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Review

Uranium(VI) bio-coordination chemistry from biochemical, solution and protein structural data

J. David Van Horn *, Huan Huang

Department of Chemistry, University of Missouri-Kansas City, 5110 Rockhill Rd., Kansas City, MO 64110-2446, USA

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Contents

Abstract

The biocoordination chemistry of the uranyl cation (uranium(VI), $[UO_2]^{2+}$) is assessed utilizing data from the Protein Databank, solution thermodynamic data and biochemical experiments. Uranyl cation is effectively transported in the bloodstream through interactions with carbonate and protein ligands. Under physiologic conditions, carboxylate donors from biological ligands to uranyl are expected to compete favorably against carbonate in the inner sphere of the tris-carbonato uranyl complex. Carboxylate donors from aspartate, glutamate or the carboxyl terminus in proteins make up the majority of inner-sphere interactions with uranyl in protein structures that include this cation. Other significant interactions include amide oxygen donors in the inner-sphere, and H-bonding to uranyl oxo ligands by amide N–H donors. These inner- and outer-sphere interactions are also present in structures of uranyl–amino acid complexes, and in other uranyl complexes with small molecules. In the solution state, uranyl–carboxylate interactions have been measured with thermodynamic values for stepwise conditional formation constants on the order of $\log K \approx 2$–5, similar to uranyl–acetate interactions. In addition to inner-sphere coordination, H-bonding and charge effects, as well as local chemical environmental conditions, play significant roles in the outer sphere; these interactions are somewhat less characterized in the literature.

Keywords: Uranium(VI) coordination chemistry; Uranyl cation; Solution thermodynamics; Amino acids; Peptides; Proteins

* Corresponding author. Tel.: +1 816 235 6327; fax: +1 816 235 2290.
E-mail address: vanhornd@umkc.edu (J.D. Van Horn).

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1. Introduction

1.1. General

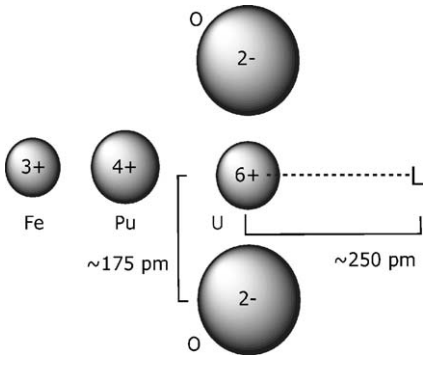
In one sense, the biocoordination chemistry of the actinides has been focused, and rightly so, on the sequestering and decorporation of these radioactive heavy metals [1–6]. As such, there has been successful research applied to the problem of decorporation agents for the actinides, and much of the attention in this area has focused on the spherical An^{4+} actinide cations, particularly plutonium(IV) [1]. Uranium(VI) as the dioxouranium(VI) (uranyl, $[UO_2]^{2+}$) cation exhibits less of an acute or chronic toxicological and radiological health risk and thus has not been studied to the extent of the other actinides [4]. A successful strategy in discovering An(IV) decorporation agents was in identifying their similarity to iron(III) and the observation that Pu(IV) effectively 'hijacks' the prevalent iron(III) transport biochemistry in biological systems [1–8]. Scheme 1 compares the charges and approximate ionic radii of Fe(III) and Pu(IV) with an ionic model for the dioxouranium(VI) cation (charge/ionic radius: Fe(III) = 4.65; Pu(IV) = 4.65; U(VI) = 8.22; adapted from Shannon [9] and Cotton [10]). The uranium-oxo bond distance suggests more than double bond character and the effective charge on U(VI) in the uranyl cation has been estimated to be +3 [11].

The unique structure of the uranyl cation, a linear dioxocation with an overall +2 charge prevents the use of effective chelating ligands that target spherical cations in three dimensions (e.g. EDTA, DTPA, etc.). Designed complexants or ligands for the uranyl cation must account for the equatorial coordination sphere available in the uranyl cation and must be able to be arranged on this equatorial plane for effective coordination.

Reviews concerning uranyl biocoordination chemistry are scarce, although some of this chemistry has been described as part of other reviews on actinide chemistry [1,12] or on general uranium coordination chemistry [13].

1.2. Scope

The scope of this review is the structural coordination chemistry and quantitative thermodynamics of the uranyl cation with biological ligands. Included is a survey of the literature surrounding uranyl biochemistry that covers the general aspects of its nephrotoxicity. The treatment is limited but incorporates the literature investigating quantitative and structural aspects of specific molecular interactions of uranyl cation with biological ligands. Inorganic phosphate and derivatives are left out of this survey, but constitute an important class of interactions under certain physiologic or environmental conditions. Chronic mechanisms of uranyl toxicity may include phosphate interactions [14].



Scheme 1.

1.3. General mechanisms of uranium toxicity

The deleterious health effects of uranium poisoning arise from biochemical interactions in vivo, and not usually via radiological effects [15]. Insoluble forms of U exhibit the least toxicity and are excreted via the digestive tract, while soluble forms of U(IV) and U(VI) do exhibit interactions with biological ligands and toxicological effects. The uranyl cation is the predominant form in vivo and is, in fact, a classic nephrotoxin (i.e. an agent that causes kidney damage and failure) used experimentally to investigate renal injury and kidney lesions [16].

It has been known since early in the 20th century that the uranyl cation binds to protein in the serum; its tissue distribution is affected by bicarbonate, and excess UO_2 has deleterious effects on the nephrons in the kidney [17,18]. Modern research studies into U toxicity and chelators for U decorporation focus on such classic chelating agents as Tiron and DTPA [2–4,6,19]. In addition, there is some study on novel U decorporation agents to ameliorate the effects of acute U poisoning [8,20,21]. However, it was noted recently that, ". . . no effective chelating agent is available for uranium, which should be considered a matter for some concern" [4].

