# At-mediated Halogen bonds: Experimental and Computational Evidences

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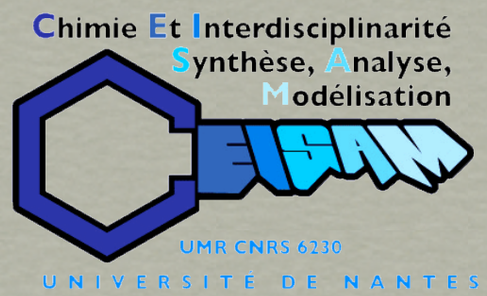
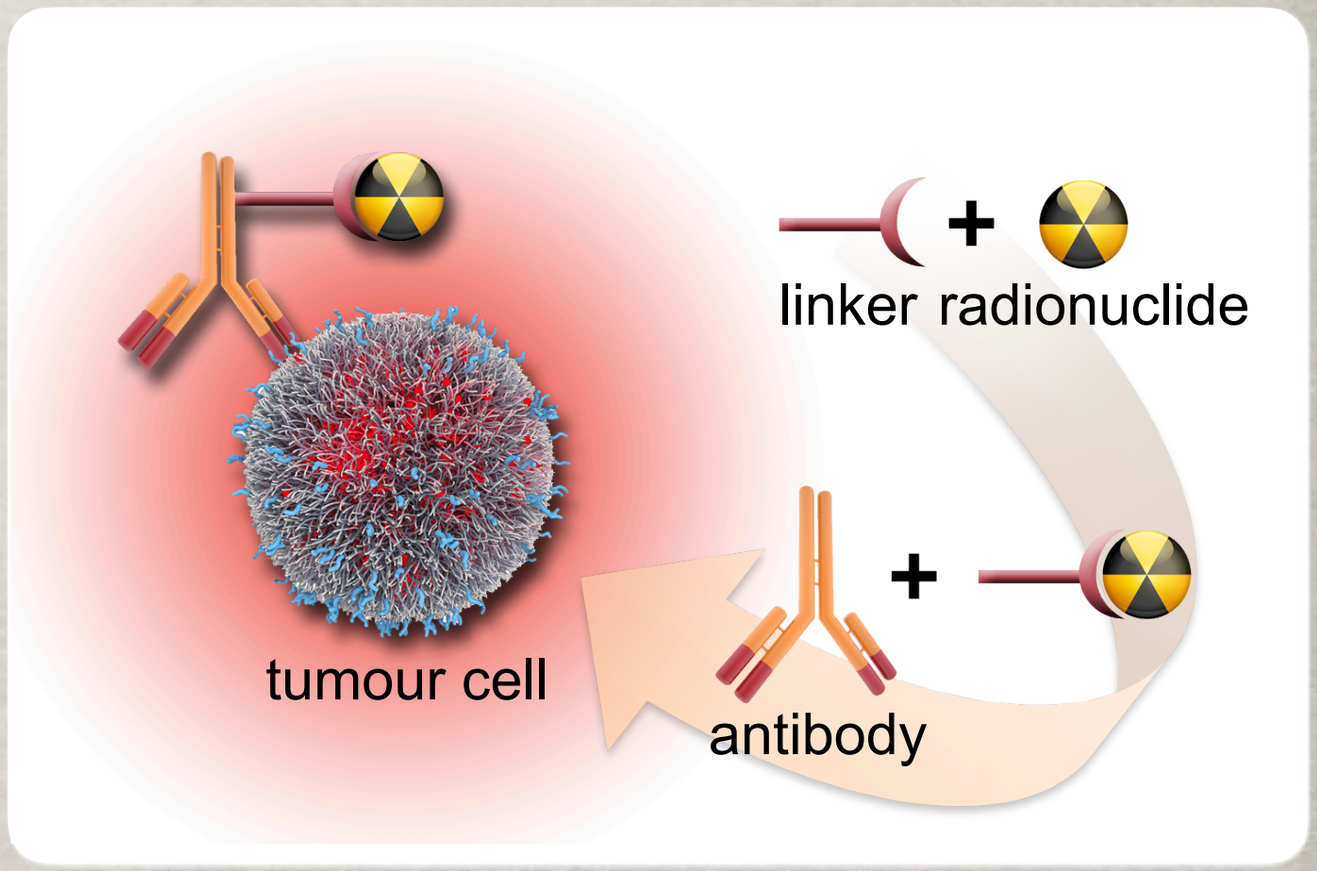



UNIVERSITÉ DE NANTES

# Context

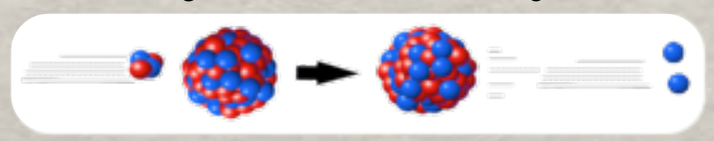
## Astatine in oncology: a wide project in Nantes area

