and electrostatic interactions. As a means to mimic these key aspects of metallobiochemistry, a burgeoning number of synthetic metal complexes have been designed to include directed noncovalent interactions in order to investigate how perturbations to a metal's secondary coordination sphere can influence the reactivity at the metal's primary coordination sphere.[1] Furthermore, directed secondary coordination sphere interactions in synthetic systems have proven to be effective for the stabilization and characterization of otherwise unstable or reactive intermediates.[2] In addition to promoting noncovalent interactions, proton-transfer reactivity can also be directed by positioned acidic/basic groups.[3] Such proton-responsive ligands are attractive features of bioinspired complexes[4] and catalysts.[5]

The recent structural elucidation of the active site of the iron-only hydrogenase enzyme revealed a derivative of 2-hydroxypyridine (2-hp) coordinated to iron.[6] This motif might reveal the blueprint of an evolutionarily designed cooperative M−L proton-responsive fragment. In addition to biological relevance, complexes containing 2-hp units feature ligand fields that may be modulated as a function of the protonation state.[7] We recently reported the coordination chemistry and catalytic reactions of complexes containing 6,6′-dihydroxyterpyridine, a rigid, proton-responsive pincer ligand incorporating the 2-hp motif, which promotes H-bonding interactions with metal-bound substrates.[8] To further extend the coordination chemistry of 2-hp-derived ligands, we targeted a framework that incorporates the 2-hp motif within an ostensibly 3-fold-symmetric ligand environment. By the incorporation of three 2-hp units into a tripodal ligand, multiple metal oxidation states and/or electronic environments should be accessible by exploiting tautomerization of the 2-hp units. Additionally, the ability to adapt to either H-bonding acceptors or donors depending on the protonation state of the ligand might be exploited to stabilize highly reactive units via noncovalent interactions. In this Communication, we present a tripodal ligand featuring 2-hp units, its subsequent coordination chemistry with Cu^I and Cu^{II} and illustrate its ability to engage in H-bonding interactions with a metal-bound ligand.[9]

The ligand tris(6-hydroxypyrid-2-ylmethyl)amine (H_3thpa) can be synthesized in three steps starting from commercially available 2-methoxy-6-methylpyridine (Scheme S1 in the Supporting Information, SI). Bromination of the pyridine methyl group[10] and subsequent condensation with ammonium carbonate afforded tris(6-methoxypyrid-2-ylmethyl)amine (tpa^{OMe}) in 45% isolated yield over two steps. Deprotection of the OCH_3 groups could not be achieved using traditional methods (acid hydrolysis, BBr_3, Me_3SiI, etc.). However, the desired hydroxyl variant can be accessed in 46% isolated yield by deprotection using 2-(diethylamino)ethanethiol hydrochloride and sodium *tert*-butoxide in refluxing dimethylformamide.

The 2-pyridone form of H_3thpa is favored in both the solution and solid state (Figure 1), as evidenced from the lack of OH

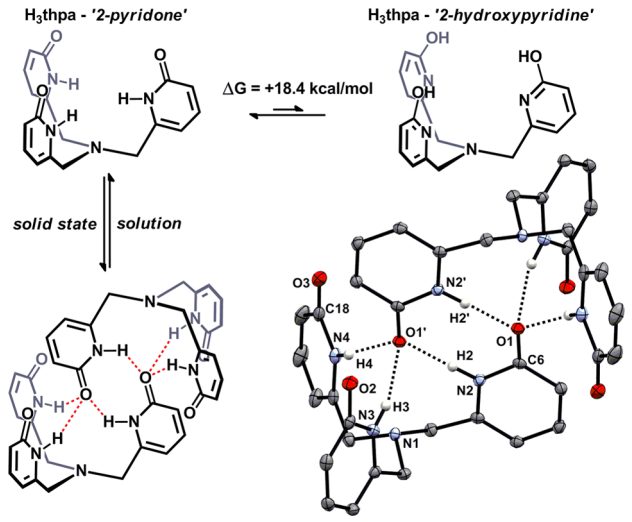

Figure 1. Tautomerization equilibrium for H_3thpa and the solid-state structure of the H_3thpa dimer (50% ellipsoids; H atoms not involved in H-bonding are omitted for clarity).

