Stable Astatine-211 labeling assisted by charge-shift bonding

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A growing attention is seen in one of the isotopes of astatine, $^{211}$At which has a half-life of 7.2h and emits high-energy $\alpha$ particle (5.9-7.4 MeV) upon decay with a short path length (80-100 μm). Application of $^{211}$At for cytotoxicity for nearby malignant cells in targeted $\alpha$ therapy of cancers is of particular interest.1 Yet, the main challenge against its successful use, is the production of an in vivo stable $^{211}$At-labelled motif that would avoid its indiscriminate release in non-targeted tissues. This is especially owing to the limited known chemistry of this rarest radioelement. Following earlier attempts to attach astatide (At*) to a soft transition metal center, we have studied $^{211}$At-labeled Rh(I), Ir(I) and Au(I) complexes of N-heterocyclic carbene (NHC, Fig. 1).2

As astatine is a heavy element ($Z = 85$), it is important to account for relativistic effects, notably spin-dependent ones in its theoretical investigation. Therefore, DFT calculations in a two-component (2c) formalism were performed. The bond dissociation energy (BDE) of the complexes in gas phase showed the bond strength in the order Rh-At < Ir-At < Au-At. This trend was confirmed in the aqueous phase where the heterolytic dissociation of the Au-At bond is more difficult by about 95 and 80 kJ/mol than those of Rh-At and Ir-At, respectively. Also, from the Gibbs free energy of halogen exchange reactions, the Au(I) complex showed superiority in terms of selectivity for astatide against competitive chloride (notable concentrations encountered in vivo), and agrees with experiment which demonstrated its good stability in human blood serum at 37°C. A deeper understanding necessitates the study of the nature of the metal-At bonds through computational means, which is otherwise difficult if not impossible experimentally. AuX (X= F - I) diatomic species were found to exhibit charge-shift bonds (CSBs), a type of bond that exists along with the classical electron-pair bond families, namely the covalent and the ionic bonds.3 Studying the diatomic AuAt bond may therefore, shed light on the investigated NHC-metal complexes. The QTAIM and ELF topological analysis were performed on the 2c spinors obtained from PBE0/dhf-TZVP-2c calculations, allowing us in particular to reveal the spin-orbit coupling (SOC) effects on the characteristics of the bonds.4

The QTAIM study of AuAt notably shows typical features of ionic bonding but without significantly charged atoms. SOC is even able to reverse the sign of the partial charges. While a significant sharing of electron-pair between Au and At is evidenced, no ELF bonding basin is found. Do these findings also characterize the metal-halogen bond in the NHC complexes and can we rationalize the trends on BDEs and Au selectivity between astatide and chloride?

![Figure 1. Studied NHC-metal complexes; *no L when M = Au(I).](image)

Keywords: astatine, relativistic DFT, spin-orbit coupling, charge-shift bonding, quantum chemical topology.