Designing the ideal uranyl ligand: a sterically-induced speciation change in complexes with thiophene-bridged, bis(3-hydroxy-N-methyl-pyridin-2-one)[1]

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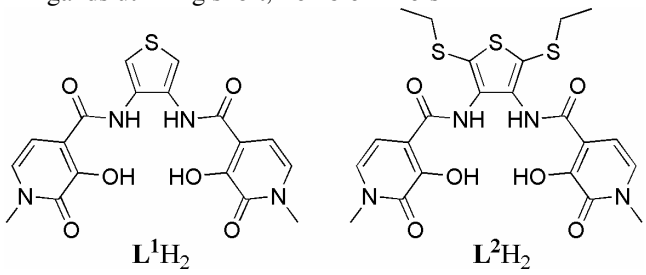
Structural characterization of a mononuclear uranyl complex with a tetradentate, thiophene-linked bis(N-methyl-3-hydroxy-pyridin-2-one) ligand reveals the most planar coordination geometry yet observed with this ligand class. Introduction of ethylsulfanyl groups onto the thiophene linker disrupts this planar, conjugated ligand arrangement, resulting in the formation of dimeric $(UO_2)_2L_2$ species in which each ligand spans two uranyl centers. Relative energy calculations reveal this tendency toward dimer formation is the result of steric interference between ethylsulfanyl substitutents and linking amides.

While nuclear power is attractive as a carbon-free energy source, the safe use of this technology requires both a low risk of contamination of environmental or biological systems with radioactive elements and the ability to deal with such contamination if it occurs.[2] Ligands that can efficiently chelate and remove actinides from the environment or *in vivo* are being developed.[3] Because uranium is the feed stock material of most nuclear power sources and is the most abundant naturally-occurring actinide, uranium chelation is of particular interest. Uranium in oxidizing conditions and *in vivo* typically adopts a hexavalent oxidation state, in which it exists as a linear, dioxo dication (uranyl, UO_2^{2+})[4] that is poorly decorporated by polyaminocarboxylic acids.[3] Unlike transition metal dioxo species, the uranyl cation maintains linearity to within a couple degrees in all of its coordination complexes, relegating coordinative variation to an equatorial plane perpendicular to the O=U=O vector. Exceptions to this behavior typically involve bulky ligands (e.g. Cp[5] or large NCN or NPN ligands[6]) in which the uranyl cation may deviate more than 11° from linearity and coordinating atoms distort out of the equatorial coordination plane. The apical oxo moieties are essentially non-reactive and are typically only observed to interact with Lewis acids in the solid state and in appropriately designed macrocyclic systems.[7-11] These properties make the uranyl cation a challenging target for selective chelation.

Recent work in our laboratory towards developing uranyl-specific chelators has focused on the use of poly-bidentate, oxygen-donating ligands incorporating synthetic analogs to siderophore chelating moieties, which are known to form high-affinity complexes with hard Lewis-acidic *f*-elements.[12] Xu *et al.* demonstrated that 3-hydroxy-N-methyl-pyridin-2-one (Me-3,2-HOPO) ligands bind the uranyl cation at four points of an equatorial pentagonal plane completed by solvent molecule coordination.[13] Chelator orientations about the uranyl are seen to depend strongly on the length of the linear ligand linker. In these complexes an intramolecular N_{amide}-H···$O_{phenolate}$ hydrogen-bonding interaction is responsible for stabilization of the deprotonated and metal-chelated ligands[14] and is optimized in ligands utilizing short, flexible linkers.[13]



$\mathbf{L^1}H_2$ $\mathbf{L^2}H_2$

Figure 1. Bis-Me-3,2-HOPO ligands 3,4-thiophene-Me-3,2-HOPO ($\mathbf{L^1}H_2$) and 2,5-bis-ethylsulfanyl-3,4-thoiophene-Me-3,2-HOPO (**2**).