A review of the literature of the toxicological effects of U (and Th, Pu, etc.) generally leads back to reviews on metal toxicity and chemistry [13,15], and they point back to the primary literature on U toxicity emanating from 'post-Manhattan Project' research [22,23]. This work identified various processes, distribution and general toxicity of uranyl species in vivo [24]. A current picture for bloodstream uranium transport is presented in Fig. 1. Generally, uranyl cation is partitioned in the serum into the uranyl bis- and tris-carbonate complexes and UO_2:protein:carbonate complexes with human serum albumin (HSA, the most abundant serum protein), transferrin (Tf, the iron transport protein) or other protein (vide infra). Of the two fractions, the uranyl–carbonate complexes are more diffusible into tissue (liver, kidneys, bones, etc.) while the portion bound to protein is the portion cleared from the serum via transport to and elimination from the kidneys.

One mechanism of uranium toxicity may relate to the disruption of the first step in glycolysis by uranyl displacing magnesium in the enzyme, hexokinase [24]. Once at the kidney, other molecular actions of uranyl appear to be the disruption of the *para*-aminohippurate transporter system [25] or damage to peritubular cell membrane [26,27]; uranyl–citrate complexes have been implicated as the cytotoxic form of U in studies with cells that model the epithelium of rat kidney [28]. Finally, a recent in vitro study reported that uranyl cation, acting as a hard Lewis acid, also causes hydrolysis reactions in the backbone of the DNA molecule [14].

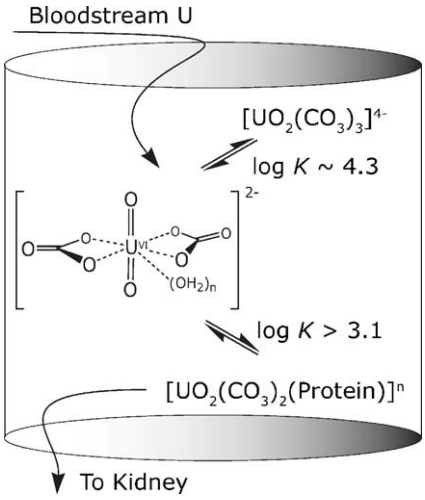


Fig. 1. Expected uranyl coordination in the bloodstream. Bis- and tris-carbonate species should predominate, but peptide or protein ligands can compete, allowing facile transport to kidney.

1.4. Quantitative uranyl–peptide and protein interactions

In serum conditions, both bis- and tris-carbonato uranyl species are expected to predominate and other inorganic interactions can be estimated from models of the inorganic speciation of uranyl in various biological fluids [29,30]. Quantitative studies on the thermodynamic stability of uranyl and other actinyl ions with proteins include uranyl–Tf [31,32] and neptunyl–Tf binding [33]. Using time-resolved laser-induced fluorescence methods, binding constants for U(VI) and Np(V) to the apo form of Tf, were reported to be $\log K \sim 16$ and $\log K < 4$, respectively, with a stoichiometry of 2:1::UO_2:Tf. The proposed complex and formation constant seem reasonable for the uranyl–Tf system in the absence of Fe(III), but further work needs to be done to establish the significance of such interactions in biological systems.

Uranyl coordination to blood plasma protein and cells has been studied in uranium miners in Hungary [34,35]; the report indicates a fairly strong interaction ($\log K_f \sim 10$–11) for uranyl-"albumin" complexes, and for uranyl association with erythrocytes (red blood cells) ($\log K_f \sim 9$). The researchers also report uranyl–amino acid association constants (vide infra) and formation constants for uranyl–DNA or –RNA complexation ($\log K_f \sim 9.7$), although without detailed experimental description.

A recent study with short, model peptides indicates that non-specific interactions between uranyl and peptide carboxylate ligands leads to ternary uranyl–peptide–carbonato species predominating at physiological pH [30]. Since ligand exchange kinetics with the uranyl cation are relatively fast, thermodynamic stability of uranyl complexes provides a reasonable basis for the molecular interactions present in the mechanism of uranyl transport in the bloodstream. The report concludes that peptide ligands with moderate affinity to uranyl ($\log K \sim 3.1$) can effectively compete with a carbonate ligand to produce ternary uranyl bis-carbonato peptide complexes. The magnitude of these "non-specific" uranyl–protein interactions is important; protein structural data (vide infra) indicate that uranyl does bind with some selectivity in protein sites, suggesting that the chemical environment seen by uranyl will affect binding and aggregation. Whether this translates to the solution phase remains to be seen, since the kinetics of ligand exchange on uranyl are fairly rapid; one can anticipate that uranyl–protein interactions will exhibit larger association constants than those for model peptides.

This picture of non-specific binding and transport of uranyl by a variety of proteins in vivo was recently corroborated by researchers screening human serum proteins for uranyl binding [36]. In this study, multidimensional chromatography coupled with a proteomic analysis, time resolved fluorescence, and mass spectrometry identified at least ten proteins with affinity for uranyl. The study specifically identified ceruloplasmin, hemopexin and two other proteins as binding uranyl with >1:1 stoichiometry after passing the metal–protein complexes through a desalting column. Also of note is the lack of a trend for uranyl binding with respect to relative protein concentration in serum or protein p*I*.

2. Structural data

2.1. Protein structures containing uranium atoms

Uranyl salts are used in protein crystallographic studies to provide a heavy atom replacement for refining protein structural data [37,38]. As such, crystal structures containing uranium atoms provide an appraisal of general aspects of uranyl bio-coordination chemistry. While used in phasing structural data, refined structures containing uranyl have not regularly been deposited into the protein data bank, resulting in very few examples of high-resolution structures and only a small overall number of structures containing U atoms. Since a protein structure resolved to 2.0 Å is about equal to the quality of a small molecule structure with weighted *R* factor around 0.20 [39], protein data sometimes presents difficulties in interpretation. Often, one or both oxo ligands may not be refined; in other cases, bond distances or geometries may not correspond to what is known from the structural coordination chemistry of uranium.

