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Bambusuril as an effective astatide sequestering agent by hydrogen bonding†

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Herein, we report a molecular cage allowing strong chelation of the ²¹¹At radioanion. Propargylated bambus[6]uril shows good affinity towards iodide and astatide radiohalides, affording promising inclusion complexes that are stable in phosphate buffered saline and human serum. Density functional theory calculations support the presence of C–H···At non-covalent cooperative interactions governing the formation of astatinated cage complexes. To our knowledge, this work is the first to report ²¹¹At-labeling using encapsulation via hydrogen bonds, which opens new perspectives in the design of ²¹¹At[−]-based radiopharmaceuticals.

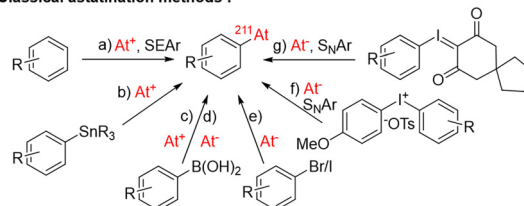
Radioisotopes of heavy halogens such as iodine I and astatine At are of significant interest in nuclear medicine for both imaging and therapeutic applications.¹ Astatine, the heaviest halogen of group 17 periodic elements, exists as 32 unstable isotopes. Among them, ²¹¹At is considered as one of the most promising α -emitting radionuclides for targeted alpha therapy in cancer treatment. ²¹¹At exhibits several favorable properties for medical applications: a simple decay scheme leading in 100% of cases to the emission of one high energy (5.9–7.4 MeV), short track (50–90 μ m) α -particle limiting irradiation of nearby healthy tissues, a short half-life (7.2 h) and a scalable production from a cheap ²⁰⁹Bi. Together, these features make ²¹¹At a radionuclide with high potential for effective targeted α -therapies.^{2,3} Consequently, several clinical trials of ²¹¹At-labeled drugs are currently underway.⁴ Among its identified oxidation states (−1, 0, 1, 5, and 7), astatide At[−] is the easiest species to obtain due to its stability in reducing media over a broad pH range.⁵ As astatine has no stable isotope, iodine, its closest halogen neighbour with similar physico-chemical properties, is commonly used as a model of At. Therefore, iodine or general halogen chemistry is often applied to astatination although differences in chemical reactivity between the two elements

have also been reported.⁶ Classical methods for At[−] labelling generally afford aryl astatine–carbon bonds either by nucleophilic or electrophilic reactions (see Fig. 1(A)). Electrophilic substitutions occur with At⁺ species including direct aromatic electrophilic substitution (SEAr, Fig. 1(a)), astatodestannylation (Fig. 1(b)), and astatodeboronation (Fig. 1(c)), while nucleophilic substitutions with At[−] species can be carried out through copper catalyzed astatodeboronation (Fig. 1(d)), halogen exchange (Fig. 1(e)), and S_NAr reactions reported with arylodonium salts (Fig. 1(f)) or spirocyclic arylodonium ylides (Fig. 1(g)).⁷

Although several radiosynthesis routes can provide astatide-aryl compounds, their potential for *in vivo* applications is questioned by the low C–At bond stability predicted by theoretical calculations⁸ and confirmed experimentally, leading to uncontrolled release of At in healthy organs.⁹ To limit de-astatination, other bonding modalities have been studied such as B–At bonds in boron clusters;¹⁰ metal–At bonds such as AtHg,¹¹ Rh(III) or Ir(III)–(16aneS₄-diol)–At,¹² and Rh(I)¹³ or Au(I)–NHC–At¹⁴ complexes, which are, apart from metal toxicity, promising strategies for At-labeling.

In this context, using host molecules, promoting noncovalent interactions with the anion guest, can be an interesting approach to capture At[−] through a host–guest complex

A) Classical astatination methods :



B) This work :

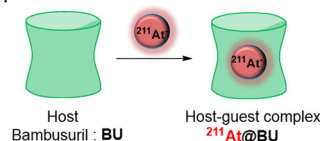


Fig. 1 (A) Classical methods for astatination, and (B) our approach.

