Title

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Synthesis and Crystallographic Characterization of the Tetravalent Actinide-DOTA Complexes, [An^{IV}(κ^8-DOTA)(DMSO)] (An = Th, U)

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Supporting Information Placeholder

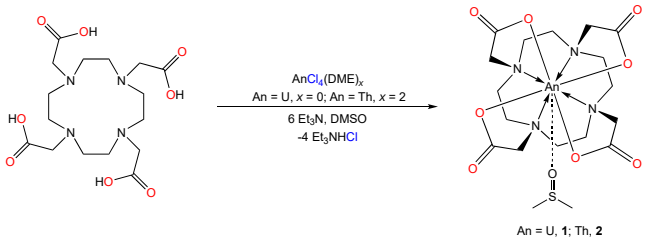
ABSTRACT:

The reaction of UCl_4 or $ThCl_4(DME)_2$ with 1,4,7,10-tetrazacyclodecane-1,4,7,10-tetraacetic acid (H_4DOTA), and 6 equiv of trimethylamine, in DMSO results in the formation of [An^{IV}(κ^8-DOTA)(DMSO)] (**1**, An = U; **2**, An = Th), which can be isolated in moderate yields after work-up. Complexes **1** and **2** are the first structurally characterized actinide DOTA complexes to feature the κ^8 binding mode for the DOTA ligand. In addition, we isolated a few crystals of [U(κ^4-H_2DOTA)(DMSO)$_4$][Cl]$_2$ (**3**). Crystallographic characterization of this material reveals that the $[H_2DOTA]^{2-}$ ligand in **3** is only coordinated to U^{4+} by its four carboxylate arms, generating an overall κ^4 binding mode. Similar complexes have been previously proposed as intermediates of H_4DOTA complexation pathway, but this intermediate had not been structurally characterized until now.

H_4DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and its derivatives form strong chelate interactions with the f elements.[1] The resulting complexes have been used for a wide variety of applications, including MRI imaging and nuclear medicine.[2-5] While lanthanide DOTA chemistry has been studied for decades,[6-10] the synthesis and characterization of actinide DOTA complexes is not well established. H_4DOTA has previously been explored as a chelator for ^{225}Ac,[11, 12] specifically for the generation of an alpha-particle therapeutic.[13, 14] The resulting complex was characterized by ITLC-GC and its stability was probed in vitro.[15] In addition, the chelation of An^{3+} by H_4DOTA has been probed by ESI-MS (An = Pu, Am),[16] as well as UV-vis spectroscopy and EXAFS (An = Pu, Am).[17] The binding constants of H_4DOTA with Am^{3+} and Cm^{3+} have also been measured,[18] and the ^{1}H NMR spectrum of [Th(DOTA)] has been recorded.[19] In contrast, only a few actinide DOTA complexes have been structurally characterized.[20] For example, only one structurally characterized Th(DOTA) complex is known, a bimetallic aquo complex: [$Th_2(H_2O)_{10}$(κ^4-H_2DOTA)$_2$][NO_3]$_4$,[20] while just two DOTA-containing uranium complexes are known: the U(IV) cluster, [U_6(μ-OH)$_4$(μ-O)$_4$(H_2O)$_8$(HDOTA)$_4$], and the 2D uranyl-coordination polymer, [$(UO_2)_2(H_2DOTA)(C_2O_4)(H_2O)_2$].[20, 21] Notably, in all three of these examples, the DOTA ligand does not bind to the metal ion via all eight of its donor atoms. In fact, to our knowledge, there are no structurally characterized actinide complexes where DOTA coordinates in its κ^8 binding mode. Critically, the structural characterization of more An(DOTA) complexes would allow us to evaluate the suitability of DOTA (and its variants) for use as a chelator in targeted alpha therapy.

Herein, we report the synthesis and crystallographic characterization of [An^{IV}(κ^8-DOTA)(DMSO)] (An = U, Th). We also report the crystallographic characterization of [U(κ^4-H_2DOTA)(DMSO)$_4$][Cl]$_2$, which is an intermediate formed along the H_4DOTA complexation pathway.

Scheme 1. Synthesis of Complexes **1** and **2**.



