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Jean-Yves Salpin, Olfa Zayene, Jun Hu, Romain Plais, Anne Gaucher, et al.. Multi-approach strategy to probe the interactions between anions and new classes of molecular receptors. 39th french days of mass spectrometry, Sep 2023, Marseille, France. hal-04247751

HAL Id: hal-04247751

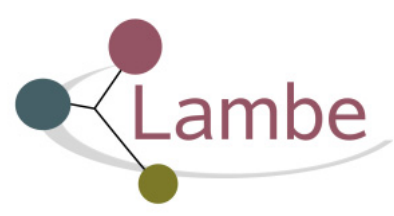
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Submitted on 18 Oct 2023

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Multi-approach strategy to probe the interactions between anions and new classes of molecular receptors



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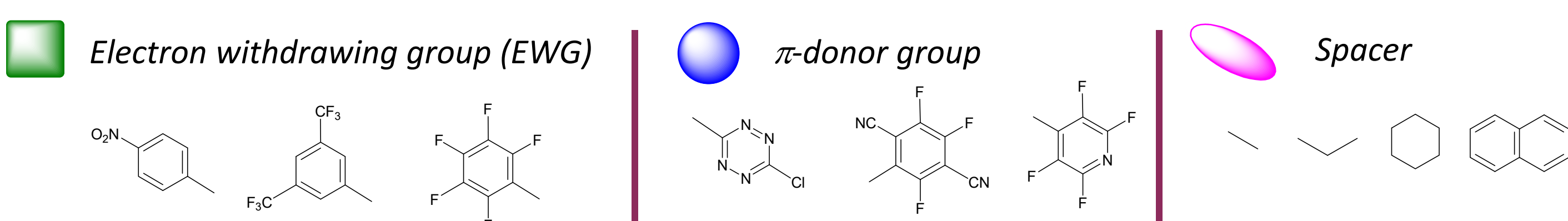
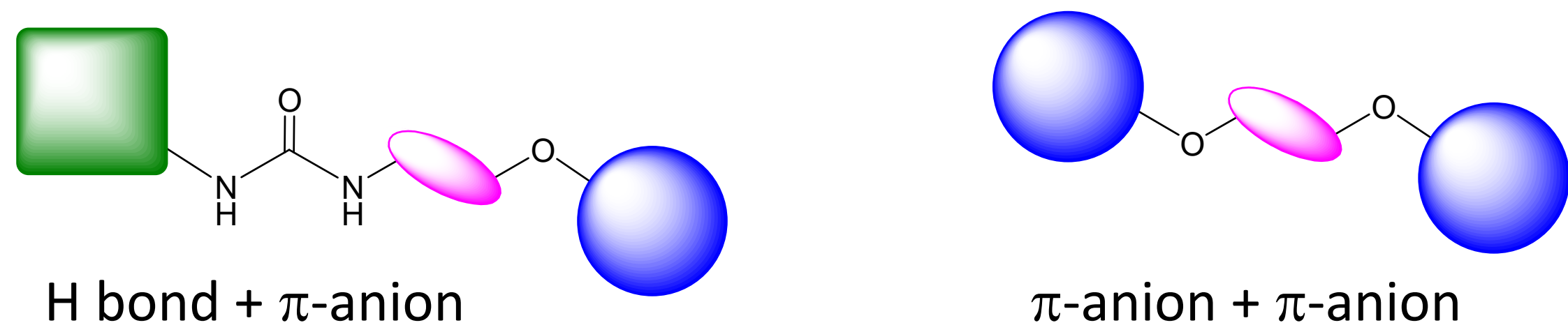
Introduction

The anion distribution across cell membranes is a major element governing biological processes in the human body. This is ensured by ion channels, membrane proteins with the capacity to selectively regulate ion flows. Disruption of these electrophysiological ion transport phenomena can lead to serious pathologies (channelopathies). One example is the deregulation of chloride ion concentration, leading in particular to cystic fibrosis.[1]