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(Fig. 1(B), this work). Nevertheless, encapsulation of anions with a large atomic radius, low charge density and low ability to engage in hydrogen bonds is an important challenge.¹⁵ In this regard, bambus[6]jurils (BUs), synthetic neutral cavitands formed by six glycoluril units connected by six methylene bridges,¹⁶ are known as the best large anion chelators, and their complexation properties for iodide, phosphate and perchlorate anions have been described.¹⁷ Surprisingly, to the best of our knowledge, the use of BUs as radioactive anion-sequestering agents has not been reported so far. In this communication, we demonstrate the ability of R₁₂BU[6] (R = propargyl) **BU 1** to act as a powerful ¹²⁵I⁻ and ²¹¹At⁻ receptor by sequestering these radioactive anions, thanks to twelve cooperative hydrogen-radioanion interactions. While our experimental data highlight the (radio)stability of the obtained radioactive complexes, DFT calculations were employed to gain deeper insight into the interaction energies between the host (**BU**) and the two radioactive guests, ¹²⁵I and ²¹¹At.

As we previously reported, **BU 1** (Scheme 1) exhibits high affinity for iodide, and crystals of I@propargyl₁₂ **BU 2** confirmed the presence of the I⁻ anion within **BU**'s cavity.¹⁸ Accordingly, **BU 1** was selected as a potential receptor for ²¹¹At⁻. First, we investigated the binding properties of Br⁻@**BU 1**¹⁹ with I⁻ by ¹H NMR titrations (see the ESI† for experimental procedures and data processing details). In CD₃CN, the stepwise addition of I⁻ to **BU 1** resulted in a slow exchange on the NMR timescale, indicating a strong affinity of **BU 1** for I⁻ ($K_a = 4.4 \times 10^3 \text{ M}^{-1}$ in CD₃CN, see Fig. S1 and S2 in the ESI†). This result is consistent with the well-established higher affinity of bambusurils for I⁻ compared to Br⁻ anions.^{17,20} The interaction between **BU 1** and I⁻ anions was also evaluated using isothermal titration calorimetry (ITC). In MeOH, **BU 1** exhibited a strong affinity for iodide ($K_a = 2.1 \times 10^6 \text{ M}^{-1}$, Fig. S3, ESI†). The ITC data clearly indicate that the formation of the I@**BU 2** complex is enthalpy-driven ($\Delta H = -20.9 \text{ kJ mol}^{-1}$) and follows a 1 : 1 binding stoichiometry (Fig. S3, ESI†).²⁰ The measured affinity for iodide is comparable to values previously reported for bambusurils.¹⁷

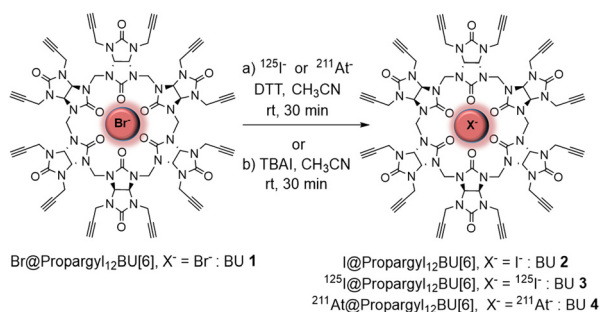
Based on these results, we investigated the complexation of ²¹¹At and ¹²⁵I radioanions (used as a model of ²¹¹At) with **BU 1** (Scheme 1). Preliminary experiments with sodium sulfite (Na₂SO₃), sodium metabisulfite (Na₂S₂O₅), and dithiothreitol

(DTT) were performed to identify a reductive agent capable of stabilizing ²¹¹At as the astatide species, amendable for the complexation reaction with **BU 1** in CH₃CN (see Table S1 and Fig. S4, ESI†). DTT appeared as the best reductive agent for astatine complexation with **BU 1**.

