

The Actinium Aqua Ion: A Century in the Making

Laura M. Thierer and Neil C. Tomson

P. Roy and Diana T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104, United States

The ^{225}Ac nucleus may hold great promise for radiotherapeutics.

Radio pharmaceuticals represent excellent opportunities for targeted anticancer therapeutics.¹ Nuclei that emit α -particles, i.e., $^4\text{He}^{2+}$, are especially attractive, since this type of decay travels only a short distance in biological tissue ($<100\ \mu\text{m}$) and deposits a large amount of energy en route (linear energy transfer $\approx 100\ \text{keV}/\mu\text{m}$, Figure 1).² The ^{225}Ac isotope is particularly appealing for this purpose. It is a pure α -emitter with a decay chain that results in the biologically innocuous ^{209}Bi isotope after proceeding through the release of two β^- - and four α -particles, the latter of which leave with an accumulated energy of 28 MeV (Figure 1). Despite the promising decay chain of ^{225}Ac for targeted alpha therapy, a host of scientific and technological questions surrounding the production, purification, coordination chemistry, and biological delivery of this isotope remain unanswered.

From a chemical perspective, more fundamental solution phase data for $\text{Ac}(\text{III})$ complexes are needed, including enthalpies and entropies of hydration, preferred coordination numbers and molecular geometries, as well as reactivity-based data, like hard/soft acid–base characteristics and relative Lewis acidities. While the study of Ac spans more than a century,³ the instability of even the element's longest-lived isotope (^{227}Ac , $t_{1/2} = 21.772(3)\ \text{y}$) has hampered the study of Ac binding and speciation in aqueous media. This contrasts with most other elements, which have well-characterized interactions with water. Main group and first-row transition metals, for instance, tend to form homoleptic aqua ions, whereas many of the heavier transition metals generate oxo products and clusters. Even for the noble gases, hydration spheres for the more polarizable elements Ar , Kr , and Xe have been explored, with argon demonstrating some solubility in water.⁴ The lanthanide aqua ions have also been well-characterized, forming a series of data that differ primarily as a function of the ionic radii of the ions.⁵

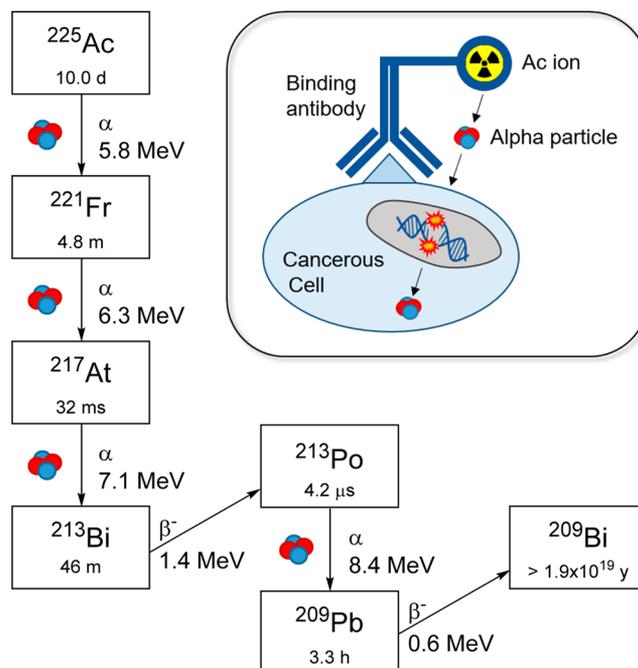


Figure 1. Nuclei that emit multiple α -particles, such as the ^{225}Ac isotope, are desirable for targeted alpha therapy due to the short distance traveled in biological tissue and large energy transfer.

For decades, it was thought that the actinides would mimic the behavior of the lanthanides,³ but research over the past several years^{6–9} has revealed differences in bonding and coordination between these elements, indicating that the $4f^n$

Before the $\text{Ac}(\text{III})$ aqua ion could be generated, a number of experimental challenges resulting from the high radioactivity of Ac had to be solved.