- top candidate for targeted alpha-immunotherapy




- production in the local cyclotron

$$^{4}_{2}\mathrm{He} + {}^{209}_{83}\mathrm{Bi} \xrightarrow{E=28\mathrm{MeV}} {}^{211}_{85}\mathrm{At} + 2\mathrm{n}$$

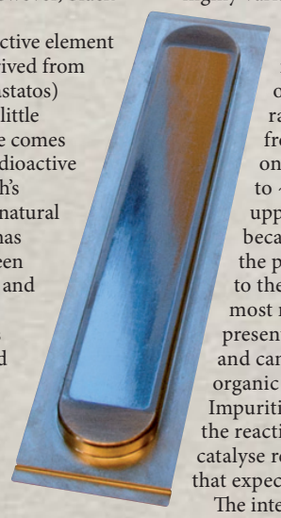


# Enigmatic astatine

**D. Scott Wilbur** points out the difficulty in studying the transient element astatine, and the need to understand its basic chemical nature to help in the development of targeted radiotherapy agents.

Since the discovery of astatine over 70 years ago[1], many of its characteristics have remained elusive. Unlike the other halogens, abundant and ubiquitous in nature, astatine is one of the rarest of all elements. This arises from the fact that it has no stable isotopes; the longest lived of its 32 known radioisotopes, $^{210}$At, has a half-life of only 8.1 hours. The rarity and radioactive nature of element 85 lends to its mystery, as it cannot be observed or weighed in a conventional sense. Even its colour is unknown; based on increasingly dark colours for halogens from fluorine to iodine, however, black seems a logical guess.

The rarity of this radioactive element is reflected in its name, derived from the Greek word αστατος (astatos) meaning 'unstable'[2]. What little astatine is present in nature comes from the decay of heavy radioactive elements found in the Earth's crust. The total amount of natural astatine at any given time has been estimated to be between a few hundred milligrams[3] and 30 g. In any case, naturally occurring astatine isotopes are too unstable, and would be too difficult to obtain, for characterization. Fortunately, the two longest-lived isotopes — $^{210}$At and $^{211}$At (half-life = 7.21 h) — can both be produced by α-beam irradiation of bismuth-209 targets (pictured, on aluminium support).



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Nevertheless, these longer-lived isotopes can only be produced in small quantities[4], which, combined with their short half-lives and high costs, have considerably limited astatine research. Of the artificial isotopes, $^{211}$At has been the primary focus of chemical studies owing to its potential in medicine.

The other 'long'-lived isotope, $^{210}$At, is not suitable because it decays into polonium-210 — the notorious radiation poison used to kill the Russian Federal Security Service officer Alexander Litvinenko in 2006, after he took political asylum in the United Kingdom.

Although some chemical data has been compiled for astatine isotopes, many physical properties have only been extrapolated. Similar to other halogens, astatine undergoes nucleophilic and electrophilic reactions. The reproducibility of some reactions however has proved highly variable. This may arise in part from the low amounts of astatine present, resulting in very high reaction dilutions. Quantities of $^{211}$At used in chemical and radiolabelling reactions range from 37 kBq to 4 GBq. These only represent from ~$4.8 \times 10^{-13}$ to ~$5.2 \times 10^{-8}$ g of $^{211}$At — and this upper limit is rarely encountered, because of the costs involved and the potential for radiation damage to the molecule being labelled. For most reactions, the quantity of $^{211}$At present ranges from $10^{-13}$–$10^{-9}$ g, and can be smaller than that of trace organic species and metals in solvents. Impurities may thus interfere with the reactions studied, and might even catalyse reaction pathways other than that expected.

The interest in $^{211}$At in medicine mentioned above arises from its potential use in systemically targeted therapy of cancers — it is one of only a few α-emitting radioisotopes considered appropriate for medical use[5], as most others can cause severe damage to internal organs. Its short path length (60–90 μm) and high-energy α-particles (6.0–7.5 MeV) are very effective in killing cells bound by a carrier-targeting agent[6]. However, a major impediment to practical applications is the low stability of astatine bonds with aromatic carbon bonds *in vivo*[7]. The development of labelling reagents containing more stable aromatic astatine–boron bonds has improved that situation, and studies evaluating bonding with other elements may further advance it.

To determine *in vivo* stability, the same cancer-targeting molecule can be labelled with $^{211}$At and (stably) with radioiodine ($^{125}$I, $^{123}$I or $^{131}$I), and the two co-injected. The concentrations of $^{211}$At in various tissues (higher lung, spleen, stomach and thyroid) indicate whether it is being released from the carrier molecule. However, even in studies in which low stomach and thyroid (neck) concentrations suggest that $^{211}$At and $^{125}$I are both stable to *in vivo* dehalogenation, very dissimilar concentrations may be observed for the two elements in other organs such as kidney and liver. This is likely to be due to variations in metabolism of the radioiodinated and astatinated molecules, or may arise from preferential clearance of the radioiodinated metabolites.