Addition of one equiv of H_4DOTA and 6 equiv of NEt_3 to a lime-green DMSO solution of UCl_4 results in a gradual color change to turquoise over the course of 1 h (Scheme 1). Work-up of the reaction mixture, followed by crystallization from DMSO/toluene results in isolation of [U^{IV}(κ^8-DOTA)(DMSO)] (**1**), as green-blue blocks in 47% yield. [Th^{IV}(κ^8-DOTA)(DMSO)] (**2**) can be made similarly, using $ThCl_4(DME)_2$ in place of UCl_4. It can be isolated in 53% yield as a white microcrystalline solid after recrystallization from hot DMSO. The rapid complexation of An^{4+} by H_4DOTA under anhydrous conditions is

notable. In acidic aqueous solutions, by contrast, complexation of Ln^{3+} by H_4DOTA can take days to weeks.[22] The successful isolation of **1** and **2** requires that the DMSO and H_4DOTA be relatively dry. If the H_4DOTA contains occluded water, we have found that the reaction results in formation of a sticky, intractable solid, which is presumably a hydroxide-bridged coordination polymer. The synthesis of the related U(IV) complex, $[U(DO3A)(DMSO)_2][Br]$ (DO3A = [4,7,10-tris-carboxymethyl-1,4,7,10-tetraazacyclododec-1-yl]-acetic acid) also requires water-free conditions.[23]

Complexes **1** and **2** are air- and water-stable. Complex **1** is soluble in DMSO and DMF, and modestly soluble in H_2O, while complex **2** is only sparingly soluble in DMSO, but modestly soluble in H_2O. They are both insoluble in CH_2Cl_2, THF, pyridine, alkanes, and aromatic solvents. Their insolubility in CH_2Cl_2 is beneficial because it permits the removal of any residual $[NEt_3H][Cl]$, should it present in the isolated material.

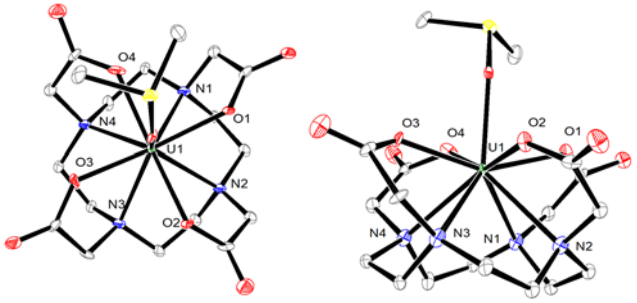


Figure 1. ORTEP diagrams of one independent molecule of $[U(\kappa^8\text{-DOTA})(DMSO)]\cdot DMSO$ (**1·DMSO**), with 50% probability ellipsoids. Hydrogen atoms and solvate molecules omitted for clarity.

Complexes **1** and **2** are isomorphous: they crystallize in the monoclinic $P2_1$ space group as DMSO solvates with two independent molecules in the unit cell. The solid-state molecular structure of one independent molecule of **1·DMSO** is shown in Figure 1. The $[DOTA]^{4-}$ ligand in **1** binds to the U^{4+} center with an octadentate coordination mode. A single DMSO ligand also coordinates to the U^{4+} center, resulting in an overall 9-coordinate geometry. The twist angles between the N_4 and O_4 faces that are formed upon DOTA coordination are 40(1)° and 38(1)° for **1** and **2**, respectively. These values are close to the ideal value of 45° expected for a capped square antiprism (SAP). Comparable values have been observed for several other $[Ln(DOTA)]^-$ complexes.[1] The average $An{-}O_{carboxylate}$ distances for **1** and **2** are 2.30 Å (range = 2.27(2) to 2.33(2) Å) and 2.36 Å (range = 2.33(2) to 2.38(2) Å), respectively. The average An–N distances for **1** and **2** are 2.72 Å (range = 2.67(2) to 2.74(2) Å) and 2.75 Å (range = 2.73(2) to 2.78(2) Å), respectively (Table 1). While no $An(\kappa^8\text{-DOTA})$ complexes have been characterized by X-ray crystallography, $[An(\kappa^8\text{-DOTA})(H_2O)]^-$ (An = Pu, Am) has been characterized by EXAFS.[17] The reported An-O (Pu-O = 2.43 ± 0.02 Å, Am-O = 2.44 ± 0.02 Å) and An-N (Pu-N = 2.67 ± 0.02 Å, Am-N = 2.68 ± 0.02 Å) distances are comparable to those observed in **1** and **2**. For further comparison, the average M-O and M-N distances in [Zr(DOTA)] are 2.13 and 2.42 Å, respectively.[24] Finally, the $An{-}O_{DMSO}$ distances for **1** and **2** are 2.38(2)/2.39(2) and 2.40(2)/2.39(2) Å, respectively. These distances are consistent with previously reported $An{-}O_{DMSO}$ distances.[23]

Table 1. Selected Metrical Parameters for **1** and **2** (Å).

