# Structural consequences of hydroxamate and tropolonate binding to iron porphyrins

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The solid-state structures of iron porphyrin hydroxamate complexes reveal an unusual monodentate $\eta^1$-O binding mode; the bidentate $\eta^2$-O,O binding of the tropolonate anion results in an apical displacement of iron of 0.80 Å from the 24-atom mean porphyrin plane.

Hydroxamic acids are ubiquitous in biology.[1] Hydroxamate groups are present in a large number of siderophores, and the hydroxamic acid functional group is a constituent of certain antibiotics, antifungal agents, tumor inhibitors, and even some food additives.[1,2] The troponoid functional group is present in a number of alkaloids and antibiotics.[3] The tropolone group has been used as a model for the antimitotics colchicine (Col) and trimethylcolchicine (Tmca), and it has been shown that some Ru and Pt complexes of Col and Tmca exhibit antitumor activity comparable to that of cisplatin.[4] The coordination chemistry of hydroxamic acids and their derivatives has been reviewed,[1,5] and the hydroxamate functional group behaves as a typical chelating (bidentate, $\eta^2$) ligand towards metals in their complexes. Hydroxamic acids can be viewed as valence isoelectronic analogs of NONOates (diazeniumdiolates),[6] in which the C–H(X) group has been replaced with the valence isoelectronic N atom.
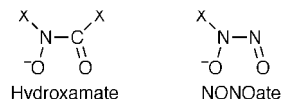


We recently reported that the Cupferron anion (Ph[$N_2O_2$]$^-$, an NONOate) binds in a bidentate mode to iron(III) porphyrins.[7] Surprisingly, there have been very few reports on the interactions of hydroxamic acids (or hydroxamates) with synthetic metalloporphyrins[8] or natural heme biomolecules,[9] and there has been no report on the interaction of tropolone with metalloporphyrins. Thus, we sought to determine the nature of binding of typically bidentate hydroxamates (with non-equivalent O-donor atoms, NO vs. CO) and the tropolonate anion (with equivalent O-donor atoms) with the metal center in metalloporphyrins. The ligands were selected to include an acyclic hydroxamic acid where the O-donor atoms could exist in *cis* or *trans* conformations, a cyclic hydroxamic acid with the O-donor atoms locked in the *cis* conformation, and tropolone where the O-donor atoms are locked in the *cis* form. We are now pleased to report our preliminary results on (i) the unambiguous determination of an unusual $\eta^1$ interaction of hydroxamates with iron(III) porphyrins, and (ii) the remarkable structural consequence of $\eta^2$ binding of the tropolone anion with an iron(III) porphyrin.

Benzohydroxamic acid (4 equiv.) was reacted with [Fe(oep)]$_2$($\mu$-O) (0.050 g, 0.042 mmol) in toluene at 70 °C for 1.5 h. Upon cooling, black microcrystals precipitated which were collected by filtration and dried to give [Fe(oep)(ONHCOPh)]·HONHCOPh (**1**·HONHCOPh) in 52% isolated yield.†‡ The molecular structure of **1**·HONHCOPh [Fig. 1(a)] reveals an unusual $\eta^1$-O binding mode for this acyclic