To explore the structural effect of linker rigidity, the uranyl complexes with two bis-Me-3,2-HOPO ligands incorporating short, rigid linkers [3,4-thiophene-Me-3,2-HOPO ($\mathbf{L^1}H_2$) and 2,5-bis-ethylsulfanyl-3,4-thoiophene-Me-3,2-HOPO ($\mathbf{L^2}H_2$), Figure 1] were synthesized. The uranyl complex with $\mathbf{L^1}$ is expected to exhibit a severely restricted coordination geometry, while that with $\mathbf{L^2}$ is intended to explore the effect of 2,5-disubstitution on the thiophene ring such as may be employed in attaching solubilizing groups or linkers to $\mathbf{L^1}$ (some degree of substituent torsion such as described by Lai *et al.* is expected).[15] In both cases, the short, relatively inflexible

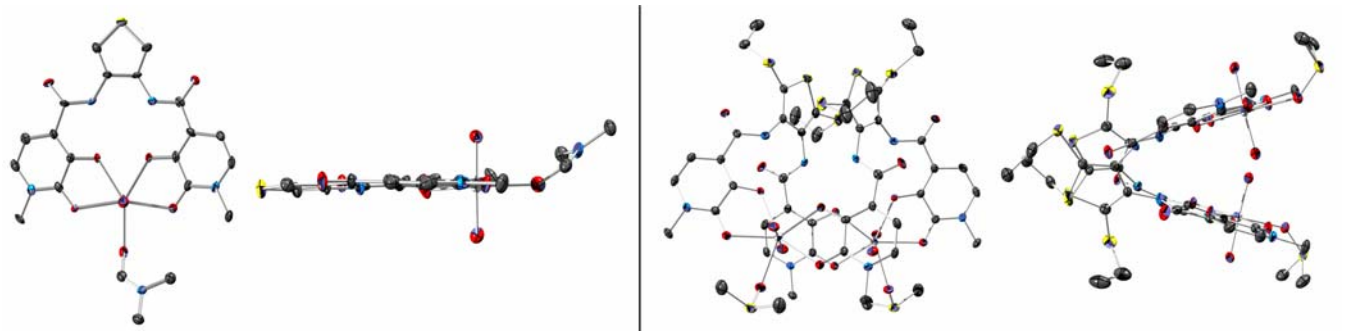


Figure 2. Top and side views of the crystal structures of $UO_2(\mathbf{L^1})$(DMF) (left) and $[UO_2(\mathbf{L^2})(DMSO)]_2$ (right). Only one of the two $[UO_2(\mathbf{L^2})(DMSO)]_2$ structures are shown due to structural similarity (solvent-free structure shown here). Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at the 50% level. Carbons are gray, oxygens red, nitrogens blue, sulfurs yellow, and uranium is silver.

linkers are intended to discourage octahedral coordination modes typical of transition and main-block elements, imparting selectivity towards the uranyl cation over other biologically relevant metal ions.

The uranyl complexes with $\mathbf{L^1}$ and $\mathbf{L^2}$ were synthesized in DMF or DMSO by stoichiometric addition of a homogeneous ligand solution and Et_3N to a stirred solution of $UO_2(NO_3)_2{\cdot}6H_2O$, resulting in the formation of a deep red, solvated uranyl complex. Crystals of these complexes were grown from these crude solutions using vapor diffusion of MeOH at room temperature and layering of MeOH at 4 °C, respectively. These crystals were measured by single-crystal X-ray diffraction at the UC Berkeley X-ray facility, and the resultant structures are illustrated in Figure 2. $\mathbf{L^1}$ chelates the uranyl cation *via* four Me-3,2-HOPO oxygen atoms, leaving a fifth equatorial site available for DMF coordination, consistent with previous bis-Me-3,2-HOPO ligand behavior.[13] The crystallization of the uranyl complex with $\mathbf{L^2}$ resulted in two crystal morphologies, one dark red and the other orange. The latter crystal type suffered from rapid desolvation of the several methanol inclusions that X-ray diffraction subsequently revealed. The dark red crystals contained no solvent inclusions, and the uranyl complexes in both crystal morphologies exhibited similar molecular geometries: the uranyl cation is coordinated by $\mathbf{L^2}$ at four points of a pentagonal coordination plane completed by a DMSO molecule. However, unlike with $\mathbf{L^1}$, the uranyl complex with $\mathbf{L^2}$ is a $[UO_2(\mathbf{L^2})(DMSO)]_2$ dimer in which each $\mathbf{L^2}$ ligand coordinates to two uranyl cations.

