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# Recent advances in uranyl binding in proteins thanks to biomimetic peptides

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## Abstract

Uranium is an element belonging to the actinide series. It is ubiquitous in rock,  
10 soil, and water. Uranium is found in the ecosystem due to mining and milling  
industrial activities and processing to nuclear fuel, but also to the extensive use of  
phosphate fertilizers. Understanding uranium binding *in vivo* is critical, first to deepen  
our knowledge of molecular events leading to chemical toxicity, but also to provide  
new mechanistic information useful for the development of efficient decorporation  
15 treatments to be applied in case of intoxication. The most stable form in physiological  
conditions is the uranyl cation ( $\text{UO}_2^{2+}$ ), in which uranium oxidation state is +VI. This  
short review presents uranyl coordination properties and chelation, and what is  
currently known about uranium binding to proteins. Although several target proteins  
have been identified, the  $\text{UO}_2^{2+}$  binding sites have barely been identified. Biomimetic  
20 approaches using model peptides are good options to shed light on high affinity  
uranyl binding sites in proteins. A strategy based on constrained cyclodecapeptides

allowed recently to propose a tetraphosphate binding site for uranyl that provides an affinity similar to the one measured with the phosphoprotein osteopontin.

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*Keywords:* Uranyl; Proteins; Biomimetic Peptide; Decorporation; Metal Binding

## 1. Introduction

30 Uranium is an element that is ubiquitous in rock, soil, and water. It belongs to the actinide series and has the highest atomic weight among all naturally occurring elements. Natural uranium contains 99.274% U-238, 0.72% U-235 and 0.0057% U-234 by weight.<sup>[1]</sup> The United Nation scientific committee on the effect of atomic radiation (UNSCEAR) has estimated that average worldwide uranium concentration  
35 is 2.8 mg/kg in soil, 0.1 ng/m<sup>3</sup> in the ambient air and 3.0 µg/L in seawater. Ground water may also contain uranium with a concentration ranging from 0.1 to 10,000 µg/L.<sup>[2]</sup> On average 2.6 µg of uranium is uptaken in food by a 70 kg adult in Canada per day.<sup>[3]</sup> Around 90 µg of uranium are present in human body from normal intake in  
40 food and air ; approximately 66% is found in the skeleton, 16% in the liver, 8% in the kidneys and 10% in other tissues. Uranium finds its way to the ecosystem not only due to uranium mining and milling industrial activities and uranium processing to nuclear fuel, but also to the extensive use of phosphate fertilizers that contain significant amounts of natural uranium, which contributes to enrich soil and water in this toxic element.<sup>[4]</sup>

45 Natural uranium displays both chemical and radiological toxic effects. However, its radiotoxicity is related to its isotopic composition and is considered rather low compared to its chemical toxicity. Whatever its route of entry, uranium is transferred rapidly into the blood, where it binds to small biological anions (50%), proteins (30%), or erythrocytes (20%).<sup>[5]</sup> Although only 1 to 1.5% of ingested uranium is  
50 absorbed still it can cause severe health problem in long run.<sup>[6]</sup> The main target organs for uranium are kidneys and bones, the accumulation in bones being a long term phenomenon, which influences bone regulation.<sup>[7-8]</sup>

Understanding uranium binding *in vivo* is critical, first to deepen our knowledge of molecular events leading to chemical toxicity, but also to provide new mechanistic information useful for the development of efficient decorporation treatments to be applied in case of intoxication. However, the molecular mechanisms involved in uranium biological storage, transport and elimination are still not well understood. Some important proteins have been identified as uranium high affinity target, still there is very little information about the molecular interactions involved in uranium binding.

This short review will first focus on uranium coordination properties and chelation. What is currently known about uranium binding to proteins will then be detailed. Finally we will show how biomimetic approaches using short peptides shed light on high affinity uranyl binding sites in proteins.

