Project No. 11-3049

Selectivity in ligand binding to uranyl compounds: A synthetic, structural, thermodynamic and computational study

Fuel Cycle

Dr. John Arnold
University of California, Berkeley

Stephen Kung, Federal POC
Sheng Dai, Technical POC

NEUP Nuclear Energy University Programs
U.S. Department of Energy

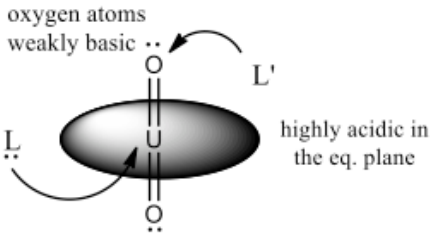
Project Title: Selectivity in ligand binding to uranyl compounds: A synthetic, structural, thermodynamic and computational study
Contract Number: 119253. **Project Number:** 11-3049
Principal Investigator: John Arnold, Department of Chemistry, University of California, Berkeley, CA 94720-1460

Background and Significance

The uranyl cation (UO_2^{2+}) is the most abundant form of uranium on the planet. It is estimated that 4.5 billion tons of uranium in this form exist in sea water. The ability to bind and extract the uranyl cation from aqueous solution while separating it from other elements would provide a limitless source of nuclear fuel. A large body of research concerns the selective recognition and extraction of uranyl. A stable molecule, the cation has a linear O=U=O geometry. The short U-O bonds (1.78 Å) arise from the combination of uranium 5f/6d and oxygen 2p orbitals. Due to the oxygen moieties being multiply bonded, these sites were not thought to be basic enough for Lewis acidic coordination to be a viable approach to sequestration.

We believe that the goal of developing a practical system for uranium separation from seawater will not be attained without new insights into our existing fundamental knowledge of actinide chemistry. We posit that detailed studies of the kinetic and thermodynamic factors that influence interactions between f-elements and ligands with a range of donor atoms is essential to any major advance in this important area. The goal of this research is thus to broaden the coordination chemistry of the uranyl ion by studying new ligand systems via synthetic, structural, thermodynamic and computational methods. We anticipate that this fundamental science will find use beyond actinide separation technologies in areas such as nuclear waste remediation and nuclear materials.

Most strategies toward uranyl sequestration involve ligands solely bonding to the uranium center equatorially in a planar geometry. Research has shown that when coordinating strong σ and π donating ligands to the equatorial plane, the added electron density softens the U(VI) center giving some Lewis basicity to the axial oxygen atoms as the U-O bond weakens. Several innovative ligand designs dually bond to both the equatorial plane and the axial oxo groups.



A ligand designed by Raymond and coworkers illustrates this approach by containing carboxylate groups as electron donors to the equatorial plane, while also containing a secondary amine to hydrogen bond with a uranyl oxygen. Such an approach is selective for the target species, as no other present cationic species would have the particular geometry of uranyl. Two reports have shown that the bonding of equatorial NCN ligands to uranyl weakens the U-O stretch frequency. This bond weakening coincides with increased Lewis basicity of the oxo ligands as illustrated by the addition $B(C_6F_5)_3$, yielding the complex $UO\{OB(C_6F_5)_3\}(NCN)_2$.

This is the first example of an oxo ligand being functionalized by borane, albeit a highly Lewis acidic one. Additionally several studies report uranyl oxo ligands interacting with transition and alkali metal cations.

The focus of this study is to synthesize uranyl complexes incorporating amidinate and guanidinate ligands. By developing a working methodology for these syntheses, there can be further investigation into more novel ligand coordination. Due to the ability of uranyl to bond with several hard electron rich ligands, it is an academic challenge to develop syntheses limiting this ligation and produce specific complexes with known coordination numbers. In this study, we use both synthetic and computational methods to investigate novel equatorial ligand coordination and how this affects the basicity of the oxo ligands. Such an understanding will later apply to designing ligands incorporating functionalities that can bind uranyl both equatorially and axially for highly selective sequestration.