hydroxamate ligand, which displays moderate hydrogen-bonding[10] [N(5A)–O(2C) 2.750(5) Å, O(1A)–O(1C) 2.673(5) Å] to a second hydroxamic acid molecule.§ The average Fe–N(por) bond length is 2.052 Å and is in the range typical of five-coordinate iron(III) high-spin porphyrins,[11] and the Fe atom is pulled out by 0.48 Å from the 24-atom porphyrin plane. Unexpectedly, the reaction of a stirred suspension of [Fe(tpivpp)Cl] in THF (in the presence of a small amount of pyridine) with a 1:1 mixture of excess benzohydroxamic acid and NaH at room temperature for 1.5 h results, after crystallization in air, in the formation of the previously reported [Fe(tpivpp)(NO$_2$)(py)] in 25% isolated yield which we identified by X-ray crystallography. This known compound was previously obtained from the reaction of [Fe(tpivpp)(NO$_2$)$_2$]$^-$ with pyridine.[12] The net formation of [Fe(tpivpp)(NO$_2$)(py)]
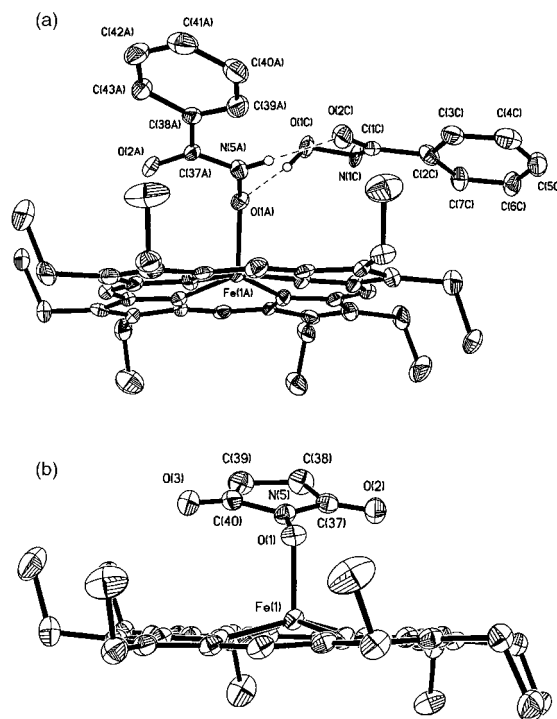


**Fig. 1** (a) Molecular structure of one of the two independent molecules of **1**·HONHCOPh. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (°) (the data for the second independent molecule are shown in square brackets): Fe(1A)–N(por) 2.049(4)–2.057(4) [2.043(4)–2.056(4)], Fe(1A)–O(1A) 1.927(4) [1.923(3)], O(1A)–N(5A) 1.377(5) [1.363(5)], N(5A)–C(37A) 1.341(6) [1.333(6)], C(37A)–O(2A) 1.235(6) [1.237(6)], O(1C)–O(1A) 2.673(5) [2.876(5)], O(2C)–N(5A) 2.750(5) [2.739(6)], O(1C)–N(1C) 1.402(5) [1.389(5)], N(1C)–C(1C) 1.309(6) [1.321(7)], C(1C)–O(2C) 1.251(6) [1.242(6)]; Fe(1A)–O(1A)–N(5A) 111.0(3) [108.3(3)], O(1A)–N(5A)–C(37A) 118.8(4) [121.3(5)]. (b) Molecular structure of **2**. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (°): Fe(1)–N(por) 2.055(2)–2.065(2), Fe(1)–O(1) 1.9163(14), O(1)–N(5) 1.367(2); Fe(1)–O(1)–N(5) 115.32(11).
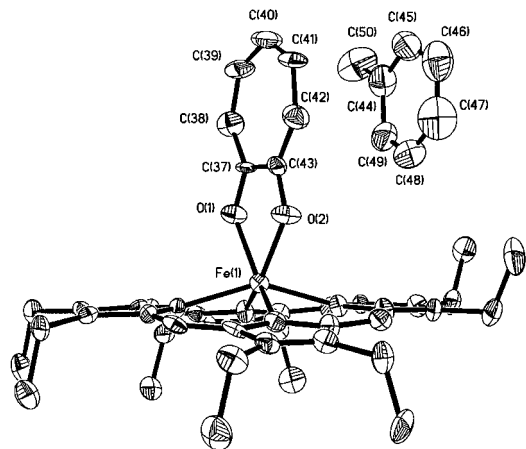
**Fig. 2** Molecular structure of **3**·C$_6$H$_5$Me. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (°): Fe–N(por) 2.088(7)–2.161(9), Fe(1)–O(1) 2.064(6), Fe(1)–O(2) 2.067(6), O(1)–C(37) 1.256(9), O(2)–C(43) 1.261(11), C(37)–C(43) 1.486(12), C(39)–C(40) 1.37(2), C(40)–C(41) 1.39(2); Fe(1)–O(1)–C(37) 120.5(6), O(1)–C(37)–C(43) 113.2(8), C(37)–C(43)–O(2) 112.3(8), C(43)–O(2)–Fe(1) 120.7(6).

