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BRIEF REPORT

Synthesis and coordination of a *tert*-butyl functionalized facially coordinating 2-histidine-1-carboxylate model ligand

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ABSTRACT

Herein, we report a bulky variant of a bis-benzimidazole carboxylate ligand. The five-position of the benzimidazole groups were substituted with tertiary butyl groups with the intention of preventing bis-ligation and oligomerization, as was observed in other studies using similar ligands. Unfortunately, even with the bulkier substituents, the new ligand still formed a bis-ligated structure. Although the new ligand did not afford the desired mono-ligated species under the conditions studied here, the preparation of the new ligand and coordination compounds provides an added design principle in the ongoing efforts of preparing structurally faithful 2-histidine-1-carboxylate model ligands in biomimetic chemistry.

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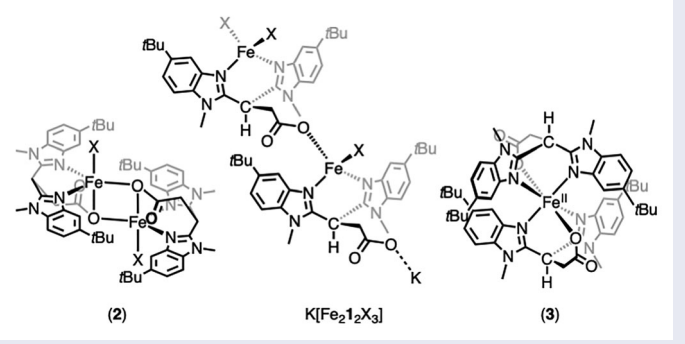

Introduction

The 2-histidine-1-carboxylate (2H1C) facial triad is a common binding motif in mononuclear nonheme iron oxygenases [1,2]. Due to its prevalence in biology, modeling 2H1C ligation is a point of interest toward gaining insight into chemical function (Figure 1) [3–5], and certain design principles have emerged. For instance, attempts at

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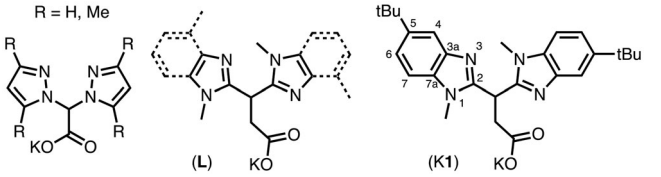


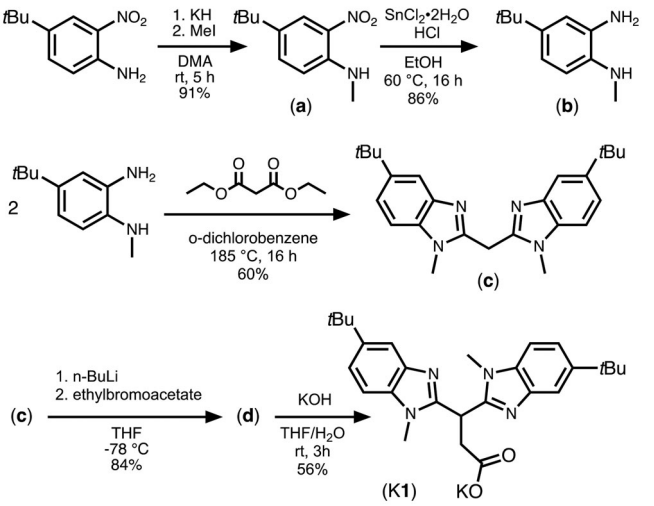
Figure 1. Examples of 2H1C model ligands.

preparing 2H1C ligation with bis-imidazole functionalized acetate ligands face difficulties because of facile decarboxylation of the ligand [6,7]. Gebbink and Burzlaff independently circumvented the challenge of ligand decarboxylation by including a CH_2 spacer between twin-imidazole (and -benzimidazole) donors and the carboxylate donor using ligand 3,3-bis(1-methyl-1*H*-imidazol-2-yl)propionate (**L**) [7,8]. This class of N,N,O ligands is exceptional in its semblance of natural 2H1C ligation [9]. Unfortunately, both imidazole and benzimidazole versions of **L** suffer from two drawbacks: namely, (a) the seven-membered ring afforded by the additional spacer group renders the ligand more labile and (b) the ligand is not sterically protected. Collectively, these facets of **L** manifest in oligomeric species formation and also bis-ligation [6,10,11].

