Design of Astatine(I) chelates for applications in targeted alpha therapy

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Astatine (Z=85) is a radioelement of major interest for targeted alpha-therapy owing to the short half-life of its ^{211}At isotope (7.2 hours) as well as its decay process leading to the emission of a single high-energy alpha particle. Stability of astatine radiolabeled complexes has been a challenge towards its medical application due to a significant degree of deastatination *in vivo*.[1] Binding "metallic" astatine, At^+, could be an alternative approach to existing radiolabeling strategies relying on astatine's halogen character.

Our goal is to guide the synthesis of multidentate ligands that specifically capture At^+, and establish an understanding of this cation's coordination chemistry. Given the heavy nature of astatine, a specific methodology has been established based on 2-component relativistic DFT calculations, with the influence of solvent taken into account. From the 2c-DFT calculations, complexation constants have been reported across a series of simple ligands containing oxygen, sulfur, selenium, nitrogen and/or phosphorus heteroatoms. Depending on the heteroatom, the nature of the bond formed with astatine can have varying degrees of covalency or ionicity. To characterize these bonds, partial charges (NPA, Hirschfeld) were calculated in combination with quantum chemical topology descriptors (QTAIM, ELF) that provide a deeper analysis of the total electron density. Furthermore, it has been demonstrated both experimentally and through modeling that there can be a formation of complexes with a 1:2 stoichiometry revealing a connection with astatine's property of being the strongest halogen bond donor [Figure 1].[2] Taking advantage of its metallic and halogen properties, various chelating agents have been designed.

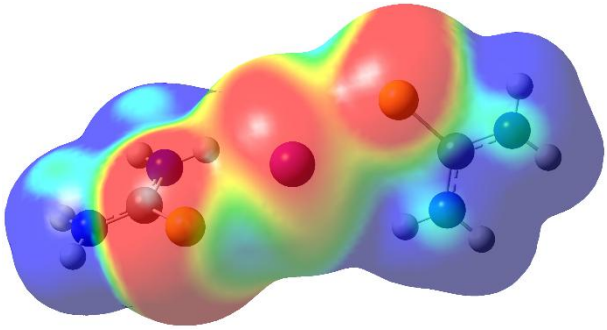

Figure 1: Electrostatic potential surface of a 1:2 stoichiometric complex (blue = low electron density, red = high electron density)

References:

[1] Guerard, F.; Maingueneau, C.; Liu, L.; Eychenne R.; Gestin, J. F.; Montavon, G.; Galland, N. Advances in the Chemistry of Astatine and Implications for the Development of Radiopharmaceuticals. Acc. Chem. Res. **54** (16), 3264–3275 (2021)

[2] Liu, L.; Rahali, S.; Maurice, R.; Gomez Pech, C.; Montavon, G.; Le Questel, J-Y.; Graton, J.; Champion, J.; Galland, G. An Expanded Halogen Bonding Scale Using Astatine. Chem. Sci. 12, 10855-10861 (2021)