A new therapeutic strategy for treating channelopathies involves the design of molecules allowing ions to be transported across lipid membranes, thereby restoring ionic currents and their physiological functions. [2] In this context, new families of receptors are being developed that combine several low-energy interactions (hydrogen, halogen and π -anion bonds). A combination of several weak interactions is likely to generate stronger and more selective bonds, thereby modulating existing properties or generating new ones. The aim of the work presented here is to characterize in detail, using a multi-approach experimental/theoretical strategy, the interaction processes at play between these new receptors and a series of target anions.[3]

Molecular receptors

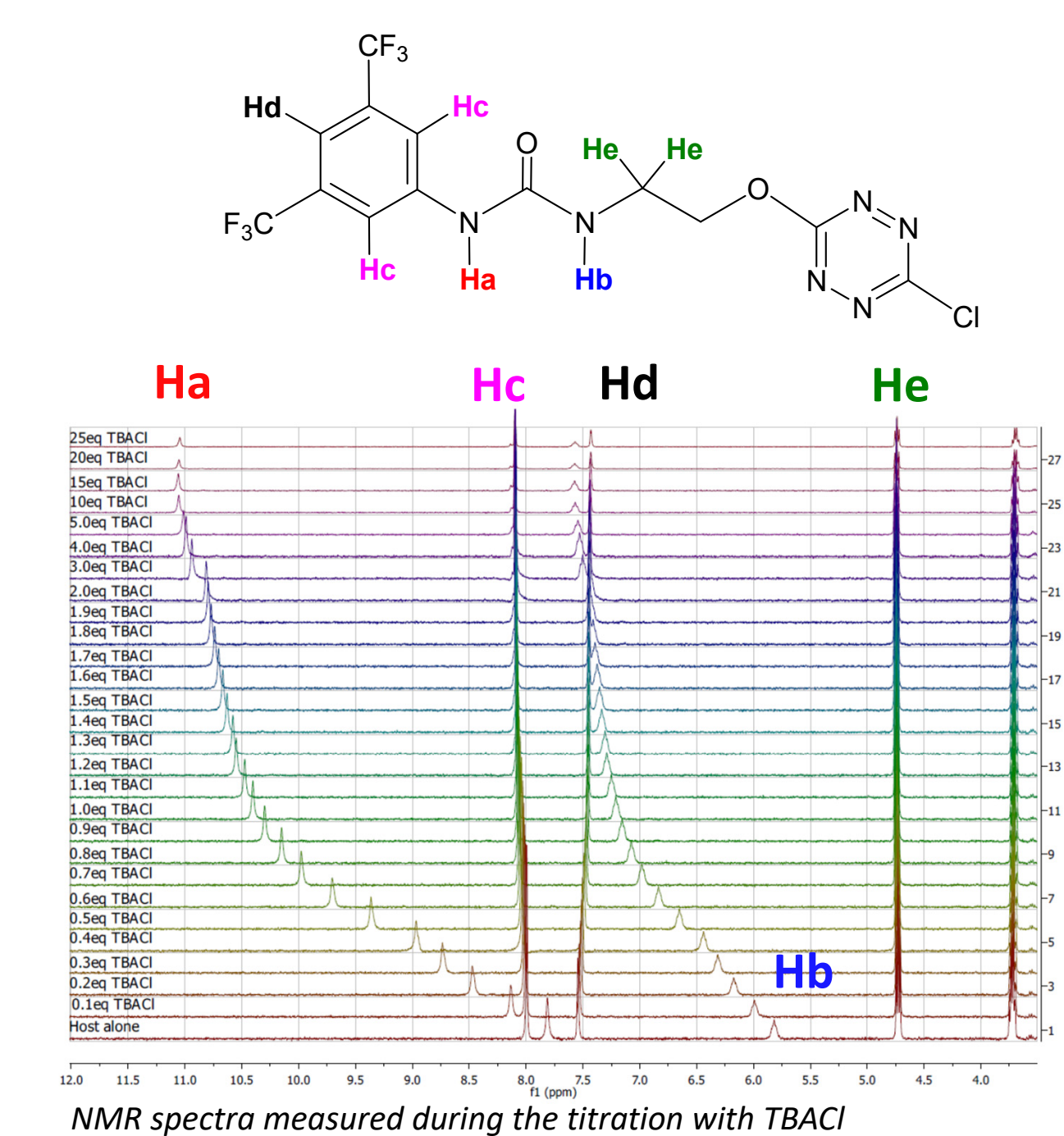
- Molecular receptors under investigation are designed to combine several types of weak interactions:



- EWG strengthen the H bonds. π -donor groups with high polarizability and positive quadrupole moment to favor π -anion interaction.

