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Astatine partitioning between nitric acid and conventional solvents: Indication of covalency in ketone complexation of AtO^+

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Astatine-211 has been produced at Texas A&M University on the K150 cyclotron, with a yield of 890 ± 80 MBq through the $^{209}Bi(\alpha,2n)^{211}At$ reaction via an 8 h bombardment with a beam current of 4–8 μA and an α-particle beam energy of 28.8 MeV. The target was then dissolved in HNO_3 and the extraction of ^{211}At was investigated into a variety of organic solvents in 1–3 M HNO_3. Extraction of ^{211}At with distribution ratios as high as 11.3 ± 0.6, 12.3 ± 0.8, 42.2 ± 2.2, 69 ± 4, and 95 ± 6 were observed for diisopropyl ether, 1-decanol, 1-octanol, 3-octanone, and methyl isobutyl ketone, respectively, while the distribution ratios for ^{207}Bi were ≤ 0.05 in all cases. The extraction of ^{211}At into both methyl isobutyl ketone and 3-octanone showed a strong, linear dependence on the HNO_3 initial aqueous concentration and better extraction than other solvents. DFT calculations show stronger binding between the carbonyl oxygen of the ketone and the At metal center.

The precarious nature of astatine's position on the periodic table, as the fifth element in the halogen series and often included as the heaviest member of the metalloids, gives rise to its diverse chemistry.[1–4] One aspect of the diverse nature of At chemistry is that it has been described to exist in six different oxidation states At^-, At^0, At^+, At^{3+}, At^{5+}, and At^{7+}; however, a thorough understanding of the speciation of each oxidation state has been elusive.[5] Moreover, as a heavy element (Z = 85), At not only has a large atomic radius (0.45 Å),[4] but also exhibits relativistic effects in its electronic structure,[2] further complicating comparison of the experiment to predicted properties based on computational models. Relativistic effects are generally divided into the scalar and the spin-dependent-terms. The scalar-term accounts for the relativistic increases in mass of the inner-core electrons, resulting from their acceleration to near the speed of light. This mass increase causes the valence *s* and *p* shells to contract into a more energetically stabilized arrangement. The spin-dependent-term accounts for interaction between the spin of the electron with magnetic fields induced by nearby charged particles and their relative motion to that of the electron. The coupling of the electron spin and orbital momentum, known as spin-orbit coupling, is similar in its order of magnitude to the scalar-term for heavy *p*-elements, like At. Consequently, spin-orbit coupling has dramatic effects on the chemical properties of At and its complexes.[6–10] Predictions accounting for the spin-orbit coupling of At have suggested changes in several properties including a roughly 10% decrease in electronegativity,[11] approximately 20% increase in the polarizability of the astatide (At^-) species,[10] the vibrational frequency of At_2 weakens by ~ 40%,[12] the reversal of the bond polarization, the dipole moment, for the H-At molecule,[13,14] among others.

Much of the diverse chemistry of At has been left unexplored,[15,16] complicated by the fact At has the lowest abundance of all naturally occurring elements on the earth, estimated at 0.07 g.[17] The low abundance of At is a result of having no stable isotopes, and relatively short half-lives for its two longest lived isotopes, roughly 7.2 h and 8.1 h for ^{211}At and ^{210}At, respectively. By and large, ^{211}At has garnered the majority of interest, with its promising application as an alpha-emitter (α-emitter) in targeted alpha therapy (TAT) drugs.[18–23] The rising interest in TAT drugs has stemmed from the remarkable clinical performance in the treatment of metastatic castration-resistant prostate cancer using the α-emitter ^{223}Ra dichloride (Xofigo®),[24] which emphasizes the need to develop α-emitting radioisotopes to label a variety of agents (typically monoclonal antibodies) with the capacity to target localized or spread malignancies adjacent to critical organs. As was pointed out by several investigators, the major impediment to the use of the α-emitting radioisotope ^{211}At in clinical trials is its limited availability.[25–27] Production of ^{211}At through high-energy spallation is not an efficient or economically feasible alternative requiring large capital investments and long processing times to extract the radioisotope. Irradiation of solid bismuth targets with α-particle beams in the 28.5–31 MeV energy range has been

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shown to produce reasonable amounts of ^{211}At through the ^{209}Bi(α,2n)^{211}At reaction.[25–27] Despite the promise of ^{211}At, there have been a limited number of studies progressing to clinical trials. The first, a study by Zalutsky *et al.*,[28] investigated the treatment of malignant brain tumors in 2008, while the second, a study by Andersson *et al.*,[21] examined the treatment of ovarian cancer in 2009. Finally, an ongoing study is being carried out for treatment of advanced hematopoietic malignancies.[18] One of the major reasons for the limited number of clinical trials is only about 30 cyclotrons world-wide have the ability to produce usable quantities of this nuclide.[19]