The bite angles of the Me-3,2-HOPO moieties to the uranyl cation average 65.6(6)° in $UO_2(\mathbf{L^1})$(DMF) and 66.4(7)° in the $[UO_2(\mathbf{L^2})(DMSO)]_2$ complexes, which correspond well to the precedent value of 66.4(4)°.[13] The equatorial $U\text{-}O_{amide/phenolate}$ bond distances in $UO_2(\mathbf{L^1})$(DMF) average 2.434(4) Å and 2.344(9) Å, respectively, while those in the solvent-containing $[UO_2(\mathbf{L^2})(DMSO)]_2$ dimer structure are 2.44(3) Å and 2.36(2) Å. These bond lengths also correspond well to precedent and are consistent with an expected stronger U-O bond with the more electronegative phenolate oxygen compared to the formally neutral amide oxygen. In the solvent-free $[UO_2(\mathbf{L^2})(DMSO)]_2$ structure, however, one Me-3,2-HOPO moiety reverses this trend, with the $U\text{-}O_{amide}$ bond shorter than the $U\text{-}O_{phenolate}$ bond (2.36 Å, 2.40 Å respectively). This behavior is assumed to be a solid state phenomenon that attests to the coordinative flexibility in these dimeric complexes. The intramolecular $N_{amide}\text{-}O_{phenolate}$ distances in the uranyl complexes with $\mathbf{L^1}$ and $\mathbf{L^2}$ range between 2.61 Å and 2.80 Å, attesting to a strong intramolecular hydrogen bonding interaction characteristic of Raymond group ligands.[14]

The equatorial $O_{phenolate}\text{-}U\text{-}O_{phenolate}$ angle in uranyl complexes with bis-Me-3,2-HOPO ligands has been shown to vary significantly with linker length, and can be considered an overall "ligand bite angle.".[13] The ligand bite angle in $UO_2(\mathbf{L^1})$(DMF) of 65.2° is much smaller than the 72° of the ideal pentagon, and the smallest angle yet observed with bis-Me-3,2-HOPO ligands. While this results in a relatively exposed uranyl center, the equatorial coordination of $\mathbf{L^1}$ is nearly planar; the Me-3,2-HOPO rings deviate only 5.8° from co-planarity and only 2.8° and 7.1° degrees from the uranyl coordination plane defined by the five coordinating oxygen atoms. This planar geometry is complementary to the equatorial coordination tendencies of the uranyl cation,[4] is the best yet observed with bis-Me-3,2-HOPO ligands, and is most likely caused by the extended bond conjugation in **1**. The "ligand bite angles" observed in the $[UO_2(\mathbf{L^2})(DMSO)]_2$ structures are no longer subject to the short inter-moiety proximity imposed by the thiophene linker due to the spanning behavior of $\mathbf{L^2}$. As a result, the ligand bite angles in $[UO_2(\mathbf{L^2})(DMSO)]_2$ structures range between 79.0° and 83.2°, which are much larger than that in $UO_2(\mathbf{L^1})$(DMF) and approach that observed with the larger 4Li-Me-3,2-HOPO ligand (79°).[13]

The only structural difference between $\mathbf{L^1}$H and $\mathbf{L^2}$H is the presence of the ethylsulfanyl substituents on the thiophene linker, and are thus the most likely cause for the lack of ligand conjugation that leads to the dimeric $[UO_2(\mathbf{L^2})(DMSO)]_2$ structures. The $O_{amide}\text{-}S_{ethylsulfanyl}$ distances between substituents on the same sides of the thiophene rings range between 2.90 Å and 5.01 Å, depending on the degree of amide twist observed; the minimum value of 2.90 Å is less than the sum of the sulfur and oxygen Van der Waals radii (3.3 Å).

The energetic influence of the ethylsulfanyl substitution was investigated by molecular dynamics calculations in which one amide in a simplified thiophene-3,4-bis-amide was rotated about the $N_{amide}\text{-}C_{thiophene}$ bond through a full 360° rotation at 5° intervals, relaxing the geometry at each

step to convergence. A rotation of 0° corresponds to a co-planar amide moiety in the conformation seen in the $UO_2(\mathbf{L^1})$(DMF) structure. This calculation was performed in the absence and presence of ethylsulfanyl substituents *ortho* to the amide moieties; the results for both calculations are shown in Figure 3. Sharp drops in relative energy upon incremental amide rotation are a consequence of significant rearrangement of the neighboring amide, typically facilitating a new hydrogen-bonding interaction.