Table 1 presents a summary of entries containing uranium atoms from the RSCB Protein Data Bank [40–42]; a spreadsheet containing uranyl–protein data utilized in this review is included as Supplementary data. The coordination donors present include aspartyl and glutamyl carboxylate, tyrosinate and amide oxygen donors. Some lower resolution structures imply imidazole and amino donors, but these results are somewhat ambiguous in light of uranium coordination chemistry in solution and from structural characterization. The highest resolution structures include refinement of the oxo ligands on the uranium(VI) metal center. Other data refines the oxo ligands but at distances inconsistent (e.g. 1.9 Å) with the structure of the uranyl cation. Finally, the majority of structures have located and refined metal atoms but do not include oxo ligands.

A few representative structures provide an overview of expected coordination to uranyl in protein structures. An example [43] of a mononuclear site at high-resolution (1.6 Å), containing aspartyl and amide-O atom donors, is presented in Fig. 2;

Table 1
Summary of protein structure entries which include "uranium" or "uranyl" (data taken from the Protein Databank)

PDB code	Resolution (Å)	No. of structural U atoms	Oxo ligands refined	Reference
1EFQ	**1.6**	**1**	**Y**	[43]
1HUU	2.0	0		[44]
1AA0	2.2	0		[45]
1OLA	2.1	2		[46]
1FNB	1.7	0		[47]
1NCG	1.9	0		[48]
1NCH	2.1	0		[48]
1NCI	**1.9**	**1**	**Y**	[48]
1EDG	1.6	0		[49]
1OLC	**2.1**	**8**	**U1–U5**	[50]
2OLB	1.4	8		[50]
1ANV	2.7	4		[51]
1JET	1.2	8		[52]
1JEU	1.25	8		[52]
1JEV	1.3	8		[52]
1B46	1.8	8		[53]
1B4Z	1.75	8		[53]
2RKM	1.8	8		[53]
1AUQ	2.3	1		[54]
1NCJ	3.4	1		[55]
1CT9	**2.0**	**16**	**U1102; U1122 (only 1 oxo)**	[56]
1BZO	2.1	2		[57]
1B3F	1.8	8		[58]
1B3G, 1B3L, 1B05 and 10 others	1.75–2.3	Varies, 1, 2, 8, 9 or 11		[58]
1B0H	1.9	8		[59]
1B1H-1B7H	1.8–2.0	8		[59]
1FE4	**1.75**	**1**	**Y**	[60]
1MVW	3.4	0		[61]
1O1A–1O1G; 1O18-1O19	All 3.4	0		[61]
1T9H	**1.6**	**8**	**Y**	[62]
1T0U	2.2	0		[63]
1UYJ	2.6	12		[64]

Entries in boldface type indicate refined U═O distances.

a solvent water molecule has also been refined at an appropriate distance for inner-sphere coordination. The uranyl cation is bound in a turn structure with a sequence of DKPGQPP (contacts underlined); the loop also contains a normal O···H–N H-bond (Lys to Gln) that may be classified as a Type II β-turn. The oxo ligands have been refined with unusually long U–O distances (1.858 and 1.861 Å); the contacts with the carboxylato donor of the Asp side chain are not symmetric (2.406 and 2.629 Å), which agrees with small molecule structures (vide infra).

Protein structures containing uranyl exhibit a variety of H-bond interactions relevant to uranyl coordination; some of these are illustrated in Fig. 3. In the high-resolution structure (1NCI, 1.9 Å [48]) that this data is taken from, the oxo ligands have been refined to expected U═O distances (1.743 and 1.739 Å), and the carboxylate donors are coordinated in a monodentate fashion. This coordination site exhibits the major H-bonding motifs expected in uranyl biocoordination. First, oxo to solvent: here, a solvent molecule (H_2O) is located 3.579 Å from the oxo ligand. Solvent can also be H-bonded to additional solvent, or to protein donors or acceptors (not illustrated). Second, N–H amide donors: the distances in this site suggest two amide N atoms are close enough (3.323 and 3.597 Å) to act as H-bond donors, but the lower one appears to have an incorrect geometry for effective H-bonding. Finally, amide NH on side chains: this site contains an amide NH_2 from an asparagine side chain located 3.493 Å from the oxo ligand.

H-bonding interactions to uranyl oxo ligands are ubiquitous across protein structures that contain uranyl. Even in structures that do not refine the oxo ligand, H-bond donors are often present at appropriate distance and are geometrically directed to the position in space where the oxo ligand is anticipated.

A lower resolution structure (2.0 Å) with representative tyrosinate and phosphate ligands is illustrated in Scheme 2 [56]. The bond distances and geometrical arrangements of the uranyl coordination spheres are dissatisfying in this structure, and only one oxo ligand is refined on the U atom illustrated, but the structure suggests that further examples will be found including the coordination of cofactors and phenolate ligands to uranyl in biological systems.

Given the conditions encountered in biological systems, uranyl hydrolysis and aggregation is expected to be encountered [12]. In this regard, the structure of an adenovirus DNA-binding protein (1ANV, 2.7 Å) is of particular interest as it includes a trinuclear uranium cluster [51]. Unfortunately, oxo and bridging ligands are not refined in the cluster that lies in an acidic pocket at the interface of three protein subunits in the structure. However, as Scheme 3 illustrates, the structure implies a bridging side chain carboxylate donor; other bridging (hydroxo or