Condensed phase studies

NMR titration (exemple with TBACl)

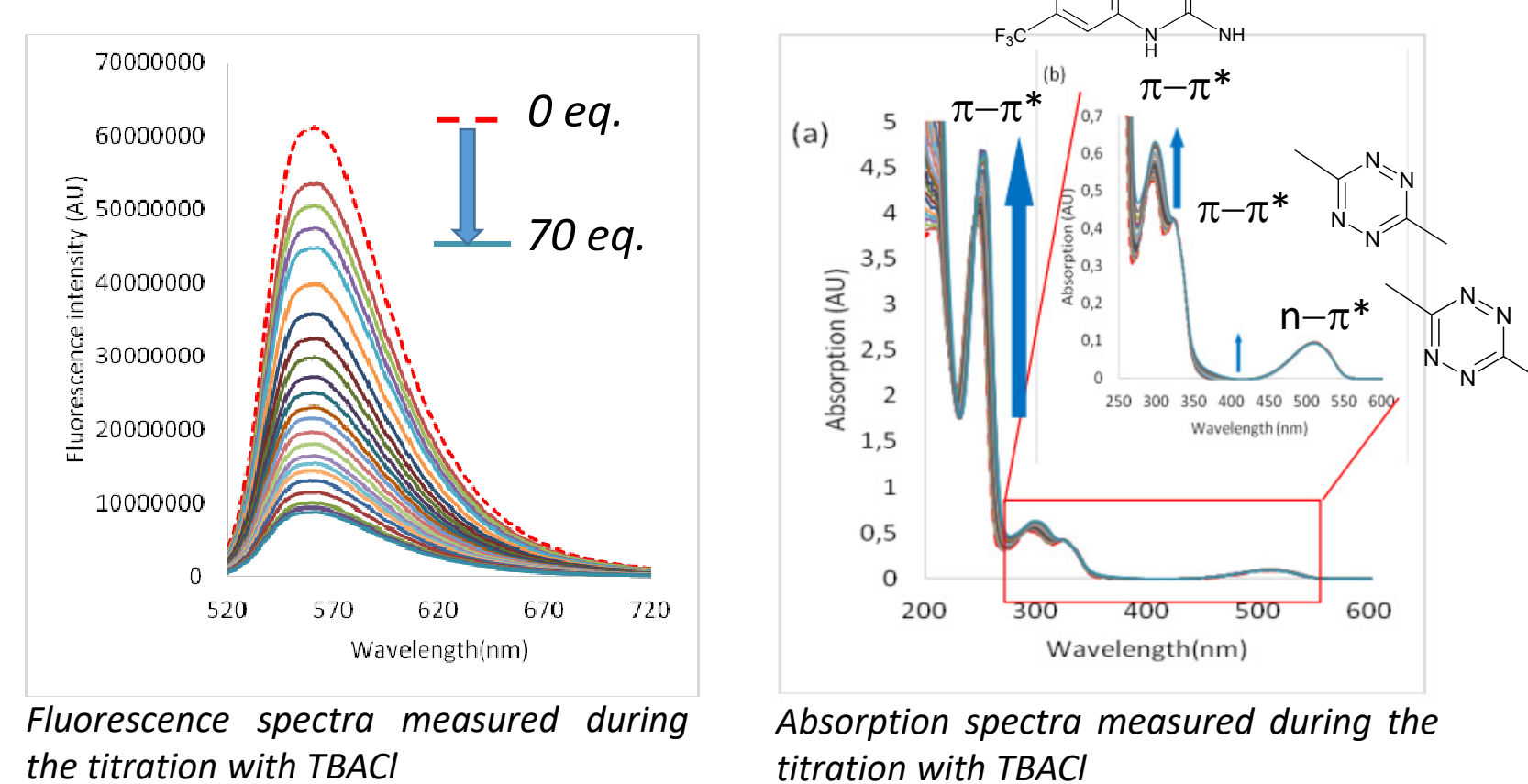


- Large downfield shifts of urea protons observed, indicative of hydrogen bonds established. Strongest interaction with Ha.
- Results consistent with a 1:1 stoichiometry.
- Binding constants and affinity order can be deduced from titration.
- Highest affinity : $\text{Cl}^- (> \text{Br}^- > \text{I}^- \approx \text{SCN}^-)$