from benzohydroxamic acid is remarkable and, to the best of our knowledge, is the first report of a hydroxamate effectively donating its 'NO' group to a metal center.¶

The related reaction of *N*-hydroxysuccinimide HONC$_4$H$_4$O$_2$ (4 equiv.) with [Fe(oep)]$_2$(μ-O) (0.060 g, 0.050 mmol) in hot toluene gave, after work-up, [Fe(oep)(η$^1$-ONC$_4$H$_4$O$_2$)] **2** in 78% isolated yield.†‖ The molecular structure is shown in Fig. 1(b), and the η$^1$-O binding mode of the hydroxamate ligand is also revealed, this time with no additional hydrogen-bonding interactions that stabilize this binding mode. The carbonyl O atoms do not interact with the metal center, with (carbonyl)O-to-Fe distances of 3.85 Å [O(3)] and 3.79 Å [O(2)]. The Fe atom is apically displaced by 0.44 Å from the 24-atom porphyrin plane towards the axial ligand.

We then employed tropolone in these reactions in order to obtain an η$^2$-O,O binding mode of the axial ligand. The reaction of tropolone with [Fe(oep)]$_2$(μ-O) in hot toluene gave, after work-up, dark purple microcrystals of [Fe(oep)(η$^2$-OC$_7$H$_5$-O)]·toluene (**3**·C$_6$H$_5$Me) in 86% isolated yield.†** The molecular structure of **3**·C$_6$H$_5$Me is shown in Fig. 2. The most noticeable features of the structure are (i) the tropolonate ligand is bound to the iron center in a bidentate mode, with essentially equivalent Fe–O distances and an O–Fe–O bite angle of 73.1(2)°,†† (ii) the tropolone plane is nearly coincident with a (por)N–Fe–N(por) plane containing diagonal porphyrin nitrogens, (iii) the toluene molecule is coplanar with the tropolone ligand and is in close proximity (*ca.* 3.5 Å) to it, and most importantly (iv) the Fe atom is apically displaced by 0.80 Å from the 24-atom plane** of the porphyrin towards the tropolone ligand! To the best of our knowledge, this is the *largest* reported mean displacement of an Fe atom from a porphyrin plane. In comparison, related displacements of 0.69, 0.60 and 0.61 Å have been observed for [Fe{t(*p*-OMe)pp}{η$^2$-ONN(Ph)O}],[7] [Fe(tpp)(η$^2$-O$_2$NO)],[15] and [Fe(tpivpp)(η$^2$-O$_2$NO)],[16] respectively.

## Notes and references

† All three compounds give satisfactory elemental analyses (±0.4%) for C, H and N: tpivpp = picket fence porphyrinato dianion. Crystal data were collected on Bruker (Siemens) P4 diffractometers with Mo-Kα radiation ($\lambda$ = 0.71073 Å). The structures were solved using the SHELXTL system and refined by full-matrix least squares on $F^2$ using all reflections. The X-ray structural study of **1**·HONHCOPh was performed at the University of Wisconsin using a SMART/CCD system, and the studies for **2**·C$_6$H$_5$Me and **3**·C$_6$H$_5$Me were performed at the University of Oklahoma.

‡ *Data for* **1**·HONHCOPh: IR (KBr, cm$^{-1}$): $\nu_{CO}$ = 1632 br; also 2965m, 2929w, 2870w, 1575s, 1515w, 1469s, 1451s, 1373m, 1312m, 1269m, 1216w, 1147s, 1111w, 1056m, 1016s, 982m, 958s, 916w, 894m, 841m, 795w, 748w, 731w, 697s, 677w. UV–VIS [$\lambda$/nm ($\varepsilon$/mM$^{-1}$ cm$^{-1}$), 1.10 × 10$^{-5}$ M in benzene]: 351(40), 394(74), 488(8). *Crystal data*: C$_{50}$H$_{57}$FeN$_6$O$_4$, $M$ = 861.87, monoclinic, $P2_1/c$, $a$ = 26.165(5), $b$ = 14.2716(18), $c$ = 24.375(4) Å, $\beta$ = 99.390(2)°, $V$ = 8980(3) Å$^3$, $Z$ = 8, $D_c$ = 1.275 g cm$^{-3}$, $T$ = 138(2) K. Final $R1$ = 0.0746 (GOF = 0.956) for 7645 'observed' reflections with $I > 2\sigma(I)$. The structure contains two independent molecules which have similar geometry [Fig. 1(a)]. CCDC 182/1388.