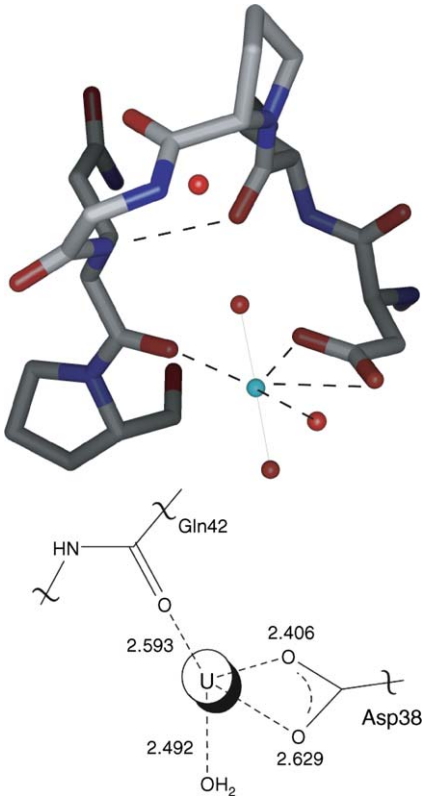


Fig. 2. Peptide turn structure (PDB: 1EFQ) coordinated to uranyl with amide-O and aspartate side chain coordination. The lower figure is a Newman projection through the oxo ligands and includes inner-sphere coordination distances and the approximate geometry of the ligands around the uranyl cation.

oxo) ligands, and the U-oxo ligands should be expected in such an arrangement even if not refined (vide infra).

Finally, the most recent structure deposited into the PDB with structural uranyl units contains a multinuclear array with bridging acetate, hydroxo and carboxylato donors [62]. This 1.6 Å structure (PDB: 1T9H) was solved by using uranyl and platinum heavy-atom derivatives, contains well-defined uranyl units and coordination, and presents the strongest evidence for histidine imidazole coordination to uranyl (Fig. 4). In this structure, there are three histidine-U cluster intermolecular contacts between a His_6-tag on an adjacent protein molecule in the crystal lattice and the cluster of uranyl cations in the cleft of the protein. The con-

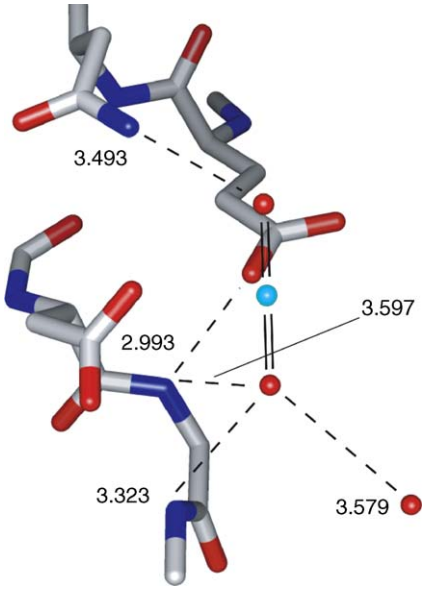


Fig. 3. An illustration (1NCI) of H-bonding schemes in uranyl protein structures. Present are oxo-solvent, oxo-backbone amide and oxo amide side chain interactions with appropriate geometrical and distance constraints.

TYR 357
{U=O, 1.941}
O
2.723
O
O
U
O
P
O
Adenosine
O
O
2.841
2.462
ASP 384

Scheme 2.

ASP 429
2.819
U
O
3.376
2.686
4.096
O
2.396
U
U
2.255
O
3.586
2.882
O
GLU 225

Scheme 3.

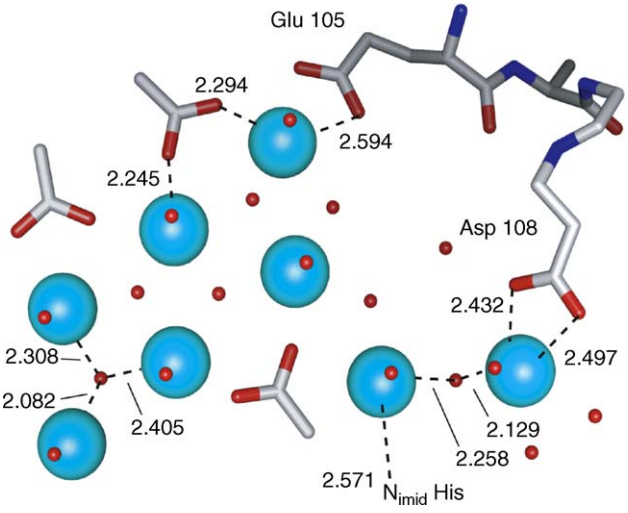


Fig. 4. Multinuclear cluster in a cleft of a heavy-atom derivative of the *yloQ* protein (PDB: 1T9H, 1.6 Å). The cluster provides examples of oxo, acetato, hydroxo bridging moieties, and is anchored to the protein with two bidentate side chain carboxylato donors; view from top, U atoms are large spheres. Select bond distances in Å.

tacts are at 2.571 Å (N_{imid}–U), 4.138 Å and 5.943 Å (NH_{imid}–U) along with other carboxylato and H-bonding interactions. The first of the imidazole-uranium contacts is *within* expected coordination distance to uranyl and has a favorable geometry for coordination to the uranyl equatorial plane (Fig. 4). The other two contacts lie below the plane of the cluster illustrated in Fig. 4 and exhibit U···N distances expected for H-bonding contacts to the oxo ligands of the uranyl unit rather than inner-sphere coordination. As indicated above and refined in the protein structure, the first contact is with the imidazole π (N-δ^1) atom (imine), while the other two contacts are with the imidazole τ (N-ε^2) atom ("NH").

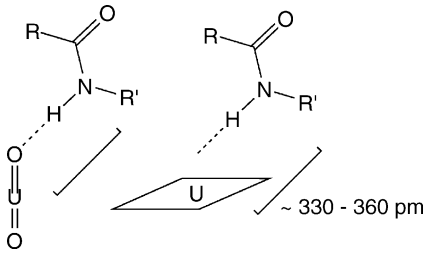
2.2. Sequence information

The data in the PDB also lends itself to analysis, using the 56 entries that include uranium, of sequence information surrounding the uranyl cation binding sites. Acidic amino acids (Asp and Glu) or a free carboxylate terminus are indicated as binding uranium in most of the reported crystal structures. A compilation of the relevant peptide sequences around uranyl binding sites is shown in Table 2. As an aside, sites for uranyl include donors close in sequence in structures including loops or turns, or far apart in a given sequence in coordination site that include donors from different chains, subunits or molecules. As expected, carboxylate donors (D = Asp, E = Glu) predominate with aspartate represented about 50% more often than glutamate. The other donors represented are a handful of the other types of amino acids available for coordination.

