Design and Synthesis of a Novel Triptycene-Based Ligand for Modeling Carboxylate-Bridged Diiron Enzyme Active Sites

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Design and Synthesis of a Novel Triptycene-based Ligand for Modeling Carboxylate-Bridged Diiron Enzyme Active Sites

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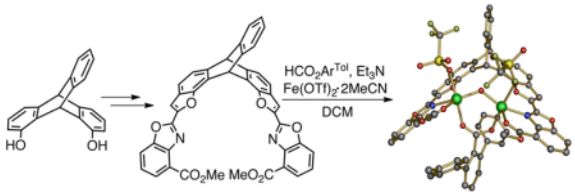
Abstract



A novel triptycene-based ligand with a pre-organized framework was designed to model carboxylate-bridged diiron activesites in bacterial multicomponent monooxygenase (BMM) hydroxylase enzymes. The synthesis of the bis(benzoxazole)-appended ligand L1 depicted was accomplished in 11 steps. Reaction of L1 with iron(II) triflate and a carboxylate source afforded the desired diiron(II) complex [Fe_2L1 (μ-OH) (μ-O_2CAr^{Tol})$(OTf)_2$].

Enzymes that contain carboxylate-bridged diiron cores belong to an important family of metalloproteins,[1–4] examples of which include the bacterial multicomponent monooxygenases (BMMs),[5–9] ribonucleotide reductase (RNR-R2),[10,11] and Δ^9-desaturase (Δ^9-D).[12,13] These metalloproteins can activate dioxygen to catalyze several remarkable chemical transformations, such as the conversion of methane to methanol. Within this family of proteins, the chemistry occurs at a diiron core supported by terminal and bridging carboxylate ligands, water and/or hydroxyl groups, and two histidine donors arranged in a *syn* fashion with respect to the diiron vector. These ligands generate a well organized cavity in the apo forms of many such metalloproteins and readily generate a diiron core upon exposure to an iron source.[14,15] The carboxylate bridge that is orthogonal to the Fe_2N_2 plane plays a key role in maintaining the structural integrity of the dinuclear center during catalysis.

Synthetic efforts to mimic the active sites of these diiron enzymes, such as that in soluble methane monooxygenase hydroxylase (sMMOH)[5] (Figure 1), have generated a diverse assortment of model compounds,[16–21] but reproducing both the structure and function of the carboxylate-bridged diiron unit in a single biomimetic platform has not yet been achieved. To obtain more accurate diiron protein models, we have designed advanced ligand frameworks that are sufficiently pre-organized to afford the desired coordination geometry upon metallation with iron salts.[22–25] Ultimately, we wish to construct a diiron compound

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Supporting Information. Detailed experimental procedures, compound characterization, and the results of ^{1}H and ^{13}C NMR spectroscopic and single crystal X-ray diffraction studies. This material is available free of charge via the Internet at http://pubs.acs.org.

having two *syn N*-donors, an oxygen-rich environment, and a covalently-tethered bridging carboxylate, and which can hydroxylate hydrocarbons under mild conditions using O_2.

With the aid of modeling studies using SPARTAN, we selected the triptycene unit as a platform to approach these goals. As depicted in Figure 2, two *N*,*O*-donor arms (**La**, red) can be connected to two wings of triptycene to bind a diiron core. An additional carboxylate can be incorporated into the ligand framework by attachment to the third wing of the backbone to deliver the bridging ligand internally. **La** with a simple triptycene backbone, however, is too compact to accommodate the desired diiron unit, for the positions marked by "X" are separated by only 4.5 Å. To increase the distance between two metal-binding arms the backbone unit **Lb,** containing furan rings fused to the triptycene group, was introduced (X···X = 8.1 Å). By attaching two benzoxazole *N*,*O*-donor arms to **Lb**, the ligand **L** was conceived (Figure 2). Although triptycenes have been known since Bartlett's first synthesis in 1942,[26,27] its use to generate ligands for assembling multinuclear metal coordination compounds has not yet been seriously explored. We describe in the present work the synthesis of a new class of dinucleating ligands based on triptycene and their use in generating a carboxylate-bridged diiron complex.