Plais et al. *ChemPhysChem* 21, 1249-1257 (2020)

UV/Vis and fluorescence spectroscopy

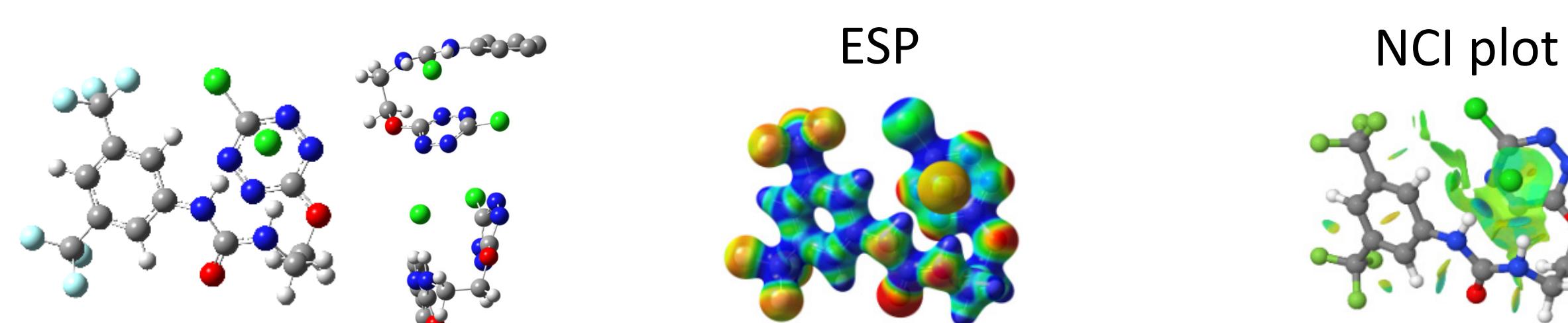
- Quenching of fluorescence is indicative of interaction with the tetrazine moiety.
- Absorption spectra: stronger variations upon titration of the bands associated with the phenylurea moiety.



- Conclusion : both sites interact but the major interaction involved in the complexation of anions is hydrogen bonding with urea.

Quantum chemical calculations

DFT studies either in the gas phase or with explicit solvent model (ACN)