Table 2
Unique sequences around uranyl binding sites derived from the PDB (the selection includes the central binding residue, and generally ±5 amino acid residues)

PDB code	Sequence
1CT9	.ALHMY**D**CARANK
1UYJ	AVMGD**E**LIVKV
1B4Z	DKPLTF**D**LLYNT.
1ANV	EDLDA**D**LISDK
1CT9	.EETVR**K**LLALHM
1CT9	EVFGG**Y**LYFHK
1BZO	FPWTD**D**NHKGD
1OLA	GAKLV**E**PEWFK
1QKA	GAYKL**K**NWVVN
1CT9	GEGSD**E**VFGGY
1ANV	GGPNC**D**FKISA
1FE4	GGVKY**D**IDLPN
1B1H	GVQLA**D**KQTLV
1OLA	HQGTF**D**VARAG
1ANV	KEHVI**E**MDVTS
1B7H	KPLTF**D**LLYNT
1UYJ	KSDLN**E**DGTIN
1QKA	KTVIN**Q**VTYLP
1ANV	KTWLN**E**EHRGL
1EFQ	LAWYQ**D**KPGQP
1CT9	LSGGL**D**SSIIS
1OLC[a]	LYIIK**H**_____
1OLC	LYNTS**D**LHKKL
1JET	NNMPI**E**LFQKL
1UYJ	NNPKV**E**LDGEP
1NCI	PINLP**E**NSRGP
1EFQ	QDKPG**Q**PPKLL
1BZO	SCASS**E**KDGKV
1CT9	SGEGS**D**EVFGG
1B51	TPPYT**D**GAKLV
1UYJ	TVPFN**E**TGVSL
1AUQ	VAVVEY**H**DGS**H**AYIGL
1NCJ[a]	VITVT**D**_____
1NCI	VTKPL**D**RELIA
1CT9	YGVLL**S**GGLDS

[a] Binding at the carboxyl-terminus.



Scheme 4.

An evaluation of the determinant sequences around uranyl binding sites shows no sequence specificity for binding. This may have been anticipated given the nonspecific nature expected for uranyl cation with protein structures from the solution data mentioned above and they suggest that specificity is dictated by the environment surrounding the uranyl binding site and outer sphere interactions. Of note are critical H-bonding interactions between uranyl oxo ligands and amide N–H main chain donors (vide supra). As mentioned, beyond a central acidic residue, there is no obvious sequence consensus for uranyl binding sites. However, these data are a random collection of entries posted to the PDB, and do not necessarily reflect the expected key players in actinyl transport in vivo.

Even in structures without oxo ligands, refined H-bond donors are located at the appropriate distance and geometry suitable for amide H-bond donors that would be expected to be participating in coordinating the uranyl atom to the protein center (Scheme 4). This status suggests that specificity in uranyl binding is dependent on protein binding site environments rather than coordination motifs and that second sphere interactions, whether they be charge–charge, hydrogen bonding, etc., play a significant role in determining where uranyl cation will bind in a particular protein.

Given the low priority of uranium biochemistry, protein crystallographers have not studied structures that may be important from a uranyl toxicological or transport regime. As a leading candidate for uranyl transport, serum albumin as well as other serum and transport proteins such as transferrin, hemopexin and ceruloplasmin [36], are key proteins of interest for future studies with included uranium. Other analyses, solved structures and additional solution thermodynamic data may allow the prediction of uranium binding sites in protein structures in the near future.

2.3. Uranyl–amino acid structural data

The generally low thermodynamic stability of the uranyl carboxylate interactions and propensity for uranyl hydrolysis

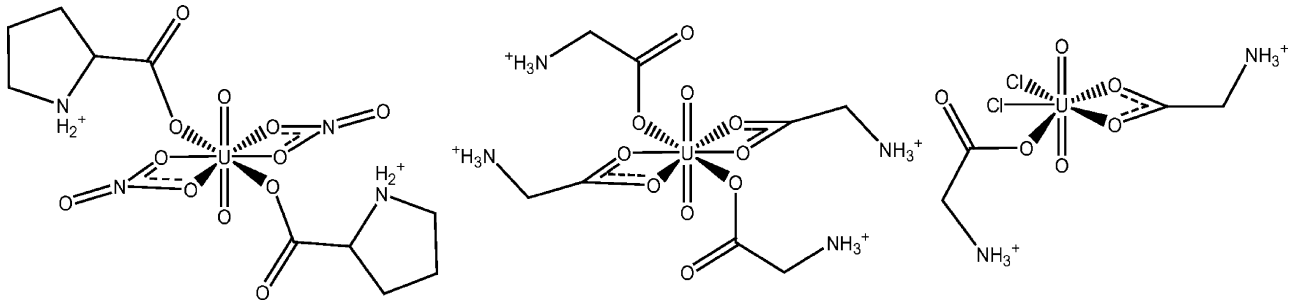


Fig. 5. Uranyl amino acid structures with typical mono- and bi-dentate carboxylato ligands (proline, left; glycine, center and right).

appears to inhibit the structural determination of many amino acid complexes. Of the twenty common amino acids, there are only uranyl structures with two of those, proline and glycine [65–67]. The structure with proline exhibits monodentate coordination to the carboxylate while the two examples of uranyl glycinato complexes both exhibit mono- and bidentate coordination by the carboxylate donors to the uranyl core (Fig. 5). Other uranyl–amino acid complexes with γ-aminobutanoic acid [68] and iminodiacetic acid (IDA) are reported in literature [69,70]. Of the two examples with IDA, one is a mononuclear complex and the other is a dinuclear uranyl complex with bridging hydroxo ligands.