Although commercially available ¹²⁵I is provided as sodium iodide in basic solution (NaOH), DTT was added to the ¹²⁵I[NaI] solution to study the complexation under the same experimental conditions as those used for ²¹¹At. The non-radioactive iodinated complex I@propargyl₁₂**BU 2**¹⁸ was first prepared as an analytical reference of ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** radiocomplexes. **BU 2** was synthesized from Br⁻@**BU 1** and TBAI (tetrabutylammonium iodide) in CH₃CN (90% yield), as reported in Scheme 1, conditions (b). Then, radiolabelled complexes ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** were prepared from **BU 1** (1.2 mM in CH₃CN) by adding a solution of ¹²⁵I or ²¹¹At in the presence of DTT (see ESI† and Fig. S5 for details). After 30 min at room temperature, the complexes ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** were obtained in very good radiochemical yields (RCYs), 99% and 90%, respectively. These results showed that the radiocomplexation reactions of ¹²⁵I and ²¹¹At are rapid and that the radiolabelled complexes **BU 3–4** are stable and detectable at trace radionuclide concentrations, demonstrating the capacity of **BU 1** to efficiently encapsulate radioactive iodide and astatide anions. Complexes **BU 3–4** were identified by radio-HPLC analysis. As expected, nearly identical retention times were obtained for ²¹¹At@**BU 4**, ¹²⁵I@**BU 3** and non-radioactive iodinated reference I@**BU 2** (see Fig. S6, ESI†).

Subsequently, various **BU** concentrations and solvents were studied as they can influence radioanion complexation (see Fig. S7–S10, ESI†). ¹²⁵I and ²¹¹At radioanions reacted at room temperature for 30 min with varying concentrations of **BU 1** in CH₃CN, CH₂Cl₂ or CHCl₃ solutions (see Fig. 2(A) and (B)). Starting from **BU 1** (a concentration of 293.9 μM), the corresponding complexes ²¹¹At@**BU 4** (Fig. 2(A) and Fig. S7, ESI†) and ¹²⁵I@**BU 3** (Fig. 2(B) and Fig. S8 and S9, ESI†) were obtained in high RCYs (90%, 88%, and 91%) for ²¹¹At@**BU 4** and (99%, 99%, and 99%) for ¹²⁵I@**BU 3** in CH₃CN, CH₂Cl₂, and CHCl₃, respectively. The efficient complexation of ²¹¹At@**BU 4** in CHCl₃ is very promising as purified ²¹¹At is frequently delivered in CHCl₃. Given the limited radiolabelling reactions described in CHCl₃, complexation can be performed immediately after astatide purification, avoiding the additional concentration evaporation step usually required. We observed that ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** complexes are formed within 10 min of reaction, indicating rapid anion capture kinetics (Fig. S9 and S10, ESI†). The radiolabelled ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** complexes were subsequently purified on a silica cartridge before further evaluation (see the ESI† for details).

Then, the stabilities of radiocomplexes ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** were evaluated in human blood serum (HS) at 37 °C and phosphate buffered saline (PBS) at room temperature (see Fig. 2(C), (D) and Fig. S11–S14, ESI†). In fact, as bambusurils have a strong affinity for anions, PBS is an interesting medium to study as it contains chlorides, at the same concentration and same pH (7.4) as in the blood, which are potential competitors of At⁻. Both ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** showed



Scheme 1 Synthesis of ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** radiocomplexes (conditions a) and I@**BU 2** (conditions b).



