



O-53 Theoretical and experimental study of astatine-metal bonds: towards new ^{211}At -labelling approaches based on transition metal complexes

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04. Chemistry of Other Radioisotopes

Title:

Theoretical and experimental study of astatine-metal bonds: towards new ^{211}At -labelling approaches based on transition metal complexes

Abstract:

Objectives:

Astatine-211 ($T_{1/2} = 7.2\text{h}$, 1α particle/decay) is considered as a highly promising radioisotope for targeted alpha therapy. Currently, the most common method to link astatine-211 to a vector is the formation of a carbon-astatine bond. However, in vivo studies often highlight a lack of stability with released astatine-211 trapped by non-targeted organs and subsequent irradiation of healthy tissues. [1] Our aim is to develop an alternative bonding modality based on the formation of At-metal bonds, the rationale being that the astatide anion (At^-) being a soft Lewis base, it is expected to bind strongly to soft metals according to the HSAB theory.

Methods:

Rhodium(I), iridium(I) and gold(I) were initially selected according to their soft metal character. *N*-heterocyclic carbenes (NHC) were chosen as ligands since they show a high modularity in terms

of steric and electronic effects (Fig. 1A), and they strongly stabilize low valent metals. [2] In addition, anti-infectious or anticancer properties have been reported for such complexes. [3]

Series of complexes were prepared with the NHC's substituents varied from electron withdrawing to electron donating and from low to high steric hindrance. Chloride was chosen as the metal ligand to act as a leaving group for ^{211}At -labelling. After chloride to astatide exchange, the obtained compounds with most favourable RCYs were tested for their stability in various media. In parallel, molecular modelling investigations have helped to compensate the lack of stable astatine isotope that limits its experimental study. Accordingly, the complexes geometries and At–metal bond descriptors were determined by relativistic DFT calculations to estimate stabilities.

Results:

Molecular modelling showed that the bond dissociation energy ranges from 504.6 to 624.6 kJ/mol when $\text{M} = \text{Rh}(\text{I})$ to $\text{Au}(\text{I})$, respectively and $\text{R1} = \text{R2} = p\text{-nitrophenyl}$. (Fig. 1B) In addition, astatine displacement by chlorine that may occur in vivo due to the high chloride concentration appears less favourable for $\text{Au}(\text{I})$ ($\Delta G^* = +7.4$ kJ/mol) than for $\text{Rh}(\text{I})$ ($\Delta G^* = -0.3$ kJ/mol). $\text{Ir}(\text{I})$ is closer to $\text{Rh}(\text{I})$ than $\text{Au}(\text{I})$ results. The superiority of $\text{Au}(\text{I})$ complexes was also observed in our first experimental results with quantitative labelling of $\text{Au}(\text{I})$ -compounds using simple conditions (acetonitrile, 80°C , 30 min), (Fig. 1C) while other metals requested more complex conditions (iodide as carrier, phase transfer agents) to get only moderate RCYs. Accordingly, stability assays were performed with $\text{Au}(\text{I})$ compound **2** in 0.1M NaCl solution, PBS and human blood serum, for at least 7h without degradation detected.

Conclusions:

Both theoretical and experimental studies highlight the superiority of the At– $\text{Au}(\text{I})$ bond. These results warrant the design of bifunctional $\text{Au}(\text{I})$ complexes for bioconjugation to relevant vectors in vivo studies.

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- [2] M.N Hopkinson *et al.*, Nature, 2014, 510, 485-496
- [3] L. Oehninger *et al.*, Dalton Trans., 2013, 42, 3269-3284

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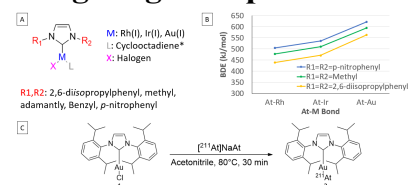


Figure 1: (A) General structure of NHC complexes studied [$^*\text{No L when } \text{M} = \text{Au}(\text{I})$] (B) $^{211}\text{At-M}$ bond dissociation energy of $\text{Rh}(\text{I})$, $\text{Ir}(\text{I})$, $\text{Au}(\text{I})$ complexes calculated at the 3c-PBEO/dhf-TZVP-3c level of theory (C) Gold(I) NHC complex radiolabelling procedure.

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