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## 2. Uranium coordination chemistry

Uranium exists in different oxidation states such as U(III), U(IV), U(V) and U(VI), the +IV and +VI oxidation states being the most important in natural environments. However, the most stable form of U in physiological conditions is the uranyl cation ( $\text{UO}_2^{2+}$ ), in which U oxidation state is +VI. This cation has a peculiar geometry with two oxo groups in a linear O-U-O arrangement and an overall +2 charge. As other f-elements of the lanthanide or actinide series, it is classified as a hard Lewis acid with a high affinity for hard oxygen donors in Pearson's classification.<sup>[9]</sup> For this reason uranyl resembles to some extent the hard cation  $\text{Ca}^{2+}$ , which it can replace in bones. However, despite some similarities the coordination properties of  $\text{Ca}^{2+}$  and  $\text{UO}_2^{2+}$  are highly different. Indeed, whereas  $\text{Ca}^{2+}$  is isotropic, the presence of the two oxo groups

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in the  $\text{UO}_2^{2+}$  cation forces the coordination of ligands – four to six – in its equatorial plane perpendicular to the O-U-O axis as shown in Figure 1.

80      Insert Figure 1

In water, hydrolysis of the uranyl cation is significant and begins at about  $\text{pH} = 3$ . In diluted solutions the first hydrolysis product is  $\text{UO}_2(\text{OH})^+$ , at higher concentrations polymeric U(VI) species such as  $(\text{UO}_2)_2(\text{OH})_2^{2+}$ ,  $(\text{UO}_2)_3(\text{OH})_5^+$  and  $(\text{UO}_2)_3(\text{OH})_4^{2+}$  are  
85      predominant in solution. Therefore, studies in water solution in physiological pH-range, have to take into account properly the formation of the hydroxo complexes.

Uranyl forms stable complexes with carbonate, a significant anion *in vivo*. Three monomeric complexes are formed:  $\text{UO}_2(\text{CO}_3)$ ,  $\text{UO}_2(\text{CO}_3)_2^{2-}$ , and  $\text{UO}_2(\text{CO}_3)_3^{4-}$ . The structure of the triscarbonato complex is a typical example of uranyl coordination in  
90      the equatorial plane as shown in Figure 2, where the six equatorial O atoms from the three carbonate anions are approximately planar (Figure 2).<sup>[10]</sup>

Insert Figure 2.

95      The peculiar geometry of the uranyl cation makes its affinity very low for classical polyaminopolycarboxylate ligands such as EDTA and DTPA, which are very efficient chelating agents for spherical cations such as  $\text{Fe}^{3+}$ ,  $\text{Ln}^{3+}$ ,  $\text{Am}^{3+}$  or  $\text{Pu}^{4+}$ .<sup>[5, 11]</sup> The design of ligands specific for uranyl has therefore to take into account its particular geometry and chemical architectures able to organize four to six hard donor groups in

100 the equatorial plane of the cation were elaborated. The most efficient uranophile  
chelating agents are multidentate ligands containing anionic oxygen donors.

Siderophores, which are natural organic compounds complexing  $\text{Fe}^{3+}$  in bacteria,  
have been taken as a source of inspiration to design efficient actinide chelating agents.  
Binding subunits like catecholates, hydroxamates and hydroxypyridinonates have  
105 been assembled in multidentate compounds. Among all the chelating molecules  
recently reviewed,<sup>[12]</sup> the two siderophore-inspired hydroxypyridonate ligands, 3,4,3-  
LI(1,2-HOPO) and 5-LIO(Me-3,2-HOPO) shown in Figure 3,<sup>[11, 13]</sup> revealed the most  
promising for actinide decorporation. Indeed, they were demonstrated to efficiently  
promote Pu(IV) elimination *in vivo*,<sup>[14]</sup> and should also be promising for uranium  
110 decorporation.<sup>[15]</sup> However, more limited effects were observed for both molecules  
when attempting to remove uranium from bones.<sup>[16]</sup> Analogues of desferrithiocin [(S)-  
4,5-dihydro-2-(3-hydroxy-2-pyridinyl)-4-methyl-4-thiazolecarboxylic acid, DFT], a  
natural tridentate iron chelator have also been tested for uranium decorporation in  
rodents. At least one of these compounds was demonstrated to clear uranium globally,  
115 as well as from the kidney and the bone.<sup>[17]</sup>

Insert Figure 3.