bands and an intense amide C═O band in the solid state (1659 cm^{-1}) and solution (1669 cm^{-1}) IR spectra. Density functional theory (DFT) calculations[11] support this tautomeric form and reveal that the pyridone form is favored by 18.4 kcal/mol (Figure 1). The solid-state structure of H_3thpa is presented in Figure 1 and is best described as a dimer formed via intermolecular H-

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bonding interactions. The carbonyl group of one H_3thpa molecule resides within the binding pocket of its symmetry-generated duplicate and forms three H-bonds with pseudo-3-fold symmetry around O1′. The C−O distances in the solid-state structure of H_3thpa [1.235(2), 1.236(2), and 1.264(2) Å] are consistent with amide-type C═O double bonds. Additionally, one arm of H_3thpa exhibits a slightly elongated C−O distance [C6−O1: 1.264(2) Å] due to a "base-pair-like" H-bonding interaction between O1 and N2′−H2′. In contrast to the chemically dissimilar amide environments noted above, the ^{1}H NMR spectrum of H_3thpa reveals 3-fold symmetry, which suggests distinct solution and solid-state stuctures.

Although the amide tautomer was isolated, we hypothesized that metalation would induce tautomerization to the 2-hp form. In a trigonal-bipyramidal (TBP) coordination environment, the hydroxyl groups of H_3thpa are ideally suited to interact with a metal-bound substrate. Given the rich coordination chemistry of copper with polyamine ligands,[12] we targeted a copper(I) halide complex supported by the H_3thpa ligand to examine the influence of H-bonding interactions on the metal primary coordination sphere. The reaction of CuCl and H_3thpa in benzene at 70 °C affords a yellow slurry, which after filtration and concentration provides CuCl(H_3thpa) (**1**). The solid-state IR spectrum of **1** confirms tautomerization of the ligand upon metalation: a new OH band is present at 3139 cm^{-1}, and the amide C═O band is absent. Yellow crystals of **1** were subjected to an X-ray diffraction (XRD) experiment. The solid-state structure of **1** is depicted in Figure 2 and reveals a TBP

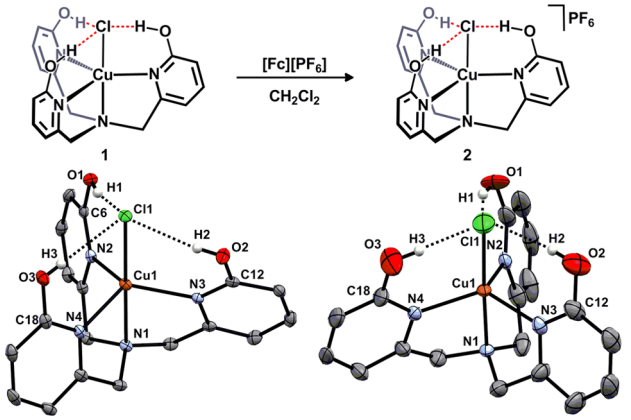

Figure 2. Synthesis and solid-state structures of **1** (50% ellipsoids; H atoms not involved in H-bonding are omitted) and **2** (30% ellipsoids; H atoms not involved in H-bonding and the anion are omitted). Selected bond distances for **1** (Å): Cu1−Cl1 2.5661(6), Cu1−N1 2.283(2), and **2** (Å): Cu1−Cl1 2.263(2), Cu1−N1 1.990(3).

coordination geometry about Cu (τ = 0.95).[13] A comparison of the Cu−Cl bond distance with the parent CuCl(tpa) [2.3976(5) Å][14] reveals an elongated Cu−Cl bond distance of 2.5661(6) Å in **1**. The lengthened Cu−Cl bond is consistent with H-bonding interactions between the three hydroxyl groups of H_3thpa and the Cl ligand [O---Cl separations: 3.045(2), 3.057(2), and 3.042(2) Å].[4c,15] As a result of these H-bonding interactions, the Cu1−N1 distance in **1** is also shortened relative to that of CuCl(tpa) [2.283(2) vs 2.437(1) Å, respectively].[14] The C−O bond distances [1.335(3), 1.334(3), and 1.344(3) Å] are also consistent with single C−O bonds, further confirming the tautomeric form.

