Title: The Structure and Bonding of a Radium Coordination Compound in the Solid-State

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Abstract: The structure and bonding of radium (Ra) is poorly understood because of challenges arising from its radioactivity and scarcity. Herein, we report the first synthesis and characterization of a molecular Ra^{2+} compound in the solid state by single crystal X-ray diffraction, using dibenzo-30-crown-10 (DB30C10) and ^{226}Ra. Our study reveals an 11-coordinate Ra^{2+} structure arising from the 10 donor atoms of DB30C10 and a bound water molecule, whereas identical crystallization conditions with barium (Ba^{2+}) yielded a 10-coordinate "Pac-Man" structure lacking water. The Ra—O_{water} bond distance is significantly longer than would be predicted from the ionic radius of Ra^{2+}. Collectively, these findings support greater water lability in Ra^{2+} complexes and demonstrate that Ra^{2+} chemistry cannot always be predicted using Ba^{2+}. Our results will be valuable in guiding both the design of new chelators and future characterization efforts for this underexplored metal ion.

Introduction: Alpha particle-emitting radioisotopes of radium (Ra), actinium (Ac), and other heavy elements have garnered tremendous interest for their potential use in cancer therapy.[1–6] Of the alpha emitters currently under investigation, only ^{223}Ra ($t_{1/2} = 11.43$ d) is approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA).[7] It is administered as unchelated $^{223}RaCl_2$ in the drug XOFIGO® and is used to treat patients with castration-resistant prostate cancer that has metastasized to the bone.[8,9] Because of the chemical similarity it shares with the calcium ion (Ca^{2+}), $^{223}Ra^{2+}$ naturally accumulates in areas of increased bone turnover associated with metastases, where its alpha-particle emissions irradiate and destroy cancer cells.[10–12] Despite the success of ^{223}Ra for this indication, its more widespread application for the treatment of visceral cancers has remained hindered because of the difficulty in stabilizing this radiometal within a tumor-targeted molecular construct.[13–19] The lability of Ra^{2+} complexes arises because Ra^{2+} forms ionic, rather than covalent, bonds with ligands, which are weakened by the low charge density of this large alkaline earth ion (8-coordinate ionic radius = 1.48 Å).[20] As such, a chelator that can deliver ^{223}Ra to soft-tissue tumors remains elusive.

To overcome this obstacle and drive forward the development of chelators that can effectively stabilize ^{223}Ra for targeted alpha therapy (TAT), a better understanding of the structure and bonding of the Ra^{2+} ion within coordination complexes is required. Of the few solid-state structural studies reported to date for Ra^{2+}, efforts have been confined to the synthesis of simple inorganic Ra^{2+} compounds and their characterization by X-ray powder diffraction (pXRD).[21–26] Although pXRD can rapidly provide data on the symmetry properties of microcrystalline samples and enable a general comparison of the structural similarities between complexes of Ra^{2+} and its congeners (e.g., Ba^{2+}, Sr^{2+}, and Ca^{2+}), this technique is unable to provide precise information regarding metal-ligand bond distances

and coordination geometries about the metal center.[27] Furthermore, the ionic salts studied to date offer limited insight into the behavior and structural organization of Ra^{2+} with larger, multidentate molecular chelators used in nuclear medicine.[6,14,28–31] Solution-state characterization of Ra^{2+} also lags behind most other metals in the Periodic Table, such that the experimental hydration structure of the Ra–aquo ion was only revealed in 2022 using extended X-ray absorption fine structure (EXAFS) spectroscopy.[32] These fundamental studies of Ra^{2+} have been sparsely reported because all its isotopes are short-lived, highly radioactive, and available only in small quantities. These features render them difficult to obtain and handle safely on the macroscopic scale necessary for conventional structural characterization studies. Consequently, even 125 years after its first discovery, insight into the coordination chemistry of Ra^{2+} is still remarkably scarce.