A readily scalable route with high synthetic efficiency is desired in order to prepare gram-quantity of **L1**. A four-step column-free synthesis of 1,8-dihydroxytriptycene (DHT) (**4**) was accomplished starting from the commercially available reagent 1,8-dihydroxyanthraquinone. As shown in Scheme 1, methylation of 1,8-dihydroxyanthraquinone using dimethyl sulfate (~3.5 equiv) gave 1,8-dimethoxyanthraquinone (**1**) in 95% yield. Crude **1** was directly reduced by zinc dust in refluxing 10% aqueous NaOH, affording 1,8-dimethoxyanthracene (**2**) in 96% yield after recrystallization from DCM. To minimize the potentially explosive benzyne intermediate generated during the Diels-Alder reaction in the next step, only ~5 g of precursor **2** was used each time in the reaction. After several runs, the combined crude mixture was subjected to crystallization from acetone, affording 1,8-dimethoxytriptycene (**3**) in 67% yield. Lastly, deprotection of 1,8-dimethoxytriptycene (**3**) using BBr_3 in anhydrous DCM, after recrystallization from acetone, gave pure 1,8-dihydroxytriptycene (DHT, 80%) (**4**). This four-step column-free synthesis afforded **4** in 49% overall yield.

Next, we attempted ortho-formylation of **4** to obtain dialdehyde **7** as a precursor to benzofuran **8** via alkylation-condensation (see Scheme S1, Supporting Information). Although intermediates **6** and **7** were successfully obtained, the latter could not be converted to the desired product **8**, primarily due to steric hindrance from both the neighboring triptycene framework and the aldehydes on the ortho-positions of the phenols during the first, alkylation, step.

To circumvent the difficulty described above, other synthetic routes toward the construction of 2-functionalized benzofuran were explored. The propargyl group of an aryl propargyl ether in the presence of CsF under high temperature can rearrange to the *ortho* position of the aryl ring to afford 2-methyl benzofuran after cyclization.[28] As shown in Scheme 3, allylation of **4** with propargyl bromide was achieved using acetone as the solvent, giving **9** in 93% isolated yield. Application of the reported[28] condition to prepare the dipropargyl ether **9** afforded **10** in 23%~25% yield. Although many attempts were made to optimize this Claisen rearrangement/benzofuran formation step, no improvement in yield was achieved. Presumably, the highly reactive allene species **i** generated in the Claisen rearrangement step can participate in unproductive side reactions (Scheme 2). Treatment with SeO_2 led to the benzylic oxidation of 2-methyl benzofuran **10** to dialdehyde **11** in excellent yield (92%). Further oxidation of dialdehyde **11** to diacid **12** was accomplished using $NaClO_2$ and 30% H_2O_2 buffered with NaH_2PO_4,[29] giving 95% of the diacid **12** after acidification with concentrated HCl.

After successful construction of diacid **12**, attempts were made to attach the *N*,*O*-donor arms to the benzofuran rings. In order to do so, an aniline moiety must be coupled to the carboxylic acid unit of **12** through an amide bond linkage. Compound **12** was treated with various amide coupling reagents, including neat $SOCl_2$, oxalyl chloride/DMF, carbonyl diimidazole (CDI), DCC, and HATU, but none of these conditions afforded the desired compound **13**. Fortunately, reaction of **12** with excess amounts of pyridine (40 equiv) and thionyl chloride (40 equiv) in anhydrous DCM could successfully convert diacid **12** to the benzoyl chloride intermediate **ii**. After removal of the volatiles, the resulting crude product was treated with methyl (3-hydroxy)anthranilate in DCM, giving diamide **13** in 58% overall yield in two steps. Lastly, cyclization of diamide **13** to form benzoxazole **L1** was achieved in 85% isolated yield using 2 equiv of *p*-$TsOH{\cdot}H_2O$ in refluxing acetic acid. The overall yield of **L1** from 1,8-dihydroxyanthraquinone is ~4.9%.

