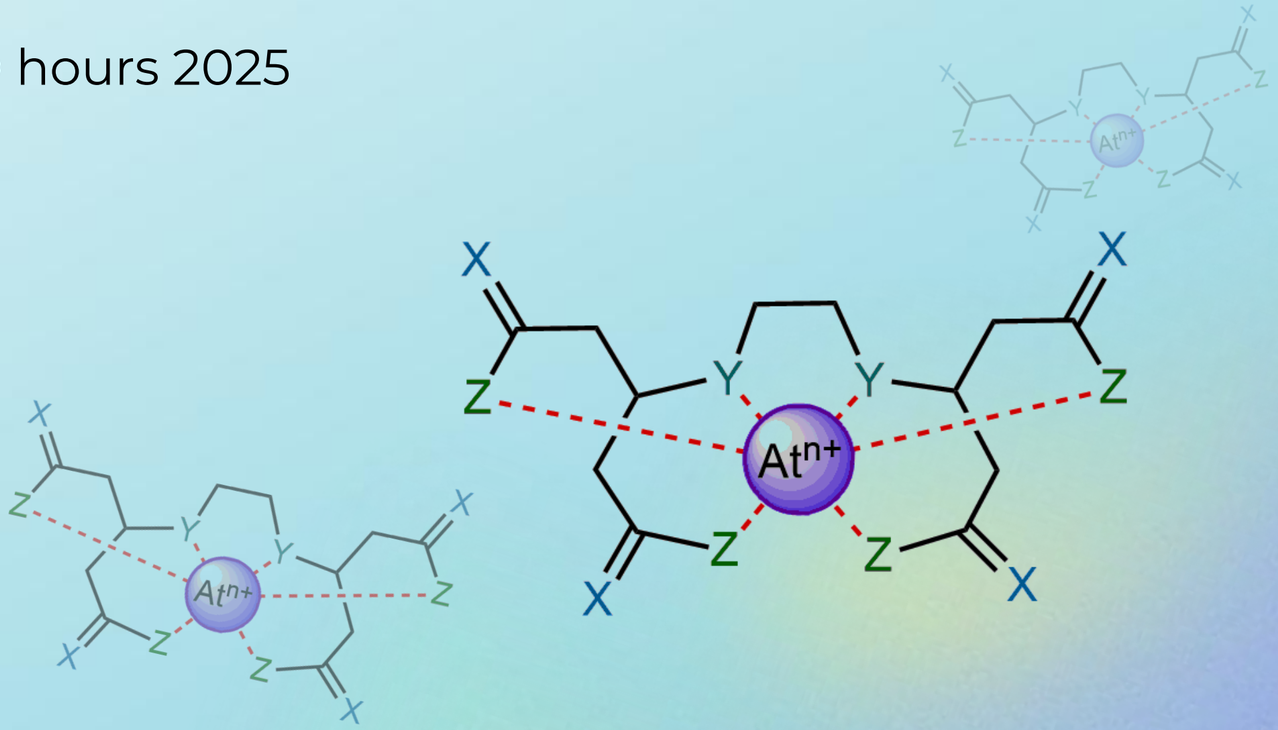
Design and evaluation of ligands for complexation of astatine-211

Subatech PhD hours 2025



Directed by :
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Supervised by Lu Liu(IPHC)