The structure with proline is hexacoordinate (not counting oxo ligands) and exhibits monodentate coordination from the prolyl carboxylate donor, with nitrate ligands completing the coordination sphere around the uranyl cation. The overall complex is neutral, with the negative charges balanced by the secondary ammonium group present on the proline ligand. The crystal is optically active and triclinic, with a space group of $P1$; each unit cell contains one $[UO_2(Pro)_2(NO_3)_2]$ formula composition.

A comparison of the uranyl glycinato structures reveals a number of differences between the two structures, but both contain mono- and bidentate carboxylate donors. The bis-glycinatodichloro uranyl complex is pentacoordinate (*sans* oxo), and exhibits a distorted pentagonal bipyramidyl geometry. The bis complex is neutral overall with the extra chloride ligands balanced by the positive ammonium groups of the glycinate ligands; the crystal system is monoclinic, in the $P2_1/c$ space group. The coordination of the bidentate carboxylate is not symmetric, with a difference of about 0.03 Å in the carboxylate O–U distances (2.516(5) Å versus 2.487(5) Å). This asymmetry is comparable to that seen in other uranyl carboxylate complexes and in uranyl protein structures.

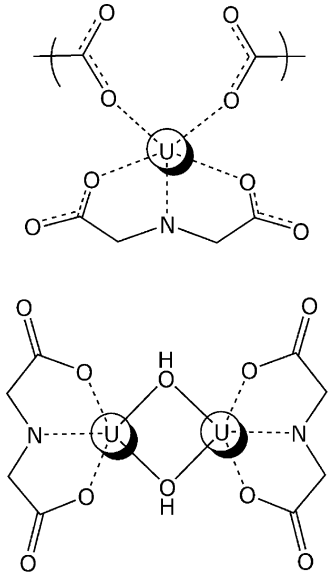
The tetrakis-glycinato structure is hexacoordinate with an almost symmetrical hexagonal bipyramidyl coordination sphere with alternating bidentate and monodentate carboxylato donors that define an equatorial plane around uranyl. The tetrakis complex has overall positive charge due to the zwitterionic nature of the glycine ligands, and is found in the space group, $P\bar{1}$. The unit cell of the crystal contains two cations; each exhibits asymmetric bidentate carboxylate coordination. There are also intermolecular H-bonding contacts (N···O distance ∼2.79 Å) between ammonium groups and the uncoordinated O atom of the monodentate glycine ligands.

Related to these structures is a tris-carboxylato uranyl complex with bidentate γ-aminobutanoic acid ligands [68]. This structure crystallizes in a triclinic crystal, is found in the $P1$ space group, and also has two cations per unit cell. The α-amino acid ligands in this complex are arranged around the uranyl unit in a distorted hexagonal arrangement with the bidentate carboxylato groups coordinated asymmetrically with U–O distances ranging from 2.45 to 2.48 Å. It appears that the asymmetry in bidentate carboxylate coordination is greater in protein structures ($\Delta \approx 0.2$–0.3 Å) than in those structures surveyed here ($\Delta \approx 0.03$–0.04 Å), but this may be related to the resolution of the different structures.

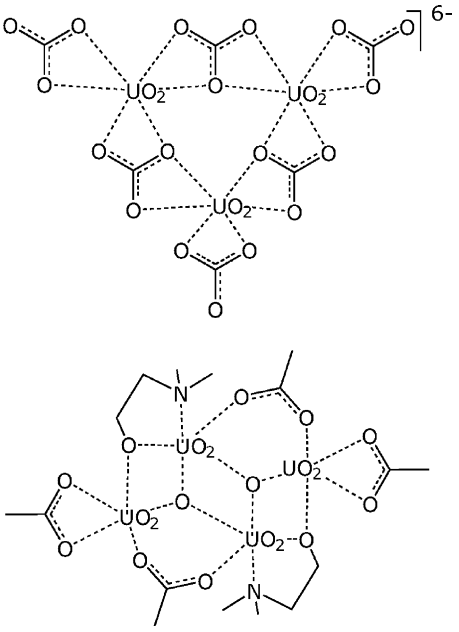
Finally, structures with iminodiacetato ligands also exhibit both monodentate and bidentate carboxylate coordination in structures with the uranyl cation and in some instances donation from the secondary amino group [69,70]. There are also bridging interactions between more than one uranyl cation in structures with the iminodiacetato ligand. Scheme 5 illustrates a Newman projection through the oxo ligands of these complexes' structures.

2.4. Multinuclear structures

Given the presence of multinuclear uranyl clusters in protein structures suggests that suitable protein sites may enhance



Scheme 5.



Scheme 6.

the formation of such multinuclear species or trap hydrolyzed uranyl species. Unfortunately, the data provided by those protein structures with uranyl clusters has been of low resolution until recently, and most structures with multinuclear clusters do not have refined oxo or bridging ligands. For comparison, two structurally characterized multinuclear uranyl clusters with carbonate or carboxylate ligands are presented here.

First, a trinuclear uranyl hexacarbonato cluster has been described using a variety of complementary experiments [71]. This species may be important in carbonate solution and resembles a trimer of the uranyl tris-carbonato anion; the cluster crystallizes as two anions per unit cell in a triclinic crystal with a space group, $P\bar{1}$ (Scheme 6, top). Second, a tetranuclear complex containing both bridging carboxylate and oxo ligands has been reported [72]. This structure actually contains four modes of coordination to the uranyl units of the cluster: (1) bridging acetate, (2) μ_3 oxo, (3) bidentate carboxylato and (4) a bridging μ_2-dimethylaminoethanolate ligand (Scheme 6, bottom). These structures may serve as models for multinuclear uranyl clusters found in protein structures (Scheme 3 and Fig. 4, respectively).