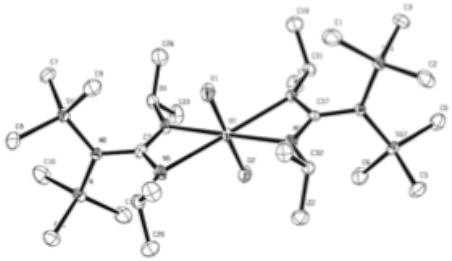
In a new sub-project, we began work last fall with Professor Matt Francis to investigate a new means of addressing the concept of selectivity in uranyl binding. Previous reports have shown that near-perfect separation of the lanthanide ions can be achieved using HPLC supports that are chemically modified to display organic ligands. However, these examples have only been demonstrated on small samples (1 - 10 mg) using expensive packing materials and high pressure, preventing their use on industrial process scale. As a low-cost alternative simple cation exchange methods have been used to facilitate large-scale lanthanide purification, but these approaches would clearly benefit from increased resolving power. In the proposed work, we will work with the Francis group to generate efficient and durable chromatography supports for lanthanide separation by (1) identifying robust peptoid-based ligands capable of binding different lanthanides with variable affinities, and (2) developing practical synthetic methods for the attachment of these ligands to Dowex ion exchange resins. The success of these approaches will yield a series of cheap, durable, high-capacity supports capable of separating complex lanthanide mixtures using simple equipment that can be readily adapted from existing water purification technology. To accelerate the discovery process, we will instead prepare small libraries of support ligands and find the structures within it that have the greatest separation potential. The peptoid backbone has been chosen for the first set of molecules to be evaluated, as these complex structures can be synthesized using efficient and inexpensive chemical strategies. The ligands comprising the library will present the uranyl ion with a widely varying collection of multidentate binders.

Lewis acid binding to uranyl complexes

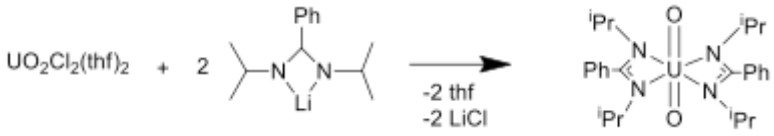
Due to the limited precedent set forth in literature, we focused on binding the uranyl cation with anionic NCN ligands such as amidinates and guanidinates. These anionic ligands can soften the U(VI) center, affecting the U-O bond length. The pathway chosen for the preparation of uranyl guanidinates was the reaction of a uranyl amide with carbodiimide to undergo a migratory insertion. The uranyl amide UO2[N(SiMe3)2]2(thf)2 was prepared according to a published procedure by adding two equivalents of KN(SiMe3)2 to a slurry of UO2Cl2(thf)2. The addition of one equivalent of N,N-diisopropylcarbodiimide to UO2[N(SiMe3)2]2(thf)2 in toluene yields a product coinciding with an immediate color change from orange to red.

The reaction of two equivalents N,N-diisopropylcarbodiimide and UO2[N(SiMe3)2]2(thf)2 in toluene at 60°C for 24 h afforded the uranyl bis(guanidinate) 2, isolated as a clean red powder. 1H NMR resonances were observed for 2 at δ 5.77, 1.73, and 0.37 with the respective integration ratio 1:6:9. The heptet resonance at 5.77 ppm corresponding to the isopropyl methine nuclei is strikingly downfield and is discussed later on.
Both reactions coincide with color changes similar to those reported for the addition of amidinate ligands to uranyl. Unlike the reported addition of two amidinate ligands onto uranyl, no THF remains coordinated to the uranium in either uranyl guanidinate species 1 or 2. This suggests some ease in coordinating highly Lewis acidic species to the uranyl oxo ligands, as there are no competitive Lewis bases present in the product.

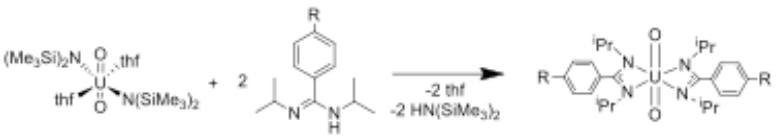
Crystals of 2 suitable for X-ray diffraction were grown from ether at -40 °C and confirm the structure analyzed from NMR spectroscopy. The uranyl unit remains almost linear (O1−U1−O2, 179.03°). The U-O bond lengths are typical for neutral complexes (1.769(3) Å and 1.774(3) Å).



Complexes of uranyl amidinates with both planar and non-planar equatorial coordination geometries have been reported. Four equivalents of amidinate salts are added to uranyl chloride to form uranyl bis(amidinate), and as many as three amidinate ligands can bond the uranyl cation with higher equivalent additions of amidinate salt. To further investigate the cause of the interesting 1H NMR resonance of the isopropyl methine proton at 5.77 ppm of the uranyl bis(guanidinate) 2, we turned to another NCN ligand class, amdinates. We synthesized a series of uranyl bis(amidinate) complexes containing isopropyl groups similar in design to 2. Complex 4 was synthesized by the salt metathesis of uranyl chloride with a known lithium amidinate. Although 4 was isolated cleanly, there was a considerable amount of the anionic "ate" complex in the raw product.