In addition to the interest from the radiopharmaceutical community, the recent discovery of element 117, tennessine (Ts),[29,30] has increased the general interest in At as a homologue to this super-heavy element.[1,2,31] While Ts has yet to display halogen-like chemical properties,[32] a better understanding of At could influence experimental design, increasing the opportunity to observe the chemical behavior of Ts.[14,33] In either case, whether developing chemical mechanisms for radiopharmaceutical applications or exploring the frontiers of the periodic table, a rapid and simple approach to At recovery and isolation would be advantageous to expanding the body of knowledge leading to new discoveries with this interesting element. In the current work, we present our recent findings on the extraction of At from nitric acid systems, which indicate covalency in the interaction of an organic ligand with the extracted At species. Additionally, this is a first step towards reducing the time required to recover ^{211}At from an irradiated target to a fraction of current approaches being utilized.[34–37]

To begin with, ^{211}At was produced on the K150 variable energy cyclotron at Texas A&M via the ^{209}Bi(α,2n)^{211}At nuclear reaction by α-particle bombardment of a natural Bi metal water-cooled target on an Al substrate for approximately 8 h with a beam current of 4–8 μA and an α-particle beam energy of 28.8 MeV. Following the α-particle bombardment, roughly one third of the target was dissolved in 15 mL of 10.5 M HNO_3. This solution was then sampled and the production yield was determined to be 890 ± 80 MBq of ^{211}At at the end of bombardment. The remainder of the solution was spiked with 2.65 kBq of ^{207}Bi and diluted to 20 mL. The resulting solution was comprised of 750 mM Bi (132 Bq mL^{-1} ^{207}Bi) and 14.8 kBq mL^{-1} ^{211}At with a HNO_3 concentration of 5.6 M. The production rate of ^{211}At, 42 ± 4 MBq h^{-1} pμA^{-1}, was a factor of 1.2–3.4× larger than previous attempts at Texas A&M[38] and was comparable to the ~50 and ~64 MBq h^{-1} pμA^{-1} at UWMCF Scanditronix MC-50 positive-ion source cyclotron[39] and at the cyclotron of the CNRS at the CEMHTI[40], respectively.

As mentioned earlier, the short half-life of ^{211}At ($t_{1/2}$ ~7.2 h) necessitates rapid chemistry to achieve a separation from the host matrix, Bi metal in the case of the cyclotron-produced, ^{209}Bi(α,2n)^{211}At nuclear reaction. In order to realize this rapid chemistry, a series of extractions from HNO_3 at various concentrations into several organic solvents were investigated. First, simple straight-chain alcohols, 1-octanol and 1-decanol, were used to extract ^{211}At from 1–3 M HNO_3, as shown in Fig. 1. The extraction of ^{211}At into 1-octanol yielded distribution ratio (D) values of roughly 37.9 ± 2.3, 42.0 ± 2.2, and 38.9 ± 2.1 at HNO_3 concentrations of 1, 2, and 3 M, respectively; which were comparable to those observed by Ekberg *et al.*,[41] roughly 34 in 1 M HNO_3 and 35 in 2 M HNO_3. Thus, the overall trends were similar, with the maximum extraction occurring around 2 M HNO_3. Conversely, the D-values for ^{207}Bi into 1-octanol were ≤ 0.05 for all three acidities, which corresponds to all the activity being present in the aqueous phase, while the amount of ^{207}Bi was below the detection limit in the organic phase. Increasing the aliphatic chain-length from C_8 to C_{10} negatively impacted the extraction of ^{211}At, with D-values of 12.3 ± 0.8 in 1 M HNO_3, 8.4 ± 0.4 in 2 M HNO_3, and 4.6 ± 0.2 in 3 M HNO_3, reducing the extractability by a factor of roughly 3, 5, and 9-fold, respectively. Additionally, the maximum extraction into 1-decanol appears to occur ≤1 M HNO_3, as the decrease in D-value is linear as the HNO_3 concentration is increased from 1 to 3 M. Again, these results are in agreement with Ekberg and co-workers,[41] as the maximum extraction was observed in 4 M HNO_3 for hexanol (C_6), indicating an interplay between the influence of aliphatic chain-length and HNO_3 concentration on the maximum extraction. The D-values for ^{207}Bi were ≤ 0.05 into 1-decanol. While the exact mechanism of metal extraction along with the HNO_3[42] is still unknown, it seems the more non-polar nature of 1-decanol inhibits extraction (see Table S1). This is most likely a result originating from the requirement of maintaining charge balance, which necessitates the difficult co-extraction of the nitrate counter anion into the organic phase along with the cationic At species. Assuming At(III) the AtO^+ molecular cation is the extracted species, as Champion *et al.*[3] have suggested based on experimental data coupled with DFT calculations, the following equilibrium describes the extraction:

$$AtO^+ + NO_3^- \rightleftharpoons \overline{AtO(NO_3)} \qquad (1)$$

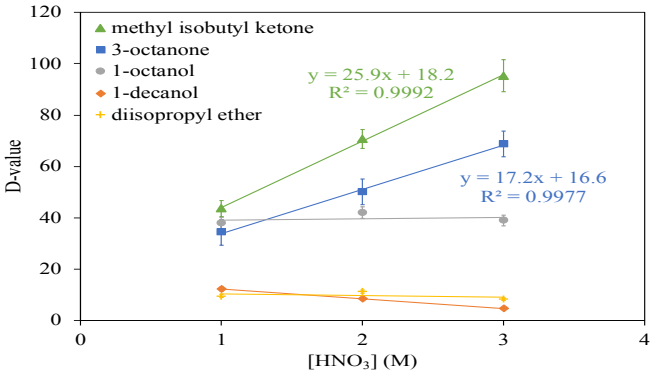

Fig. 1 D-values of the extraction of ^{211}At into different organic solvents as a function of initial aqueous HNO_3 concentration. Solid lines for visual aid. Note D-values for Bi were ≤ 0.05 in all cases.

Both Ekberg *et al*. and Champion *et al.* have concluded the AtO^+ species prefers a more polar solvent, a conclusion also supported by current findings.

To test this further, a less polar solvent, diisopropyl ether, and a more polar solvent, methyl isobutyl ketone, were investigated (see Table S1). As expected, the ^{211}At extraction into diisopropyl ether was in the range of the 1-decanol, with the ^{207}Bi continuing to remain in the aqueous phase (D-value

≤ 0.05). More interestingly, ^{211}At behaved significantly different in the methyl isobutyl ketone system compared to the other solvent systems studied, displaying a strong HNO_3 dependence. The ^{211}At extraction into methyl isobutyl ketone was slightly higher from that of 1-octanol in 1 M HNO_3, while the D-values increase by a factor of roughly 1.7x and 2.4x when the HNO_3 concentration is increased to 2 and 3 M, respectively. These result are in line with Alliot *et al*.[40] who also observed a strong affinity of At by methyl isobutyl ketone, however, no discussion on the impact of acidity the extraction or the interaction which may be occurring was offered. The ^{207}Bi, on the other hand, showed similar behavior as the other systems studied, with very low D-values, ≤0.05. A second ketone, 3-octanone, with a polarity similar to 1-octanol (see Table S1), was then tested to determine if solvation effects of the more polar methyl isobutyl ketone was the driving force for the extraction or if the carbonyl functional group of the ketones were playing a major role. As with methyl isobutyl ketone, ^{211}At extraction into 3-octanone appears to be similar to that of 1-octanol in 1 M HNO_3, while the D-values increase by a factor of roughly 1.2x and 1.8x when the HNO_3 concentration is increased to 2 and 3 M, respectively. Again, the ^{207}Bi remained in the aqueous phase (D-value ≤ 0.05). The enhanced extraction of AtO^+ by ketones over alcohols has also been demonstrated by employing DFT calculations, which showed the free energy of binding for acetone to be 4.6 kcal mol^{-1} stronger than that for isopropyl alcohol. The predicted ketone AtO^+ will be discussed in detail below.

