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COMMUNICATION

Synthesis and characterization of a tris(2-hydroxyphenyl)methane-based cryptand and its triiron(III) complex†

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Reaction of tris(5-amino-2-ethoxy-3-isopropylphenyl) methane and pyridine-2,6-dicarbonyl-dichloride affords a multi-dentate cryptand in 48% yield. Metallation with iron(III) chloride results in a substantial conformational change of this ligand to give a trianionic triiron(III) complex. Ferric cations line the periphery of the internal cavity with each adopting a square pyramidal N_3Cl_2 coordination environment.

Proteins that catalyze multielectron redox reactions combine a tailored active site pocket with multimetallic assemblies, where the metal clusters provide the redox equivalents to drive the reaction, and the active site enforces substrate selectivity.[1] The design of synthetic catalysts to replicate the reactivity of metalloproteins is a long standing research goal with substantial focus on the synthesis and properties of metal complexes that are structural mimics of enzymatic metal clusters. However, these structural analogues[2] have yet to operate as effective catalysts for multielectron redox reactions.[3]

The design of molecular receptors that selectively recognize specific analytes is well-developed in organic synthesis.[4,5] These types of molecules are constructed with a carefully tailored binding site that recognizes the target analyte selectively based on size, as dictated by the shape and volume of the binding site relative to the target molecule, and electrostatic or hydrogen bonding interactions between functional groups incorporated on the interior surface of the binding cavity and complementary groups on the analyte. Metal ions, such as copper(II), have been incorporated into organic receptors, where the metal ion serves as a Lewis acid for analyte recognition rather than as a redox-active catalytic centre.[6] Realizing the interplay between the active site and metal cofactors in enzyme systems, our approach focuses on incorporating multiple metal coordination sites into molecular receptors as a means to combine metal cooperativity with substrate selectivity.

Previously, multimetallic complexes of cofacial diporphyrins, pacman porphyrins, and bis(TREN) cryptands, among others, have been carefully designed to preorganize metal centers around an active site, in which the ligand orients accessible metal coordination sites to react with substrates cooperatively.[7] Rational catalyst design, however, requires synthetic control of the electronic and structural properties of the metal centres, which cannot be achieved without sacrificing synthetic ease or yield for porphyrin- and TREN-based ligands. Despite these drawbacks, macrobicycles remain attractive candidates because libraries of multimetallic complexes can be readily synthesized using a modular approach. We sought to develop macrobicyclic ligands, in which synthetic precursors with versatile functional groups could be easily accessed. In this regard, tris(2-hydroxyphenyl)methanes are an ideal candidate because the synthesis of these triarylmethanes tolerates various functionalities on the reactant phenol and salicylaldehyde.[8] Here we report the synthesis and metallation of the first cryptand to be synthesized from tris(5-amino-2-ethoxy-3-isopropylphenyl)methane and the corresponding triiron(III) complex. This result demonstrates a route to potentially create tunable ligands for metal clusters by varying the functional groups on the phenols and salicylaldehyde.

Reaction of phenol **1** and salicylaldehyde **2**[8] with thionyl chloride in methanol affords the substituted triphenoxymethane **3** (Scheme 1).[9] From prior reports, we anticipated that the alkoxy groups would preferentially align to one molecular face with the nitro-substituents in **4** oriented to the opposite face.[9,10] Alkylation followed by nitration afforded **4**, and subsequent reduction yielded our desired building block **5** in multigram quantities.[9,11] Ease of purification for each synthetic step compensated for the low overall yield of **5**. Condensation of two equivalents of **5** with three of pyridine-2,6-dicarbonyl dichloride afforded the desired cryptand H_6**L** in 48% yield (Scheme 1). We attribute the unusually high yield for the final step in our synthetic route to the alignment of the amines to one molecular face, which has been proposed for cyclophanes assembled from 1,3,5-triethylbenzene.[12]

From the single crystal X-ray structure, the pyridine dicarboxamide arms of H_6**L** adopt a propeller arrangement and preassemble around a 126 Å^3 central cavity (Fig. 1).[13] The distances between the amide nitrogen atoms range from 6.577(4) Å for N6–N3 to 7.130(3) Å for N9–N3.‡ Expectedly, these metrics are similar to the distances between similar substituents in compounds analogous to **5**, suggesting that distances between metal