To avoid the evolution of anion "ate" complexes, the uranyl bis(amidinate) compounds 5-7 were targeted by reaction of uranyl bisamide with a series of designed amidines.
The trifluoromethyl-substituted complex 7 was isolated as a THF- adduct, containing one tetrahydrofuran molecule per complex when solvent was removed under high vacuum as observed by 1H NMR. Both complexes 5 and 6 contained no THF when solvent was removed. Our inability to remove THF from 7 is likely because the trifluoromethyl-substitued amidinate groups do not donate enough electron density to the uranium center for it to release THF. By using electron-withdrawing (EWG) and electron-donating groups (EDG), we hope to tune the electron-donating ability of the amidinate ligands to the uranyl center. Doing this could affect the uranium-oxygen bond

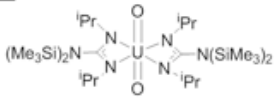


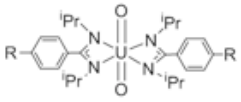
R= Me **(5)**,
R= F **(6)**,
R= CF_3 **(7)**

distances of uranyl as the uranium receives varying degrees of electron density from its equatorial ligands. Such differences in the U-O bonding would likely lead to differences in binding strength of Lewis acids bonding to the oxo moieties. The O=U=O symmetric stretches of the complexes would provide some basis for comparing how our tuning affects the uranyl oxo basicity. The O=U=O symmetric stretching frequencies of the uranyl bis(amidinate) complexes are higher than that of the uranyl bis(guanidinate). Overall, the stretching frequencies of the different complexes do not vary greatly, and it is likely they all have very similar U-O bond distances.

Similar to the 1H NMR resonance of the isopropyl methine protons in the uranyl bis(guanidinate), the isopropyl methine protons of the uranyl bis(amidinate) complexes all exhibit particularly downfield 1H NMR resonances.

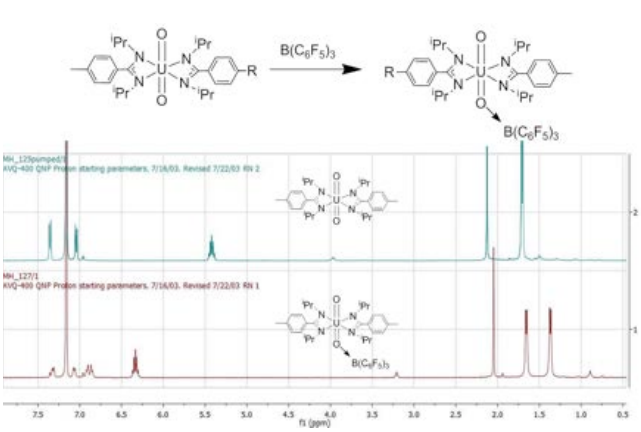
Complex	δ (ppm vs. TMS) $CH(Me)_2$
Uranyl bis(guanidinate) complex	
2	5.77
Uranyl bis(amidinate) complexes	
5	5.42
4	5.34
6	5.11
7•thf	4.79



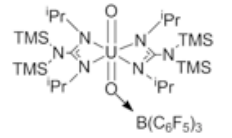


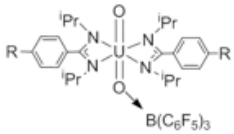
R= H **(4)**, Me **(5)**, F **(6)**, CF_3 **(7)**

The same guanidinate used in our experiment was used as a ligand on ytterbium by Weng et al. The reported resonance of the isopropyl methine proton in their complex Yb(guan)3 was at 2.15 ppm, far upfield to our observed shift, with all other 1H and 13C NMR shifts being similar to our experimental values. Likewise, the lithium amidinate salt used to synthesize complex 4 produced a 1H NMR isopropyl methine resonance at 3.00 ppm, noticeably upfield of that observed in the spectroscopy of 5. The isopropyl methine shifts of all our uranyl complexes showed heptets considerably downfield of those of similar compounds, even though the complexes are diamagnetic. It is likely the downfield resonances arise from spin-orbit (SO) effects from the heavy uranium nucleus. Kaupp et al. predicted hydrides bonded to U(VI) as having giant SO effects which were predicted to have 1H NMR shifts as downfield as 146.4 ppm. Although these compounds have hydrogen nuclei directly bonded to uranium, we should and do see lesser spin-orbit coupling at the isopropyl methine protons. Due to a Fermi-contact type mechanism, we see downfield shifts at every atom at odd-numbered positions from the uranium center, and slight upfield shifts at every even-numbered



Complex	δ (ppm vs. TMS) $CH(Me)_2$
Uranyl bis(guanidinate) adducts	
2·$B(C_6F_5)_3$	6.76
Uranyl bis(amidinate) adducts	
5·$B(C_6F_5)_3$	6.33
4·$B(C_6F_5)_3$	6.24





R= H **(4**·$B(C_6F_5)_3$**)**
Me **(5**·$B(C_6F_5)_3$**)**

position. Because the hydrogen nuclei are at a

third position away from the uranium center, it follows that the isopropyl methine carbon should experi ence a slight upfield shift (2- 4 ppm) as it is two positions from the heavy actinide.