The solution structure (CD_2Cl_2) confirms the retention of C_3 symmetry of **1**, by the chemical equivalence of the three pyridine arms, as monitored by ^{1}H NMR spectroscopy. In contrast to reports of the dynamic solution behavior of Cu(tpa)X (X = Cl$^-$ or Br$^-$) at room temperature,[16] the solution structure of **1** remains static, as evidenced by the narrow peak widths of the methylene resonances at room temperature ($\nu_{1/2}$ = 3.3 Hz; Figure S3 in the SI) and invariance when measured from +40 to −50 °C.[17] The OH resonances of **1** also appear as a single, sharp resonance at 10.57 ppm ($\nu_{1/2}$ = 6.8 Hz). The static solution behavior is consistent with persistent H-bonding interactions, which engage the axial Cl ligand and prevent dissociation.

On the basis of the highly directed interactions observed for **1**, we sought to investigate how the H-bonding manifold would be modified upon electronic perturbation. The cyclic voltammogram of **1** displayed a reversible Cu$^{I/II}$ redox wave centered at 95 mV vs SCE (Figure S4 in the SI). Accordingly, oxidation of **1** was effected with 1 equiv of ferrocenium hexafluorophosphate to afford the copper(II) complex **2** (Figure 2). The X-band EPR spectrum of **2** (Figure S7 in the SI) features an "inverse-axial" spectrum ($g_\parallel$ = 2.010, $A_\parallel$ = 81 G, $g_\perp$ = 2.165, and $A_\perp$ = 64 G) consistent with a Cu^{II} ion in a TBP coordination environment.[18] As further confirmation of the solution-state structure, the electronic absorption spectrum of **2** (Figure S8 in the SI) exhibits d−d bands consistent with TBP geometry in solution [λ_{max} = 913 nm (300 mol^{-1} cm^{-1}), 740 nm (90 mol^{-1} cm^{-1})].[18]

Green crystals of **2** were subjected to an XRD experiment.[11] The solid-state structure of **2** is depicted in Figure 2 and reveals a TBP geometry (τ = 0.93) similar to that of **1**, with key differences. The Cu−Cl bond in **2** [2.263(2) Å] is, as expected, much shorter than that in **1**. The O---Cl separations [2.876(6), 2.912(5), and 2.997(5) Å] are also consistent with intramolecular H-bonding interactions as in **1**.[15] A comparison with the corresponding CuCl(tpa)$^+$ complex reveals a marginal elongation of the Cu−Cl distance in **2** [2.263(2) vs 2.233(2) Å, respectively].[19,20] These results indicate that H-bonding between the OH groups and the Cl ligand may be weaker in **2** compared to **1** because of decreased electron density at the Cl ligand adjacent to a more electropositive Cu^{II} ion. The Cu1−N1 distance in **2** is also drastically shortened [1.990(3) Å] in relation to **1**, consistent with the increased electrophilicity at Cu.

In order to further quantify the effects of H-bonding interactions of H_3thpa, **1**, and **2** and the effects on substrate binding, DFT calculations were employed. Optimization and frequency calculations were performed on the hydroxy tautomer of H_3thpa to determine the OH stretching frequency in the absence of intermolecular H-bonds (3620 cm^{-1}). Similarly, the asymmetric OH stretching frequencies for **1** and **2** were calculated as 3228 and 3377 cm^{-1}, respectively. Although the absolute frequency shift was overestimated[4c] compared to the experimental values for **1** and **2** (3139 and 3273 cm^{-1}; Table S2 in the SI), the difference in shifts upon oxidation of **1** to **2** is well reproduced by the calculations ($\Delta\nu$ = 149 vs 134 cm^{-1}). The bathochromic shift of the OH bands relative to free H_3thpa is consistent with H-bonding interactions: a shift arising from electron donation from the Cl ligand into the OH σ^* orbitals, thus weakening the bond. In **1**, the OH stretch is even further shifted than that in **2**, consistent with stronger H-bonding interactions in **1** due to the increased nucleophilic character on the Cl atom.[4c,21] The shift of the OH bands, relative to free H_3thpa, can be used to approximate the strength of the H-bonding interactions using a methodology described by Iogansen et al., yielding values of 6.1 kcal/mol for **1** and 4.8 kcal/mol for **2**