Complex	1	2
av. An–O	2.30	2.36
av. An–N	2.72	2.75
$An{-}O_{DMSO}$	2.38(2), 2.39(2)	2.40(2), 2.39(2)
$An{-}O_{plane}$	0.565(7)	0.555(8)
$An{-}N_{plane}$	1.72(1)	1.75(1)
Twist angle (°)	40(1)	38(1)

The room temperature ^{1}H NMR spectrum of **1** in D_2O exhibits six paramagnetically shifted proton environments between 38.54 and -55.61 ppm (Figure S1 in the supporting information). The sharp singlets at 21.74 and -55.61 ppm are assigned to the two acetate proton environments. These assignments we made by comparison with the NMR spectral data reported for $[Eu(DOTA)(H_2O)]^-$.[25] The four remaining peaks are assignable to the four unique proton environments of the cyclen ring. Three of these peaks, at 38.54, 19.32, and 5.76 ppm, are doublets with J_{HH} = 15 Hz, while the fourth (0.76 ppm) is a singlet. The presence of six peaks of equal intensity makes it appear that complex **1** is in the slow-exchange regime at this temperature.[6] Inspection of the ^{1}H NMR spectrum of [Zr(DOTA)] suggests that it is also in the slow-exchange regime.[24]

The room temperature ^{1}H NMR spectrum of **2** in D_2O exhibits five very broad resonances, ranging from 3.87 ppm to 2.84 ppm, suggestive of a fluxional system. Consistent with this hypothesis, upon heating this sample to 65 °C, these five resonances transform into three broad resonances, at 4.23, 3.77, and 3.33 ppm. These values are in good agreement with those previously reported for $[Th(\kappa^8\text{-DOTA})(H_2O)]$ generated *in situ*.[19] Similar behavior was observed for $[La(DOTA)(H_2O)]^-$, and was explained by invoking the inversion of the cyclen ring.[6] The $^{13}C\{^1H\}$ NMR spectra of **2** also features evidence of fluxionality. At room temperature, its $^{13}C\{^1H\}$ NMR spectrum features resonances at 55.22 and 57.09 ppm, which are assignable to two unique cyclen methylene environments (Figure S4 in the supporting information). Upon warming to 45 °C, the two methylene resonances coalesce into a single peak (Figure S5 in the supporting information). Using the two-site exchange approximation, the

activation barrier ($\Delta G_c^{\ddagger}$) for ring inversion was calculated to be 61 kJ/mol.[26] For comparison, $\Delta G_c^{\ddagger}$ = 61 kJ/mol and 64 kJ/mol for cyclen ring inversion in [La(DOTA)(H_2O)]$^-$ and [Eu(DOTA)(H_2O)]$^-$, respectively.[25, 27]

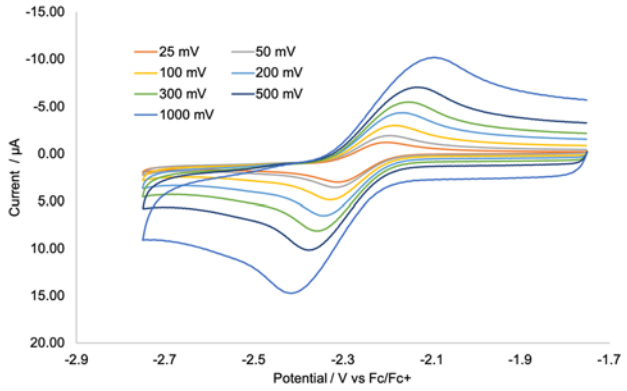


Figure 2. Scan rate dependent cyclic voltamogram of complex **1** (vs. Fc/Fc^+). Measured in DMSO with 0.1 M $[NBu_4][BPh_4]$ as the supporting electrolyte.