To probe the basicity of the oxo moieties in our uranyl complexes, we monitored their binding of the strongly acidic B(C6F5)3 by 1H NMR. This coordination was observable by 1H and 19F NMR spectroscopy even while the adducts were in benzene solution. Similar to the reaction reported by Sarsfield et al., the formation of the U=O-B bond is indicated by an immediate solution color change from bright red to deep magenta. Upon addition of B(C6F5)3, there is a large downfield shift of the isopropyl methine hydrogen nuclei from 5.42 ppm to 6.33 ppm. This same downfield shift is present when other uranyl complexes coordinate with B(C6F5)3 as depicted by Table 2.

The binding of the borane to the oxo moiety pulls electron density away from the uranium center, resulting in a contraction of the U-N bonds in the compounds. This phenomenon was observed by Sarsfield et al. and can be confirmed in the future by X-ray crystallography of the isolated borane adducts. Such a change seems to produce larger spin-orbit coupling of the uranium nucleus with the isopropyl methine hydrogen nuclei. Computed shifts (Peter Hrobárik/Kaupp group) of some of the compounds using PBE and PBE0 exchange-correlation functionals are shown in Table 3 along with their experimental SO coupling contributions.
The spin-orbit effects on the isopropyl methine resonances are actually predicted computationally as well as their approximate downfield shifts. The computations also exhibit an increase spin-orbit coupling upon coordination with borane. These relativistic effects are not fully understood, so our synthesized uranyl compounds may help to elucidate some characteristics of spin-orbit effects arising from heavy atoms.

Other Lewis acids could bind to the uranyl oxo much like the very acidic borane. The next compound used for the task was Al(C6F5)3, a stronger electrophile than B(C6F5)3. Multinuclear NMR spectroscopy (1H, 19F) indicated the triarylaluminum nucleophile successfully binded to the uranyl bis(amidinate) 5. Although the same color change to deep magenta was observed, NMR spectroscopy revealed the evolution of minor products likely arising from the aluminum pulling off amidinate ligands. In the 1H NMR spectrum, a heptet corresponding to the isopropyl methine was observed downfield at 6.48 ppm. It is worth noting that this shift is even further downfield of the isopropyl methine shift of the borane adduct 5•B(C6F5)3. This is likely due to higher SO coupling due to a shorter contraction of the N-U bonds.

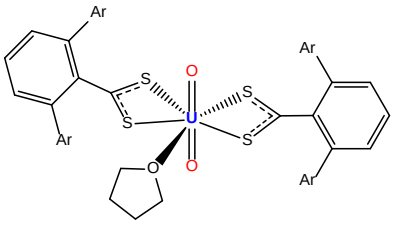
Terphenyl uranyl complexes

Terphenyl groups, especially meta-terphenyl groups, can be attached to a variety of binding moieties to create very sterically-hindered ligands for binding to different metal ions. Different functionalities can be places both at the binding site and on the terphenyl groups at various positions to tune the steric and electronic properties of the ligands. Carboxylate terphenyls have been used to bind uranyl, with simple terphenyl carboxylates as well as assemblies of three terphenyls into a larger ligand that forms hydrogen bonds with one of the terminal oxo groups based on the hydrogen bond donors above the equatorial plane. Such ligands have the potential to be used for sequestration of uranyl from sea water or other systems due to their selectivity and affinity for uranyl due to these structural features.

Rather than using hydrogen bonding to interact with the oxo groups of uranyl, stronger Lewis acid groups may be able to be used as well. The Lewis acid-base interactions can be stronger than hydrogen bonds, and it has been shown that boranes do interact with terminal oxo groups (above). The size of the space created by the terphenyls can be adjusted depending on the side groups on the ligand, to potentially influence the nature of interactions possible with Lewis acids, or other molecules such as solvents.