The X-ray crystal structure of **L1** is shown in Figure-S2. Both benzoxazole arms are co-planar with the benzofuran rings of the triptycene backbone, suggesting that the two aromatic subunits are in conjugation. One of the benzoxazole arms has its *N*,*O*-donor side pointing to the C-9 methine of the triptycene backbone, whereas the other is pointed away. The distance between N1 and O4 is 6.421 Å, which falls within the 5.5–7.5 Å separation necessary for binding two metal ions.[18] These *N*,*O*-donor arms can rotate around the C–C single bond between the benzoxazole and benzofuran units, and are expected to form dinuclear species upon reaction with iron salts.

Red crystals of X-ray diffraction quality were obtained by vapor diffusion of Et_2O into a DCM solution containing **L1**, $Fe(OTf)_2{\cdot}2MeCN$ (2 equiv), wet Et_3N (2 equiv), and 2,6-di(*p*-tolyl)benzoic acid (HO_2CAr^{Tol}) (2 equiv). As shown in Figure 3, the formula of the compound is $[Fe_2\mathbf{L1}(\mu\text{-}OH)(\mu\text{-}O_2CAr^{Tol})(OTf)_2]$. Selected bond distances and angles are listed in Figure 3. The complex has a diiron core coordinated by two benzoxazole *N*,*O*-donors. A bridging carboxylate ligand and a bridging hydroxyl group form a six-membered ring that includes the two iron atoms. In addition, each iron atom has a terminal triflate group bound trans to the bridging carboxylate, affording a neutral complex.[30] The Fe–Fe distance in this complex is 3.443 Å, which is very close to that in reduced sMMOH (~ 3.4 Å).[5]

In summary, a new triptycene-based ligand framework has been designed and synthesized. The bis-furan fused triptycene backbone, together with carefully chosen benzoxazole *N*,*O*-donor arms, provides a unique pre-organized platform, which can readily bind two irons in the presence of an external carboxylate. There is no significant conformational change in the framework between free ligand **L1** and that in the diiron complex, indicating the desired pre-organized character of the ligand platform. Our ongoing research focuses on the investigation of this complex with molecular oxygen as well as further elaboration of the *N*,*O*-donor arm to create a hydrophobic pocket for substrate binding. The synthesis of ligand **L** with a pendent carboxylate on the third wing of the triptycene backbone is also underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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30. Note: the details of this complex as well as its reactivity with molecular oxygen will be reported in a subsequent paper.

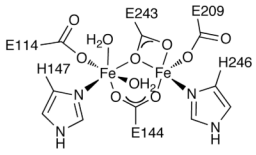


Figure 1.
Reduced state of the diiron core of sMMOH.

