

Advancing Chelation Chemistry for Actinium and Other +3 f-Elements, Am, Cm, La.

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Investigation of explicit solvent water coordination.

Single water molecules – Full optimization. Figure S1 shows the full geometry optimization of the $M(\text{DOTA})^{1-}$ and $M(\text{DOTP})^{5-}$ complexes including a single water molecule. For $M(\text{DOTA})^{1-}$ complexes, the water molecule remains coordinated to the metal ions, but the positions of the hydrogen atoms on the water molecule vary, most likely due to slight interactions with the acetate functional groups. In $M(\text{DOTP})^{5-}$, however, the water molecules lose coordination to the metal ions and instead are hydrogen bonded to two phosphonate functional groups for all metals. This is probably due to the -2 charge on the phosphonate groups and lack of explicit water molecules in the simulation.

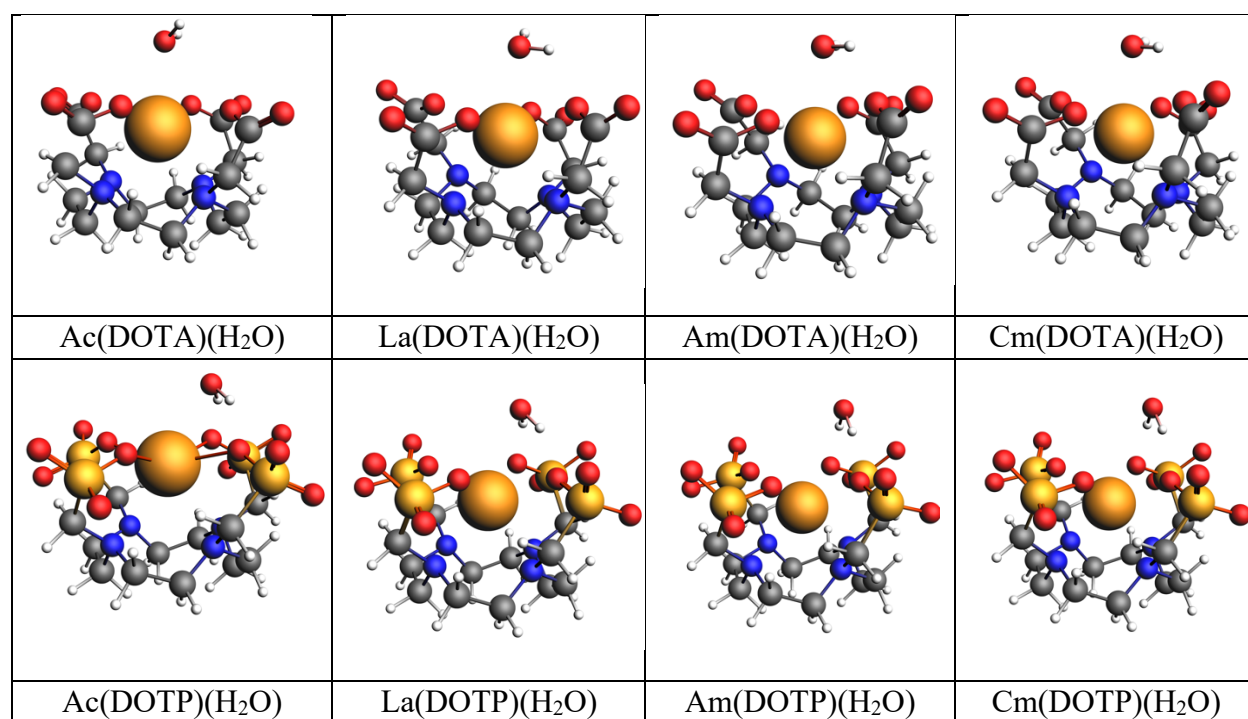


Figure S1. geometry optimization of the $M(\text{DOTA})^{1-}$ and $M(\text{DOTP})^{5-}$ complexes including a single water molecule

Three water molecules – Full optimization. Performing full optimizations with a single water molecule proved difficult, due to the effect of the negatively charged functional group on the arms of the chelator that can interact with the water molecules. In solution, there would be many water molecules coordinating to the functional groups from the solvent, allowing an additional water molecule to coordinate to the metal without being pulled to the side by the acetate/phosphonate groups. However, explicitly modeling enough water molecules to have even one solvation shell around the large $M(\text{DOTA})^{1-}$ and $M(\text{DOTP})^{5-}$ complexes was infeasible for this study. Several approximate models for water coordination were explored.

