



Molecular modelling towards stable Astatine-211 labelling for targeted alpha therapy

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Context



²¹¹At in targeted alpha therapy













Halogen bonding





non-covalent highly directional interaction between covalently bonded halogen and a Lewis base

Experimental investigation with At:



initial At distribution

new distribution



 $pK_{BAtI} > pK_{BI_2}$

suggests At as the stronger XB donor

Molecular modelling: characterize the interaction in B…Atl



- most stable XB-complexes involve At
- first evidence of At-mediated XB

Comparison between experiment and modelling



- good agreement between pK_{BAtl} values
- confirmation of experimental formation of At-mediated XB complexes
- At is the strongest XB donor

Nat. Chem. 2018, 10, 428–234. Chem. Eur. J. 2020, 26, 3713–3717 Chem. Sci. 2021, 12, 10855–10861

Part II

Understanding *in vivo* stability of astatoaryl prosthetic groups



SAB as prosthetic group

Ο ²¹¹At⁺ Ö 211A 211 SAB

SAGMB as alternative prosthetic group

higher in vivo stability than SAB

in vivo high release of free At

why, and what is the mechanism of deastatination







Known enzymatic deiodination mechanism





- ΔG_{298K}^0 for **At-Ph 25.6 kJ/mol more favorable** than for **I-Ph**
- less dehalogenation experimentally for SIB vs SAB
- possible enzymatic deastatination ?

Possible interacting groups



XB interaction energy only significant for selenocysteine and aspartate

Possible interacting groups



Thermodynamics of the deastatination

mechanism for aspartate:



mechanism for selenocysteine:



 ΔG_{298K}^{0} more favorable for SeCys (-122.8 kJ/mol)

SeCys prime deastatination suspect



How about deastatination in SAGMB?



40% of Boltzmann population



no halogen bonding

SeCys interaction with SAGMB?



- SeCys only interacts through guanidinium
- deastatination mechanism not applicable (no XB)

Part III

An alternative ²¹¹At-labelling based on soft metal complexes



Metal – NHC complexes as BCA

Concept:

- At- should bind strongly with soft metal centers
- *N*-heterocyclic carbene: flexible, stabilizing



M: Rh(I), Ir(I), Au(I)

L: cyclooctadiene (for M = Rh, Ir)

R₁,R₂: 2,6-di*i*sopropylphenyl, methyl, adamantyl, benzyl, *p*-nitrophenyl

X: ²¹¹At, I, CI

Objectives:

- identify complex with sufficient M At strength
- identify complex that allow radiolabelling

Towards a robust ²¹¹At-labelling of metal – NHC complexes

Estimate of M-X bond strength



٠

- Au-At is the strongest bond ٠
- same trend irrespective of R₁ & R₂ ٠

800

Halogen exchange reaction



 $25 \qquad R1=R2=o-diiPr-Ph$ $5 \qquad X=1$ $5 \qquad X=1$ $5 \qquad Lower is better$ $-15 \qquad Rh(1) \qquad Ir(1) \qquad Au(1)$

selectivity in favor of At- only for Au-complexes



experimental facts:

- chlorinated precursor results to 95 \pm 3 % RCY

• iodinated precursor results to 26 ± 6 % RCY



Nature of Au – At bonding



q(Au) = -0.02q(At) = -0.32

not consistent with ionic interaction! Electron Localization Function: 3D space partitioned into volumes



V(Au,At) absent: it can not be covalent!



Braïda et al. (Molecules 2022, 27, 490): charge-shift bonding in Au-X (X=CI, Br, F)

Wang et al. (Phys. Chem. Lett. 2023, 14, 5226) also charge-shift bonding in Au-I

delocalization index, δ : measure of electron pair sharing CS bonding feature: δ higher than formal bond order $\delta = 1.49$

charge-shift bonding character in Au - At

Conclusion

- ☆ caution must be taken of At-labelled compounds' ability for XB interactions
 - one pattent submitted
- ☆ Au is predicted to efficiently bind At: excellent RCY with Au-NHC complex
 - ▶ try more soft metals, modify NHC-ring...
- * molecular modelling as a guide is demonstrated!

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Thank you for your attention!

Method

2-component relativistic DFT

At (Z=85): relativistic effects are important

Functionals:¹ PBE0; PW6B95 Basis sets: dhf-TZVP-2c & ECP60MDF

Solvation: CPCM-UAHF

Bonding analysis: QTAIM & ELF

$$\widehat{H} = \sum_{i} \left[\sigma_{0} \widehat{h}^{0}(i) + \vec{\sigma} \cdot \vec{h}_{SO}(i) \right] + V_{ee} + V_{NN}$$
• inner-core charge
• RECP scalar effect
one – electron SO operator
(parameterized with 4c cal.)

orbitals constructed from 2c spinors:

$$\varphi_{i}(r) = \begin{pmatrix} \varphi_{i\alpha}(r) \\ \varphi_{i\beta}(r) \end{pmatrix} = \begin{pmatrix} \sum_{\mu} c^{\alpha}_{i\mu} \chi_{\mu}(r) \\ \sum_{\mu} c^{\beta}_{i\mu} \chi_{\mu}(r) \end{pmatrix}$$

1. Galland, et al. J. Comput. Chem. 2016, 37, 1345-1354

Bonding analysis strategy

Electron density calculated from occupied 2c-spinors: $\rho(r) = \sum_{i}^{occ} \varphi_{i\alpha}^{*}(r) \varphi_{i\alpha}(r) + \varphi_{i\beta}^{*}(r) \varphi_{i\beta}(r)$

QTAIM

partition molecular space into topological basins via $\nabla \rho(r)$ atomic population: $\overline{N}[\Omega] = \int_{\Omega} \rho(r) dr$ atomic charge: $q(A) = Z(A) - \overline{N}[\Omega]$ DI: $\delta(\Omega_A, \Omega_B) = 2 \sum_i \sum_i n_i^{1/2} n_j^{1/2} \langle \varphi_i | \varphi_j \rangle_{\Omega_A} \langle \varphi_i | \varphi_j \rangle_{\Omega_B}$ classification based on indicators from virial theorem: $\frac{1}{4}\nabla^2 \rho(r) = 2G(r) + V(r)$ $\nabla^2 \rho_b$ $|V_{h}|/2G_{h} < 1$ $|V_{h}|/2G_{h}>1$ $\rho_h \ge 0.2$ au $\rho_b \leq 0.1$ au shared-shell regular CS pure CS covalency no-covalency $|V_b|/G_b$

ELF

ELF:
$$\eta(r) = \frac{1}{1 + \chi^2(r)}$$

Pauli KE density: energy due to redistribution of electrons in accordance with Pauli principle

$$\chi(r) = \frac{\tau_p}{\tau_h} = \frac{\tau(r) - \frac{1}{8} \frac{|\nabla \rho(r)|^2}{\rho(r)}}{c_F \rho(r)^{5/3}}$$

$$\tau(r) \text{ positive definite local KE} of noninteracting electrons}$$

KE density of UEG of same electron density

3D molecular space partitioned into volumes



Results

Bonding analysis: Quantum Theory of Atoms In Molecule

molecular space partitioned into topological basins via $\nabla \rho(r)$



it can not be ionic!

Charge-shift bonding

• bonding arising from minimization of lone pair bond-weakening effect (LPBWE):