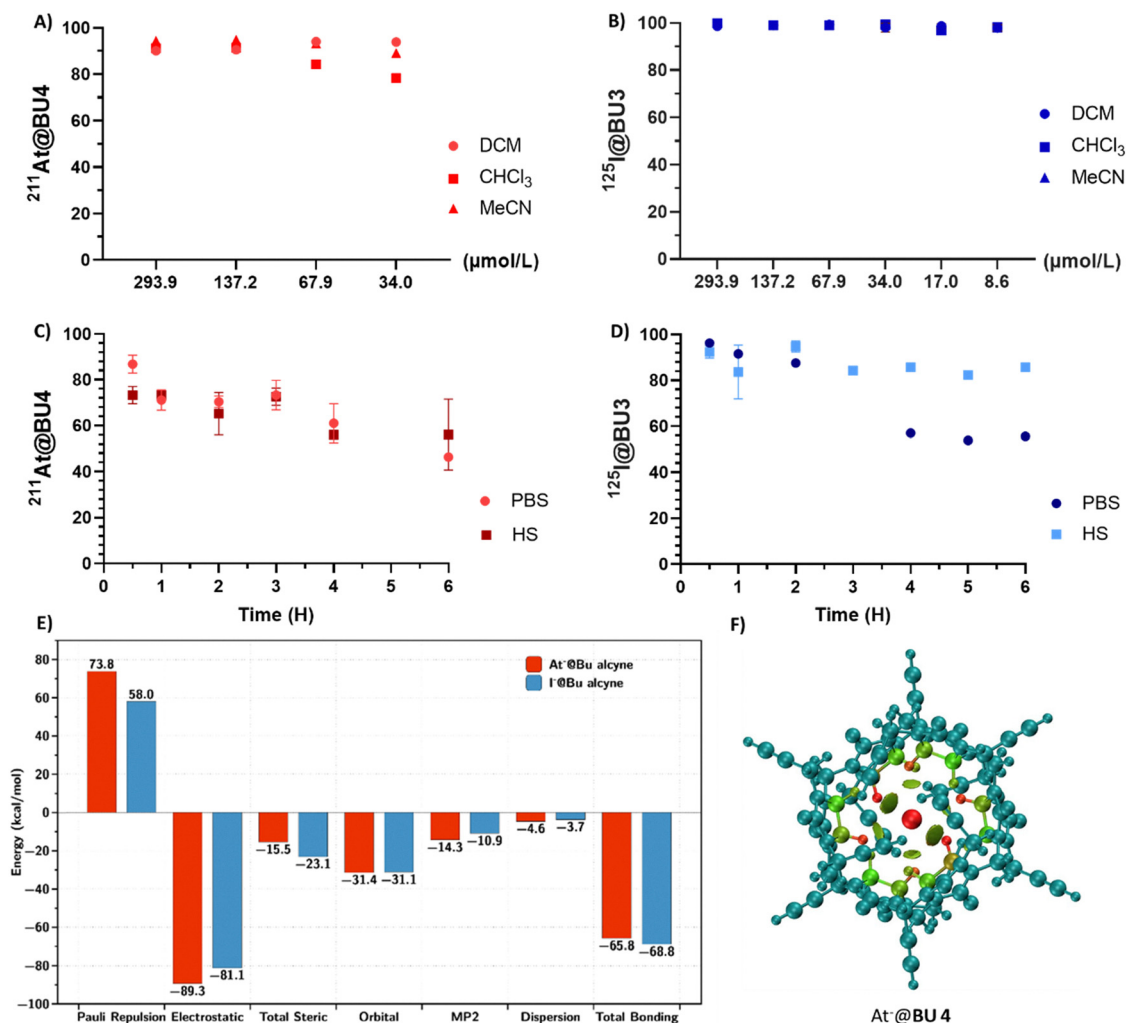


Fig. 2 (A) Influence of the **BU 1** concentration on radiolabelling of ²¹¹At in DCM (●), CHCl₃ (■), and CH₃CN (▲); (B) influence of the **BU 1** concentration on radiolabelling of ¹²⁵I in DCM (●), CHCl₃ (■), and CH₃CN (▲), standard conditions: 0.5–1.5 MBq, DTT (0.16 μmol), at rt for 30 min, with RCY determined by TLC; (C) stability study of ²¹¹At@**BU 4** in PBS (●) and in HS (■) at 37 °C; (D) stability study of ¹²⁵I@**BU 3** in PBS (●) and in HS (■) at 37 °C with RCY (%) as a function of time (hours); (E) bonding energy analysis using ZORA-DFT with the revDOD-PBE-D4 functional, focusing on interactions between At⁻/I⁻ and **BU 1** fragments (see the ESI† for details); (F) isosurface map to visualize C–H···At non-covalent interactions in **BU 4**; for ease of reading, only H atom interactions with **At** are shown. The molecular structure is color-coded according to the contribution of various atoms to the interfragment interaction, using a blue-green-red color scale. Atoms appearing in red indicate a greater involvement in the **At-BU** cage interaction, highlighting regions of stronger interactions.

some dehalogenation in PBS but remained mostly intact after 6 h of incubation (60% and 55%, respectively, see Fig. 2(C), (D) and Fig. S11, S12, ESI†). In HS, the stability of the complexes was higher than in PBS, again with a slight superiority of ¹²⁵I@**BU 3** over ²¹¹At@**BU 4** (80% and 70% of intact complex after 6 h, respectively, see Fig. 2(C) and (D) and Fig. S13 and S14, ESI†). Overall, observing the retention of ¹²⁵I and ²¹¹At in the **BU**'s cage over several hours validates our complexation concept and the strong encapsulation of these halides.