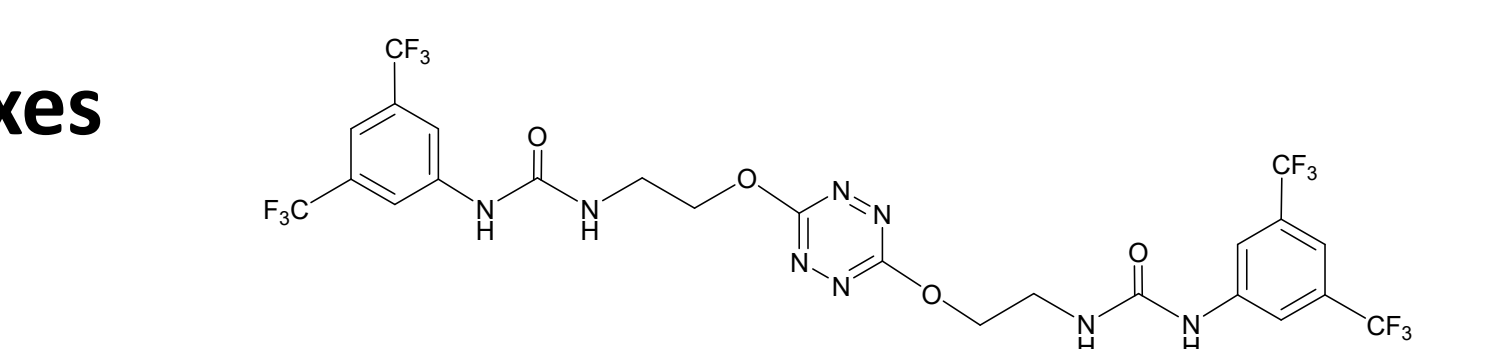
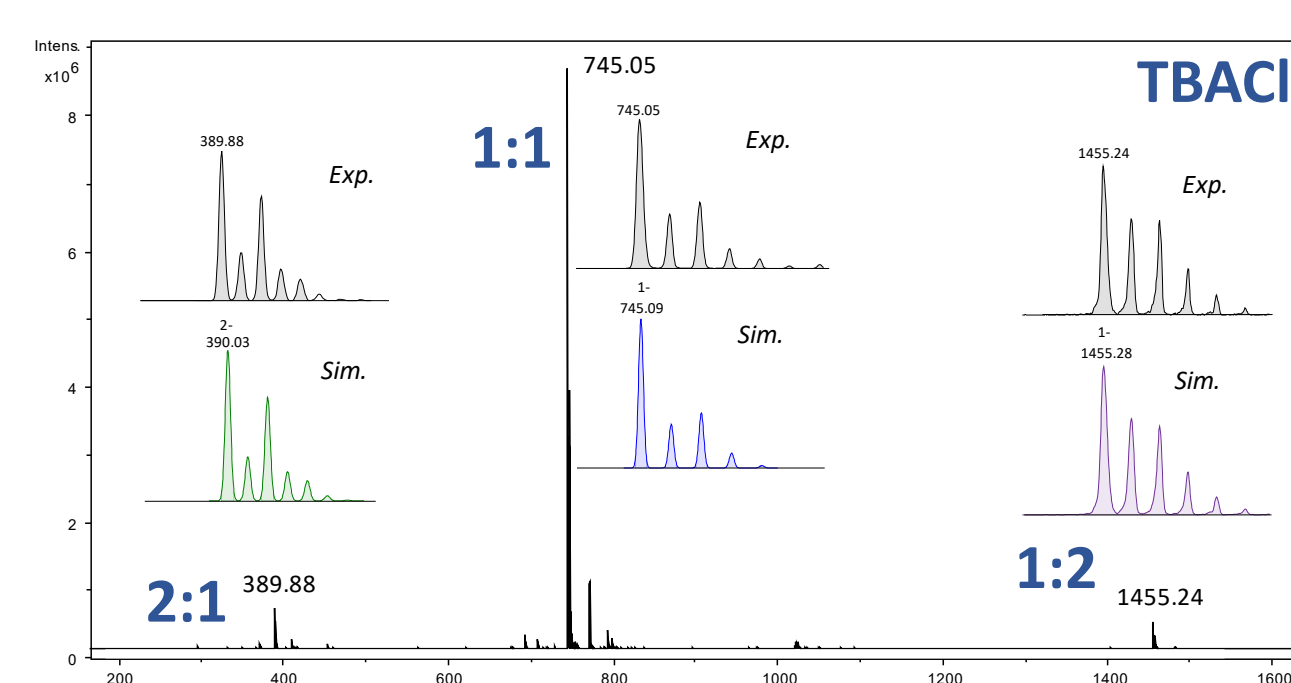
- Calculations : binding scheme combining H bond and π -anion interaction.
- Electrostatic potential (ESP) : presence of electrodeficient regions that can bind the anion.
- NCI plots evidence defined dish-shaped surfaces allowing visualization of anion- π interactions.

Methodology

- Study of the interactions with anions by mixing the receptors with n-tetrabutylammonium salts (TBAX).
- Anions with different geometries (halides, NO_3^- , SCN^- , PF_6^- ,...)
- Titration experiments by adding increasing number of equivalents of TBAX.
- Mass spectrometry : electrospray ionization applied to equimolar solutions (10^{-4} M or 10^{-5} M) of receptor/TBAX in ACN/ H_2O (90/10). MS and MSⁿ spectra acquired on an Amazon Speed ETD ion trap (negative mode).