Uranyl exhibits a large affinity for phosphate and therefore ligands with  
120 phosphonate binding units were also explored starting with the simplest basic  
compound, 1-hydroxyethane-1,10-diphosphonic acid (HEDP), which is already  
approved for medical use. Indeed, HEDP is used for the treatment of Paget's disease  
and allows slow down the process of bone remodeling that is abnormally excessive in

patients.<sup>[18]</sup> Numerous molecules carrying several biphosphonate functions anchored  
125 on various chemical scaffolds were also developed for specific uranyl binding and  
decorporation.<sup>[19-20]</sup> Remarkable  $\text{UO}_2^{2+}$ -binding abilities were reported for some  
tripodal ligands such as the tren derivatives shown in Figure 3.<sup>[20]</sup> However uranyl  
complexes were demonstrated not to be eliminated in rodents.

### 130 **3. Interaction of uranyl with protein**

Uranyl binding to proteins is also expected to involve hard oxygen donors that are  
mainly found in the side chains of amino acids but also in the protein backbone.  
Carboxylate donors are present in the side-chains of aspartates (Asp) or glutamates  
(Glu) and in the carboxyl-terminus of the peptide chain. The phenolate function  
135 appears in the aromatic amino acid tyrosine (Tyr) and phosphate hard donors belong  
to phosphorous amino acids namely phospho-serine and -threonine (pSer and  
pThr).<sup>[21]</sup> The coordination of the nitrogen atom of the imidazole cycle of histidine has  
also been observed in an engineered protein.<sup>[22]</sup>

Several  $\text{UO}_2^{2+}$  target proteins have been identified and studied over the past  
140 decades.<sup>[23-29]</sup> The two abundant serum proteins, transferrin and albumin, were  
thought to be the major targets of  $\text{UO}_2^{2+}$  in blood during a long time and were  
extensively studied as uranium targets *in vivo*.<sup>[8, 23-24, 30-31]</sup> Structural analysis of the  
uranyl binding site in transferrin indicates significant differences with the  $\text{Fe}^{3+}$   
binding site, the nitrogen donor from the imidazole belonging to a histidine residue  
145 being replaced by an oxygen donor arising from a peptide carbonyl function.<sup>[23]</sup> Over  
the past decades, thanks to the development of powerful analytical tools<sup>[26-29]</sup>  
compatible with the lability of uranyl-protein complexes and also to *in silico*



approaches<sup>[25, 32]</sup>, other significant uranyl target proteins could be identified. Vidaud et al. designed a surface plasmon resonance experiment (SPR) using the immobilization of a specific monoclonal antibody raised against the uranyl complex with 1,10-phenanthroline-2,9-dicarboxylic acid (DCP)<sup>[27, 29]</sup> to screen and select high affinity uranyl-binding proteins. Among those, fetuin and osteopontin are two proteins involved in bone regulation that demonstrate particularly large affinities for uranyl.

Fetuin, despite its low concentration could be one of the major target protein of uranyl in the serum, even considering the significantly larger concentrations of albumin and transferrin.<sup>[33]</sup> Chromatographic and spectroscopic approaches have revealed that this protein can bind three  $\text{UO}_2^{2+}$  at three different binding sites. The sequence of the protein is rich in oxygen-containing residues and although the metal-binding sites are not identified,  $\text{UO}_2^{2+}$  is expected to be mainly bound to the side-chains of aspartates and glutamates.<sup>[33]</sup>

Osteopontin showed an affinity for uranyl similar to fetuin. It is an intrinsically disordered protein mainly found in the organic bone matrix, which is involved in the organo-mineral homeostasis of the bone.<sup>[34]</sup> Osteopontin has many phosphorylation sites and has been demonstrated to complex up to 6  $\text{UO}_2^{2+}$  cations at physiological pH.<sup>[34]</sup> Phosphorylation plays a role in uranyl complexation since the affinity drops significantly (10- to 100-fold) when the protein is dephosphorylated. Interestingly, Extended X-Ray Absorption Fine Structure (EXAFS) experiments performed on a complex of  $\text{UO}_2^{2+}$  with an osteopontin fragment shows that a phosphorylated group is involved in the complexation of the metal ion.<sup>[35]</sup>

More recently, the affinity of these two proteins for uranyl could be measured thanks to Capillary Electrophoresis coupled to Inductively Coupled Plasma Mass

Spectrometry (CE-ICPMS). Fetuin and osteopontin display very similar conditional stability constant at physiological pH ( $10^{11.4-11.5}$ ), although their structures, sequences and expected uranyl binding sites are very different.<sup>[36-37]</sup>

175 In another context, aiming at uranium recovery or extraction from sea water, a uranyl-binding protein has been *de novo* designed by computational screening based on the known scaffolds in the Protein DataBank (PDB). One protein that consists of three  $\alpha$ -helices in a tight bundle demonstrates a particularly high affinity for uranyl ( $10^{12}$ ) with more than 10,000-fold selectivity over  $\text{Ca}^{2+}$ .<sup>[38]</sup> This metalloprotein design  
180 represents an important step toward developing strategies to extract uranium from the ocean.

