Neutral acetohydroxamic acid coordination to a mononuclear Ni(II) center stabilized by an intramolecular hydrogen-bonding interaction[†]

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Treatment of a new chelate ligand having both amide- and phenyl-appended pyridyl moieties with Ni(ClO₄)₂·6H₂O and acetohydroxamic acid in methanol solution results in the production of a novel pseudo-octahedral Ni(II) complex having a neutral acetohydroxamic acid ligand stabilized by a hydrogen-bonding interaction.

The acetohydroxamato monoanion (AHA⁻) is a well-known inhibitor of several metalloenzymes, including urease enzymes from plants and bacteria, which contain a binuclear Ni(II) center within the active site.¹⁻⁵ AHA⁻ inhibition of Klebsiella aerogeness and Bacillus pasteurii ureases has been suggested to involve initial formation of a weak enzyme/inhibitor complex (E-I, Scheme 1) having coordination of a neutral acetohydroxamic acid (AHA) molecule at a single Ni(II) ion.⁶⁻⁸ Stabilization of the E-I species may involve formation of a hydrogen-bonding interaction involving the bridging hydroxyl group.⁸ This E-I complex is then proposed to slowly convert to a more stable E-I* structure (Scheme 1), which exhibits a bridging coordination mode for the hydroxamato monoanion, a structural motif that has also been identified in model systems.9,10 In regard to the E-I species, to our knowledge, a structurally characterized complex having neutral acetohydroxamic acid coordination has not previously been reported for any transition metal ion.¹¹ Herein we report the preparation and characterization of a novel synthetic mononuclear Ni(II) complex having a coordinated neutral acetohydroxamic acid ligand, the hydroxyl proton of which forms a moderate hydrogenbonding interaction with a noncoordinated pyridyl nitrogen of the supporting chelate ligand.

A new chelate ligand, *N*,*N*-bis[(6-phenyl-2-pyridyl)methyl]-*N*-[(6-pivaloylamido-2-pyridyl)methyl]amine (bppppa) having both amide-¹² and aryl-substituted pyridyl moieties was assembled as shown in Scheme 2. Admixture of this ligand with equimolar amounts of Ni(ClO₄)₂·6H₂O and acetohydroxamic acid in



† Electronic supplementary information (ESI) available: Experimental section, Figs. S1 and S2. See http://www.rsc.org/suppdata/cc/b4/b413683g/ *berreau@cc.usu.edu

CH₃OH solution, followed by recrystallization *via* Et₂O diffusion into a CH₃CN : CH₃OH solution of the complex at ambient temperature resulted in the deposition of purple block crystals of [(bpppa)Ni(HONHC(O)CH₃)](ClO₄)₂ (1) in 72% yield. Complex 1 has been characterized by X-ray crystallography, elemental analysis, FTIR, UV-vis, and a solution magnetic moment measurement.

X-Ray crystallographic analysis of 1 revealed a mononuclear pseudo-octahedral Ni(II) center and a tetradentate N₃O-donor coordination mode for the bppppa chelate ligand with one phenylappended pyridyl moiety noncoordinated (Fig. 1).[‡] The N-H and O-H hydrogen atoms of the acetohydroxamic acid ligand, as well as the amide N-H hydrogen of the bppppa ligand, were located and refined independently. Importantly, the noncoordinated pyridyl nitrogen acts as a hydrogen bond acceptor for the Ni(II)-coordinated hydroxyl group of the acid. This hydrogen bond may be classified as moderate based on the short heteroatom distance [O(2)-H(2)···N(5) 2.518(3) Å] and a somewhat acute bond angle [158(5)°].¹³ A similar hydrogen-bonding interaction has been reported involving a Mn(II)-coordinated methanol ligand and a noncoordinated phenyl-appended pyridyl moiety in [(6- Ph_2TPA)Mn(CH₃OH)₃](ClO₄)₂ {6-Ph₂TPA = N,N-bis[(6-phenyl-2-pyridyl)methyl]-N-[(2-pyridyl)methyl]amine}.14

The Ni–O(H) distance involving the hydroxamic acid ligand is elongated in 1 by ${\sim}0.072$ Å relative to that found in a structurally



 $[(\text{bppppa})\text{Ni}(\text{HONHC}(\text{O})\text{CH}_3)](\text{ClO}_4)_2,\,\textbf{1}$

Scheme 2



Fig. 1 ORTEP representation of the cationic portion of 1. All ellipsoids are drawn at the 35% probability level. All hydrogen atoms except the N-H and O-H protons not shown for clarity. Selected bond lengths (Å) and angles (°): Ni(1)-N(2) 2.027(3), Ni(1)-N(3) 2.130(3), Ni(1)-N(4) 2.128(3), Ni(1)-O(1) 2.040(2), Ni(1)-O(2) 2.091(2), Ni(1)-O(3) 2.037(2), O(2)-Ni(1)-O(3) 79.71(9).