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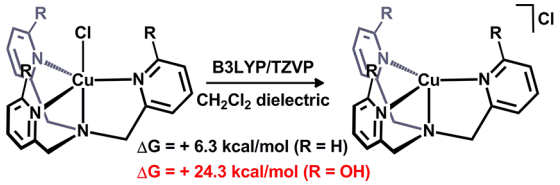
per H-bond.[21,22] As a structural manifestation of the H-bonding effects, the Cu−Cl bond in **2** is significantly shorter, and likely stronger, than the Cu−Cl bond in **1**. The weakening of the Cu−Cl bond in **1** enhances the ionic nature of the Cl ligand and promotes stronger donation into the OH σ^* orbital.

The structural data allude to an axial Cu−Cl bond whose stability might be regulated by secondary interactions. To further quantify this effect, we examined the thermodynamics of the H-bonding interactions in **1** using CuCl(tpa) to benchmark our studies. The ionization reaction shown in eq 1 was investigated



(1)

for both complexes. For CuCl(tpa), dissociation of the Cl ligand to afford the axially vacant $[Cu(tpa)]^+$ was found to be an overall uphill reaction by 6.3 kcal/mol. For **1**, chloride dissociation to afford $[Cu(H_3thpa)]^+$ was endergonic by 24.3 kcal/mol. While the Cu−Cl bond distance in **1** is significantly lengthened in comparison to CuCl(tpa), vide supra, the results from our calculations demonstrate that chloride dissociation from **1** is energetically more costly than that in CuCl(tpa). This difference (18 kcal/mol) is likely attributable to chloride stabilization through noncovalent interactions and can be used to estimate an upper limit of the strength of the H-bonding interactions in **1** (~6 kcal/mol per H-bond). Furthermore, the C_3 symmetry of **1** is maintained in solution. In contrast, dissociation of the pyridyl arms has been reported for Cu(tpa)Cl.[16] These data are consistent with stabilization of the primary coordination geometry of **1** via H-bonds to the Cl ligand, which are responsible for maintaining the 3-fold-symmetric structure.

In conclusion, we have described H_3thpa, a tripodal ligand that, when fully protonated, presents three H-bond donors to a metal-bound substrate. Our results demonstrate that the H-bonds enforce 3-fold symmetry for copper(I/II) halide complexes in the solution and solid state and significantly stabilize the Cu−Cl bond. Additionally, our calculations along with vibrational data show that the strength of the H-bonding interactions between the Cu−Cl and OH groups of H_3thpa are significantly influenced by the oxidation state of Cu and that ~18 kcal/mol is an upper estimate for the strength of these noncovalent interactions in **1**. Further experiments to utilize H_3thpa to facilitate the binding/activation of small molecules are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Widger, L. R.; Davies, C. G.; Yang, T.; Siegler, M. A.; Troeppner, O.; Jameson, G. N. L.; Ivanović-Burmazović, I.; Goldberg, D. P. *J. Am. Chem. Soc.* **2014**, *136*, 2699. (b) Cheruzel, L. E.; Cecil, M. R.; Edison, S. E.; Mashuta, M. S.; Baldwin, M. J.; Buchanan, R. M. *Inorg. Chem.* **2006**, *45*, 3191. (c) Tubbs, K. J.; Fuller, A. L.; Bennett, B.; Arif, A. M.; Berreau, L. M. *Inorg. Chem.* **2003**, *42*, 4790. (d) Feng, G.; Mareque-Rivas, J. C.; Williams, N. H. *Chem. Commun.* **2006**, 1845. (e) Shook, R. L.; Borovik, A. S. *Chem. Commun.* **2008**, 6095. (f) Tutusaus, O.; Ni, C.; Szymczak, N. K. *J. Am. Chem. Soc.* **2013**, *135*, 3403. (g) Wada, A.; Honda, Y.; Yamaguchi, S.; Nagatomo, S.; Kitagawa, T.; Jitsukawa, K.; Masuda, H. *Inorg. Chem.* **2004**, *43*, 5725. (h) Berreau, L. M. *Eur. J. Inorg. Chem.* **2006**, 273.

(2) Borovik, A. S. *Acc. Chem. Res.* **2004**, *38*, 54.