Despite recent advances in the identification of uranyl-binding proteins, the nature of the binding sites and of the residues involved in coordination are still unknown. Therefore, biomimetic peptides have been proposed as simple and efficient tools to  
185 study uranyl- binding sites in proteins and mimic these large biological molecules.

#### **4. Biomimetic approaches to shed light on uranyl binding sites**

Peptides are straightforward models of proteins that can be used to decipher molecular interactions with selected sequences present in these large biomolecules.  
190 Since peptides are based on amino acid residues, which are building blocks of proteins, they can reproduce the metal binding sites with the same types of donors. Short linear peptide sequences are usually lacking structure with a backbone conformation where the residues are oriented randomly. However the peptide backbone can be organized by introducing constrained amino acid such as the cyclic

195 proline to promote turn formation. Moreover, some secondary structural elements  
such as helices or  $\beta$ -sheets can be promoted in longer or cyclic peptides.

Biomimetic peptides have been exploited to study interactions of proteins with  
endogenous metals as well as toxic ones. Therefore depending on the nature of the  
metal-binding site to model, namely residues involved in metal coordination, but also  
200 location with respect to the whole protein, solvent-exposed loop or highly constrained  
buried site, different types of peptides have been designed and studied for metal  
chelation. Peptide design includes simple linear sequences extracted from the protein  
structure,<sup>[39-45]</sup> short peptides with hairpin turns<sup>[46-47]</sup> and cyclic peptides.<sup>[48-55]</sup>  
Supramolecular peptide assemblies such as three-stranded coiled coils have also been  
205 used to produce functional metalloenzymes.<sup>[56-57]</sup> Importantly, metal-peptide  
interactions can be studied in water close to physiological pH, which is crucial to get  
data relevant to biological systems.

Since  $\text{UO}_2^{2+}$  binding sites have barely been identified in proteins, biomimetic  
approaches are especially attractive to shed light on the binding sites that are  
210 triggering uranium toxicity.

#### *4.1. Linear model peptides*

Linear sequences are usually selected to get mimics of specific fragments of a  
protein. However, they can also be chosen *de novo* to measure the impact of some  
215 specific amino acids or amino acid combination on metal binding. For instance,  
polyaspartate pentapeptides with two or three Asp were studied for uranyl binding as  
aspartate-rich sequences in proteins.<sup>[58]</sup> The thermodynamic parameters of the  
complexation reaction were correlated to structural predictions based on DFT

(Density functional theory) calculations and spectroscopic data. The stability of the  
220 uranyl-peptide complexes was mainly enhanced through enthalpy depending on steric  
constraints. However these experiments were conducted at pH 3.5 to avoid uranyl  
hydrolysis and precipitation. Therefore, it is difficult to extrapolate this behavior to  
physiological conditions.

The role of phosphate coordination attracted a lot of attention since  
225 phosphoproteins such as osteopontin were demonstrated to be relevant uranyl target *in*  
*vivo* and to efficiently coordinate uranyl.<sup>[34, 37]</sup> Ca-binding proteins, like calmodulin,  
were used as starting points to engineer uranyl-binding EF-Hand peptides.<sup>[59-60]</sup>  
Interestingly, the specific phosphorylation of one tyrosine residue in the Ca-binding  
loop of one domain of the protein has been demonstrated to significantly enhance  
230 uranyl binding. The polyphosphorylated sequence pSDEpSDE present in osteopontin  
is thought to be involved in bone mineralization<sup>[61]</sup> as well as in calcium and uranyl  
binding due to both carboxylate and phosphate groups from the side-chains of  
Asp/Glu and pSer, respectively. Hence, the hexapeptide pSDEpSDE was studied for  
its uranyl chelating ability.<sup>[35]</sup> Importantly, the data obtained with this peptide are very  
235 similar to the protein and EXAFS demonstrated the coordination of one phosphate  
group to uranyl. Uranyl-binding to the bovine milk protein  $\beta$ -casein was compared to  
selected model peptides representing the amino acid sequence 13–16 of  $\beta$ -casein. The  
phosphoryl-containing sequences form uranyl complexes of significantly higher  
stability than the structure-analog phosphoryl-free sequences.<sup>[62]</sup>

