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## Structural characterization of actinide-calmodulin complexes by NMR spectroscopy

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Actinides are radioactive metals of high importance in civil and military nuclear industries. They can be found in the environment due to historical dissemination resulting from atmospheric nuclear weapon tests. Moreover, in the context of nuclear waste disposal and nuclear facilities dismantling, the handling of actinides poses a risk of contamination for the operators. Given their strong radiotoxicity, it is essential to investigate their behavior within the human body. While the targeted organs are well-known, the transport mechanism and molecular interactions remain unidentified. Proteins have been identified as actinide targets in the event of human contamination. Although the literature on the interactions between actinides and proteins is scarce, metalloproteomic studies have shown that several calcium-binding proteins have a strong affinity for actinides<sup>1</sup>. As a model for all calcium-binding protein, the calcium-modulated protein (calmodulin) was chosen for its EF-hand motif site, which is widely present in calcium-binding proteins. Loïc Daronnat investigated the interaction of plutonium(IV) with several variants of the calmodulin and observed various behaviors of the plutonium depending on the variant of calmodulin used<sup>2</sup>: the formation of a Pu(IV)-calmodulin complex, the formation of a Pu(III)-calmodulin complex and the formation of hexanuclear clusters of plutonium.

CaME (Engineered Calmodulin) is a variant of calmodulin developed especially to bind plutonium(IV). This variant has an extra carboxylate ligand in its complexation loop (shown in figure 1), increasing its affinity for actinides IV. This particular variant was the only which did not promote the formation of plutonium clusters. Instead, it only generated 1:1 complexes. Additionally, an unexpected change of the oxidation state of plutonium (from IV to III) was noticed in presence of CaME.<sup>3</sup> To get a better understanding of this behavior, a deepened characterization of the species formed between CaME and actinides have been undertaken. This work aims to characterize the complexes formed between CaME and actinides (Th, U, Np, Pu), using different experimental techniques. Electrospray Ionization Mass Spectrometry was used to determine the stoichiometry of the complexes and UV-Vis-NIR Spectroscopy was used to characterize the environment of the actinide. Structural data were obtained through two or three-dimensional NMR spectroscopy. For that, an extra batch of CaME was synthesized and enriched with <sup>13</sup>C and <sup>15</sup>N, allowing for <sup>1</sup>H-<sup>13</sup>C-<sup>15</sup>N NMR analysis. The comparison of the RMN spectra of the protein and the complexes formed will allow to identify the amino acids involved in the coordination sphere of the metallic ions.

### References

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- 2) Daronnat, L. Doctorat Ph D thesis of the Montpellier University, 2023
- 3) Daronnat, L. *Inorg. Chem.* 2023, 62 (21), 8334–8346