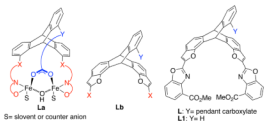


Figure 2.
Ligand design

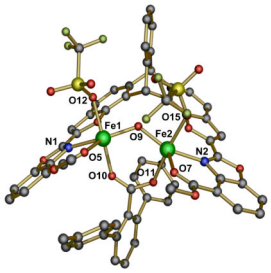
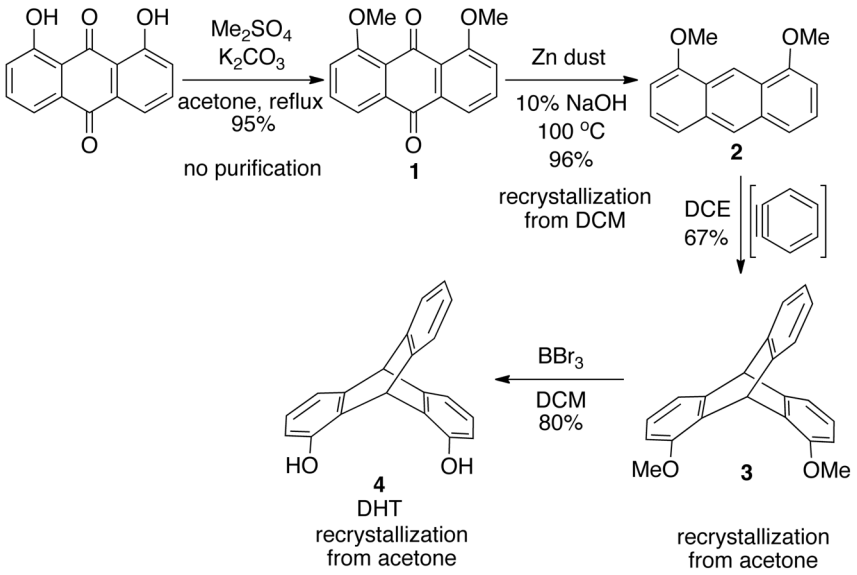
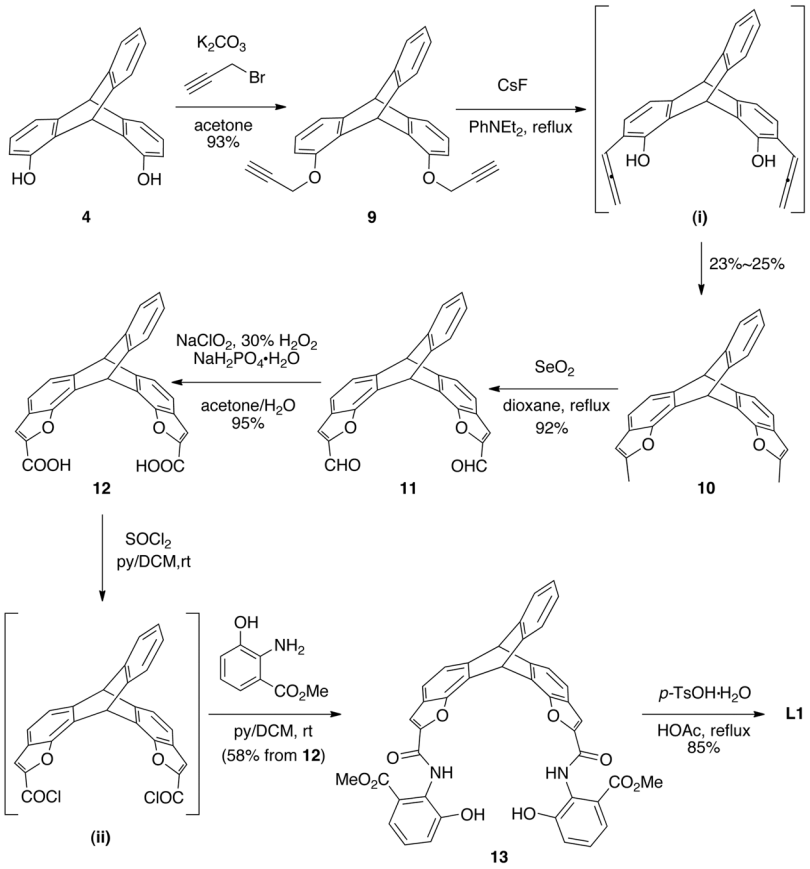


Figure 3.

X-ray crystal structure of complex [Fe_2**L1**(μ-OH)(μ-O_2CAr^{Tol})$(OTf)_2$]. Selected bond distances (Å) and angles (degree): Fe(1)–Fe(2) = 3.443; Fe(1)–N(1) = 2.139(6); Fe(1)–O(5) = 2.114(6); Fe(1)–O(9) = 1.949(5); Fe(1)–O(10) = 2.071(5); Fe(1)–O(12) = 2.147(5); Fe(2)–N(2) = 2.116(6); Fe(2)–O(7) = 2.107(5); Fe(2)–O(9) = 1.944(5); Fe(2)–O(11) = 2.059(5); Fe(2)–O(15) = 2.207(5); Fe(1)–O(9)–Fe(2) = 124.4(3); N(1)–Fe(1)–O(9) = 154.1(2); N(2)–Fe(2)–O(9) = 149.6(2).



Scheme 1.
Column-free synthesis of DHT **4**



Scheme 2.
Synthesis of ligand **L1** from **4**