240 All these studies point to the decisive role of phosphate in uranyl coordination with  
proteins. However short linear peptides extracted from the protein sequence cannot  
mimic the overall contribution of the protein if residues far apart in the sequence

contribute to the metal binding site. Hence, to estimate and possibly quantify amino acids' contribution to uranyl binding in proteins, another approach exploiting cyclic peptides has been proposed in our team during the past few years, our ultimate objective being to propose relevant structures for uranyl binding sites found in proteins.

#### 4.2. Cyclic model peptides

Peptides with constraining structural elements able to pre-orient metal-binding groups to the metal center show higher affinity for metal cations than random-coil equivalents, if the design is adapted to the metal properties, i.e. nature of donor atoms and coordination geometry. Indeed, this strategy pre-organizes to some extent the peptide for metal binding, thereby minimizing the structural reorganization needed for complexation.

Therefore we looked at peptide structures that could orient at least four amino acid side-chains bearing hard oxygen donors to the equatorial plane of the dioxo uranyl cation, to form complexes, which could be considered as models of the uranyl bound form in proteins. Previous studies in the literature demonstrated that cyclic decapeptides with two Pro-Gly  $\beta$ -turn inducers display a controlled conformation with a  $\beta$ -sheet structure that defines two distinct faces, with the "upper" face containing four amino acid side-chains oriented in the same direction (Figure 4, inset).<sup>[63-65]</sup>

Insert Figure 4.

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Our group adapted this design to hard metal coordination in a first series of compounds named **pS<sub>0</sub>** by introducing acidic residues, Asp and Glu, in positions 1, 3, 6 and 8 to promote metal coordination on the upper face of the peptide scaffold.<sup>[53, 66]</sup> The introduction of a tryptophan residue in position 7 with the indole group oriented on the lower face allowed us to measure the equilibrium constant thanks to the indole fluorescence quenching upon uranyl complex formation. To be able to appropriately compare the equilibrium constants for uranyl complexes' formation, within the peptide series and also with proteins, we designed a competition experiment from pH 6 to pH 7.4, using iminodiacetic acid, which avoids uranyl hydrolysis. This first series of cyclic peptides was demonstrated to form 1:1 uranyl-peptide complexes with larger stability at physiological pH ( $\log K^{\text{pH } 6} = 8.2$ ) than the corresponding linear peptides. The cyclic decapeptide with four Glu building blocks showed the largest equilibrium constant with respect to Asp-containing peptides due to the stronger Lewis basicity of the carboxylate side chain of the Glu residues and probably to the larger flexibility of the latter side chain. Besides, the  $\beta$ -sheet structure and the presence of four coordinating amino acids in position 1, 3, 6 and 8 were demonstrated to be key parameters for large affinity.

The influence of phosphorylation was then investigated in successive generations of peptides with one to four phosphoserines (pSer) depicted in Figure 4. The building block pSer was chosen as the phosphorylated amino acid since the majority of the phosphorylated sites in human osteopontin are serine (Ser) residues alongside a few threonine (Thr) residues. Starting with the prototype peptide sequence **pS<sub>0</sub>** - that coordinates  $\text{UO}_2^{2+}$  with four carboxylate groups from glutamate residues<sup>[66]</sup> - we gradually replaced acidic residues by pSer leading to peptides with one pSer<sup>[67]</sup> such

290 as **pS<sub>1</sub>**, two pSer<sup>[68]</sup> such as **pS<sub>18</sub>**, three pSer in **pS<sub>168</sub>** and four pSer in **pS<sub>1368</sub>**.<sup>[69]</sup> The density of phosphate residues has a crucial influence on UO<sub>2</sub><sup>2+</sup> complex speciation and stability. First, whereas peptides **pS<sub>0</sub>**, **pS<sub>1</sub>** and **pS<sub>18</sub>** form exclusively 1:1 (UO<sub>2</sub>)<sub>2</sub>P complexes, peptides containing three and four pSer, **pS<sub>168</sub>** and **pS<sub>1368</sub>** both trap two UO<sub>2</sub><sup>2+</sup> ions in bimetallic complexes (UO<sub>2</sub>)<sub>2</sub>P.<sup>[69]</sup>