MS studies

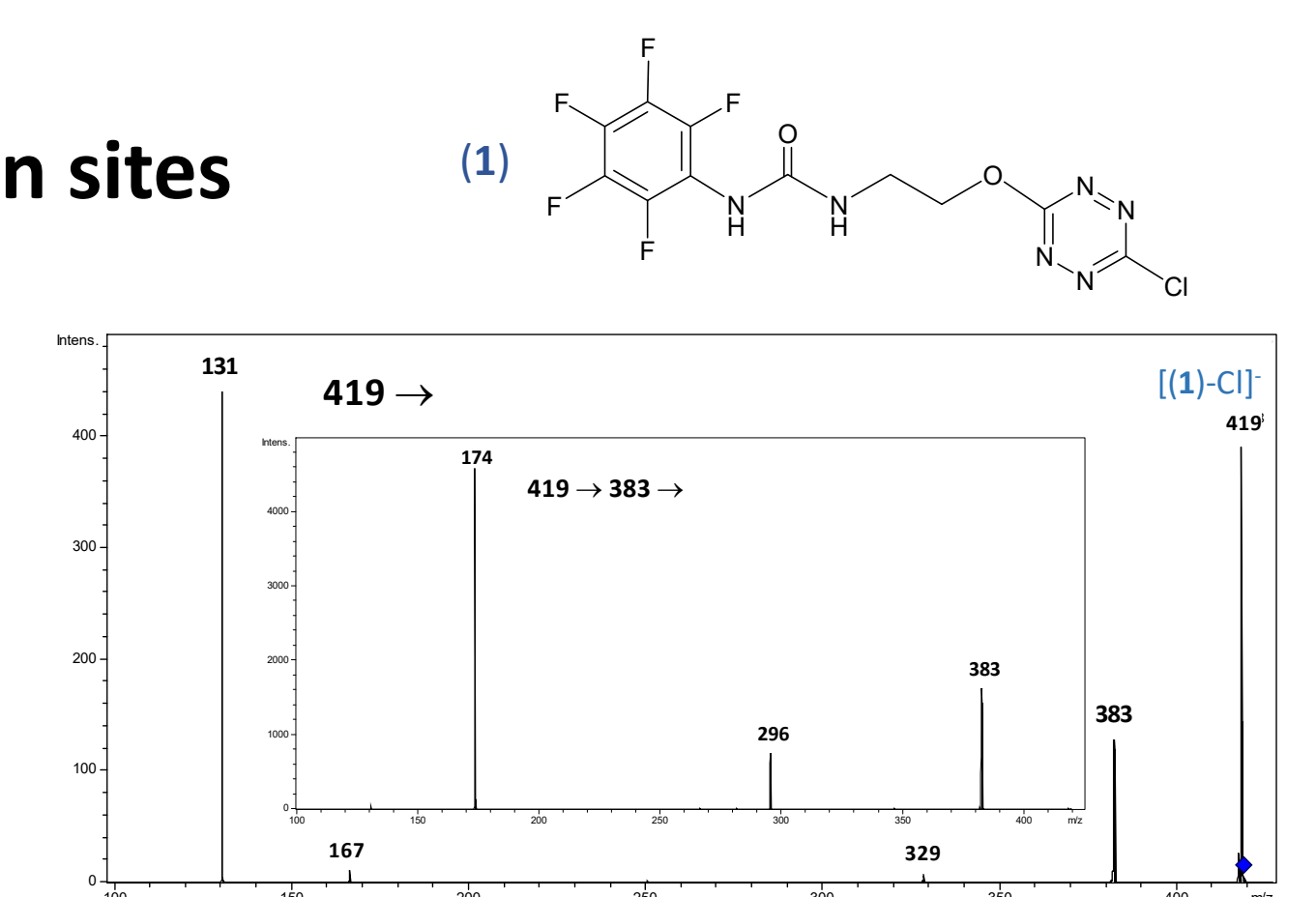
MS : stoichiometry of the complexes



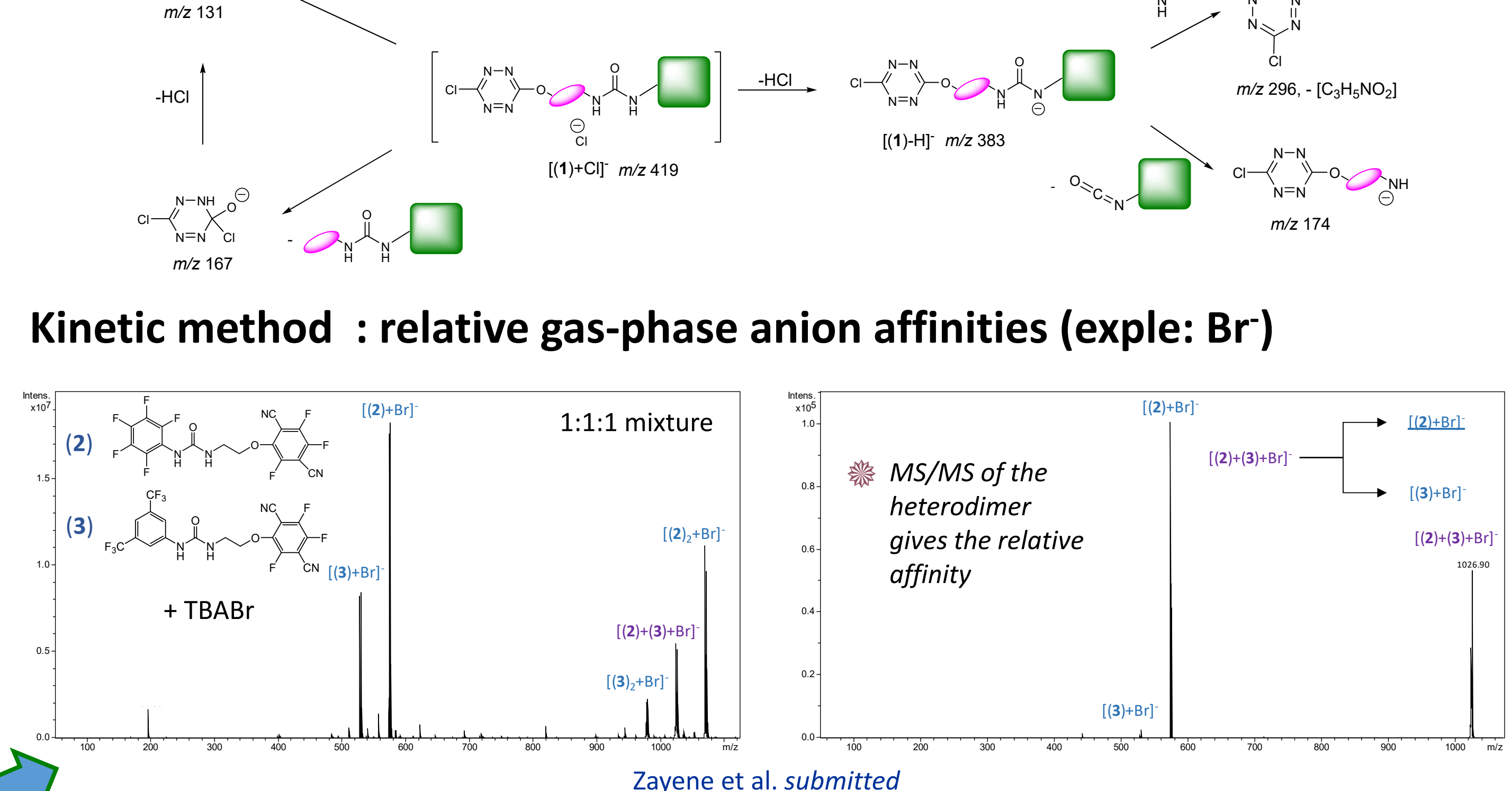
- Dominant stoichiometry : 1:1, in agreement with NMR data.
- Doubly-charged anions can be observed for big receptors.

MSⁿ : information about the interaction sites

- MS/MS data show that the anion interacts with both the urea and the tetrazine moieties. Agreement with calculations and condensed phase studies.
- The extent of deprotonation (-HX) is correlated to the gas-phase acidity of HX.



Kinetic method : relative gas-phase anion affinities (exple: Br⁻)



Conclusions

- Nice agreement between condensed phase and gas-phase studies.
- Very rich unimolecular chemistry upon collision.
- A cooperative effect between H bond and π -anion interactions is observed for several receptors.

References

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- T. Sato et al. *J. Biol. Chem.* 273, 21455-21462 (1998)
- R. Plais et al. *Eur. J. Org. Chem.* 26, e202201281 (2023)