2.5. Uranyl oxo H-bonding

The common occurrence of the oxo ligand as an H-bond acceptor in uranyl protein complexes suggests that this is a common feature in uranyl structures in small molecules as well. In fact, a careful look at the Cambridge database indicates that there are a number of structures which include distances between uranyl oxo ligands and hydrogen bond donors that should be considered hydrogen bonds in these structures. In structural cases, there are examples of inter- and intramolecular hydrogen bonding between the uranyl oxo group and amino or amido hydrogen bond donors [73–76]; hydrogen-bonding interactions with solvent are also present. Solvent interactions are present both in small molecular structures and in protein structures, as seen above.

Uranyl-oxo ligands, as H-bond acceptors, should not be considered unusual, and may play a significant role in the biocoordination and transport of the uranyl cation. While prevalent, these interactions have not been significantly commented on in the literature except in a few cases [77–82]. The potential for hydrogen-bonding interactions to influence coordination to uranyl cation has not been lost on Raymond and co-workers, who published a series of papers [77–82] that included the idea of "stereognostic interactions" between metal cations, which lead to their effective sequestration in suitably designed ligands. Their ligand design for uranyl focused on a tripodal scaffold of donors to coordinate uranyl in the equatorial plane with an H-bond donor in an axial position. Infrared spectroscopy was used to evaluate hydrogen-bonding interactions between uranyl oxo and the ligand.

3. Solution thermodynamic data

3.1. General

Solution data on the thermodynamic stability of the uranyl cation with biological ligands, and particularly the amino acids, are rather limited, but has been evaluated by various research groups over the past 50 years. The hard Lewis-acid character of uranium(VI) in the uranyl cation suggests that oxygen donors would be preferred in its coordination sphere, and that electrostatic forces are a good first approximation for understanding uranyl–ligand interactions. As illustrated above, small molecule and protein X-ray data indicate this preference for oxygen donors with uranyl cation. In addition to carboxylate, the other major donors represented in small molecule structures include phenolate ligands, imine donors from Schiff base ligands or aromatic N-heterocycles [83]. It has been suggested that the effective charge on uranium in the uranyl cation is approximately +3 [11]. Given the [Rn] electronic configuration of U(VI), one anticipates that electrostatic interactions will predominate in the coordination chemistry of the uranyl cation.

Select conditional stability constants for 1:1 metal–ligand complexes of uranyl with biological ligands are presented in Table 3. The data are not an exhaustive, critical list, but represents select data for uranyl–amino acid interactions at ionic strengths around 0.1, and provide a general overview of expected solution interactions of uranyl with peptides and proteins, or other ligands in biological conditions.

3.2. Acetate and carbonate

For comparison, the first three entries of Table 3 contain stepwise association constants between uranyl and the carbonate and acetate ligands [84–86]. These two ligands may serve as endpoints for the thermodynamic range potentially available for carboxylate donors with the uranyl cation. Acetate represents a typical carboxylate interaction with uranyl with $\log K \sim 2$–5 depending on conditions. Carbonate appears to be ideally suited in a geometric, structural and electronic sense to coordinate

Table 3
Select conditional solution thermodynamic data for uranyl-amino acid and other ligands

Entry	Ligand	Species[a]	log K or log β(*)[b]	Conditions	Reference
1	Carbonate	110	10.1	Extrapol. to $\mu = 0$; 25 °C	[84]
		120	7.0	Extrapol. to $\mu = 0$; 25 °C	[84]
		130	4.3	Extrapol. to $\mu = 0$; 25 °C	[84]
2	Acetate	110	2.12	1 M $NaClO_4$; 25 °C	[85]
		120	1.65	1 M $NaClO_4$; 25 °C	[85]
		130	1.29	1 M $NaClO_4$; 25 °C	[85]
3	Acetate	110	4.56	0.1 M $NaClO_4$; 25 °C	[86]
4	Glycine	122	2.14*	0.1 M $NaClO_4$; 30 °C	[87]
	β-Alanine	122	3.49*	0.1 M $NaClO_4$; 30 °C	[87]
	4-Aminobutyrate	122	4.44*	0.1 M $NaClO_4$; 30 °C	[87]
	Isobutyrate	120	5.66*	0.1 M $NaClO_4$; 30 °C	[87]
5	Alanine	110	2.03	0.1 M $NaClO_4$; 30 °C	[88]
	Valine	110	2.01	0.1 M $NaClO_4$; 30 °C	[88]
	4-Aminobutyrate	110	2.43	0.1 M $NaClO_4$; 30 °C	[88]
	4-Aminobutyrate	120	2.15	0.1 M $NaClO_4$; 30 °C	[88]
6	Acetate	110	2.70	$\mu = 0.2$, KNO_3; 25 °C	[89]
	Succinate	110 (?)	2.62	$\mu = 0.2$, KNO_3; 25 °C	[89]
	Aspartate	111	2.61	$\mu = 0.2$, KNO_3; 25 °C	[89]
	Glutamate	111	2.66	$\mu = 0.2$, KNO_3; 25 °C	[89]
7	Glycine amide	110 (?)	5.15*	$\mu = 0.15$–0.25; 25 °C	[90]
	Histidine[c]	111 (?)	7.71*	$\mu = 0.15$–0.25; 25 °C	[90]
	Histidine methyl ester[c]	110 (?)	5.76*	$\mu = 0.15$–0.25; 25 °C	[90]
8	Aspartate	110 (?)	8.71	0.1 M $NaClO_4$; 30 °C	[91]
	Glutamate	110 (?)	8.43	0.1 M $NaClO_4$; 30 °C	[91]
	Aspartate	Ternary[d]	2.99–5.10	0.1 M $NaClO_4$; 30 °C	[91]
	Glutamate	Ternary[d]	2.98–4.52	0.1 M $NaClO_4$; 30 °C	[91]
9	GlyGly	110	6.72	0.1 M $NaClO_4$; 31 °C	[93]
	Asparagine	110	7.23	0.1 M $NaClO_4$; 31 °C	[93]
	Valine	110	7.97	0.1 M $NaClO_4$; 31 °C	[93]
	Alanine	110	8.55	0.1 M $NaClO_4$; 31 °C	[93]
10	Glutamate	110	8.30[e]	0.1 M $KClO_4$; 25 °C	[92]
		120	6.37[e]	0.1 M $KClO_4$; 25 °C	[92]
11	GlyGlyHis	Ternary[f]	2.2	0.1 M Na_2CO_3; 25 °C	[30]
	AspAlaHisLys	Ternary[f]	3.1	0.1 M Na_2CO_3; 25 °C	[30]