295 Interestingly, the equilibrium constants for the formation of the monometallic complexes at physiological pH,  $\log\beta_{11}^{\text{pH } 7.4}$ , increase linearly with the number of phosphate residues with an enhancement of 0.8 orders of magnitude in the constant for each phosphate group added (See values for the  $\log\beta_{11}^{\text{pH } 7.4}$  in Figure 4). Importantly, the peptide with four phosphate residues, **pS<sub>1368</sub>** displays an affinity  
300 constant for UO<sub>2</sub><sup>2+</sup> equivalent to that reported for the first binding site of the phosphoprotein osteopontin at physiological pH: 10<sup>11.3</sup> for **pS<sub>1368</sub>** vs 10<sup>11.5</sup> for osteopontin.<sup>[37]</sup> This phosphate-rich peptide is therefore proposed as a relevant model of UO<sub>2</sub><sup>2+</sup> coordination in the UO<sub>2</sub><sup>2+</sup>-osteopontin complex. Indeed the apo-protein is known to have no specific structure, however its backbone is flexible-enough to  
305 organize four phosphate coordinating residues from various positions in the protein sequence to produce an optimal arrangement in the equatorial plane of UO<sub>2</sub><sup>2+</sup>.

The series of cyclic peptides was also investigated with Ca<sup>2+</sup>, an important endogenous cation competing for UO<sub>2</sub><sup>2+</sup> in vivo. The preference of Ca<sup>2+</sup> for acidic sequences with respect to phosphate ones was evidenced by comparing the  
310 equilibrium constants which are typically 10<sup>4</sup> with **pS<sub>0</sub>** and 10<sup>2</sup> with **pS<sub>1368</sub>**. Therefore phosphate-rich cyclopeptides are highly selective for the dioxo UO<sub>2</sub><sup>2+</sup> cation, an important feature for the development of decorporation agents.

## 5. Conclusion

315 Uranium is a toxic metal exhibiting both radiological and chemical toxicity. Its relevant form *in vivo* is the linear dioxo cation uranyl  $\text{UO}_2^{2+}$ , which is a hard acid with a large affinity for oxygen donors. Its specific geometry promotes coordination of ligands in the equatorial plane perpendicular to the O-U-O axis. Several target proteins of uranyl have been identified such as albumin, transferrin and the high  
320 affinity fetuin and osteopontin, which are both involved in bone regulation. However the binding sites of uranyl are still not known although this molecular information is a key-parameter to understand toxicity mechanisms and design efficient decorporation agents. Biomimetic approaches using model peptides have been develop to shed light on coordination of uranyl *in vivo* and to identify its binding sites. Cyclic peptides,  
325 which are able to orient four amino acid side-chains in the equatorial plane of uranyl were de novo designed and the complexes, formed at physiological pH, mimic the bound-form of the uranyl protein complexes. Thanks to this approach, a tetraphosphate site that provides an affinity similar to the one measured with osteopontin, is now proposed for uranyl binding to phosphoprotein. Interestingly,  
330 phosphate-rich cyclic peptides are highly selective for uranyl with respect to calcium, a major competing cation for binding to phosphoproteins like osteopontin. The coordination of other biological metal cations such as Cu(II), Zn(II), Fe(II) or Fe(III) should also be investigated in the future to determine the overall selectivity of such peptides, an important feature for the development of decorporation agent based on  
335 phosphopeptides.

## Conflicts of Interest



The authors declare no conflicts of interest.

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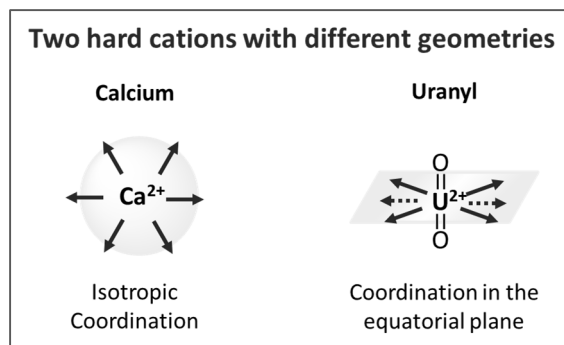
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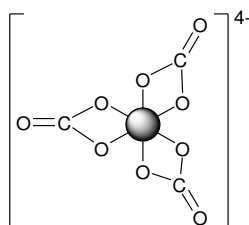
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## Figures and captions