$\text{Ln}(\text{III})$ ions are often a poor model for predicting the properties of the $5f^n$ $\text{An}(\text{III})$ ions.⁹ Even within the actinide series, it is now well-established that the bonding and reactivity can vary dramatically across the row.^{4,9} This difference formed the basis of a recent study by Batista,

Published: March 7, 2017

Kozimor, and co-workers from Los Alamos National Laboratory (LANL), wherein it was found that AcCl_3 retains its chloride ligands in an 11 M HCl solution—a departure from the behavior of the transuranic species AmCl_3 , which forms a dicationic aquo complex.¹⁰ The LANL group's study simultaneously reported the first bond length to Ac, providing a true landmark in the study of this element. This same team is now reporting for the first time the characterization of the Ac(III) aqua ion, a study that provides much-needed, fundamental data that will be useful in the development of chelating agents tailored to the specific size, shape, and Lewis acidity of Ac(III).¹¹

Before the Ac(III) aqua ion could be generated, a number of experimental challenges resulting from the high radioactivity of Ac had to be solved. Use of the more stable ^{227}Ac isotope diminished the radiological hazard and increased the handling time of the samples. Still, the scarcity of ^{227}Ac necessitated the use of microgram scale quantities of Ac. To aid the isolation of Ac from solution, the material was coprecipitated with Lu(III), yielding a solid mixture of $\text{Lu}(\text{OH})_3$ and $\text{Ac}(\text{OH})_3$. The products were then centrifuged and redissolved in dilute aqueous triflic acid, generating a solution of $\text{Lu}(\text{H}_2\text{O})_x^{3+}$ and $\text{Ac}(\text{H}_2\text{O})_x^{3+}$ suitable for extended X-ray absorption fine structure (EXAFS) spectroscopy and X-ray absorption near-edge structure (XANES) spectroscopy measurements (Figure 2). These techniques

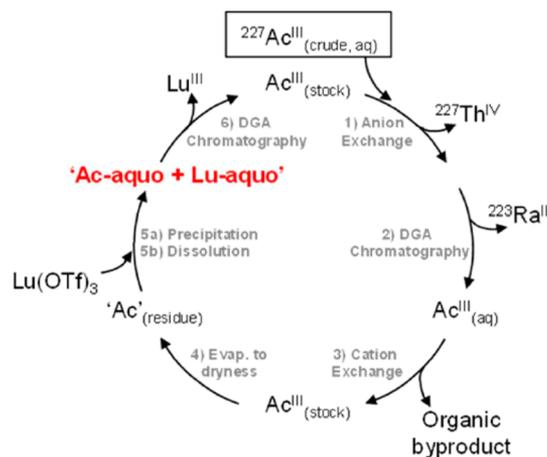


Figure 2. Actinium purification and XAFS sample preparation procedure. Reproduced with permission from ref 11. Copyright 2017 American Chemical Society.

give element-specific information on the coordination environment surrounding the metal center, including the number, identity, and bond lengths of the metal's ligands.

The experimental Ac L_3 -edge EXAFS data were interpreted through models developed using molecular dynamics density functional theory (MD-DFT). The model surrounded

a single Ac(III) ion with 64 water molecules and a uniform, neutralizing background charge. The coordination sphere of the metal ion was then tracked over 8 ps. The model calculated a narrow distribution of coordinated water molecules, finding 9 aquo ligands at an average distance of 2.7 Å. When the $\text{Ac}(\text{H}_2\text{O})_8^{3+}$ and $\text{Ac}(\text{H}_2\text{O})_{10}^{3+}$ complexes were inserted into the simulation, they quickly rearranged to $\text{Ac}(\text{H}_2\text{O})_9^{3+}$. The geometry of the $\text{Ac}(\text{H}_2\text{O})_9^{3+}$ model was then used to generate a calculated EXAFS spectrum, which fit the measured EXAFS data nicely. This similarity results from the good agreement between the predicted (2.61–2.76 Å) and measured (2.63(1) Å) Ac–O bond distances as well as the predicted and measured number of oxygen atoms within the primary coordination sphere of Ac(III). The large number of aquo ligands is consistent with the large atomic radius of the Ac(III) ion. Related solution-phase experiments on actinide (U–Cf) +3 ions find coordination numbers ranging from 7.0 to 10.3. In this case, a larger coordination number for Ac(III) may be expected due to the periodic trend toward larger ionic radii for the earlier actinides.