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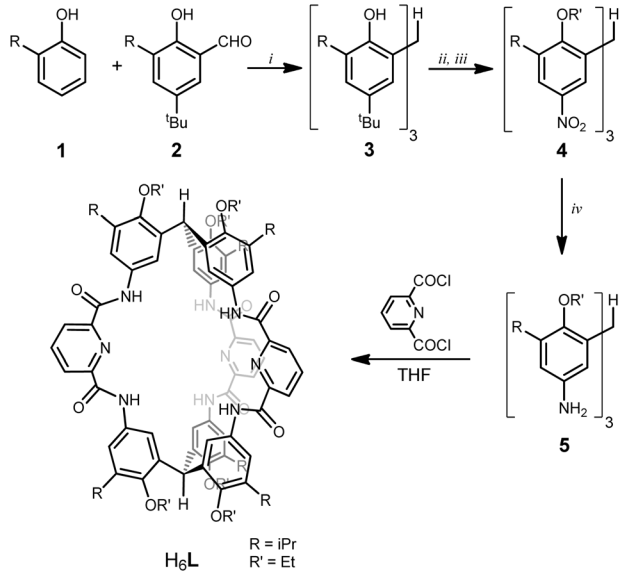

Scheme 1 Synthesis of the multi-dentate cryptand, $H_6\mathbf{L}$. (i) $SOCl_2$, MeOH (ii) EtI, NaH, DMF, (iii) HNO_3, TFA, DCM (iv) RANEY Ni, $H_{2(g)}$, THF/EtOH.

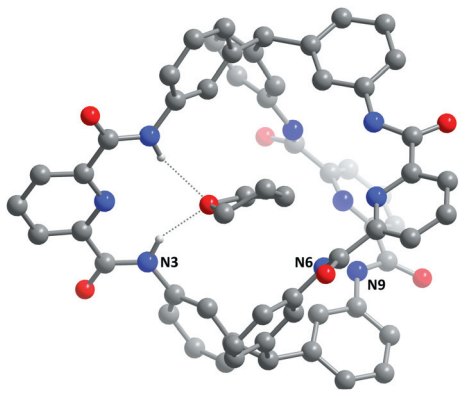

Fig. 1 Crystal structure of $H_6\mathbf{L}\cdot(THF)_3(H_2O)_2$. The ligand adopts a propeller-like structure in which the three pyridine dicarboxamide arms define an internal cavity. A guest THF molecule is held within the cavity by two hydrogen bonds. C, N, O and H atoms are represented by grey, blue, red and light gray spheres, respectively. Isopropyl chains, ethoxy groups, hydrogen atoms (except the two that are depicted), and non-coordinated solvent molecules were omitted for clarity.

binding sites can be varied by rational choice of the tripodal triamine. Guest solvent molecules occupy the central cavity and grooves between the arms of $H_6\mathbf{L}$. The THF guest within the cavity forms hydrogen bonds with two amides on one pyridine dicarboxamide arm with N–H···O bond distances of 2.35(3) and 2.14(3) Å and angles of 146(3)° and 158(3)°, which are comparable to those for interactions between THF and other amides.[14] The four remaining amides from the other pyridine dicarboxamide arms form hydrogen bonds with THF and water molecules, all of which occupy the grooves between ligand arms (Fig. S3†).

Treatment of a THF solution of $H_6\mathbf{L}$ with potassium hexamethyldisilazide followed by ferric chloride at −78 °C afforded the dark red–brown trianionic $[(FeCl_2)_3\mathbf{L}]^{3-}$ complex. In ESI (−)/MS of the product solution,[15] ions corresponding to triiron

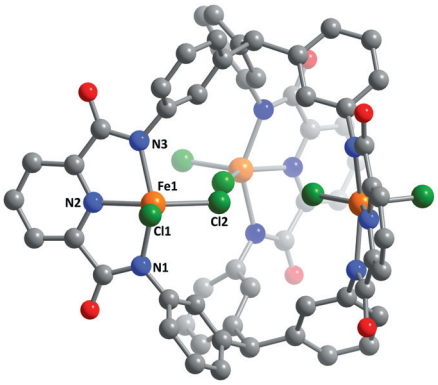

Fig. 2 A portion of the crystal structure of $[K(MeCN)_2]_3[(FeCl_2)_3\mathbf{L}]$ depicting the triiron(III) anionic complex. The iron centers all adopt a square pyramidal coordination environment and surround the central cavity. The two tris(alkoxyphenyl)methane caps adopt opposite propeller conformations in contrast to the free ligand. Fe, Cl, C, N, and O atoms are represented by orange, green, grey, red and blue spheres, respectively. Isopropyl chains, ethoxy groups, K^+ ions, H-atoms and solvent molecules are omitted for clarity.

(III) complexes are observed, including the potassium adduct of the parent complex, $K[(FeCl_2)_3\mathbf{L}]^{2-}$, as well as species in which one or more chloride ligands are substituted for hydroxide. In the UV-visible absorption spectrum of the product complex, we observe a strong absorption band centred at 294 nm (ε = 43 900 M^{-1} cm^{-1}) and a broad feature in the visible region (524 nm, ε = 3980 M^{-1} cm^{-1}). These absorption maxima are comparable to those reported for other ferric complexes of substituted pyridine-2,6-dicarboxamides.[16,17] Attempts to deprotonate the $H_6\mathbf{L}$ with stronger bases, such as methyllithium, were unsuccessful and afforded only a mixture of products. Although related triarylmethanes undergo oxidation *via* formal hydride loss at the methine carbon atom,[10b] the ^{1}H-NMR spectra of reaction mixtures suggest that this proton can be abstracted by stronger bases, subsequently leading to ligand decomposition.