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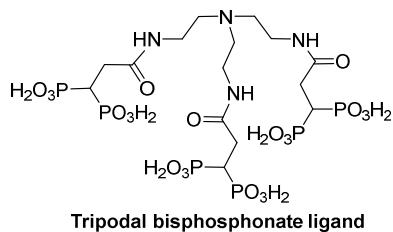
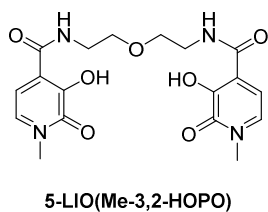
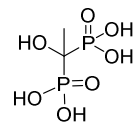
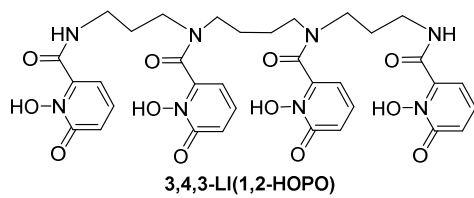
**Figure 1.** Coordination geometry of uranyl compared to calcium.



490 **Figure 2.** Top view of equatorial uranyl coordination in the  $\text{UO}_2(\text{CO}_3)_3^{4-}$  complex.

The two bowl represents the uranyl cation with the two oxo oxygen atoms perpendicular to the figure.

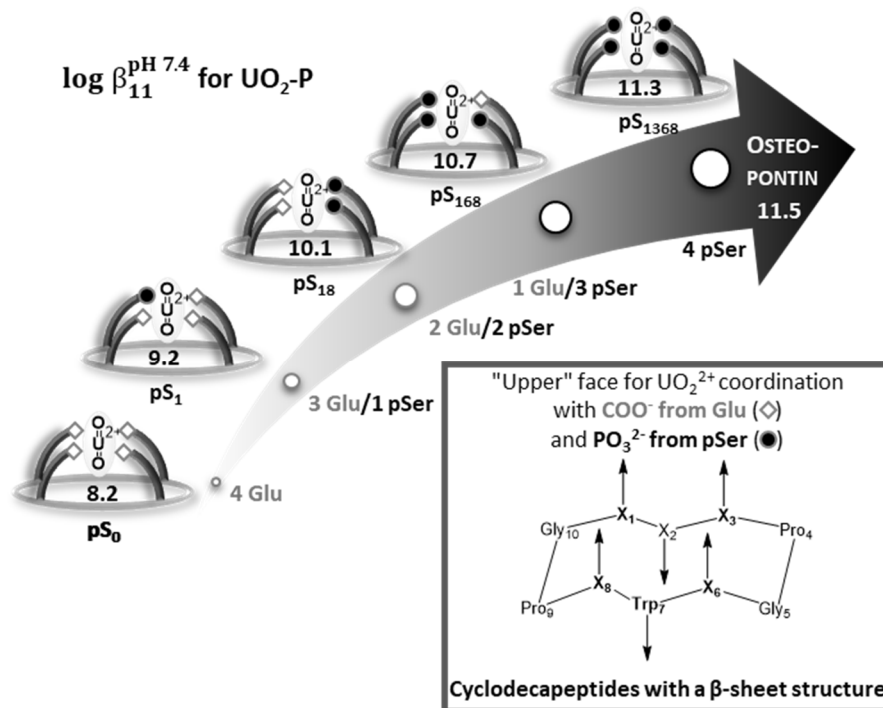




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**Figure 3.** Some classical uranyl complexing molecules

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**Figure 4.** Conditional stability constants for the formation of uranyl complexes at pH 7.4 with the series of biomimetic cyclic decapeptides increase significantly with the number of pSer residues to reach the value measured for osteopontin. Inset: Design of the peptides.

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## Graphical Abstract :

Considering uranium toxicity and its industrial and agricultural use, it is crucial to  
510 understanding the molecular mechanisms responsible for uranium toxicity.  
Biomimetic approaches with model peptides have therefore been developed to shed  
light on uranyl binding sites in proteins that are barely known and to identify its  
coordination.

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