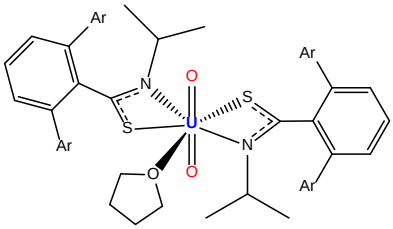
The terphenyl structure can be used to create a series of bidentate ligands, with oxygen, nitrogen, and sulfur donors, to give a series of ligands with similar geometries but varying electronic properties. The synthesis for all these ligands use the same techniques to introduce the anionic binding group. If these complexes with uranyl or other actinde species can be synthesized, the set of analogous complexes can provide insights into the nature and strengths of actinide-ligand binding, particularly with sulfur ligands.

Work has been continued with Lewis acid binding to uranyl complexes, and the uranyl dithioacid and thioamide complexes have been synthesized. However, they do not show reactivity with the Lewis acid $B(C_6F_5)_3$ that was previously used with smaller amidine and guanidine complexes. This is likely due to the steric hindrance from the terphenyl groups with such a large Lewis acid. An analogous set of ligands, based on a mesityl group, have been synthesized and synthesis and characterization of complexes is underway.



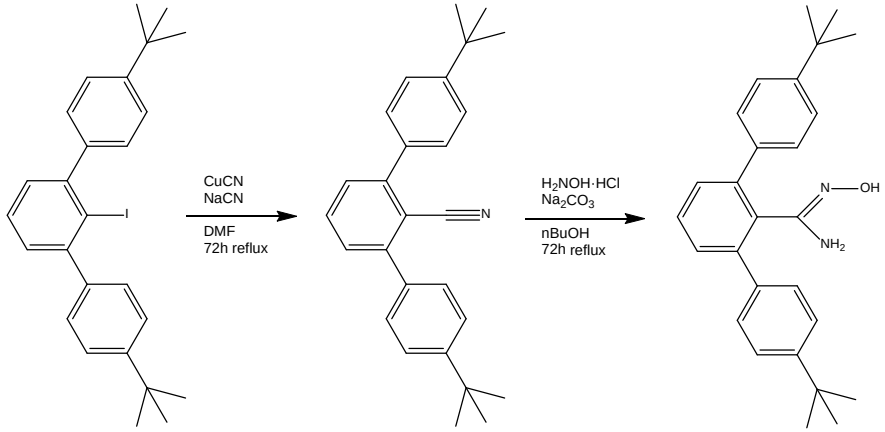
orange-red crystals

Terphenyl and other sterically hindered amidoximes are being synthesized, to investigate the role of sterics and backbone geometry in uranyl binding. These are related to some of the other terphenyl ligand complexes that we have been synthesizing. Complexes of metals with these large amidoximes can give insight into the structures and binding of uranyl complexes with amidoximes, since their large steric bulk may limit the ability of multiple ligands to bind. Additionally, these may also be potential building blocks for peptoid libraries, since a modular approach can also be used to examine binding on uranyl away from the terphenyl groups.



orange-red crystals

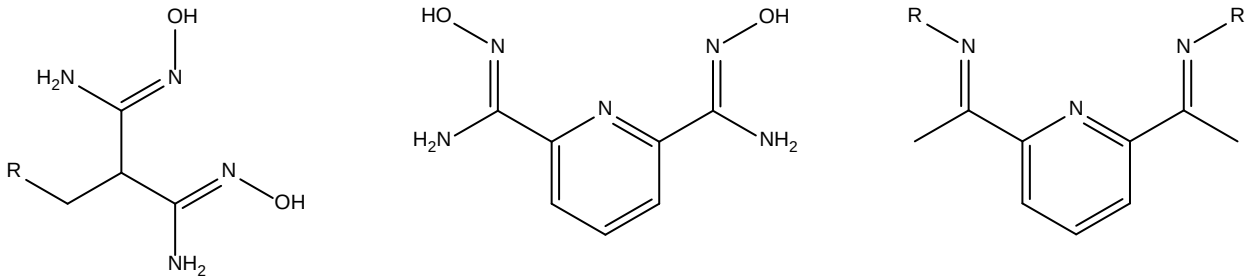
Several synthetic routes have been attempted from the terphenyl iodide and the aniline. Direct conversion from the iodide to the nitrile under several different sets of conditions has not been successful, likely due to the steric bulk of the outer aromatic groups. The aldehyde can be synthesized as an intermediate, however, conversion to the nitrile was not successful for the same reason. Diazotization of the terphenyl aniline followed by treatment with cyanide resulted in the unexpected product of the protonated terphenyl. Further investigation and other synthetic routes to obtain the terphenyl amidoxime will be investigated, such as dehydration of a primary amide. Terphenyl ligands with different substitution patterns may also be more successful in this reaction.