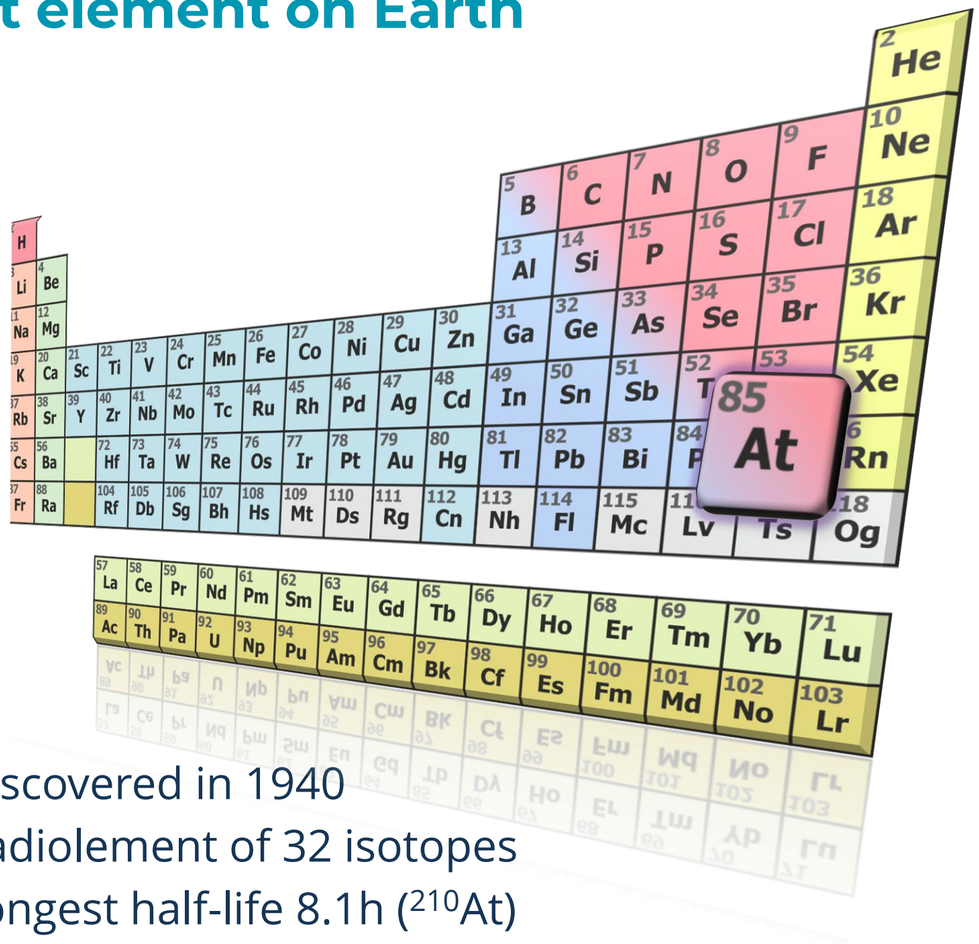
Camille Custodio

13/03/2025

Contents

Element 85 : Astatine

Rarest element on Earth

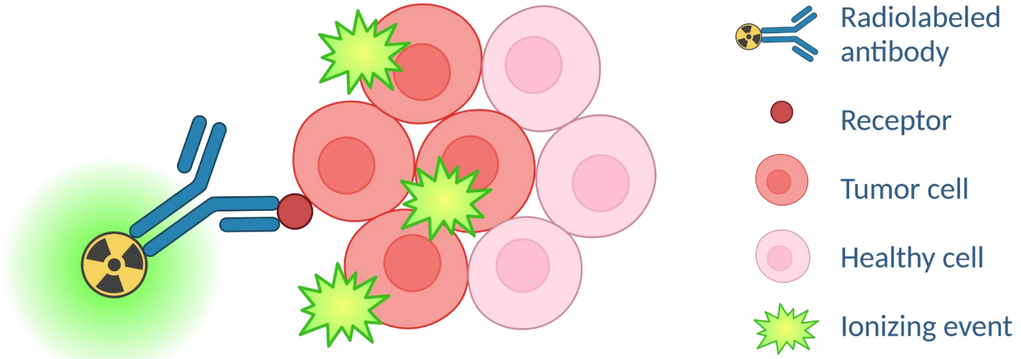


- Discovered in 1940
- Radiolement of 32 isotopes
- Longest half-life 8.1h (^{210}At)
- ^{211}At half-life : 7.21h