§ The related [Fe{t(*p*-Me)pp}(L)] (L = benzohydroxamate, Cupferrate) complexes were proposed on the basis of IR spectroscopy to contain monodentate axial ligands[5] although we have shown by X-ray crystallography that the [Fe(por)(Cupferrate)] [por = tpp, t(*p*-OMe)pp] complexes display bidentate η$^2$-O,O coordination of the axial cupferrate ligands.[7]

¶ The acid-catalyzed hydrolysis of hydroxamic acids to give hydroxylamines and the parent carboxylic acids has been reviewed.[13]

‖ *Data for* **2**: IR (KBr, cm$^{-1}$): $\nu_{CO}$ = 1703s; also 2964s, 2933s, 2871m, 1469m, 1456m, 1436w, 1373m, 1315w, 1268m, 1212s, 1147m, 1110w, 1055m, 1015m, 982w, 958s, 916w, 840m, 748w, 729m, 698w, 656w, 475w. UV–VIS [$\lambda$/nm ($\varepsilon$/mM$^{-1}$ cm$^{-1}$), 1.02 × 10$^{-5}$ M in benzene]: 372(74), 397(92), 500(10), 525(10), 620(7). *Crystal data*: C$_{40}$H$_{48}$FeN$_5$O$_3$·C$_6$H$_5$CH$_3$, $M$ = 794.82, triclinic, $P\bar{1}$, $a$ = 13.2595(10), $b$ = 13.2893(11), $c$ = 13.9116(11) Å, $\alpha$ = 74.034(6), $\beta$ = 69.406(5), $\gamma$ = 65.593°, $V$ = 2065.3(3) Å$^3$, $Z$ = 2, $D_c$ = 1.278 g cm$^{-3}$, $T$ = 173(2) K. Final $R1$ = 0.0461 (GOF = 1.045) for 5742 'observed' reflections with $I > 2\sigma(I)$. The structure contains a disordered toluene solvent molecule. CCDC 182/1388.

** *Data for* **3**·C$_6$H$_5$Me: IR (KBr, cm$^{-1}$): $\nu_{CO}$ 1591s; also 2965s, 2929m, 2871m, 1520s, 1495w, 1469w, 1437s, 1406m, 1366s, 1314w, 1268m, 1226s, 1218m, 1143m, 1110m, 1055s, 1013s, 980m, 954s, 914m, 877m, 842m, 748m, 738m, 729s, 714w, 695s, 543m. UV–VIS [$\lambda$/nm ($\varepsilon$/mM$^{-1}$ cm$^{-1}$), 1.01 × 10$^{-5}$ M in benzene]: 332(42), 393(76), 556(12). *Crystal data*: C$_{50}$H$_{57}$FeN$_4$O$_3$, $M$ = 801.85, monoclinic, $P2_1$, $a$ = 10.409(3), $b$ = 14.473(5), $c$ = 14.803(3) Å, $\beta$ = 109.16(2)°, $V$ = 2106.6(8) Å$^3$, $Z$ = 2, $D_c$ = 1.264 g cm$^{-3}$, $T$ = 173(2) K. Final $R1$ = 0.0706 (GOF = 1.093) for 3546 'observed' reflections with $I > 2\sigma(I)$. The esds for the displacements of the 24 individual C and N atoms from the calculated least-squares plane lie in the range 0.006–0.009 Å, with the Fe atom displaced 0.802(2) Å from this plane. CCDC 182/1388.

†† The $D_3$ symmetric [Fe(tropolonate)$_3$] complex exhibits a related O–Fe–O bite angle of 77.8°.[14]

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