To gain deeper insights into the stability of the ¹²⁵I@**BU 3** and ²¹¹At@**BU 4** complexes, density functional theory (DFT) calculations were performed. The factors affecting the stability of the **BU 1** complexes with I⁻ and At⁻ anions were analyzed using an energy decomposition approach (see Fig. 2(E) and Fig. S15, ESI† for details). For both complexes ²¹¹At@**BU 4** and

¹²⁵I@**BU 3**, similar trends were observed in the noncovalent interactions involved. The dominant contribution to the interaction energy arises from the electrostatic interaction, accounting for approximately 64% of the total attractive interactions in both complexes. This is followed by orbital interactions, contributing around 22.5% for ²¹¹At@**BU 4** and 24.5% for ¹²⁵I@**BU 3**. To a lesser extent, the MP2 interaction energies associated with the noncovalent C–H···X interaction are also notable, with values of approximately 10.9 kcal mol⁻¹ for ²¹¹At@**BU 4** compared to 8.6 kcal mol⁻¹ for ¹²⁵I@**BU 3**. Finally, dispersion interactions further contribute to the overall stability of the complexes. The total bonding energy for I⁻ and At⁻ exhibits a difference of 3 kcal mol⁻¹, with greater stabilization observed in the ¹²⁵I@**BU 3** complex (–68.8 versus –65.8 kcal mol⁻¹ for I and At, respectively). This indicates that **BU 1** has a slightly higher



affinity for iodide than for astatide. This trend has been confirmed experimentally since the **BU 1** concentration can be decreased by 8-fold ($34 \mu\text{mol L}^{-1}$) for complexation with ^{211}At and by 32-fold ($8.6 \mu\text{mol L}^{-1}$) for $^{125}\text{I}@BU 3$ formation, without affecting the RCY (see Fig. S7–S10, ESI†). Here, the difference in the stability of the two complexes ($^{211}\text{At}@BU 4$ and $^{125}\text{I}@BU 3$) could be explained by either this slightly lower affinity of At^- versus I^- or the tendency of At^- to be oxidized in the At^+ cation exhibiting no affinity for the **BU 1** cage.⁵

Quantum chemical calculations were also employed to determine the volume of the central bambusuril cavity, for both the empty **BU** cage and the anions encapsulated (see Fig. S16 and S17, ESI†). The volume of the central cavity in the empty **BU**'s cage **BU 1** was found to be 32.6 \AA . In the presence of astatide and iodide anions, the cavity volume decreased to 32.0 \AA and 31.5 \AA , respectively. The smaller cavity size observed with iodide compared to astatine suggests a stronger interaction between the iodide anion and the cage, consistent with the interaction energy analysis. Furthermore, the non-covalent $\text{C-H}\cdots\text{I}$ and $\text{C-H}\cdots\text{At}$ interactions in $\text{I}@BU 3$ and $\text{At}@BU 4$ were analyzed using Multiwfn software²¹ (Fig. 2(F) and Fig. S14, ESI†). The computed isosurfaces (green regions) clearly highlight the presence of $\text{C-H}\cdots\text{I}$ interactions (Fig. S16(a), ESI†) and $\text{C-H}\cdots\text{At}$ interactions (Fig. 2(F) and Fig. S16(b), ESI†).

In summary, we report the first radiolabelling of a **BU**[6] cage with astatine-211 and iodine-125, yielding stable $^{211}\text{At}@BU 4$ and $^{125}\text{I}@BU 3$ complexes in both organic and biologically relevant media. These experimental and theoretical results constitute the first evidence of astatide sequestration within a host molecule through hydrogen bond interactions, demonstrated here using a bambusuril cage. To our knowledge, radiopharmaceuticals based on anion chelation remain unexplored, in contrast to the widespread use of cation-complexing agents with radiometals in nuclear medicine.²² This preliminary study thus paves the way for new opportunities in the field of radiopharmaceuticals.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.†

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