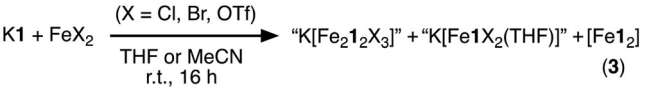
In a previous report, Gebbink and coworkers provided DFT evidence that increasing the steric factors around the iron center by methylating the benzimidazole four-position of the benzimidazole ring disfavors the bis-ligation [10]. Nevertheless, methylation at the four-position of **L** (Figure 1) did not completely prevent the formation of the bis-ligated product. Our interest in pursuing structurally faithful ligand platforms to study the chemistry of metalloenzymes inspired us to further develop bulkier variants of this ligand motif. We envisioned that *tert*-butyl groups would have substantial improvement. However, incorporation of *tert*-butyl groups in the benzimidazole four-position is not trivial because the precursors are not readily available. Additionally, our motivation was to use the new ligand in biomimetic oxygenase studies and we envisioned problems associated with intramolecular ligand oxidation related to what has been observed by others [12]. Therefore, using commercially available materials, we prepared a new ligand that contains a *tert*-butyl group on the benzimidazole five-position and this report details the synthesis and coordination chemistry of this new ligand. While the incorporation of these bulkier groups did not prevent bis-ligation from occurring, the preparation of the new ligand and its coordination complex represent a step forward in developing design principles in biomimicry of the ubiquitous 2H1C facial triad.

Synthesis of a bulky 2H1C model ligand

The commercially available sterically encumbered 4-(*tert*-butyl)-2-nitroaniline starting material was first methylated using methyl iodide following a potassium hydride deprotonation to produce 4-(*tert*-butyl)-*N*-methyl-2-nitroaniline (**a**) in 91% yield (Scheme 1). Thereafter, $SnCl_2$/HCl reduction of nitro compound in ethanol was employed to produce the diamine (**b**) in 86% yield. The diamine was then reacted with diethyl malonate to produce the bulky bis-benzimidazole compound bis(5-(*tert*-



Scheme 1. Synthesis of K**1**.



Scheme 2. Proposed product mixture from **1** + FeX_2.

butyl)-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methane (**c**) in 60% yield. Lithiation of **c** at −78 °C and subsequent treatment with ethyl bromoacetate produced the ester form of the ligand (**d**), which after isolation is separately converted through saponification to produce the potassium salt of the desired ligand potassium 3,3-bis(5-(*tert*-butyl)-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)propanoate (K**1**). The ligand can be produced in gram scale with an overall yield of 21%.

Coordination chemistry of K1 with iron(II)

Treatment of K**1** with a variety of iron salts (FeX_2; X = Cl, Br, OTf) in a 1:1 stoichiometry unfortunately did not lead to straightforward preparation of the desired product, which is the tetrahedral species [Fe**1**X] or some solvated variant of higher coordination (e.g. [Fe**1**X$(MeCN)_2$]). Instead, the products of 1:1 reaction furnished amorphous powder material that, in solution, is a mixture of species (Scheme 2; see Figures S13–S25 for spectral analyses described below).