In the quest to produce targeted therapeutics for treatment of cancer and other diseases, many of the basic chemical studies with $^{211}$At have unfortunately been set aside. Although some of its physical properties will continue to elude direct characterization, it is apparent that we need to gain a better understanding of its basic chemical and radiochemical properties to unravel the enigma of astatine. ❐

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References
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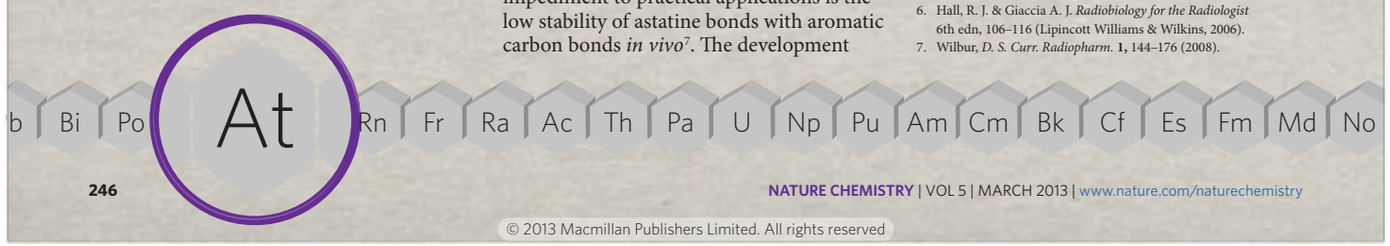




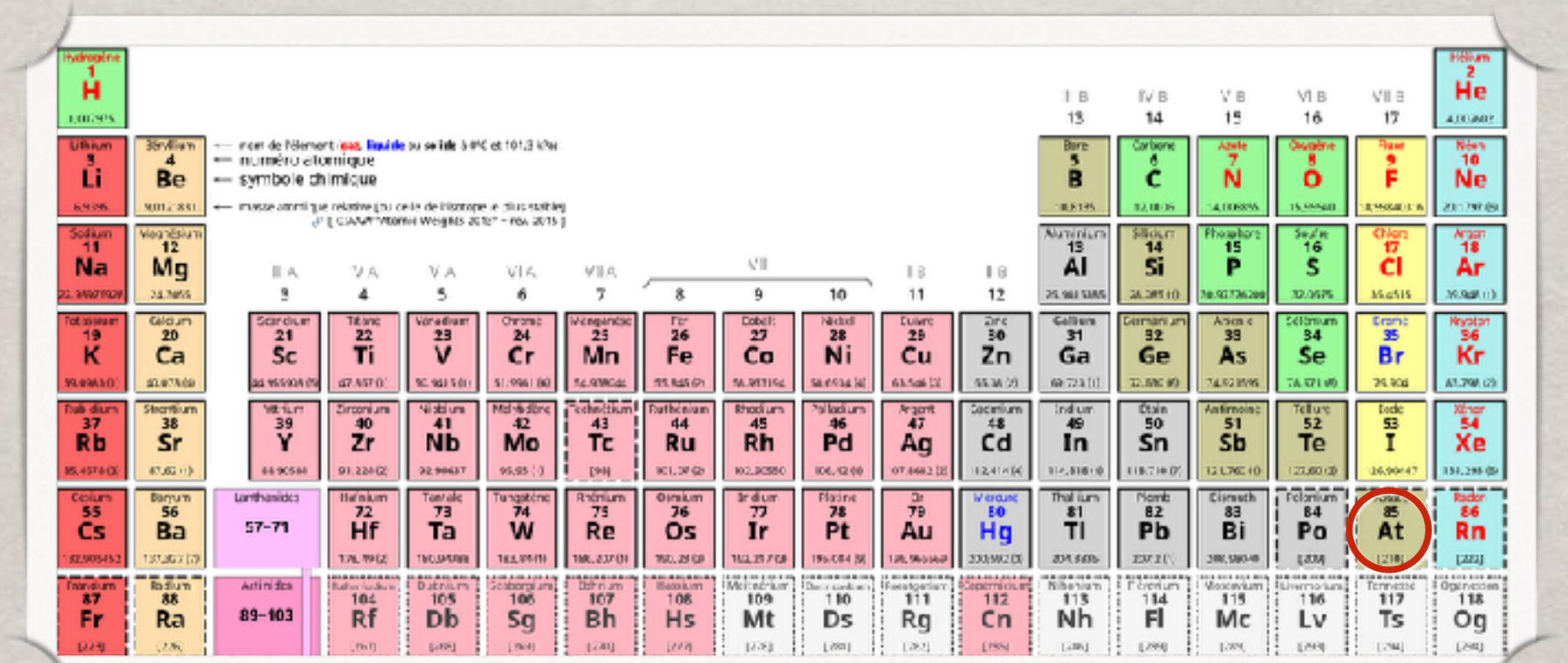



**Nature Chemistry 2013:**

«the need to understand its basic chemical nature to help in the development of targeted radiotherapy agents»
D. S. Wilbur

