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Synthesis and Crystallographic Characterization of the Tetra-valent Actinide-DOTA Complexes, [AnIV(κ8-DOTA)(DMSO)] (An = Th, U)

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Supporting Information Placeholder

ABSTRACT:
The reaction of UCl4 or ThCl4(DME)2 with 1,4,7,10-tetraazaacyclodecane-1,4,7,10-tetraacetic acid (H4DOTA), and 6 equiv of trimethylamine, in DMSO results in the formation of [AnIV(κ8-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 κ8 binding mode for the DOTA ligand. In addition, we isolated a few crystals of [U(κ4-H2DOTA)(DMSO)4][Cl]2 (3). Crystallographic characterization of this material reveals that the [H2DOTA]2- ligand in 3 is only coordinated to U4+ by its four carboxylate arms, generating an overall κ4 binding mode. Similar complexes have been previously proposed as intermediates of H4DOTA complexation pathway, but this intermediate had not been structurally characterized until now.

Scheme 1. Synthesis of Complexes 1 and 2.

Addition of one equiv of H4DOTA and 6 equiv of NEt3 to a lime-green DMSO solution of UCl4 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 [UIV(κ8-DOTA)(DMSO)] (1), as green-blue blocks in 47% yield. [ThIV(κ8-DOTA)(DMSO)] (2) can be made similarly, using ThCl4(DME)2 in place of UCl4. It can be isolated in 53% yield as a white microcrystalline solid after recrystallization from hot DMSO. The rapid complexation of An4+ by H4DOTA under anhydrous conditions is...
notable. In acidic aqueous solutions, by contrast, complexation of Ln3+ by H2DOTA can take days to weeks. The successful isolation of 1 and 2 requires that the DMSO and H2DOTA be relatively dry. If the H2DOTA 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.

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

<table>
<thead>
<tr>
<th>Complex</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>av. An–O</td>
<td>2.30</td>
<td>2.36</td>
</tr>
<tr>
<td>av. An–N</td>
<td>2.72</td>
<td>2.75</td>
</tr>
<tr>
<td>An–Oplane</td>
<td>0.565(7)</td>
<td>0.555(8)</td>
</tr>
<tr>
<td>An–Nplane</td>
<td>1.72(1)</td>
<td>1.75(1)</td>
</tr>
<tr>
<td>Twist angle (°)</td>
<td>40(1)</td>
<td>38(1)</td>
</tr>
</tbody>
</table>

The room temperature 1H NMR spectrum of 1 in D2O 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 were made by comparison with the NMR spectral data reported for [Eu(DOTA)(H2O)]. 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 JHH = 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. Inspection of the 13C{1H} NMR spectrum of [Zr(DOTA)] suggests that it is also in the slow-exchange regime.24 The room temperature 13C{1H} NMR spectra of 2 also features evidence of fluxionality. At room temperature, its 13C{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 ($\Delta G_c^{‡}$) for ring inversion was calculated to be 61 kJ/mol. For comparison, $\Delta G_c^{‡}$ = 61 kJ/mol and 64 kJ/mol for cyclen ring inversion in [La(DOTA) (H$_2$O)]$^+$ and [Eu(DOTA)(H$_2$O)]$^+$, respectively.\textsuperscript{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$^{IV}$(aq),\textsuperscript{28, 29} highlighting the ability of strongly chelating macrocyclic ligands to stabilize the An$^{IV}$ state.\textsuperscript{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.\textsuperscript{29}

Figure 3. ORTEP diagrams of [U($\kappa^4$-H$_2$DOTA)(DMSO)$_3$][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($\kappa^4$-H$_2$DOTA)(DMSO)$_3$][Cl]$_2$ (3). Complex 3 crystallizes in the orthorhombic P2$_1$2$_1$2 space group as a DMSO solvate, 3-5DMSO, and its solid-state structure is shown in Figure 3. Complex 3 features a square antiprismatic geometry with a twist angle of 44.5(3)° between the DMSO and DOTA O$_4$ planes. The [H$_2$DOTA]$^{2+}$ ligand is coordinated in a $\kappa^4$ 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($\kappa^4$-H$_2$DOTA)(H$_2$O)$_5$]$^+$ (M = Nd, Pu, Am), the four carboxylate arms are deprotonated and two nitrogen atoms are protonated.\textsuperscript{17} Significantly, the $\kappa^4$ binding mode observed for the DOTA fragment in 3 has been proposed as an intermediate binding mode along the DOTA complexation pathway.\textsuperscript{31-34} This binding mode has been detected by a variety of spectroscopies,\textsuperscript{25} 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-tetakis[methylene(2-carboxyethyl)phosphinic acid] (DOTPI) and 1,4,7,10-tetraakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane (DOTAM).\textsuperscript{35, 36}

In summary, we have synthesized and structurally characterized the first An$^{IV}$(DOTA) complexes that feature a $\kappa^8$ binding mode of the DOTA ligand. Moreover, isolation and characterization of 3 represents the first crystallographic confirmation of the previously proposed $\kappa^4$ intermediate formed during DOTA complexation. The lack of any other crystallographically-characterized $\kappa^8$-bound actinide DOTA complexes is surprising, given the long 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$^{IV}$ chelators, which will be required for a variety of applications, including targeted alpha therapy.\textsuperscript{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)

AUTHOR INFORMATION

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

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