Driven by the long-standing challenge of chelating Ra^{2+} and the desire to transform ^{223}Ra into a targeted radiotherapeutic agent for a range of cancers, we sought to shed new light on the structural chemistry of Ra^{2+} through single crystal X-ray diffraction (scXRD). This technique allows one to gain a complete picture of bond distances and angles, conformation, geometry, strain, and key binding interactions within a structure, descriptors that ultimately underly and dictate the overall stability of a metal–ligand complex. Until now, information on the structure and bonding of Ra^{2+} complexes using this traditional characterization tool has not been accessible. Here, we describe how we overcame the hurdles of working with a macroscopic quantity of ^{226}Ra to attain the first single crystal structure containing the Ra^{2+} ion, to the best of our knowledge. This structure was obtained using the macrocyclic crown ether dibenzo-30-crown-10 (DB30C10). Analysis of the Ra^{2+} complex in comparison to DB30C10 complexes of the smaller alkaline earth ion Ba^{2+} reveals significant differences in their structural conformation and bonding interactions, underscoring the divergent chemistry of these congeners. The insight garnered here into the complexation behavior and preferences of the Ra^{2+} ion will be valuable in establishing ligand design principles that promote the stabilization of $^{223}Ra^{2+}$ for TAT. It also serves as guidance for handling, synthesizing, and crystallizing $^{226}Ra^{2+}$ complexes to support future solid-state characterization efforts by researchers for this radioactive ion.

Results and Discussion

Preparation of Single Crystals. With a half-life of 1600 years, ^{226}Ra is the longest-lived radioisotope of Ra. It is available in milligram quantities but is highly radioactive because of its relatively short half-life. To place this radioactivity in context, one mole of ^{226}Ra is approximately 2.7 million times more radioactive than an equivalent amount of natural ^{238}U. Radiological concerns regarding the use of ^{226}Ra stem from the fact that its direct daughter radionuclide is Rn-222 (^{222}Rn, $t_{1/2} = 3.82$ d), a gas that poses a contamination and health risk if not contained properly. Furthermore, the decay of ^{226}Ra yields several daughter radionuclides that emit high-energy gamma rays, in addition to a total of 5 alpha particles and 4 beta particles. This ionizing radiation will cleave chemical bonds, destroying molecular species both in solution and in the solid state. Thus, any successful crystallization will need to be executed rapidly, reproducibly, and on a small scale.

To achieve this goal, we first optimized our crystallization conditions using non-radioactive Ba^{2+} as a surrogate for Ra^{2+}. We selected DB30C10 as the chelator for Ra^{2+} because it has been used previously to grow single crystals with other large, charge-diffuse metal ions such as divalent samarium (Sm^{2+}), Ba^{2+}, and potassium (K^+)[33–37], and it bears similarity to the macrocyclic chelators employed in TAT.[6,16,28–31] The **Ba1** complex was synthesized using equimolar amounts of $Ba(NO_3)_2$ and DB30C10 in H_2O or D_2O (although compounds may contain either H_2O or D_2O from synthesis, H_2O is used throughout this work for simplicity). To aid in our efforts, tetrabutylammonium tetraphenylborate (Bu_4NBPh_4, 2 equiv in CH_3CN) was added to the reaction solution to promote the exchange of NO_3^- for BPh_4^- as the charge-balancing non-coordinating counteranion. The BPh_4^- anion is commonly used to increase the crystallinity of compounds and adds significant mass to the resulting complex, which is favorable when attempting to crystallize an otherwise small amount of material. Colorless crystals formed after slow evaporation of the solution overnight (see methods) and were identified by scXRD as $[Ba(DB30C10)][BPh_4]_2·MeCN$ (**Ba1**). Our initial reaction conditions were subsequently scaled down to a metal content of 330 ng Ba^{2+} as $Ba(NO_3)_2$, from which we were able to consistently obtain single crystals.