A terphenyl amidoxime was finally synthesized from a different terphenyl (with *t*-butyl groups for solubility) using a direct Rosenmund-von Braun reaction followed by treatment with hydroxylamine at a higher temperature than usual. This amidoxime exhibits somewhat hindered rotation around the aryl-amidoxime C-C bond indicative of the sterics of the terphenyl group. Reactions to synthesize the uranyl complex as well as vanadium, lithium and other metals are in progress.

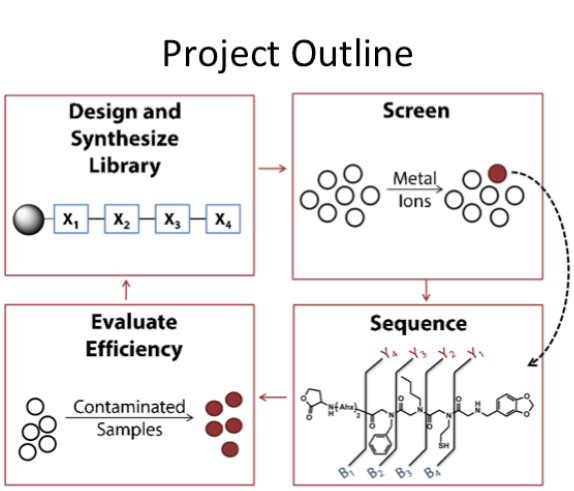
Other amidoxime ligands

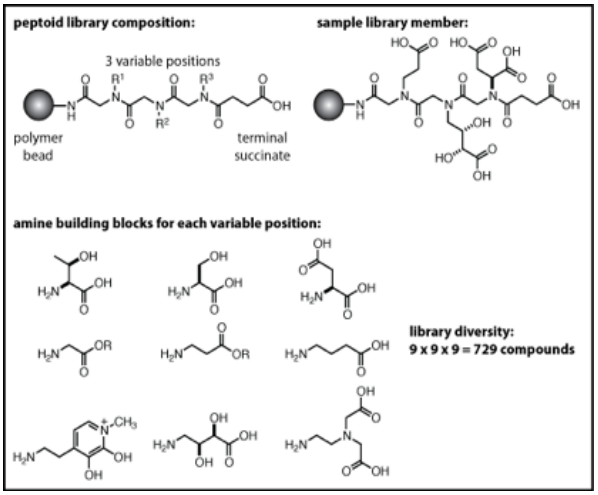
As well as the terphenyl amidoxime, other multi-functional amidoxime ligands are being investigated. The main goal of these will be do elucidate ligand features that provide selectivity for uranyl over vanadium species, and help understand what features of amidoximes enable such strong binding. These ligands will contain multiple rigid amidoxime groups, which bear some similarities to complex groups sometimes found on current amidoxime-based polymer adsorbent materials. A germinal bis(amidoxime) (left) is being synthesized, and this ligand design allows for a wide range of R groups to be incorporated into the ligand. This will provide a platform to investigate the effects of steric and electronic changes in the ligand to the uranyl binding affinity and characteristics. Another bis(amidoxime)-pyridine ligand (center) also contains a rigid arrangement of two amidoxime groups, but with a planar geometry with another nitrogen donor atom.



Additionally, with the pyridine-based ligands, the conjugation of the ligand may allow for the investigation of the redox chemistry of uranyl, by stabilizing lower oxidation states and being redox-active. Several related ligands can be synthesized, such as the analogous hydroxamic acid, oxime, and imine (right), the latter of which has already been made in previous work in the Arnold group. The synthesis of these ligands and their uranyl and vanadium complexes is currently in progress.

Combinatorial peptoid ligands





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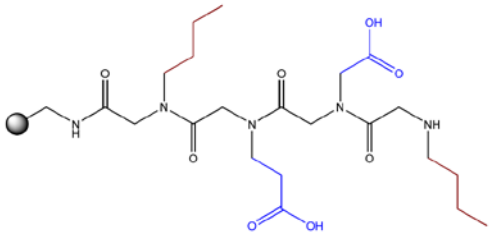
(a)