Heaviest of the **halogens…**

With **metallic** properties

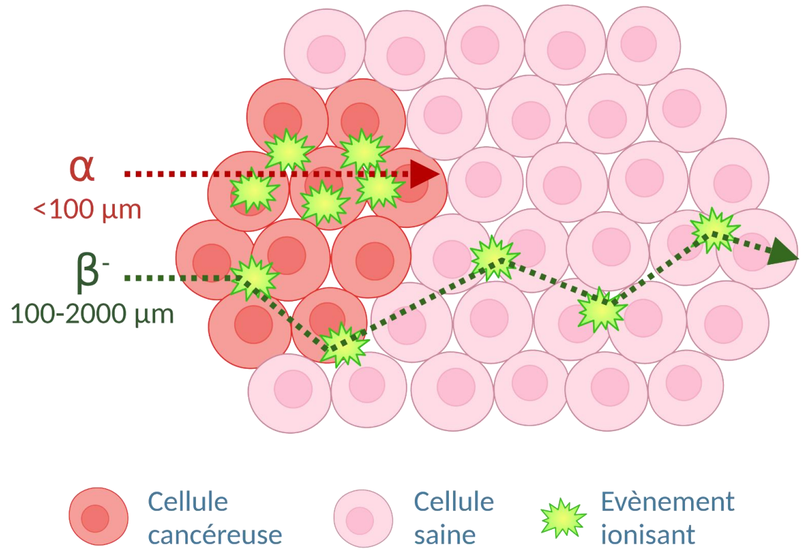
Applications in Radionuclide Therapy and theranostics



Astatine-211 for Targeted Alpha Therapy

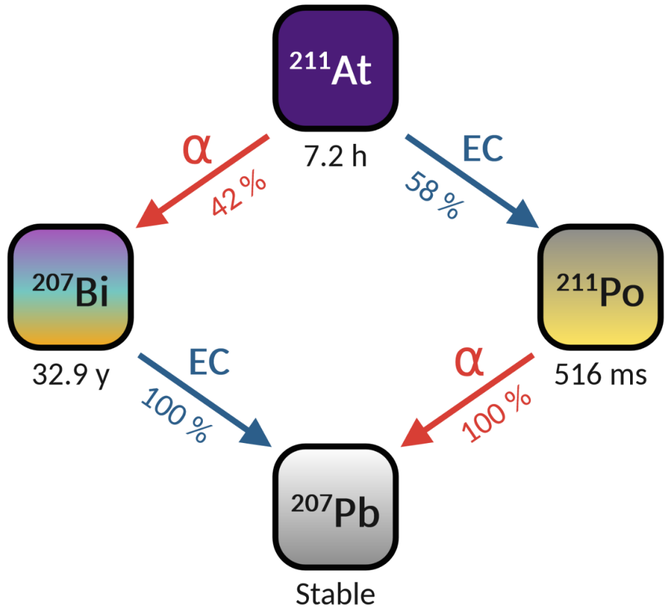
Properties of interest

- ☢ Singular alpha particle emitted by decay
- ☢ Produced in cyclotron by bismuth solid target irradiation