**no spectroscopic tools can be used to study At chemistry**

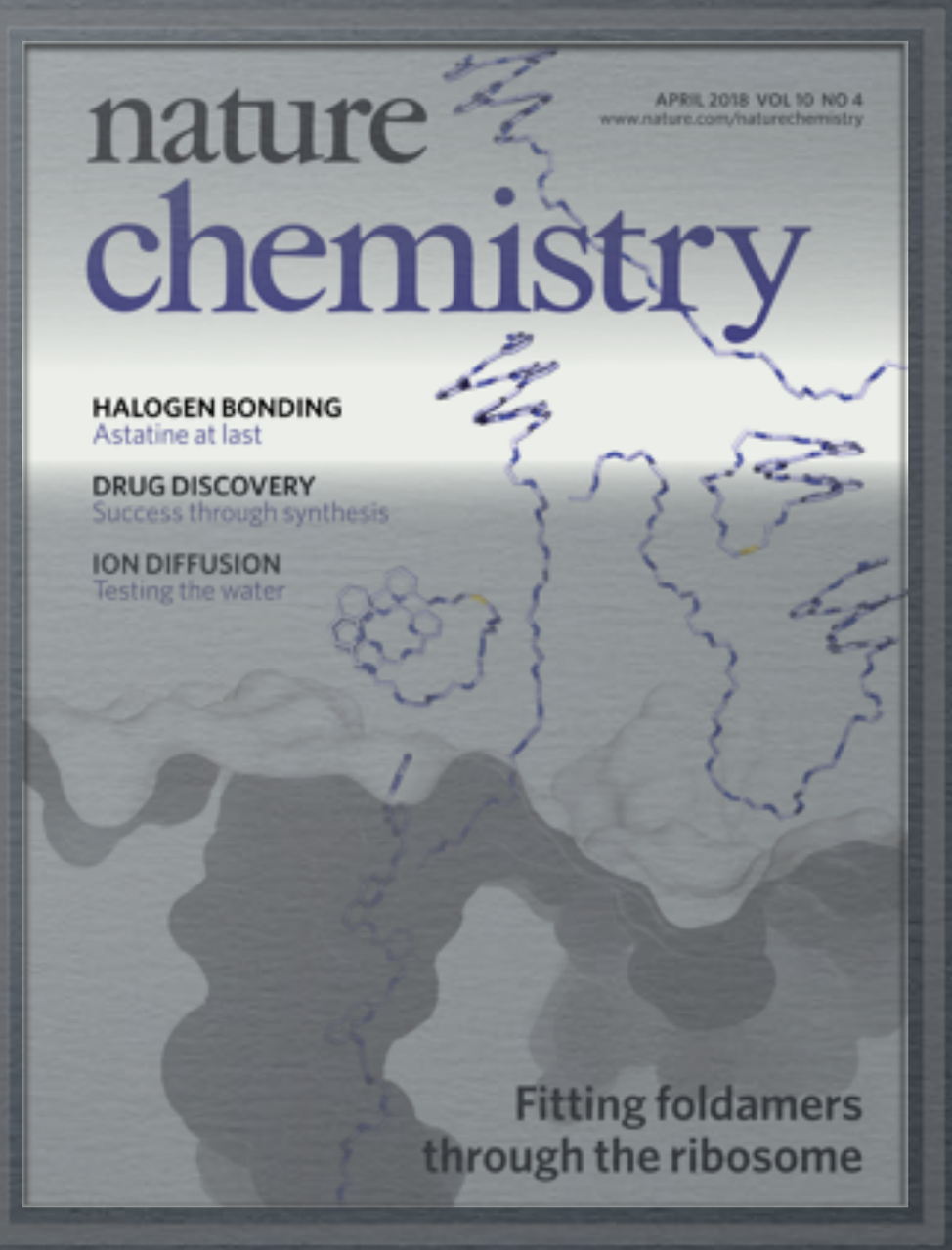
# INVESTIGATIONS VIA THEORETICAL TOOLS




**consider the special relativity**

- scalar relativistic effects
- spin-dependent effects: spin-orbit coupling

# At-Mediated Halogen Bonds (XBs)

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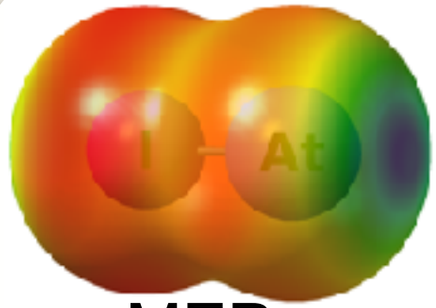
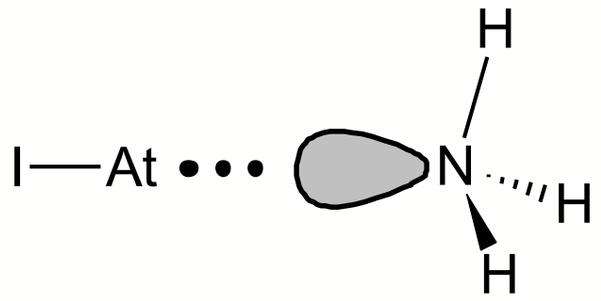
# Context

- **XB: a highly directional interaction**




MEP

« σ-hole » ⟷ interaction ⟶ nucleophilic site (Lewis base)