To keep a single water molecule centered above and coordinated to the metal ions, two additional water molecules were simulated that hydrogen bond to two functional group oxygen atoms each (see Figure S2). ΔE values were calculated using Equations S1 and S2 to determine the difference in binding between $M(\text{DOTP})^{5-}$ modeled with three water molecules and $M(\text{DOTA})^{1-}$ (with and without three water molecules). Due to the high expense of frequency calculations for large complexes, ΔG values were not calculated for these simulations. The results are similar to the main text values for Ac^{3+} and La^{3+} including a single water molecule, with $M(\text{DOTP})^{5-}$ binding to all metals around 30 kcal/mol stronger than $M(\text{DOTA})^{1-}$. For Am^{3+} and Cm^{3+} , however, a water molecule did not remain coordinated to the metal (Figure S3). This could be indicative of it being unfavorable for a water molecule to coordinate to the $M(\text{DOTP})^{5-}$ complexes with Am^{3+} or Cm^{3+} in solution.

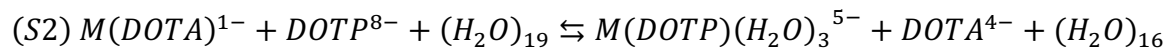
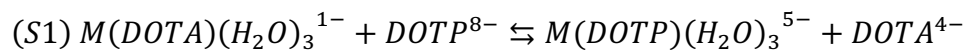


Table S1: ΔE values in kcal/mol for $M(\text{DOTP})(\text{H}_2\text{O})_3^{5-}$ using equations S1 and S2

	Eq S1	Eq S2
Ac	-26.4	-24.3
La	-36.6	-30.4
Am	No H_2O coordination	
Cm	No H_2O coordination	

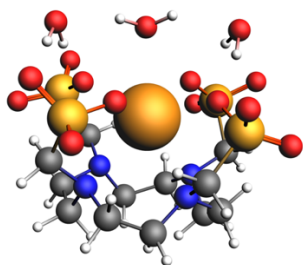


Figure S2: $\text{Ac}(\text{DOTP})(\text{H}_2\text{O})_3$ optimized geometry

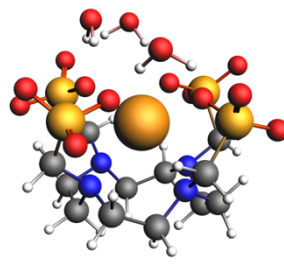


Figure S3: $\text{Cm}(\text{DOTP})(\text{H}_2\text{O})_3$ optimized geometry

Single Water Molecule – Constrained Optimization. All data reported in the main text that includes a water molecule was determined by fixing the water molecule to metal-chelator dihedral angles. This water molecule stayed centered above the metal ion with the hydrogen atoms on the water pointing away from the complex (Figure S1), as has been done in other work.¹ This method cancels out the hydrogen bonds that form between the water molecule and functional group arms, due to the lack of explicit solvation. In general, water coordination to $M(\text{DOTP})^{5-}$ complexes did not alter the stability trends observed when comparing $M(\text{DOTA})^{1-}$ and $M(\text{DOTP})^{5-}$ compounds.

Figure S4 shows the optimized geometry of $\text{Ac}(\text{DOTA})^{1-}$ with dihedral angles, (water)H-O-Ac-O(acetate), held fixed to ensure the water molecule hydrogens stayed in the "up" position. All $M(\text{DOTA})^{1-}$ and $M(\text{DOTP})^{5-}$ complexes maintained a similar geometry when optimized with these constraints. All main text energy values including water molecules are reported using constrained water geometries.

Table S2: Average interatomic distances for M(DOTP)⁵⁻ complexes with and without water molecules. All data is shown in angstroms with the uncertainty in the last digit from the standard deviation of all distances.