Comparison of ionization density of α & β- emissions

Decay scheme of ^{211}At

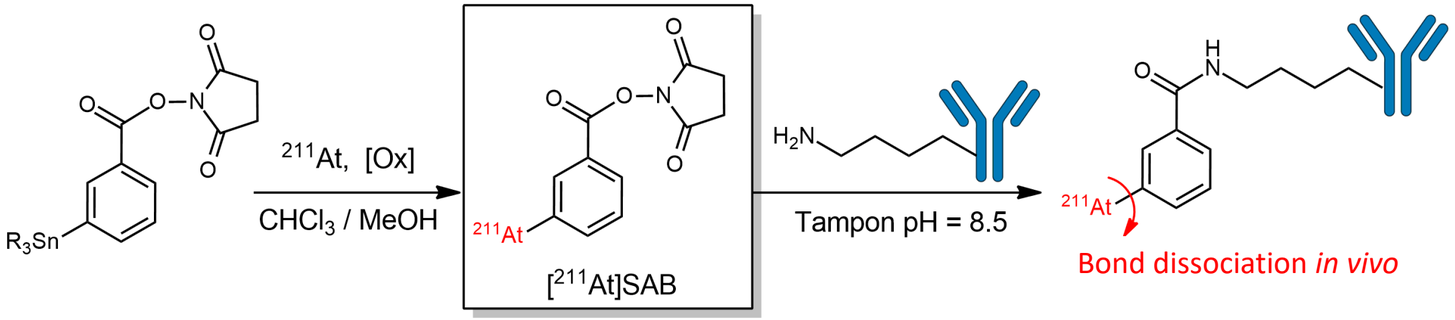


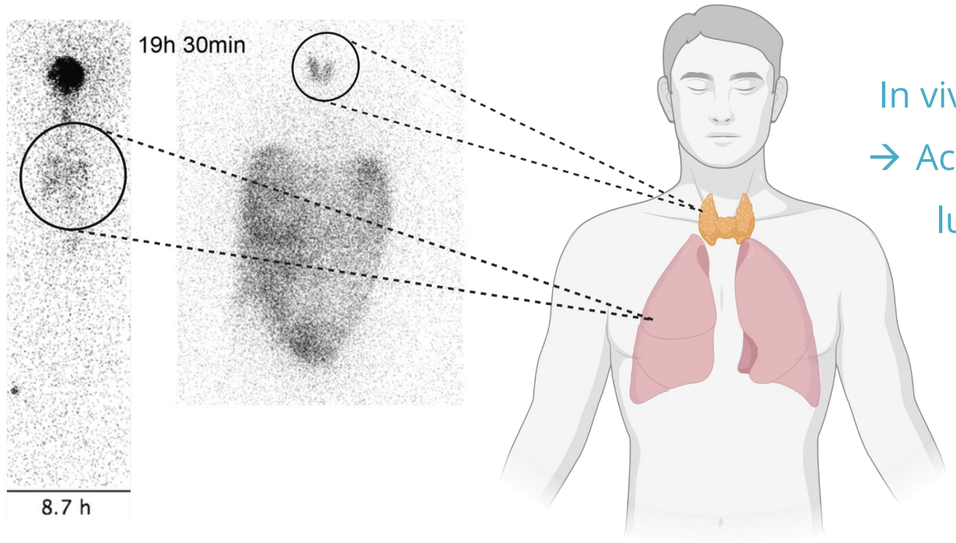
ARRONAX research cyclotron 70MeV for production of ^{211}At.

Current limitations for applications of astatine-211

Astatine as a halogen...

Radiolabeling with **SAB** : Succinimidyl Astato Benzoate





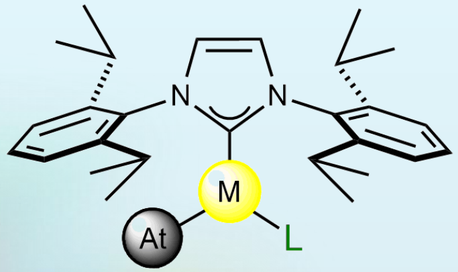
In vivo deastatination
→ Accumulation in the lungs and thyroid

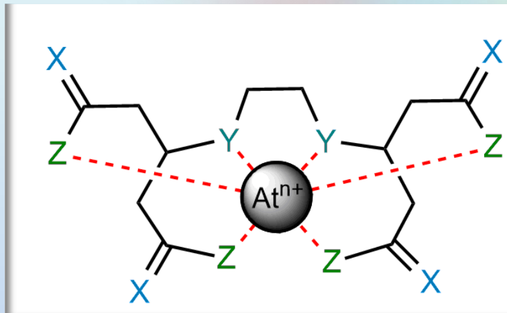
... or a metal ?