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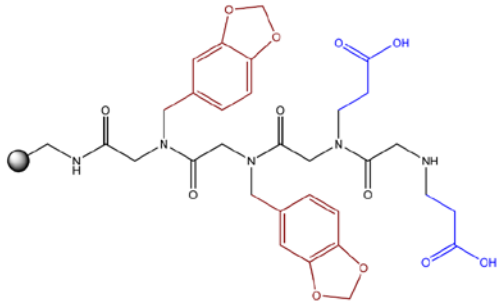
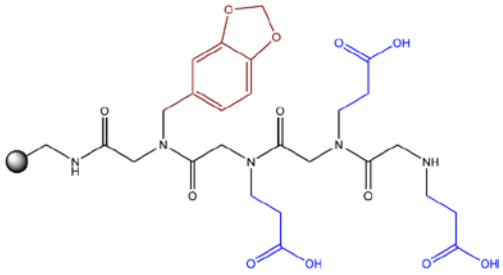


(c)



Before adding dye

3 drops of arsenazo III added

Binding seen in 2 mM uranyl acetate

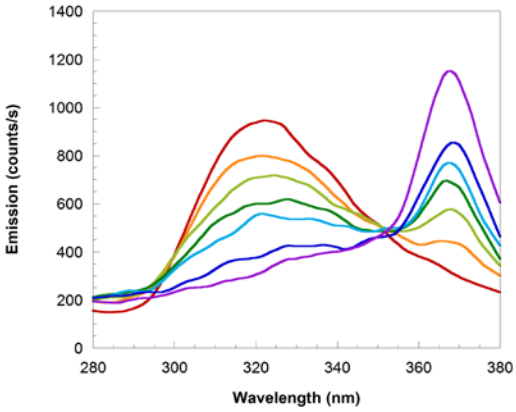
Experiments that have been used for peptoid libraries to bind other metals have been tested and adapted to investigate uranyl binding. Since the uranyl cation is not strongly colored, it is not possible to determine whether binding has occurred simply by visual inspection. We have used a dye, arsenazo III, to qualitatively determine whether uranyl is present within a peptoid bead, which can then be selected for sequencing.

A large library has been used to investigate uranyl binding. From this, three hit sequences have been identified: butylamine – β-alanine – glycine – butylamine; piperonylamine – piperonylamine – β-alanine – β-alanine; piperonylamine – β-alanine – β-alanine – β-alanine. Notably, only four amines are present in these sequences, only two of which bind to uranyl (β-alanine and glycine; the other two, butylamine and piperonylamine, are just sterics). The third sequence (c) has been synthesized on a larger scale and cleaved from the polymer bead to give the free peptoid, which is being used in other binding studies.

The peptoids are colorless, and the color of uranyl is not detectible at the low concentrations used, such that UV-Vis spectrometry cannot be used to characterize the complexes or the binding. However, fluorescence spectroscopy has been used with other uranyl species and complexes, and we are starting to use it to investigate uranyl-peptoid binding as well. The fluorescence of uranyl and related species can be used qualitatively and quantitatively to determine binding constants and probe the nature of the interactions.

The fluorescence of uranyl at very low concentrations (on the order of 100 μM) is very weak due to water quenching the fluorescence. However, the presence of other coordinating species can drastically increase the intensity and change the shape of spectra. Using phosphate as a buffer severely interferes with the fluorescence spectra, either through the formation of uranyl phosphate or other complexes, or affecting fluorescence quenching in other ways. Attempting to

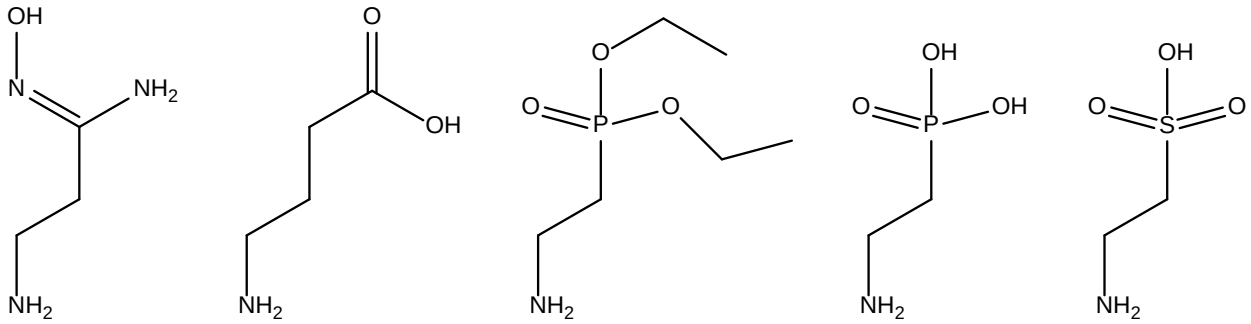
take spectra without a buffering agent has not been successful, since the pH varies over the course of an experiment, leading to variable binding strengths as well as changing fluorescence. Fluorescence experiments with a different buffer, HEPES, were performed, and by measuring the fluorescence intensity of the piperonylamine side chains (the uranyl fluorescence was very weak at the concentrations used), an approximate binding constant of $K_d \approx 670 \pm 160$ μM was obtained. Since this represents very weak binding, further experiments with these initial hit sequences were put on hold, and instead we focused more on design and synthesis of a new library.



