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

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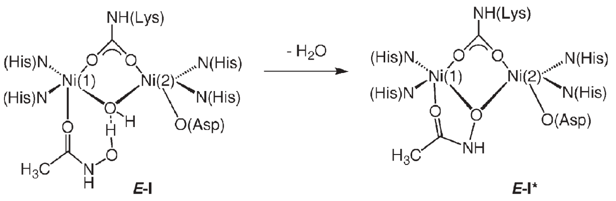
Received (in Cambridge, UK) 7th September 2004, Accepted 25th October 2004
First published as an Advance Article on the web 2nd December 2004
DOI: 10.1039/b413683g

Treatment of a new chelate ligand having both amide- and phenyl-appended pyridyl moieties with $Ni(ClO_4)_2 \cdot 6H_2O$ 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 aerogenes* 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 hydrogen-bonding interaction with a noncoordinated pyridyl nitrogen of the supporting chelate ligand.

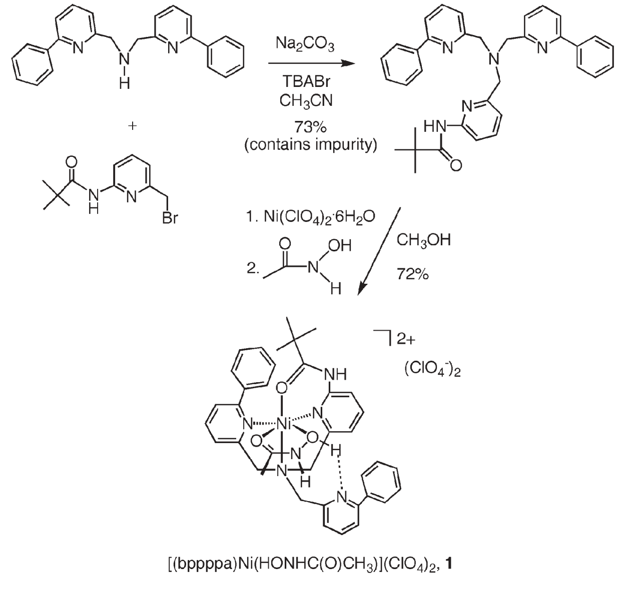
A new chelate ligand, *N*,*N*-bis[(6-phenyl-2-pyridyl)methyl]-*N*-[(6-pivaloylamido-2-pyridyl)methyl]amine (bppppa) having both amide-[12] and aryl-substituted pyridyl moieties was assembled as shown in Scheme 2. Admixture of this ligand with equimolar amounts of $Ni(ClO_4)_2 \cdot 6H_2O$ and acetohydroxamic acid in CH_3OH solution, followed by recrystallization *via* Et_2O diffusion into a $CH_3CN : CH_3OH$ solution of the complex at ambient temperature resulted in the deposition of purple block crystals of $[(bppppa)Ni(HONHC(O)CH_3)](ClO_4)_2$ (**1**) in 72% yield. Complex **1** has been characterized by X-ray crystallography, elemental analysis, FTIR, UV-vis, and a solution magnetic moment measurement.



Scheme 1

X-Ray crystallographic analysis of **1** revealed a mononuclear pseudo-octahedral Ni(II) center and a tetradentate N_3O-donor coordination mode for the bppppa chelate ligand with one phenyl-appended 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 $[(6\text{-}Ph_2TPA)Mn(CH_3OH)_3](ClO_4)_2$ {6-Ph_2TPA = *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 ~0.072 Å relative to that found in a structurally



$[(bppppa)Ni(HONHC(O)CH_3)](ClO_4)_2$, **1**

Scheme 2

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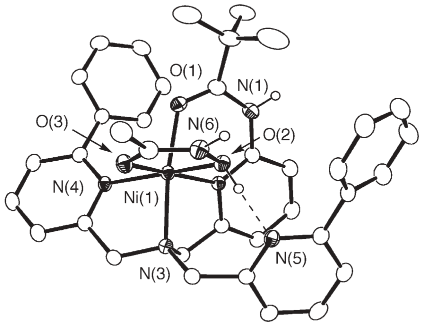

Fig. 1 ORTEP representation of the cationic portion of **1**. All ellipsoids are drawn at the 35% probability level. All hydrogen atoms except the N–H and O–H protons not shown for clarity. Selected bond lengths (Å) and angles (°): Ni(1)–N(2) 2.027(3), Ni(1)–N(3) 2.130(3), Ni(1)–N(4) 2.128(3), Ni(1)–O(1) 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 Ph$_2$TPA ligand [(6-Ph$_2$TPA)Ni(ONHC(O)CH$_3$)]ClO$_4$, [**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–N$_{PhPy}$ 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 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 $\nu_{C=O}$ vibration can be identified at 1656 cm^{-1} for the Ni(II)-coordinated bppppa amide carbonyl group (see ESI†). The $\nu_{C=O}$ 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.

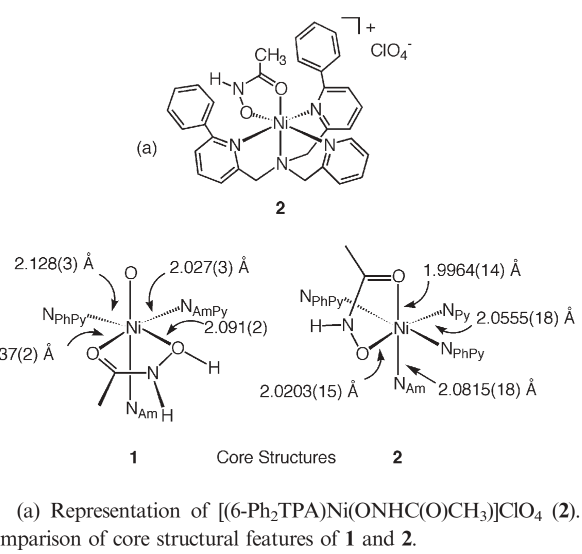

Fig. 2 (a) Representation of [(6-Ph$_2$TPA)Ni(ONHC(O)CH$_3$)]ClO$_4$ (**2**). (b) Comparison of core structural features of **1** and **2**.

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 **1** and **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 ~920 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 structurally-related 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.

We thank the National Science Foundation (CAREER Award CHE-0094066) and the Herman Frasch Foundation (501-HF02) for funding this research.

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Notes and references

‡ *Crystal data*: for **1**: $C_{38}H_{44}Cl_2N_6NiO_{12}$, M = 906.40, orthorhombic, space group *Pbca*, a = 19.2023(5), b = 34.9478(9), c = 12.2308(2) Å, V = 8207.8(3) Å^3, Z = 8, μ = 0.672 mm^{-1}. Using Mo-Kα 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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