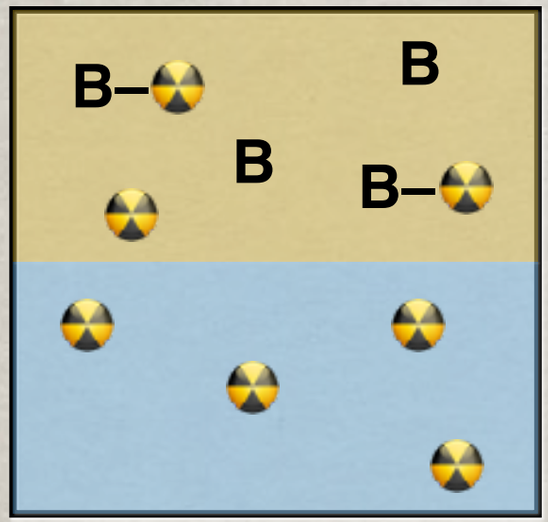



applications in many fields from bio-medicinal chemistry to materials science

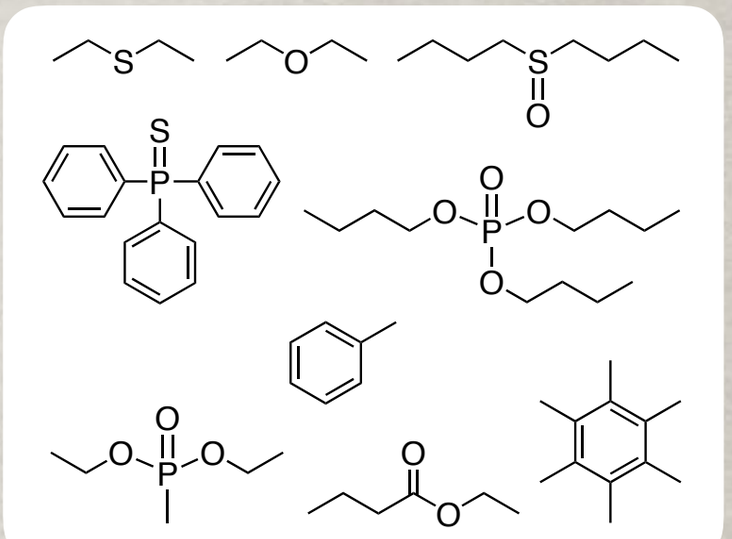
- **Astatine is potentially the strongest XB donor**