With these optimal reaction conditions in place, we executed the synthesis of the analogous Ra^{2+} complex in a radiological fume hood using $^{226}Ra(NO_3)_2$ dissolved in D_2O. Four large crystals formed after 21 h. One crystal was selected and mounted immediately on the diffractometer using an established protocol (see methods). Analysis of the data acquired by scXRD revealed the complex as $[Ra(DB30C10)(H_2O)][BPh_4]_2$ (**Ra1**) (**Figure 1**). Even with the rapid crystallization time of **Ra1**, the crystals were not colorless as expected, but were instead pale yellow. This yellowing of the crystals was likely due to radiation damage and has also been observed in $^{226}Ra(SO_4)$ pXRD samples.[26] After 48 hours, the yellow color of the crystals grew more pronounced (**Figure 2**), and additional crystals that formed over this time frame were already degraded to a quality not suitable for scXRD measurements. Collectively, these observations underscore the need for rapid formation and analysis of crystals when working with $^{226}Ra^{2+}$.

Crystallographic Analysis. **Ba1** crystallizes in the monoclinic space group C_2/c. The Ba^{2+} center is coordinated by all ten etheric oxygen (O_{ether}) donor groups of DB30C10 in a "Pac-Man" configuration (**Figure 1**).[37,38] In this configuration, the crown ether folds over onto itself, encompassing the metal center. This conformation is further stabilized by π-π stacking of the phenyl groups and has been observed previously in an isostructural divalent Sm^{2+} complex of DB30C10, $[Sm(DB30C10)][BPh_4]_2·MeCN$ (**Sm1**).[37] The crystal structures of two other Ba^{2+} complexes of DB30C10 have also been reported. These structures were obtained under different synthetic conditions and crystallized with $[Bi_2Cl_8]^-$ and $[Co(NCS)_4]^-$ as counteranions, giving rise to complexes with the formulas $[Ba(DB30C10)(H_2O)][Bi_2Cl_8]$ (**Ba2**) and $[Ba(DB30C10)(H_2O)][Co(NCS)_4]·H_2O$ (**Ba3**), respectively.[35,36] In contrast to **Ba1**, both **Ba2** and **Ba3** have a water molecule bound to the metal center, forming 11-coordinate complexes. Furthermore, the phenyl groups of DB30C10 are angled away from each other and therefore do not engage in π-π stacking. Consequently, **Ba2** and **Ba3** lack the "Pac-Man" conformation observed in **Ba1** and **Sm1**

(**Figure 3**). These differences suggest that the nature of the counteranion can affect the packing of the crystal structure, resulting in various conformations of DB30C10 around the M^{2+} center.

Notably, although the synthesis and crystallization of **Ra1** was performed identically to **Ba1**, the complexes were not isostructural. **Ra1** instead crystallized in the triclinic $P\bar{1}$ space group, and the conformation of DB30C10 in **Ra1** resembled that of **Ba2** and **Ba3** (**Figure 3**). In this case, the disparate configurations between **Ba1** and **Ra1** cannot be attributed to the presence of different counteranions in the crystal lattice because both complexes possess two outer-sphere BPh_4^- anions. Rather, these results suggest that the size of the M^{2+} center plays an important role in the conformation adopted by DB30C10. Specifically, the 8-coordinate ionic radii established for Sm^{2+} and Ba^{2+} are 1.27 Å and 1.42 Å, respectively, whereas the ionic radius of Ra^{2+} is 1.48 Å.[20] Thus, we hypothesize that the Ra^{2+} ion may be too large to be optimally accommodated by DB30C10 in the "Pac-Man" configuration.

A comparison of the interatomic distances of **Ra1** versus the conformationally similar **Ba2** and **Ba3** structures also reveals marked differences between Ra^{2+} and Ba^{2+} in the context of bonding. The $M–O_{ether}$ bond distances in **Ra1** range from 2.907(2) Å to 3.086(2) Å, which are slightly longer than the bond distances in **Ba2** and **Ba3** (2.789–3.164 Å). These longer bond distances are likely explained by the larger ionic radius of Ra^{2+} in comparison to Ba^{2+}. More pronounced, however, is the difference in the interatomic distances between the metal center and the coordinated water molecule in these structures. Specifically, the $Ba–O_{water}$ bond distances in **Ba2** and **Ba3** are 2.763 Å and 2.780 Å, respectively. By contrast, the $Ra–O_{water}$ bond distance in **Ra1** is approximately 0.14 Å longer (2.913 Å) (see **Table 1** for crystallographic data). This bond distance in **Ra1** is significantly longer than expected considering the 0.06 Å difference in ionic radii between Ba^{2+} and Ra^{2+}, which suggests that Ra^{2+} binds water more weakly than does Ba^{2+}. Our results are consistent with those reported recently for the Ra–aquo ion, for which the average $Ra–O_{water}$ bond was estimated to be 2.86 ± 0.06 Å.[19] Furthermore, when examining other alkaline earth crown ether complexes possessing coordinated water molecules, there appears to be a trend of increasing $M^{2+}–O_{water}$ bond distances and decreasing $M^{2+}–O_{water}$ binding energies with increasing ionic radii.[39–44] These trends in the alkaline earth series, coupled with the $Ra–O_{water}$ bond length reported in this work, support the concept of greater lability of bound water molecules in Ra^{2+} compounds compared to Ba^{2+} compounds.