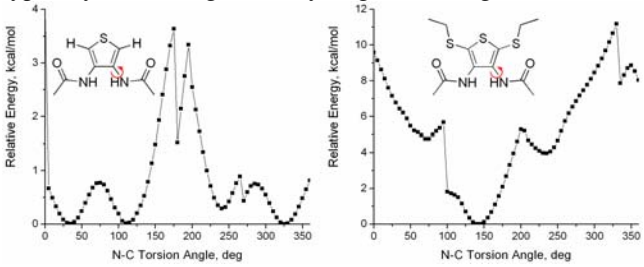


Figure 3. Relative energy calculations for rotation of an acetamide substituent about the N_{amide}-$C_{thiophene}$ bond in the presence of an *ortho* acetamide in the absence (left) and presence (right) of ethylsulfanyl substitution.

In the absence of steric influences, the amide moiety is expected to prefer conjugation to the thiophene linker (0° and 180°).[16] However, in the presence of an *ortho* amide (Figure 3, left), 180° is an energetic maximum due to steric interference between the two amides. The less than 1 kcal/mol energy difference upon rotations from 0° is a result of the combination of an energetically costly break in conjugation combined with favorable inter-amide N-H···O hydrogen bonding allowed by the free rotation of the neighboring amide. The small energy differences between these angles makes the observed 4° and 9° amide torsions in $UO_2(\mathbf{L^1})$(DMF) reasonable considering the structural influence of uranyl chelation and increased electronic conjugation in $\mathbf{L^1}$ compared to the model compound, with both factors favoring low amide torsion angles.

In the presence of ethylsulfanyl substituents the energy profile and energy differences change significantly (Figure 3, right). A 150° torsion angle is favored due to a combination of N-H···S and O···H-N hydrogen bonding interactions of one amide to the ethylsulfanyl and *ortho* amide substitutents, respectively. This conformation is not appropriate for mononuclear or dimeric complex formation, and is thus not observed in the uranyl complexes with $\mathbf{L^2}$. Torsion angles near 0° represent the highest calculated energies due primarily to a combination of steric interference between amide oxygen and ethylsulfanyl sulfur atoms, explaining why ligand $\mathbf{L^2}$ does not form mononuclear uranyl complexes as $\mathbf{L^1}$ does. Interestingly, local energy minima occur at 70° and 235° at which the amide group is significantly twisted out of conjugation with the thiophene ring. This conformation balances the unfavorable effects of steric interference with the ethylsulfanyl sulfurs and the absence of electronic conjugation to the thiophene ring, resulting in a conformation *ca*. 4 kcal/mol higher than the global minimum. This *ca*. 4 kcal/mol torsion cut-off is consistent with small molecule torsions observed in crystal structures,[17] and the predicted torsion angles correspond very well with the N_{amide}-$C_{thiophene}$ bond torsion angles exhibited in the $[UO_2(\mathbf{L^2})(DMSO)]_2$ crystal structures: (65°, 245°) for the unsolvated structure, and (59°, 239°) and (57°, 246°) for the MeOH-containing structure.

In conclusion, we have demonstrated that relatively small changes in backbone geometry can significantly change the coordination behavior of bis-Me-3,2-HOPO ligands with the uranyl cation which must be taken into account when designing uranyl-selective ligands. We have also demonstrated the first instance of uranyl dimer complex formation using bis-Me-3,2-HOPO ligands. Future work currently in progress addresses the structural and solution thermodynamic studies of thiophene- and other rigidly-linked bis-Me-3,2-HOPO ligands with the uranyl cation.

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Supporting Information Available: Experimental procedures, molecular dynamics data, tables of pertinent bond lengths and angles, crystallographic refinement details and figures, .cif files for uranyl complexes with $\mathbf{L^1}$ and $\mathbf{L^2}$. This material is available free of charge via the internet at http://pubs.acs.org.

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