- **from radiochemistry experiments**

  investigations in biphasic systems




distribution ⇨ $K_{BAtI}$



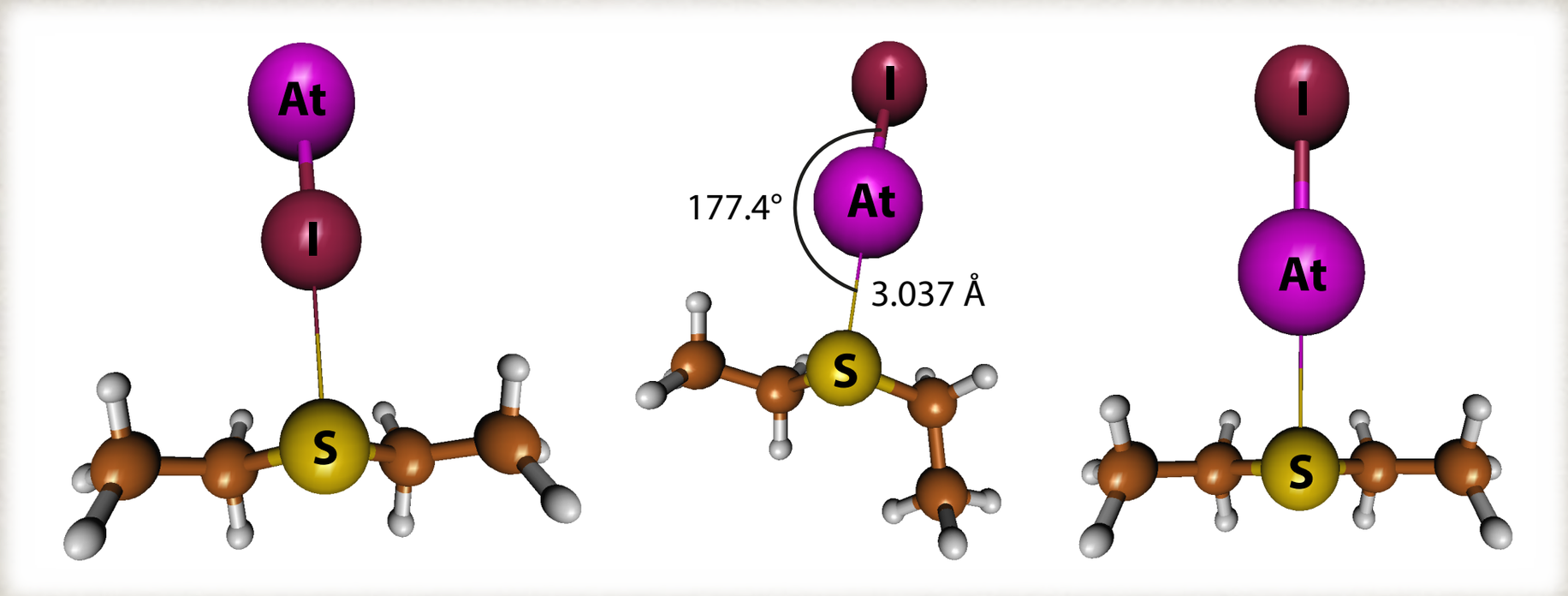

- from literature

$$\log K_{BAtI} > pK_{BI_2}$$

astatine is the prime suspect …

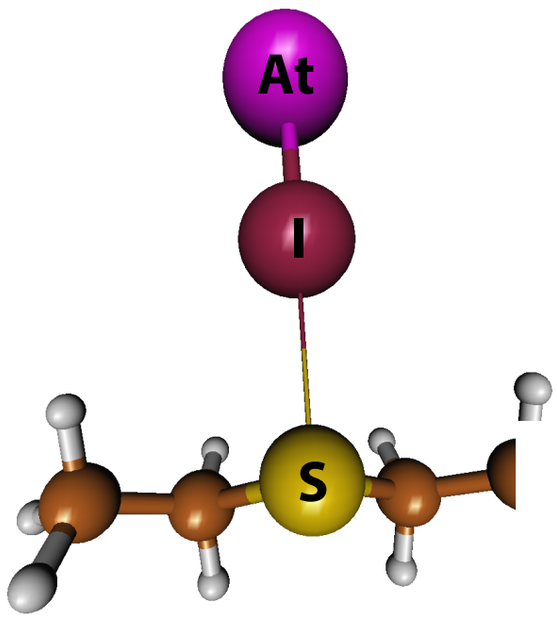
- from computational chemistry

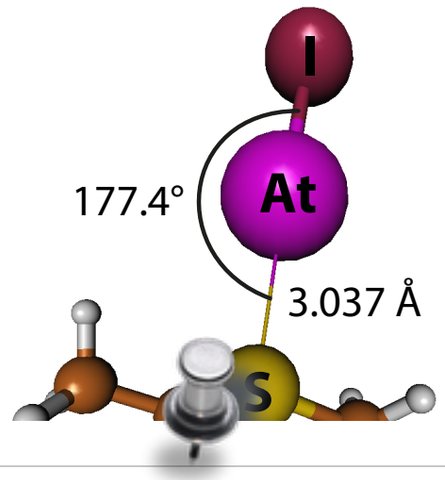
numerous XB complexes

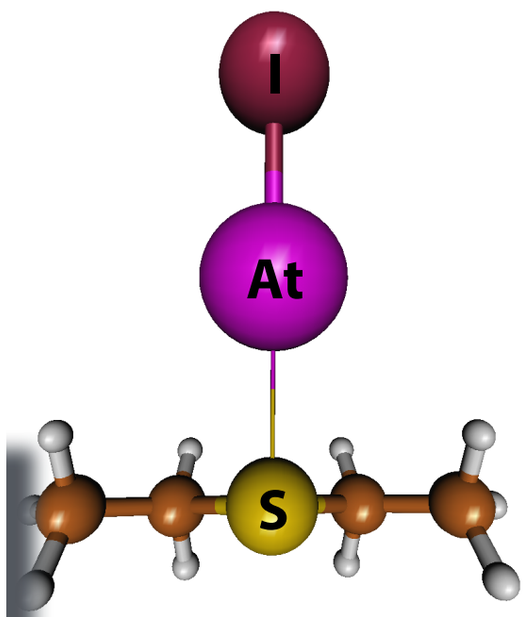


- from computational chemistry