In summary, we have prepared and characterized the first molecular Ra^{2+} coordination compound in the solid-state by scXRD, to the best of our knowledge. In comparing the Ra^{2+} complex to other crystal structures of DB30C10 complexed with Ba^{2+} and Sm^{2+}, two chemically similar divalent ions, we highlight key differences in their structural conformation and in the lability of coordinated water. Collectively, our results emphasize the disparate coordination chemistries of Ra^{2+} and Ba^{2+}, such that using Ba^{2+} as a nonradioactive surrogate to model the behavior of Ra^{2+} in studies must be done so with caution. We anticipate that the crystallization methods reported in this study will guide other researchers in their efforts to advance the solid-state chemistry of Ra^{2+}. Additionally, these

results in the solid-state complement our solution-state efforts to characterize the complexation thermodynamics of Ra^{2+} in aqueous media,[19] and we expect that the combined insight from these studies will be helpful in rationally designing new chelators for ^{223}Ra-based TAT. To advance this endeavor, efforts are ongoing in our lab to synthesize and characterize other related Ra^{2+} complexes by scXRD.

Methods:

Preparations. *Caution! ^{226}Ra is a radioactive material ($t_{1/2}$ = 1600 y) that decays to ^{222}Rn, followed by a series of short-lived bismuth, lead, and polonium daughters. All manipulations of material containing ^{226}Ra were carefully carried out in a radiological laboratory equipped with HEPA filters and continuously monitored for contamination.*

The synthesis of **Ba1** and **Ra1** were carried out in open-front fume hoods with no attempt to exclude moisture or oxygen. All reagents were used as received from the manufacturer without any further purification. $Ba(NO_3)_2$ (Fisher Scientific), D_2O (Sigma), deionized water ($\geq$18 MΩ·cm), MeCN (VWR), Bu_4NBPh_4 (Sigma), DB30C10 (Parish Chemicals), and immersion oil (Type NVH, Electron Microscopy Services) were used for the syntheses and preparations of **Ba1** and **Ra1**. ^{226}Ra (97.1% purity by mass; < 0.1% Ba) was purchased as a dried down nitrate salt from the National Isotope Development Center and used without further purification. It was delivered in a vial equipped with a septum cap. To minimize the risk of a contamination event, the solid was reconstituted with D_2O via syringe to a concentration of ~50 mM (11.3 mCi/mL) prior to uncapping the vial.

The synthesis of **Ba1** was carried out by mixing MeCN solutions of 140 μL of 17 mM DB30C10 (1.3 mg, 2.4 μmol) with 280 μL of 17 mM Bu_4NBPh_4 (2.7 mg, 4.8 μmol) in a 3 mL glass vial. Then, 150 μL of deionized water was added to the vial. After mixing, 47.5 μL of 50 mM $Ba(NO_3)_2$ (0.6 mg, 2.4 μmol) in H_2O or D_2O was added to the reaction solution, at which time a precipitate formed. The suspension was then briefly stirred to redissolve the precipitate. The vial was covered with Parafilm® and punctured once with an 18-gauge needle to allow for slow evaporation. Rectangular, colorless blocks of the formula $[Ba(DB30C10)][BPh_4]_2 \cdot MeCN$ formed overnight.