- Stable cation in water
- Association with ligands

SAt-Radio project : *Stable ^{211}At-labeled Radiopharmaceuticals for TAT*

Metal-astatine bond





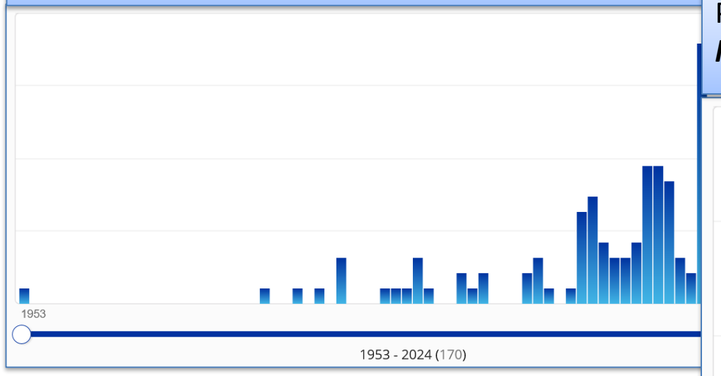
Complexation with ligand

Labeling strategies using metallic astatine

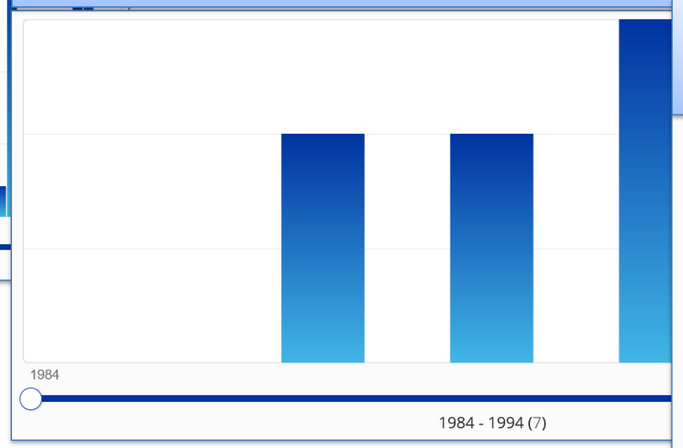
State of the art on complexation of astatine

« The number of studies dealing with the complexation properties of the cationic forms of astatine remains limited. »

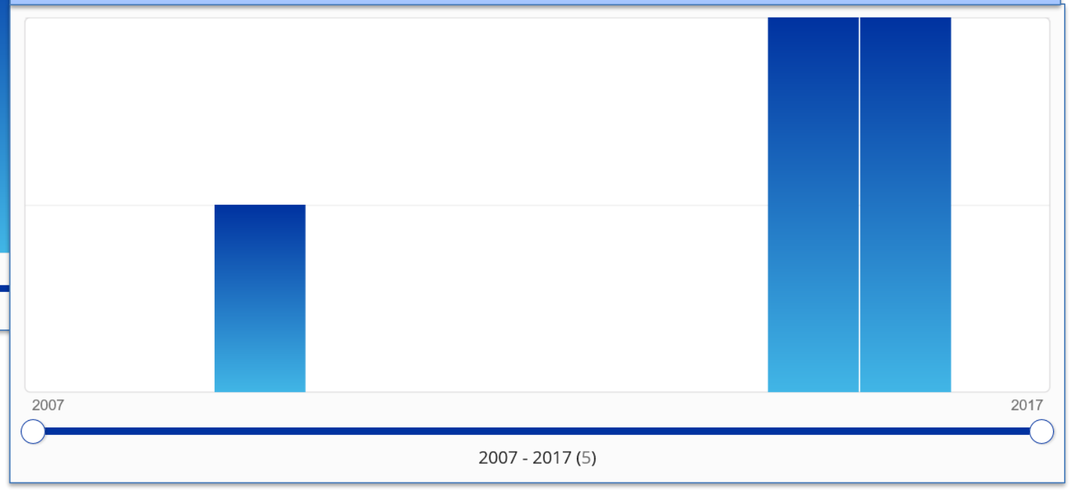
Publications returned by SciFinder to the query : ***« astatine-211 » and complex***.



Publications returned by SciFinder to the query : ***« astatine(I)» and ligand***.

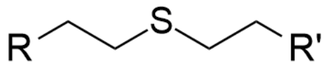


Publications returned by SciFinder to the query : ***« astatine(III) » and complex***.