Looking forward, the supply of medical isotopes from facilities like LANL combines the unique capabilities of specialized equipment for producing, isolating, and handling radioactive materials with useful imaging and therapeutic applications. Production capabilities are now reaching a level where availability of the actinium 225 isotope is not the limiting factor that it has been historically. This increased availability provides the raw material needed by Batista, Kozimor, and their team of researchers to discover the fundamental properties of these underexplored and fascinating ions. Further work in the field will undoubtedly delineate the unique chemical properties of Ac, providing a means of targeting these potent radionuclides at some of the most intractable problems facing modern medicine.

Author information

E-mail: tomson@upenn.edu.

REFERENCES

- (1) de Kruijff, R.; Wolterbeek, H.; Denkova, A. A Critical Review of Alpha Radionuclide Therapy—How to Deal with Recoiling Daughters? *Pharmaceuticals* **2015**, *8* (2), 321.
- (2) Morgenstern, A.; Bruchertseifer, F.; Apostolidis, C. Bismuth-213 and Actinium-225 – Generator Performance and Evolving Therapeutic Applications of Two Generator-Derived Alpha-Emitting Radioisotopes. *Curr. Radiopharm.* **2012**, *5* (3), 221–227.
- (3) *The chemistry of the actinide and transactinide elements*, 4th ed.; Morss, L. R., Edelstein, N. M., Fuger, J., Ed.; Springer: Dordrecht, 2010.
- (4) Richens, D. T. *The chemistry of aqua ions: synthesis, structure, and reactivity: a tour through the periodic table of the elements*; J. Wiley: Chichester, New York, 1997.

(5) Allen, P. G.; Bucher, J. J.; Shuh, D. K.; Edelstein, N. M.; Craig, I. Coordination Chemistry of Trivalent Lanthanide and Actinide Ions in Dilute and Concentrated Chloride Solutions. *Inorg. Chem.* **2000**, *39* (3), 595–601.

(6) Arnold, P. L.; Turner, Z. R. Carbon oxyanion transformations by actinide compounds and catalysts. *Nature Reviews Chemistry* **2017**, *1*, 0002.

(7) Schelter, E. J.; Wu, R.; Veauthier, J. M.; Bauer, E. D.; Booth, C. H.; Thomson, R. K.; Graves, C. R.; John, K. D.; Scott, B. L.; Thompson, J. D.; Morris, D. E.; Kiplinger, J. L. Comparative Study of f-Element Electronic Structure across a Series of Multimetallic Actinide and Lanthanoid-Actinide Complexes Possessing Redox-Active Bridging Ligands. *Inorg. Chem.* **2010**, *49* (4), 1995–2007.

(8) Neidig, M. L.; Clark, D. L.; Martin, R. L. Covalency in f-element complexes. *Coord. Chem. Rev.* **2013**, *257* (2), 394–406.

(9) Polinski, M. J.; Grant, D. J.; Wang, S.; Alekseev, E. V.; Cross, J. N.; Villa, E. M.; Depmeier, W.; Gagliardi, L.; Albrecht-Schmitt, T. E. Differentiating between Trivalent Lanthanides and Actinides. *J. Am. Chem. Soc.* **2012**, *134* (25), 10682–10692.

(10) Ferrier, M. G.; Batista, E. R.; Berg, J. M.; Birnbaum, E. R.; Cross, J. N.; Engle, J. W.; La Pierre, H. S.; Kozimor, S. A.; Lezama Pacheco, J. S.; Stein, B. W.; Stieber, S. C. E.; Wilson, J. J. Spectroscopic and computational investigation of actinium coordination chemistry. *Nat. Commun.* **2016**, *7*, 12312.

(11) Ferrier, M. G.; Stein, B. W.; Batista, E. R.; Berg, J. M.; Birnbaum, E. R.; Engle, J. W.; John, K. D.; Kozimor, S. A.; Lezama Pacheco, J. S.; Redman, L. N. Synthesis and Characterization of the Actinium Aquo Ion. *ACS Cent. Sci.* **2017**, DOI: [10.1021/acscentsci.6b00356](https://doi.org/10.1021/acscentsci.6b00356).