The synthesis of **Ra1** was performed in a HEPA-filtered fume hood using a procedure identical to that described above for **Ba1**, except that the reagents were scaled appropriately such that the same number of moles were used in both experiments. Briefly, upon addition of $Ra(NO_3)_2$ in D_2O to the reaction solution, a precipitate formed like that observed for the **Ba1** reaction. After stirring to redissolve the precipitate, the vial was covered with Parafilm® and punctured once. This method allows for slow evaporation while minimizing the risk for external contamination by any radon gas that may be released from solution. After sitting overnight, pale-yellow irregular blocks of the formula $[Ra(DB30C10)(H_2O/D_2O)][BPh_4]_2$ formed.

ScXRD Studies. X-ray diffraction measurements were performed on a Bruker D8 Venture diffractometer equipped with a Ims 3.0 molybdenum X-ray source (l = 0.71073 Å). Apex

IV software was used for data collection and unit cell determination. The crystal structure was solved using SHELX software within the *OLEX2* GUI software.[45,46] Crystals of **Ba1** were coated with immersion oil and mounted on a Mitegen Cryoloop. The collection was performed at room temperature to enable comparison to the Ra structure (*vide infra*). Crystals of **Ra1** were placed in immersion oil and then mounted to a Mitegen Cryoloop with quick setting epoxy. After the epoxy had set, a plastic sheath was epoxied to the Mitegen Cryoloop for further contamination control.[47] The epoxied Mitegen mount was surveyed for contamination before mounting on the scXRD instrument. This plastic sheath method is not optimal for cold data collections due to icing. Therefore, the collection was performed at room temperature. The CIF files within this report were archived in the Cambridge Crystal Data Center under CCDC depositions 2244265 and 2244266.

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Contributions
F. D. W. constructed and executed the synthesis, preparation, imaging, and characterization of Ra/Ba complexes. N. A. T. developed the concept of Ra scXRD and prepared the stock solution of [226]Ra. S. K. C. aided in manipulations for scXRD and [226]Ra imaging experiments. M. E. S. aided in preparing the fume hood, prepping the [226]Ra stock solution, and setting up the [226]Ra reaction.

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Ethic Declarations
The authors declare no competing interests.

Figures:

Figure 1 (left): The molecular crystal structure of (left) [Ba(DB30C10)][BPh$_4$]$_2$·MeCN (**Ba1**) and (right) [Ra(DB30C10)(H$_2$O)][BPh$_4$]$_2$ (**Ra1**). Thermal ellipsoids are drawn at the 50% probability level. The Ra^{2+} compound forms an 11-coordinate structure in comparison to the 10-coordinate Ba^{2+} structure due to an additional water molecule in the coordination sphere. Hydrogen atoms, BPh$_4$ anions, and solvent molecules have been omitted for clarity.

Figure 2. Images of **Ra1** crystals (a) picked for scXRD, (b) in immersion oil, and (c) left in the reaction solution. Crystals left in immersion oil became dark yellow after sitting for 48 hours, while crystals left in the reaction solution began degrading after 48 hours. Colorless crystals in the reaction vial were confirmed as unreacted Bu$_4$NBPh$_4$.

Figure 3. The different conformations of DB30C10 observed in complexes of Sm^{2+}, Ba^{2+}, and Ra^{2+}. Only **Sm1** (a) and **Ba1** (b) exhibit π-π stacking of the phenyl groups. The conformation of DB30C10 around the metal center is driven by cation radii and packing of the corresponding counteranions.

Table 1. Crystallographic information of complexes discussed within this work.

Compound	Space Group	Coordination Number	Average M–O_{ether} Bond Distance (Å)	M–O_{water} Bond Distance (Å)
[Sm(DB30C10)][BPh4]2[37]	*C2/c*	10	2.707	-
[Ba(DB30C10)][BPh4]2 (this work)	*C2/c*	10	2.811	-
[Ba(DB30C10)(H2O)][Bi2Cl8]2[35]	*P1̄*	11	2.939	2.763
[Ba(DB30C10)(H2O)][Co(NCS4)]2[36]	*P1̄*	11	2.943	2.780
[Ra(DB30C10)(H2O)][BPh4]2 (this work)	*P1̄*	11	2.949	2.913