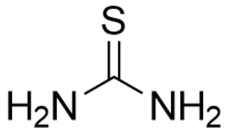
Labeling strategies using metallic astatine

Formation of At(I) complexes : Work by Dresden group (1980s)



☢ Studies of **thioethers** by Ludwig

☢ Studies of **thioureas** by Dreyer

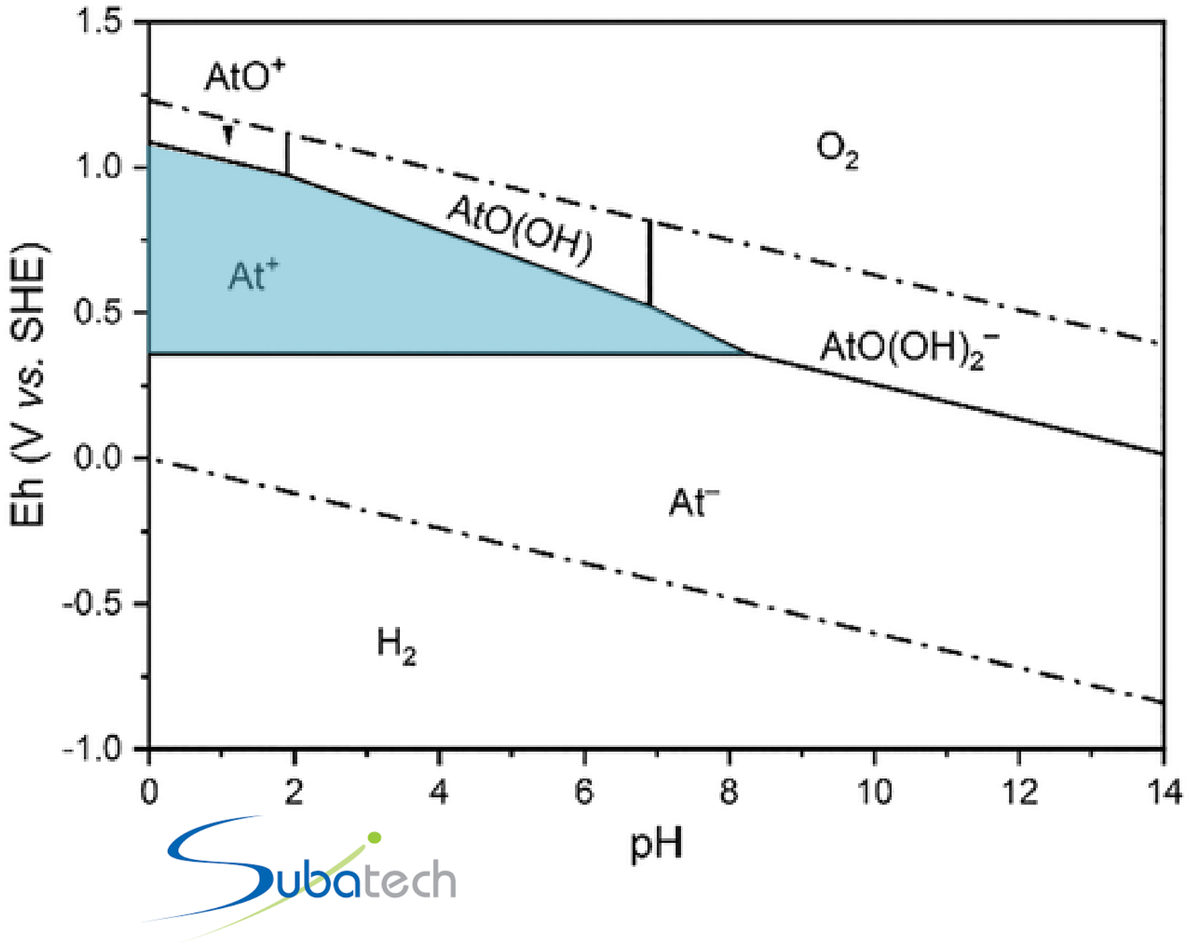


Characterization of complexes by **ionic mobility**

Recent advances :

→ Updated **Pourbaix diagram** by Subatech (Champion, 2009 and Liu, 2022)

→ Studies of ligands thiocyanate and calixarene by **competition method**



Pourbaix Diagram : Liu, L.; et al. Inorg. Chem. 2022, 61 (34), 13462–13470.