For the product(s) obtained from $FeBr_2$, an elemental analysis was obtained that is consistent with the formula KFe_2**1**$_2Br_3$. ESI mass spectral analysis of this material gave rise to two major peaks with *m/z* = 985.42442 and 1081.31410. These are formulated as the bis-ligated ion $[K(Fe\mathbf{1}_2)]^+$ (calcd. = 985.41935) and $[Fe_2\mathbf{1}_2Br]^+$ (calcd. = 1081.30892). For the product obtained from $FeCl_2$, an elemental analysis was

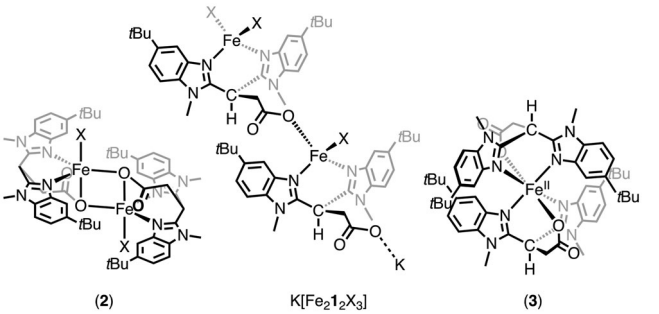
obtained that is consistent with a [K{Fe**1**Cl_2(THF)}] formulation. Analogously, ESI MS analysis of this material similarly gave rise to two major peaks with $m/z = 985.41920$ and 1037.36053. These are corresponding to the same species formulated earlier as the bis-ligated ion $[K(Fe\mathbf{1}_2)]^+$ (calcd. = 985.41935) and $[Fe_2\mathbf{1}_2Cl]^+$ (calcd. = 1037.35944). So, despite the differences in elemental analysis, the solution state speciation is similar for the products obtained from $FeCl_2$ and $FeBr_2$. This hypothesis is supported by nearly identical FTIR and ^{1}H NMR of the isolated material (Figures S24 and S25).

In contrast, the triflate ion gave different results. Although the elemental analysis was inconclusive, the HRMS furnished two major peaks with $m/z = 1151.34643$ and 1339.26588. These are assigned as $[Fe_2\mathbf{1}_2(OTf)]^+$ (calcd. = 1151.34261) and $[K\{Fe_2\mathbf{1}_2(OTf)_2\}]^+$ (calcd. = 1339.25834), none of which correspond to the bis-ligated product (calcd. = 985.41935 not present for OTf species). Furthermore, the FTIR and ^{1}H NMR spectra of the material obtained from $Fe(OTf)_2$ is different from that obtained using $FeCl_2$ or $FeBr_2$ (Figures S13 and S15). The FTIR spectra of the isolated products indicates that the carboxylate arm of the ligand is coordinated to a metal center; $\nu(COO^-) = 1583\,cm^{-1}$ for K**1** shifts to 1579, 1569 and 1563 cm^{-1} for the products isolated from $FeCl_2$, $FeBr_2$ and $Fe(OTf)_2$, respectively.

All three starting materials gave ions of the general formulation $[Fe_2\mathbf{1}_2X]^+$, which could be formulated as a dinuclear structure originating from $[Fe^{II}\mathbf{1}X]_2$ (**2**). The bridging ligand in **2** can in principle be either the X group or the carboxylate in $\mathbf{1}^-$; spectroscopic and literature precedent support the latter. For instance, the bispyrazolylacetate analog of K**1** has been used to prepare the dinuclear complex $[Fe^{II}$(bispyrazolylacetate)(Cl)$]_2$ where the carboxylate moiety of each ligand forms the bridge [13].

Additionally, evidence from ^{19}F NMR spectroscopy of the iron triflate product indicates that it is not bridging. Hagen has detailed the solution state coordination chemistry of $Fe(OTf)_2$ with Me_3-TACN using ^{19}F NMR spectroscopy and provides a guide for assessing some of the solution state speciation in this study [14]. For example, outer sphere triflate ion has a sharp signal at −80 ppm in MeCN, which broadens and shifts upfield when coordinated to iron(II), and bridging triflate ions are further shifted to ≈+60 ppm [14,15]. The $^{19}F\{^1H\}$ NMR chemical shift for the triflate product is −79 ppm and is broad (Figure S14), which falls within the range for an outer sphere triflate and the broadening of the peak suggests that the triflate anion is in equilibrium with a triflate-Fe species. Collectively, these data and comparison with literature allow us to hypothesize one of the complexes forming in solution is the dinuclear complex **2** with connectivity as shown in Scheme 3. Other oligomeric species are additionally possible given that the mass spectral and elemental analyses of the synthesized material contained potassium ions; a possible structure of an oligomer is shown in Scheme 3 whose composition is consistent with elemental analysis we obtained for $[K(Fe_2\mathbf{1}_2Br_3)]$.