(3) (a) Rosenthal, J.; Nocera, D. G. *Acc. Chem. Res.* **2007**, *40*, 543. (b) Rakowski DuBois, M.; DuBois, D. L. *Chem. Soc. Rev.* **2009**, *38*, 62.

(4) (a) Hart, J. S.; Nichol, G. S.; Love, J. B. *Dalton Trans.* **2012**, *41*, 5785. (b) Hart, J. S.; White, F. J.; Love, J. B. *Chem. Commun.* **2011**, *47*, 5711. (c) Sickerman, N. S.; Park, Y. J.; Ng, G. K. Y.; Bates, J. E.; Hilkert, M.; Ziller, J. W.; Furche, F.; Borovik, A. S. *Dalton Trans.* **2012**, *41*, 4358. (d) Park, Y. J.; Sickerman, N. S.; Ziller, J. W.; Borovik, A. S. *Chem. Commun.* **2010**, *46*, 2584.

(5) (a) Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3884. (b) Royer, A. M.; Rauchfuss, T. B.; Gray, D. L. *Organometallics* **2010**, *29*, 6763. (c) For a recent review on 2-hp-derived catalysts, see: Wang, W.-H.; Muckerman, J. T.; Fujita, E.; Himeda, Y. *New J. Chem.* **2013**, *37*, 1860. (d) DePasquale, J.; Nieto, I.; Reuther, L. E.; Herbst-Gervasoni, C. J.; Paul, J. J.; Mochalin, V.; Zeller, M.; Thomas, C. M.; Addison, A. W.; Papish, E. T. *Inorg. Chem.* **2013**, *52*, 9175. (e) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003**, *125*, 6608.

(6) (a) Hiromoto, T.; Ataka, K.; Pilak, O.; Vogt, S.; Stagni, M. S.; Meyer-Klaucke, W.; Warkentin, E.; Thauer, R. K.; Shima, S.; Ermler, U. *FEBS Lett.* **2009**, *583*, 585. (b) Hiromoto, T.; Warkentin, E.; Moll, J.; Ermler, U.; Shima, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 6457.

(7) Letko, C. S.; Rauchfuss, T. B.; Zhou, X.; Gray, D. L. *Inorg. Chem.* **2012**, *51*, 4511.

(8) Moore, C. M.; Szymczak, N. K. *Chem. Commun.* **2013**, *49*, 400.

(9) Although we have found no prior reports of H_3thpa, a related tridentate ligand was described by Rauchfuss and co-workers (ref 7).

(10) Gray, M. A.; Konopski, L.; Langlois, Y. *Synth. Commun.* **1994**, *24*, 1367.

(11) Please see the SI for details.

(12) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047.

(13) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349.

(14) Eckenhoff, W. T.; Pintauer, T. *Inorg. Chem.* **2007**, *46*, 5844.

(15) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48.

(16) (a) Eckenhoff, W. T.; Garrity, S. T.; Pintauer, T. *Eur. J. Inorg. Chem.* **2008**, 563. (b) Hsu, S. C. N.; Chien, S. S. C.; Chen, H. H. Z.; Chiang, M. Y. *J. Chin. Chem. Soc.* **2007**, *54*, 685.

(17) Sandström, J. *Dynamic NMR spectroscopy*; Academic Press Inc.: London, 1982.

(18) Hathaway, B. J.; Billing, D. E. *Coord. Chem. Rev.* **1970**, *5*, 143.

(19) Karlin, K. D.; Hayes, J. C.; Juen, S.; Hutchinson, J. P.; Zubieta, J. *Inorg. Chem.* **1982**, *21*, 4106.

(20) For a similar Cu^{II}−Cl elongation, see: Jitsukawa, K.; Harata, M.; Arii, H.; Sakurai, H.; Masuda, H. *Inorg. Chim. Acta* **2001**, *324*, 108.

(21) For a similar analysis, see: Rivas, J. C. M.; Hinchley, S. L.; Metteau, L.; Parsons, S. *Dalton Trans.* **2006**, 2316.

(22) Iogansen, A. V.; Kurkchi, G. A.; Furman, V. M.; Glazunov, V. P.; Odinokov, S. E. *Zh. Prikl. Spektrosk.* **1980**, *33*, 460.