	No H ₂ O	With H ₂ O	Δ distance with H ₂ O	M-O(H ₂ O)
Ac-O	2.514(4)	2.515(2)	0.001	2.848
Ac-N	2.92(1)	3.005(3)	0.08	
La-O	2.426(3)	2.444(3)	0.018	2.763
La-N	2.848(5)	2.944(5)	0.096	
Am-O	2.371(2)	2.376(5)	0.005	2.881
Am-N	2.761(3)	2.841(7)	0.080	
Cm-O	2.355(2)	2.364(3)	0.009	2.715
Cm-N	2.781(4)	2.892(7)	0.111	

Inter-plane Distances	No H ₂ O	With H ₂ O
Ac-O	0.99	0.78
Ac-N	1.96	2.08
O-N (Ac)	2.96	2.86
La-O	0.98	0.78
La-N	1.87	2.01
O-N (La)	2.85	2.79
Am-O	1.06	0.86
Am-N	1.76	1.88
O-N (Am)	2.81	2.74
Cm-O	1.00	0.79
Cm-N	1.79	1.95
O-N (Cm)	2.79	2.73

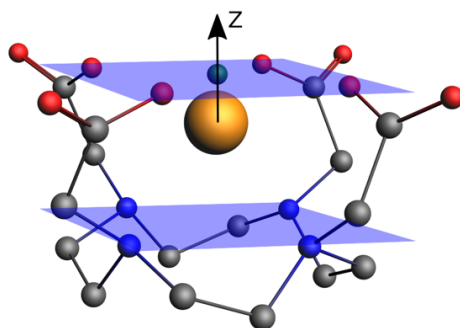


Figure S4: Depiction of oxygen and nitrogen planes in $\text{Ac}(\text{DOTA})^{1-}$ using the central point of the coordinating oxygen atoms (green sphere) and the metal ion to define the z-axis that is orthogonal to both planes. All hydrogen atoms are omitted for clarity.

The interatomic distances for M–O and M–N in $\text{M}(\text{DOTP})^{5-}$ are most similar to EXAFS data when modeled without a coordinating water molecule for all four metals (See Table above). The average distance of the water molecule to the metal is 0.14 Å longer in $\text{M}(\text{DOTP})^{5-}$ versus $\text{M}(\text{DOTA})^{1-}$ complexes. The increased M–O(H_2O) distance suggests that a water molecule is less likely to be bound to $\text{M}(\text{DOTP})^{5-}$ complexes with Ac, Am, Cm, or La compared to $\text{M}(\text{DOTA})^{1-}$ complexes.

Thermodynamic stability calculations also show disfavor for water coordination to $\text{M}(\text{DOTP})^{5-}$ complexes, especially with Am and Cm. Water coordination to $\text{M}(\text{DOTA})^{1-}$ or $\text{M}(\text{DOTP})^{5-}$ seems to have little effect on the stability of Ac complexes (range of less than 6 kcal/mol for equations 1-4 in main document) compared to the other metals tested (average range of 21 kcal/mol). This may indicate that water molecules have a higher exchange rate when $\text{M} = \text{Ac}$ compared to $\text{M} = \text{La}$, Am, or Cm.

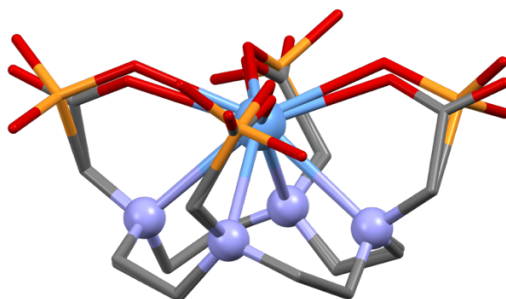


Figure S5: Overlay of optimized Ac(DOTA)^{1-} and Ac(DOTP)^{5-} geometries.

The DOTP ligand contains the larger phosphorous atom shown in orange sticks.