Diffusion of diethyl ether into an acetonitrile solution of the product afforded dark red–brown crystals of $[K(MeCN)_2]_3[(FeCl_2)_3\mathbf{L}]$ (Fig. 2).§ In the molecular structure of the complex, the iron–iron distance is 6.723(2) Å and the distance between the chloride donors housed within the interior of the complex is 3.413(3) Å. Each potassium cation is coordinated by two acetonitrile molecules from the crystallization solvent and two oxygen donors – one from an amide and the other from the ethoxy group on an adjacent ligand arm (Fig. 3, O1 and O4A). From the large metal–metal distances and absence of bridging ligands between the iron centres, we expected minimal electronic communication between the metal centres in the complex.

The steric demands of $H_6\mathbf{L}$ enforce a 1 : 1 stoichiometry for each pyridine-2,6-dicarboxamide donor and iron(III) cation, which has not been realized for monometallic ferric complexes employing phenyl-substituted pyridine-2,6-dicarboxamide ligands.[16–18] In $[(FeCl_2)_3\mathbf{L}]^{3-}$, each arm coordinates one iron(III) with the metal adopting a slightly distorted square pyramidal coordination geometry (τ = 0.05 with a 0.9% tetragonal distortion[19]) (Fig. 3). The basal plane is comprised of the pyridyl N-atom, two deprotonated carboxamides and one chloride anion, with an axial chloride donor completing the primary

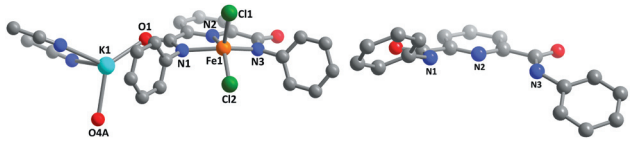

Fig. 3 Portions of the crystal structures of $[K(MeCN)_2]_3[(FeCl_2)_3\mathbf{L}]$ (left) and $H_6\mathbf{L}$ (right) depicting the conformational changes upon metallation. The pyridyl ring in the metal complex is almost perpendicular to the neighbouring phenyl rings (left) whereas the angles between the planes of two phenyl rings and the pyridyl are 36° and 50° in $H_6\mathbf{L}$ (right). Each K^+ cation is coordinated to two acetonitrile molecules from the crystallization solvent, and two O-atoms from an amide (O1) and an ethoxy group (O4A). Fe, Cl, K, C, N and O atoms are represented as orange, green, sky blue, gray, blue and red, respectively. H-atoms and solvent are omitted for clarity.

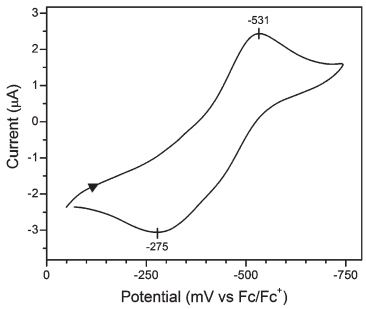

Fig. 4 Cyclic voltammogram of $[K(MeCN)_2]_3[(Fe^{III}Cl_2)_3\mathbf{L}]$. Scan rate of 100 mV s^{-1} using 2 mm Pt working, Pt wire counter, and Ag/Ag^+ reference electrode in 0.1 M Bu_4NPF_6 DMF solution.

coordination sphere. The metal ion sits 0.570(2) Å above the N_3Cl plane, comparable to other square pyramidal iron(III) complexes with N_3-donor sets.[20] The N_{amide}–Fe bond distances of 2.064(5) and 2.104(5) Å and the N_{amide}–Fe–N_{amide} bond angle of 145.1(2)° are similar to those reported for the high-spin $[Fe(PyPSMe)_2]^-$ complex.[17] Consistent with these structural similarities to the high-spin complex, a room temperature magnetic moment of 10.08 μ_B was determined for $[(FeCl_2)_3\mathbf{L}]^{3-}$ by Evan's method using the parallel field formula,[21] which agrees with three $S = 3/2$ ferric ions. Coordination of the K^+ cation to O1 likely weakens the donor strength of N1, and results in the longer N_{amide}–Fe bond distance as compared to N3–Fe bond.