numerous XB complexes



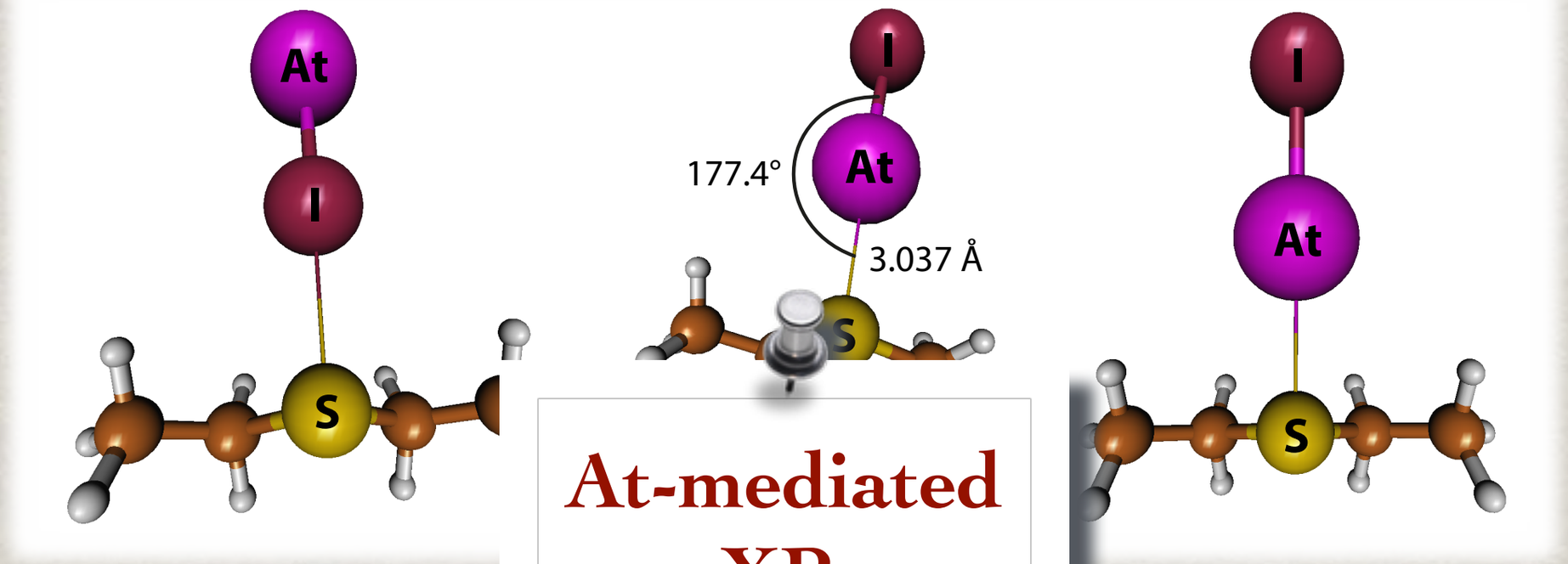




**At-mediated XBs**

- from computational chemistry

numerous XB complexes

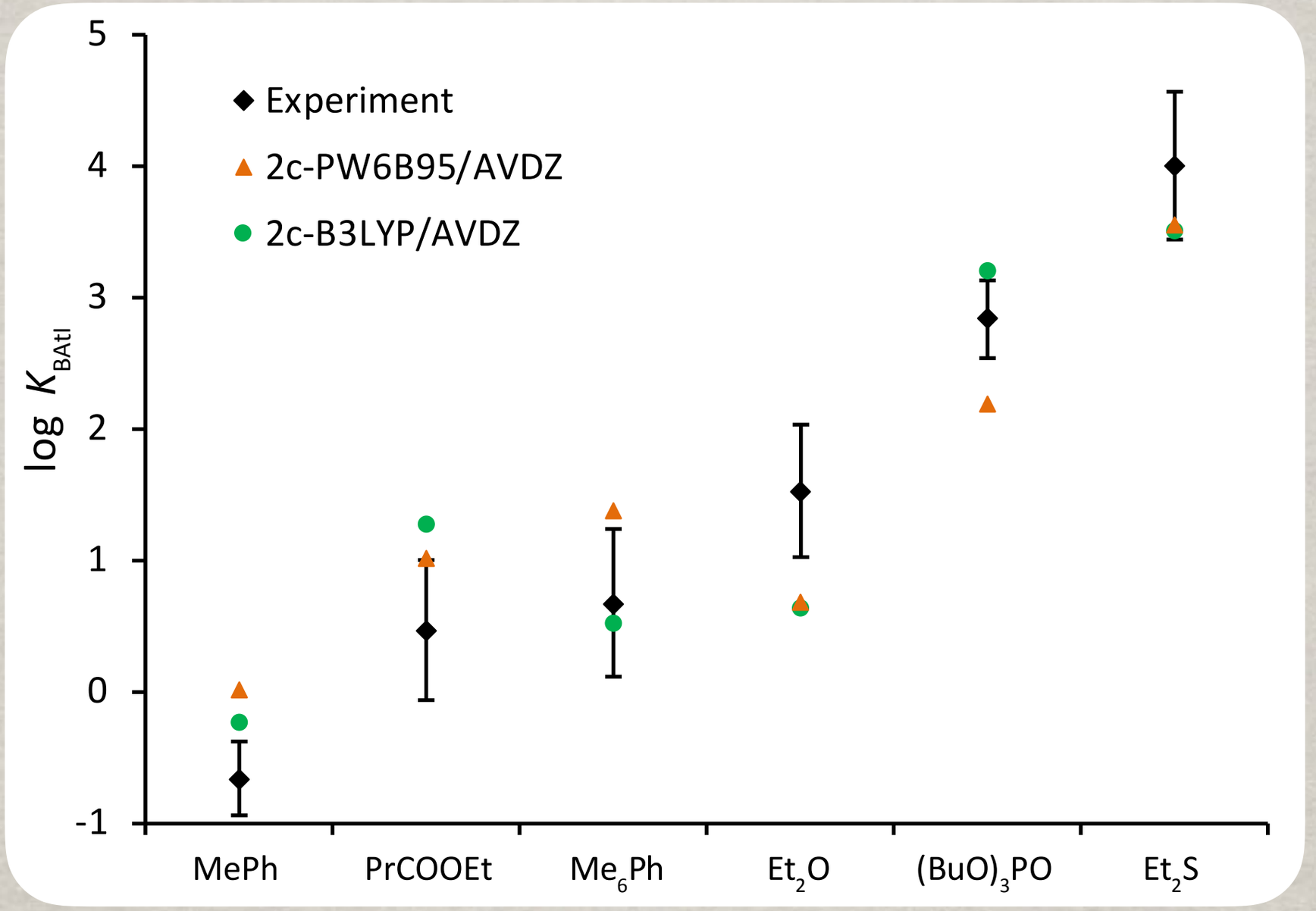



**At-mediated XBs**

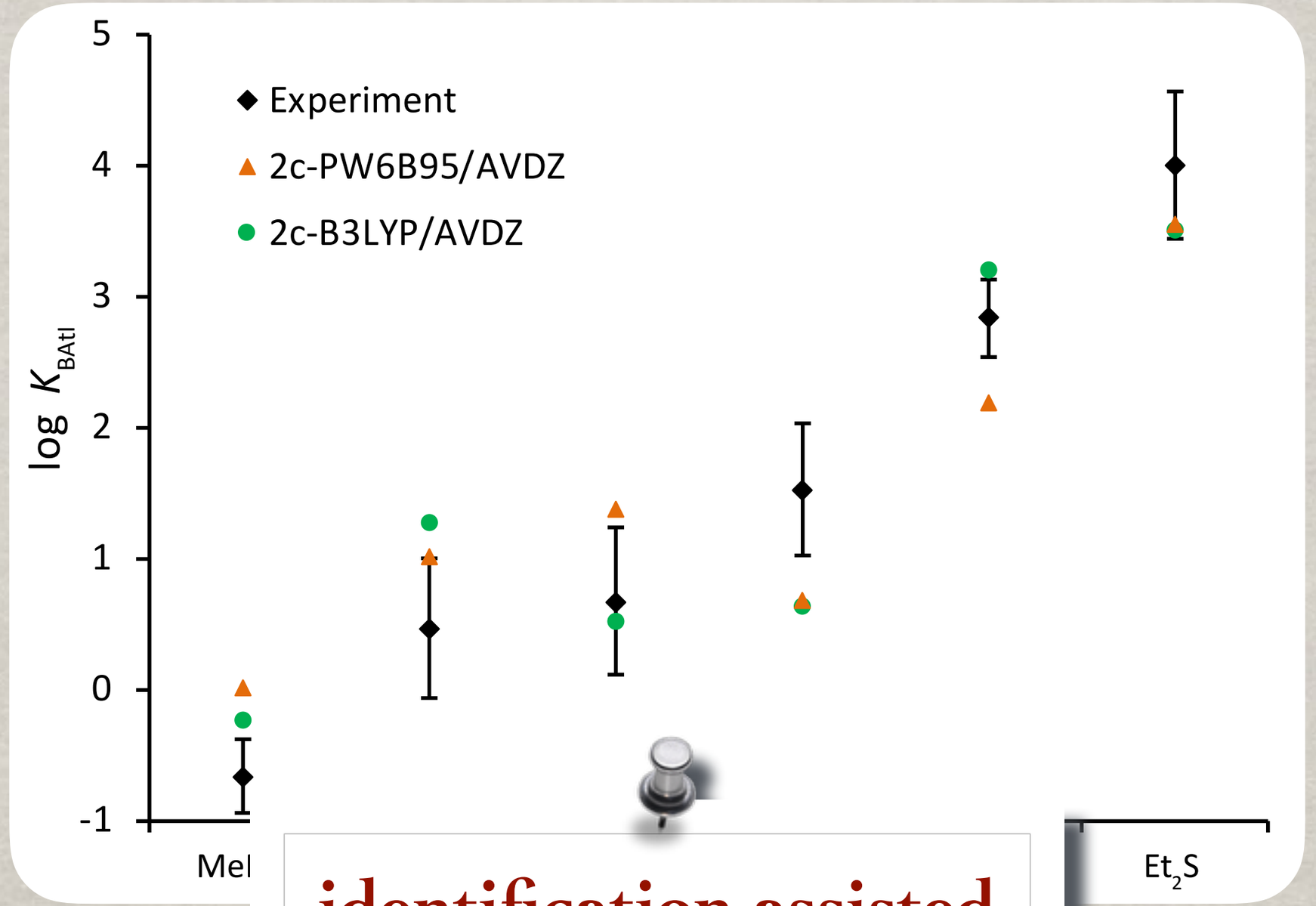
exchange reactions

$$B_1\cdots AtI + B_2 \leftrightharpoons B_2\cdots AtI + B_1$$

$$\Rightarrow \log K_{B_2AtI} = \log K_{exc} + \log K_{B_1AtI}$$




overall good agreement (MAE=3.1 kJ/mol)




**identification assisted by QM calculations**

overall g kJ/mol)

# Perspectives

- Extend the range of the XB basicity scale
- Influence of relativistic effects on At-mediated XBs
- At-mediated XBs relevant to targeted alpha-immunotherapy

# ACKNOWLEDGEMENTS

## organisations

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ANR

INVESTISSEMENTS D'AVENIR

Région PAYS DE LA LOIRE

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