In one attempt to liberate the potassium ions from mixture and force precipitation of single crystals, 18-crown-6 was added to a 1:1 reaction between $FeBr_2$ and K**1**. This caused a light-yellow solid (**3**) to precipitate from the THF reaction mixture. The solid was partially soluble in warm 6:1 acetonitrile and methanol solvent mixture that afforded crystals suitable for diffraction after diffusion of diethyl ether over a period of three weeks. The molecular structure **3** co-crystalized with a MeOH solvent molecule,



Scheme 3. Possible solution state structures.

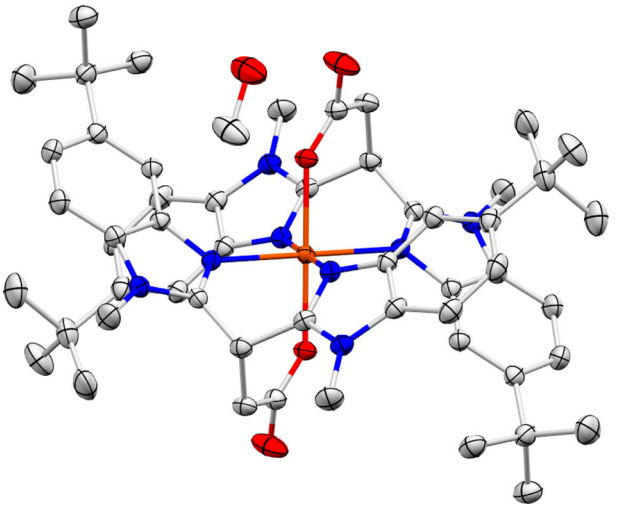


Figure 2. Molecular structure of **3**•MeOH with ellipsoids shown at 50% probability; H-atoms are not shown. Color scheme: orange = Fe; blue = N; red = O; grey = C.

which was identified in the FTIR spectrum of the crystals (Figure S27). The FTIR spectrum of **3** was identical to the one obtained from the insoluble product of treating a 1:2 mixture of $FeBr_2$ and K**1** in methanol. As noted earlier, the HRMS (i.e. $m/z = 985.41935$) confirmed that the bis-ligated species is present in solution for both 1:1 and 1:2 K**1**:Fe stoichiometries.

The crystal structure of **3** contains two molecules of **1** coordinated to the metal center (Figure 2). The structure is similar to previously reported neutral coordination complexes prepared by coordination of imidazole and other benzimidazole variants of the ligand to iron(II) and copper(II) where the carboxylate arms are coordinated trans to each other [7,11]. Nevertheless, complex **3** is the first reported structure of a neutral coordination complexes of the benzimidazole variant with iron(II). The methanol molecule that is co-crystalized with **3** forms a hydrogen bond with the non-coordinated carboxylate oxygen.

In conclusion, incorporation of the *tert*-butyl groups did not prevent bis-ligation from occurring. However, **3** represents the first example of any crystallographically

characterized Fe(II) complex with a bis-benzimidazole carboxylate ligand. While not conclusive, we propose that incorporation of the *tert*-butyl group narrowed the solution speciation that enabled the crystallization. Nevertheless, incorporation of the *tert*-butyl was not enough to temper the diverse coordination enabled by this ligand class. Further coordination studies using Fe(III) may result in the desired mono-ligated product and is ongoing.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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