We also recorded the cyclic voltammogram of complex **1** in DMSO at a variety of scan rates, using either $[NBu_4][PF_6]$ or $[NBu_4][BPh_4]$ as supporting electrolyte. The cyclic voltammogram (with $[NBu_4][BPh_4]$ as supporting electrolyte) features a reversible redox feature with $E_{1/2}$ = -2.26 V (vs. Fc/Fc^+) (Figure 2). We have assigned this feature to a U(IV)/U(III) reduction event. Not surprisingly, this value is much decreased from the reported reduction potential of -0.58 V (vs. SHE) for U^{4+}(aq),[28, 29] highlighting the ability of strongly chelating macrocyclic ligands to stabilize the An^{4+} state.[30] Using $[NBu_4][PF_6]$ as supporting electrolyte, we observe the presence of a quasi-reversible feature at +0.44 V (vs. Fc/Fc^+) (Figure S9 in the supporting information). This feature becomes increasingly reversible with increasing scan rates and has been assigned as a U(IV)/U(V) oxidation event.[29]

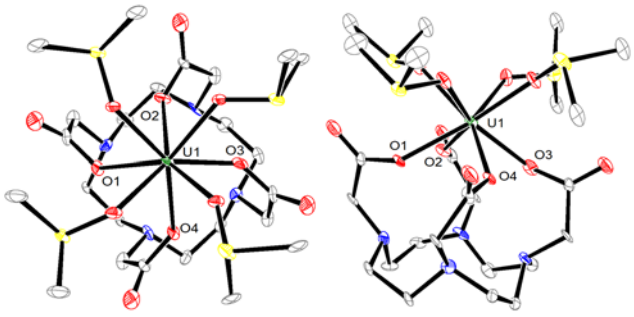


Figure 3. ORTEP diagrams of [U(κ^4-H_2DOTA)$(DMSO)_4$][Cl]$_2$ (**3·5DMSO**), with 50% probability ellipsoids. Hydrogen atoms, chloride counterions, and solvent molecules have been omitted for clarity. Selected bond distances (Å): U1−O1 = 2.39(1), U1−O2 = 2.27(1), U1−O3 = 2.36(1), U1−O4 = 2.29(1), av. U−O_{DMSO} = 2.37.

In one instance, during an attempt to crystallize **1** we grew a few green-brown blocks. An X-ray crystallographic analysis of these crystals revealed them to be [U(κ^4-H_2DOTA)$(DMSO)_4$][Cl]$_2$ (**3**). Complex **3** crystallizes in the orthorhombic $P2_12_12$ space group as a DMSO solvate, **3·5DMSO**, and its solid-state structure is shown in Figure 3. Complex **3** features a square antiprismatic geometry with a twist angle of 44.5(3)° between the DMSO and DOTA O_4 planes. The $[H_2DOTA]^{2-}$ ligand is coordinated in a κ^4 fashion via all four carboxylate arms. Four DMSO ligands are also coordinated to the uranium center. Two outer sphere Cl^- ions, required to maintain charge balance, are also found in the structure. The average U-$O_{carboxylate}$ distance is 2.33 Å (range: 2.27(1) - 2.39(1) Å) and the average U-O_{DMSO} distance is 2.37 Å (range: 2.32(1) to 2.42(1) Å). While the two labile DOTA protons could not be located in the difference Fourier map, in the calculated structures of the related complexes, [M(κ^4-H_2DOTA)$(H_2O)_5]^+$ (M = Nd, Pu, Am), the four carboxylate arms are deprotonated and two nitrogen atoms are protonated.[17] Significantly, the κ^4 binding mode observed for the DOTA fragment in **3** has been proposed as an intermediate binding mode along the DOTA complexation pathway.[31-34] This binding mode has been detected by a variety of spectroscopies,[22] but the observation of **3** represents the first time that it has been characterized by X-ray crystallography. That said, it should be noted that this binding mode has been observed for a handful of DOTA derivatives, including 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis[methylene(2-carboxyethyl)phosphinic acid] (DOTPI) and 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane (DOTAM).[35, 36]

In summary, we have synthesized and structurally characterized the first An^{IV}(DOTA) complexes that feature a κ^8 binding mode of the DOTA ligand. Moreover, isolation and characterization of **3** represents the first crystallographic confirmation of the previously proposed κ^4 intermediate formed during DOTA complexation. The lack of any other crystallographically-characterized κ^8-bound actinide DOTA complexes is surprising, given the long f element history of this ligand. In this regard, we attribute our success to use of non-aqueous reaction and crystallization conditions, which results in fast metal complexation and the inhibition of hydrolysis. Ultimately, we believe this work will accelerate the development of potent An^{4+} chelators, which will be required for a variety of applications, including targeted alpha therapy.[14, 37, 38]

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Crystallographic details for **1**−**3** (CIF)
Experimental procedures and spectral data for complexes **1**−**3** (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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[An^{IV}(κ^8-DOTA)(DMSO)] (An = Th, U) are the first structurally characterized actinide DOTA complexes to feature the κ^8 binding mode for the DOTA ligand.