

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, ²¹¹At which has a half-life of 7.2h and emits high-energy α particle (5.9-7.4 MeV) upon decay with a short path length (80-100 μ m). Application of ²¹¹At for cytotoxicity for nearby malignant cells in targeted α therapy of cancers is of particular interest.¹ Yet, the main challenge against its successful use, is the production of an in vivo stable ²¹¹At-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 ²¹¹At-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).

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

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