related pseudo-octahedral Ni(II) hydroxamato (AHA⁻) complex of the Ph₂TPA ligand [(6-Ph₂TPA)Ni(ONHC(O)CH₃)]ClO₄, [2, Fig. 2(a), Ni(1)-O(2) 2.0203(15) Å].¹⁴ The Ni-O bond distance involving the acetohydroxamic acid carbonyl oxygen in 1 [Ni(1)-O(3) 2.037(2) Å] is also slightly longer than the analogous bond in 2 [1.9964(14) Å]. Within the hydroxamic acid/AHA⁻ units in 1 and 2, the C-O and C-N bond distances are very similar, with the largest difference outside experimental error being ~ 0.005 Å in the C-N bond. Overall, these combined structural parameters indicate that the neutral hydroxamic acid binds more weakly to the mononuclear Ni(II) center in 1 than does the monoanionic acetohydroxamato ligand (AHA⁻) in 2. Finally, we note that the average Ni–O bond distance for 1 (2.06 Å) is slightly longer than that of 2 (2.01 Å) and the symmetric Ni–O distance (2.0 Å) in acetohydroxamato-inhibited urease from Bacillus pasteurii.8,14

In regard to the structural features of 1 versus 2, it is also worth noting that the shorter Ni-NPhPy distance in 1 [2.128(3) Å] as compared to those found in 2 [2.2630(17)/2.2292(17) Å] suggests the presence of a more Lewis acidic Ni(II) center in 1, consistent with the coordination of the neutral acetohydroxamic ligand.

The solid state infrared spectra of 1 and 2 differ in several ways. For example, as shown in Fig. S1(a), the region of



Core Structures

Fig. 2 (a) Representation of [(6-Ph₂TPA)Ni(ONHC(O)CH₃)]ClO₄ (2). (b) Comparison of core structural features of 1 and 2.

3800-2600 cm⁻¹ for 1 contains a broader, more intense feature than is found for 2 under identical conditions (see ESI⁺). This is consistent with the presence of the additional hydroxamic acid -OH and amide NH (within the bppppa ligand) moieties in 1, both of which participate in hydrogen-bonding interactions. In Fig. S1(b), a $v_{C=0}$ vibration can be identified at 1656 cm⁻¹ for the Ni(II)-coordinated bppppa amide carbonyl group (see ESI[†]). The $v_{C=O}$ vibration for the acetohydroxamic acid/AHA⁻ carbonyl groups in 1 and 2 should be present near 1600 cm^{-1} . However, this region in both complexes is complicated by a pyridyl ring vibration, which precludes conclusive assignments.

The energy of the $^3A_{2g}$ \rightarrow $^3T_{1g}(F)$ and $^3A_{2g}$ \rightarrow $^3T_{2g}(F)$ transitions differ in the electronic absorption spectra of ${\bf 1}$ and ${\bf 2}$ (see ESI[†], Fig. S2) in dry acetonitrile solution.¹⁵ The former transition is shifted to slightly higher energy in 1 (570 nm vs. 585 nm in 2). In addition, whereas in 1 the latter transition is found at $\sim 920 \text{ cm}^{-1}$, in 2 this feature is shifted into the near-IR region.

In summary, we have found that a novel mononuclear Ni(II) complex having neutral acetohydroxamic acid coordination may be isolated using a chelate ligand that provides an internal hydrogen bond acceptor. The structural and spectroscopic properties of 1 are notably different from those of a structurallyrelated Ni(II) complex of the acetohydroxamato anion (2). This work provides the first chemical precedent upon which to evaluate acetohydroxamic acid versus acetohydroxamato anion coordination to a Ni(II) center, a topic that is important toward fully understanding the inhibition properties of urease enzymes.

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Notes and references

Crystal data: for 1: C₃₈H₄₄Cl₂N₆NiO₁₂, M = 906.40, orthorhombic, space group *Pbca*, a = 19.2023(5), b = 34.9478(9), c = 12.2308(2) Å, $\hat{V} = 8207.8(3)$ Å³, Z = 8, $\mu = 0.672$ mm⁻¹. Using Mo-Ka radiation (0.71073 Å), a total of 16542 reflections were collected (4.84 $< 2\theta < 54.96$) of which 9172 were independent. Refinement converged to $R_1 = 0.0555$, $wR_2 = 0.1229 (I > 2\sigma I)$ and $R_1 = 0.0962$, $wR_2 = 0.1440$ (all data). Complex 1 crystallized with one molecule of noncoordinated methanol per formula unit. CCDC 250014. See http://www.rsc.org/suppdata/cc/b4/b413683g/ for crystallographic data in CIF or other electronic format.

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