The overall behavior of ^{211}At extraction in both the 3-octanone and methyl isobutyl ketone systems was similar, showing a linear relationship between ^{211}At D-values and the initial HNO_3 concentration in the aqueous phase between 1–3 M HNO_3, while the slope of the methyl isobutyl ketone system was roughly 50% steeper than that of the 3-octanone system. The direct correlation between D-values of ^{211}At into both methyl isobutyl ketone and 3-octanone as a function of HNO_3 concentration may indicate an interaction between the ketone and At metal center. Currently, the nature of such an interaction is not completely clear. Density functional calculations (DFT, computational details in SI) show a strong donor-acceptor interaction between the empty π* orbital of the AtO^+ and the 'sp^2' O lone pair of the acetone (see Fig. 2). The NBO analysis of the AtO+_isopropanol (see Fig. S5) indicates its sp3 O lone pair donates 0.11 fewer electrons to AtO+ than the sp2 O lone pair orbital in AtO+_acetone. This interaction is 4.6 kcal/mol stronger than the corresponding interaction of the AtO^+ with the 'sp^3' O lone pair of isopropyl alcohol, while the solvent corrected Gibbs free energy of binding (see Table S3) is still larger for AtO^+_acetone than for AtO^+_isopropanol by 2.1 kcal/mol. Thus, ketones show significantly strong binding to AtO^+, which leads to better extraction. Again, the exact mechanism of AtO^+ extraction is unknown, but a brief discussion on the nature of the interface is offered. At the H_2O-organic interface the organic molecules will have their polar end (oxygen) in (at) the H_2O layer. The AtO^+ and NO_3^- will be solvent separated in the H_2O layer so the early, and key interaction, of these species with respect to extraction of AtO^+ will be the binding of AtO^+ with the oxygen of the organic molecule. The movement of the AtO^+ into the organic layer will necessarily need to be accompanied by the NO_3^-, but this last interaction will not be the key to the extraction.

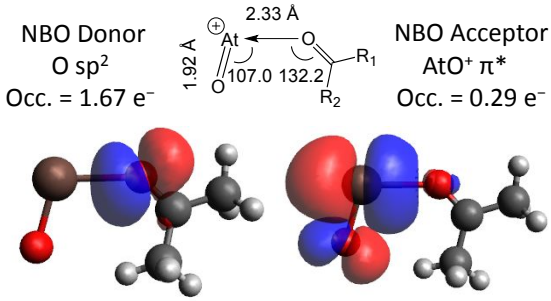

Fig. 2 The DFT geometry for the singlet state of the AtO^+ acetone complex (top center) shows a strongly bent structure that suggests an At–O bond formed from the donation of an lone pair (sp^2) into the π* orbital of AtO^+. The natural bond orbital (NBO) analysis of this AtO^+ acetone complex confirms a donor-acceptor bond in which ~0.3 electrons are donated from the O lone pair (left) to the previously empty AtO^+ π* orbital (right).

In conclusion, the K150 cyclotron at Texas A&M has been utilized to produce ^{211}At through the ^{209}Bi(α,2n)^{211}At reaction via α-beam bombardment at 28.8 MeV and the target was dissolved in nitric acid to produce an ^{211}At stock solution. The extraction of ^{211}At, presumably as the AtO^+ molecular cation, into five organic solvents has been studied as a function of HNO_3 aqueous concentration. The organic solvents were selected for their difference in polarity, with the *a priori* assumption that increased polarity would enhance extraction, an effect confirmed within this study. However, of greater significance, there appears to be an interaction between the ketone frontier orbitals with the π* AtO^+ molecular orbital, which may be evidence of covalency in the coordination of the At metal center by the ketone ligand. These results help validate the loss of degeneracy in the π* highest occupied molecular orbital (HOMO) to produce a closed shell configuration, which has been predicted computationally. Future studies will endeavor to elucidate the AtO^+ covalency by studying other ligands with π-donor and π-acceptor properties. The effective extraction of At out of HNO_3 could drastically reduce the amount of time required to purify and isolate At for future investigations.

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Conflicts of interest

The authors declare the following competing financial interest(s): J.D.B., E.E.T., and L.A.M. and S.J.Y. have filed a provisional patent application relating to this work.

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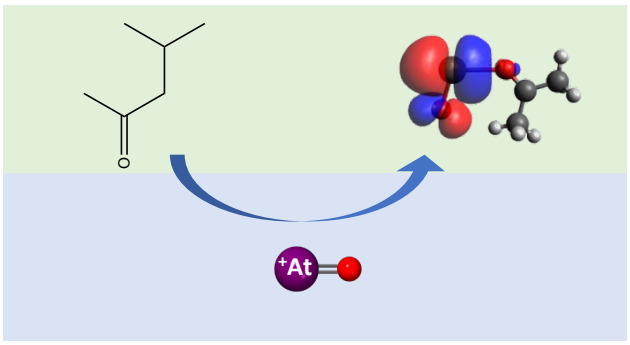

The extraction of ^{211}At into ketones out of 1–3 M nitric acid show better extraction than other solvents, with DFT calculations showing stronger binding between the carbonyl oxygen of the ketone and the At metal center.