All M(DOTP)^{5-} complexes showed a preference for the twisted square antiprism (TSAP) structure. La(DOTP)^{5-} in the square antiprism (SAP) geometry showed an increase in energy of 9 kcal/mol. M-O and M-N bond lengths and other distances of interest for M(DOTA)^{1-} and M(DOTP)^{5-} complexes are shown Tables S2. For all metal ions investigated, the M-O distance decreases by an average of 0.04 Å when moving from M(DOTA)^{1-} to M(DOTP)^{5-} and the M-N distances increase by 0.09 Å. Since phosphorous atoms are larger than carbon atoms and form longer bonds, the phosphonate arms move further above the metal ion than the acetate groups, but the oxygen atoms are able to reach in closer to the metal ion as shown in Figure S5.

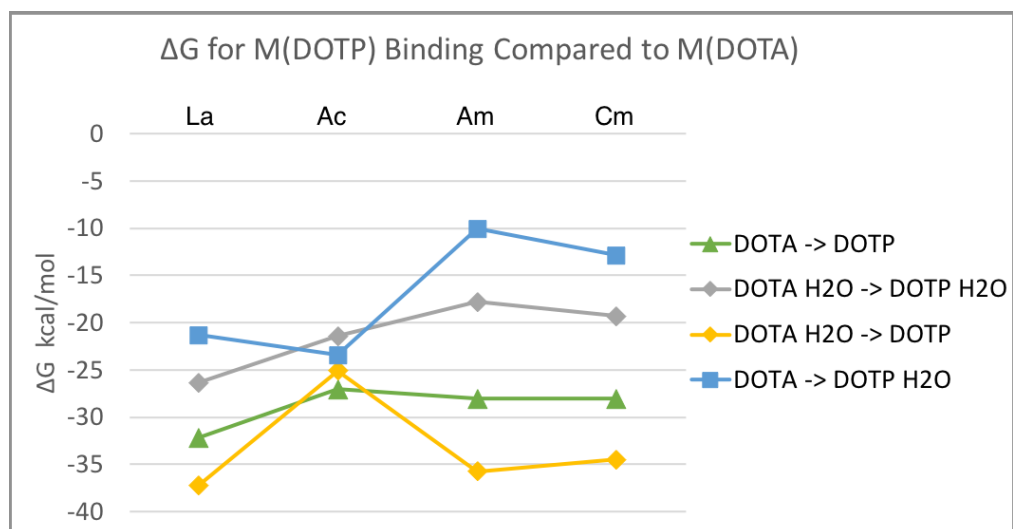


Figure S6: Plot of ΔG values for metal exchange between $M(\text{DOTA})^{1-}$ and $M(\text{DOTP})^{5-}$ for $M = \text{Ac}, \text{Am}, \text{Cm}, \text{and La}$. Green triangles, grey diamonds, yellow circles, and blue squares correspond to Equations 1-4, respectively.

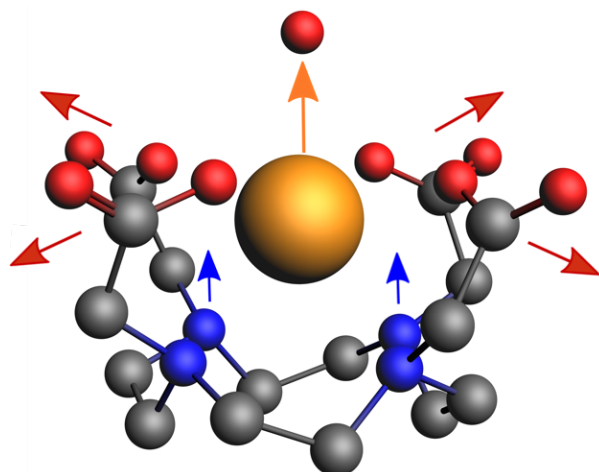


Figure S7: Depiction showing how the $\text{Ac}(\text{DOTA})^{5-}$ structure changes when water binds Ac^{3+} . Hydrogen atoms are not shown for clarity.

REFERENCES.

- (1) Deblonde, G. J.-P.; Kelley, M. P.; Su, J.; Batista, E. R.; Yang, P.; Booth, C. H.; Abergel, R. J. Spectroscopic and Computational Characterization of Diethylenetriaminepentaacetic Acid/Transplutonium Chelates: Evidencing Heterogeneity in the Heavy Actinide(III) Series. *Angew. Chem. Int. Ed.* **2018**, 57 (17), 4521–4526.