[a] Species are indicated in an "MLH" format.
[b] log K represents the stepwise association constant for the addition of ligand to metal; log β represents a cumulative association constant.
[c] A species anticipated for glycine amide histidine and styrene methyl ester are the 1:1 uranyl ligand complex but are not specified in the reference.
[d] The ternary structures of aspartate and glutamate are those with other acid ligands such as quinolinate, picolinate, etc.
[e] Entry 10 specifically lists these data as being the stepwise association constant for the 1:1 metal–ligand complexes and the 1:2 metal–ligand complex.
[f] The ternary complexes of the peptides GGH and DAHK are the uranyl bis-carbonate-peptide species.

uranyl with a high initial stepwise constant (log $K_{ML} \sim 10$). The cumulative formation constants of the bis- and tris-carbonato complexes lead to these uranyl species predominating under many environmental and biological conditions.

3.3. Uranyl–amino acid interactions

Entries 4–6 are representative data for amino acid–uranyl interactions [87–89]. These data, taken together, represent the interaction of a single carboxylate to uranyl interaction, or of the formation of ML_2 type complexes; these are in keeping with values obtained for the interaction of acetate with uranyl under similar conditions. Of note is the systematic increase in thermodynamic stability in a series of amino acids going from the α-amino acid, glycine, to β-alanine and to γ-amino butyric acid (entry 4). The observed charge effect in this series of data suggests charge–charge interactions between nearby positively charged ammonium groups and the carboxylate donor, or with the uranyl cation, destabilize the complex by 0.2–0.5 log units. The other entries provide values for a typical uranyl–carboxylate association constant (log $K \sim 2.0$) with an α-amino group present, and association constants for uranyl interactions with Asp and Glu side chain carboxyl groups (log $K \sim 2.6$).

Early work suggested that the histidine imidazole side chain could be a donor to the uranyl cation (entry 7) [90]. These values were obtained via solvent extraction studies, and are a bit hard to interpret as to the species indicated; of interest is the difference of about 2 log units between the association constant of "uranyl

histidine" and "uranyl histidine methyl ester", which is about the magnitude of a uranyl carboxylate interaction as seen in the other entries. There is the suggestion of histidine imidazole donors in the protein databank (vide supra), which suggests this experiment (or similar) with histidine should be repeated and extended.

Some solution data also present problematic interpretations as to which species are being postulated for measurements reported (e.g. entries 8–10 [91–93]). In question is the possibility of interactions between α-amino groups (or amino donors in general) and the uranyl cation. Some data seem to suggest a large stepwise association constant that has been interpreted as being amino (RNH_2)–uranyl coordination. However, given the lack of significant structural data with uranyl coordinated to primary amino groups, this interpretation may be seriously in question. Other data, such as that in entry 8, for formation of aspartate- or glutamate-uranyl species call into question the nature of the interaction being measured in these systems. Again, it is interesting that the identified stepwise association step for ternary species (UO_2:acid:amino acid; acid = picolinic, quinolinic) in entry 8 is in keeping with the other observed single carboxylate stepwise association constants with uranyl. The magnitude of the interactions presented in entry 8 suggests that these reported constants may represent cumulative association constants (possibly an M:L:H::1:1:1 species) that include the proton association constant in the overall reported value.

In addition, entry 9 illustrates again some of the problematic data in reports of uranyl bioligand interactions. The reported values are presumably the stepwise association constant between a metal and peptide or amino acid complex. But the magnitude of these constants suggests possibly a 1:2 cumulative formation constant or some other process going on in these systems. Other reports [92] that present unusual or impossible association constants for uranyl–amino acid interactions may also be a misinterpretation of the expected species in the reported experiments. For comparison, thorium (IV)-carboxylate amino acid interactions are on the order of $\log K_{ML}$ of 7–9, but the final entry (No. 10) for glutamate binding to carboxylate appears to be inconsistent with observed values from other systems.

Finally, some recent work has reported on the association constants for ternary uranyl carboxylate complexes with peptides [30]. The interactions measured in these systems (Table 3, entry 11) are again on the order of expected interactions between uranyl and carboxylate donors. These data also hint at a charge effect operating in uranyl peptide or uranyl ligand complexes; specifically, charge neutralization to form an overall neutral species in solution (compare to $[UO_2(CO_3)]^0$, above).

4. Conclusions

Taken together, these data suggest a significant range of binding interactions between uranyl and amino acids, peptides or protein donor groups. One may expect significant contributions from aspartyl and glutamyl side chain carboxylate donors, as is realized in data from the PDB. The thermodynamic stability of uranyl biocoordination ranges from interactions with amino acid carboxylates ($\log K \sim 2$–3+) to fairly strong interactions reported with protein ($\log K_f \sim 10$ or 16). A significant gap remains in the overall picture of uranyl interactions with biological ligands; solution studies are needed to identify ligands in the range of stability that spans the above thermodynamic limits. The contribution of H-bonding, charge effects and other second sphere interactions in uranyl-biocomplexes needs to be evaluated. Donors such as tyrosinate can also be expected in small molecule–uranyl solution interactions. Future investigations into amino acid interactions should include uranyl–histidine and uranyl–tyrosine interactions to evaluate imidazole and tyrosyl ligand donors to the uranyl cation. Despite the difficulties of uranyl hydrolysis, it appears that the coordination chemistry of the uranyl cation at pH ∼ 7 will be a fascinating area of study in the next decades.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ccr.2005.09.010.

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