Comparison of the structures of the $[(FeCl_2)_3\mathbf{L}]^{3-}$ and the as-synthesized ligand reveals a significant structural change upon metal binding. In $H_6\mathbf{L}$, both triphenoxymethane caps have the same chirality and the amide groups in each arm are not coplanar with either the pyridyl or phenyl rings (Fig. 3, right). Consequently, the angles between the planes of neighbouring pyridyl and phenyl aromatic rings are 36° and 50°, with almost an up-down conformation for the two phenyl rings relative to the pyridyl one. After deprotonation and metallation, however, the angles between these aromatic ring planes increase to 75° and 83° with concomitant reorganization from the helical arrangement in $H_6\mathbf{L}$ to one in which the two triphenoxymethane caps adopts opposite propeller conformations (Fig. 2 and 3). The almost perpendicular disposition of the pyridyl ring *versus* the two neighbouring phenyl rings in $[(FeCl_2)_3\mathbf{L}]^{3-}$ is consistent with that observed for monometallic complexes of substituted *N*, *N*′-diphenylpyridine-2,6-dicarboxamide.[16,17] This structural change consequently rotates the equatorial chloride away from the interior cavity, and could be an important feature for substrate access and/or product egress in future efforts. The significant ligand reorganization after metallation is reminiscent of the conformational changes observed during catalytic turnover in many enzyme systems[22] as well as the structural changes reported for molecular devices.[23] Methods to exploit this rearrangement to enhance reactivity or to respond to external stimuli are currently being explored.

The cyclic voltammogram of $[K(MeCN)_2]_3[(FeCl_2)_3\mathbf{L}]$ in anhydrous DMF shows a quasi-reversible response with $E_{\frac{1}{2}} = -403$ mV (*vs.* $Fc–Fc^+$) assigned to the Fe^{III}–Fe^{II} couple, which is comparable to the value reported by Mukherjee and co-workers for a bis(pyridine-2,6-dicarboxamido)iron(III) complex (Fig. 4).[16] The large ΔE_p of 256 mV is consistent with a structural change upon reduction,[24] although we cannot discount weak electrostatic coupling between the metal centres, which may give rise to three overlapping waves. No change was observed in the amplitude of either the cathodic or anodic waves after repeated scanning, suggesting that there is no ligand or complex decomposition during the reaction. Electrochemical data collected on $H_6\mathbf{L}$ and the potassium salt of $\mathbf{L}^{6-}$, which was generated *in situ* with KHMDS, support our assignment of this process as metal-based (Fig. S7†). From magnetic susceptibility measurements on $[K(MeCN)_2]_3[(FeCl_2)_3\mathbf{L}]$, the saturation value of $\chi_M T$ at room temperature of 7.4 emu K mol^{-1} is comparable to the expected theoretical value for three isolated $S = 3/2$ iron (III) centres (Fig. S10†).

In conclusion, we have reported the synthesis and characterization of a tris(hydroxyphenyl)methane-based cryptand and its corresponding trianionic triiron(III) complex. For the former, the ligand arms preassemble a central void space, capable of accommodating guest species. The triiron(III) complex serves as a synthetic proof of principle as the metal cations decorate the internal cavity, and are primed to react cooperatively with a bound substrate. Although the metal centers appear to be site-isolated in the iron(III) complex, we are exploring routes to displace the equatorial chloride ligands to allow substrates to bind and bridge the metal centres and turn on cooperativity. Preliminary work suggests that the chloride–chloride distance depends on the metal oxidation state, opening the possibility of designing complexes as redox-dependent host–guest systems.

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Notes and references

‡ **Crystal data for $H_6\mathbf{L}\cdot(THF)_3\cdot(H_2O)_2$**: $C_{101}H_{129}N_9O_{17}$, $M = 1714.13$, triclinic, space group $P\bar{1}$, $a = 17.9708(2)$, $b = 19.0228(3)$, $c = 19.2837(3)$ Å, $\alpha = 73.327(1)°$, $\beta = 67.465(1)°$, $\gamma = 66.260(1)°$, $V = 5504.7(1)$ $Å^3$, $Z = 2$, $T = 100$ K. 67 204 reflections collected, 18 677 independent reflections, 9470 reflections with ($I > 2\sigma(I)$), R_1 ($I > 2\sigma(I)$) = 0.1096, wR_2 (all data) = 0.1609.

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§ **Crystal data for $[K(MeCN)_2]_3[(FeCl_2)_3L]$**: $C_{101.5}H_{107}Cl_6Fe_3K_3N_{15.5}O_{12}$, M = 2233.58, cubic, space group $P2_13$, $a = b = c$ = 22.853 (2) Å, $\alpha = \beta = \gamma = 90°$, V = 11934(1) Å^3, Z = 4, T = 100 K, 5832 reflections collected, 5832 independent reflections, 4639 reflections with ($I > 2\sigma(I)$), R_1 ($I > 2\sigma(I)$) = 0.0794, wR_2 (all data) = 0.1684.

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