Using data from the binding experiments as well as molecular modeling, we hope to determine what could improve upon the peptoid sequences and library. Changing the length of the sequence, incorporating different amines, and (possibly) changing the amide backbone length to increase spacing between peptoid amines will be investigated for optimization of the peptoid sequences to attempt binding with lower concentrations of uranyl.

New peptoid library

A new peptoid library is being designed, and the library members are in the process of being synthesized. In addition to some of the sub-monomers used in previous libraries, the sub-monomers shown below will be used. These groups are suitable for testing for uranyl binding, since they are anionic, and some of them may have a relatively strong affinity for uranyl over other metals. However, they will need to be protected before being used in peptoid synthesis. Of these, the phosphonate, sulfonate, and carboxylic acid have not been incorporated into peptoid sequences before, however, similar units with different chain lengths have been. The amidoxime monomer has never been used, but will be especially valuable for this project, since they are already known to be good binders of uranyl and sequences incorporating this unit can help discover uranyl-binding motifs that may be valuable in other ligands.



The synthesis of these protected sub-monomers is nearly complete; synthesis of the *t*-butyl phosphonate and carboxylate are complete. Synthesis of the amidoxime is in progress, and different protecting groups for the amine during synthesis have been tested. Phthalimide, tosylamide, and fluoreneyl protecting groups have been tested, however, hydroxylamine treatment and deprotection reactions have not been able to produce pure product. The remaining submonomers are now being tested for incorporation efficiency and conditions, since a very high incorporation efficiency is needed to reliably synthesize and test the combinatorial library.

Incorporation of the amidoxime group may be difficult, as side reactions with the peptide bond coupling agents may be problematic. For this reason, the amidoxime may need to be protected, likely with an alkyl group at the more nucleophilic oxygen atom. A synthesis for installing a *t*-butyl group has been devised, by adaptation of a procedure normally used in esterification reactions, and it has been used with simple test substrates. Now that this has been established, it will be used with the peptoid submonomer as well. Using an *O*-substituted hydroxylamine has also been tested, however, this synthetic strategy has not been successful in synthesis of these protected amidoximes.

Currently, incorporation of the nitrile is being tested. The same incorporation conditions as for other monomers are being used initially. There has been some success with incorporation, but more tests are being done to ensure these reactions are near-quantitative. After this, hydroxylamine treatment will be explored, as solvent, time, and concentration can be varied to increase amidoxime yield but minimize side reactions.

In addition to the use of new submonomers, new aspects of the library design are being explored and their feasibility investigated. In particular, the use of turn units for non-linear peptoids (DFT has shown that a linear backbone is favored, and energy is needed to overcome this) such as piperazine or proline are being investigated computationally and experimentally. Dedicated fluorophores for more accurate quantitative analysis for binding are being explored as well.

DFT Studies

In collaboration with Dr. Sinisa Vukovic, work on DFT calculations for the peptoid-uranyl complexes has been continued. Optimized structures have been generated for a peptoid sequence representative of the initial hits, consisting of a peptoid containing three carboxylate groups. Using DFT, we can predict solution-state binding modes and geometries, since experimental characterization of this is difficult. From these calculations, we have found that the most favorable binding mode contains only two carboxylates binding, rather than all three. The peptoid backbone prefers to be linear and it is somewhat rigid, so tridentate binding is slightly less favored due to the backbone needing to bend to accommodate all three carboxylates around uranyl.

In March, Mr. Parker had the opportunity to travel to Oak Ridge National Lab to learn about DFT calculations on peptoid sequences and uranyl binding from Dr. Sinisa Vukovic. This trip was very valuable in determining how DFT can and will be used in future peptoid studies, and its general applicability to this project. In the future, we will be able to perform DFT

calculations on other binding sequences and possibly be able to use this to predict binding to future libraries.

Preliminary work has been done to predict possible binding modes and geometries for peptoid sequences containing amidoxime groups and assess possible binding modes for the new library. In particular, some possible binding structures have been identified as having a suitable geometry for binding, containing amidoximes as well as other library members. This has confirmed that the sub-monomers that will be incorporated are suitable for this application, and more sequences will be investigated after library synthesis and initial testing.