Thesis subject : complexation of metallic astatine

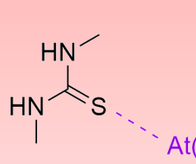
Design and evaluation of ligands for complexation of astatine-211

Screening of ligands → library of molecules established from :

- Literature
- Computational chemistry

Selection of small ligands → formation of polydentate ligands

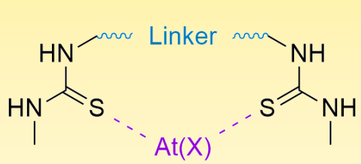
Monodentate ligands



→ *Ligand selection*

Step 1

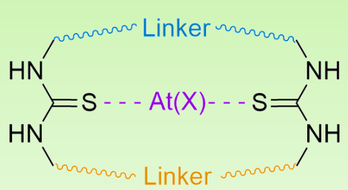
Preorganized bidentate ligands



→ *Chelate effect*

Step 2

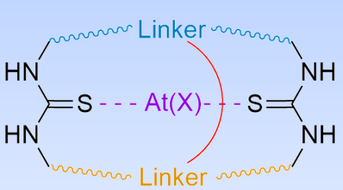
Macrocyclic ligands



→ *Structure variations*

Step 3

Formation of cryptants

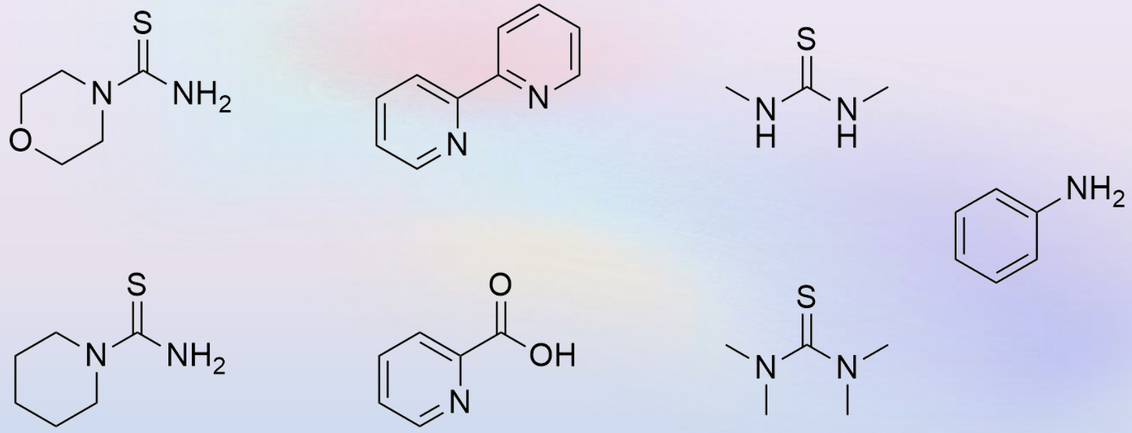


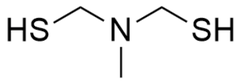
→ *Retention of At⁺*

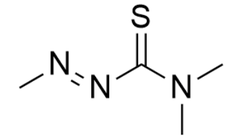
Screening of model ligands

Ligands selection for screening based on available litterature

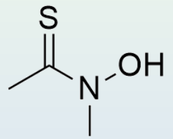
Commercially available

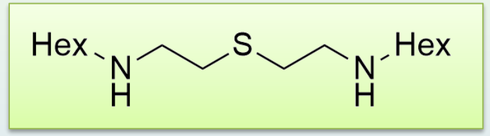


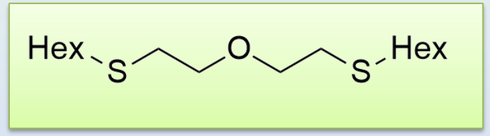


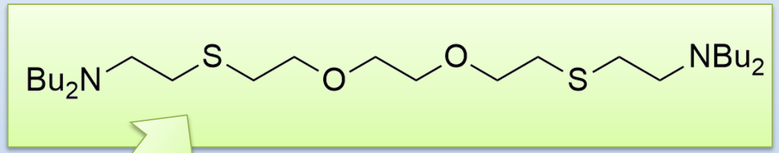


For synthesis





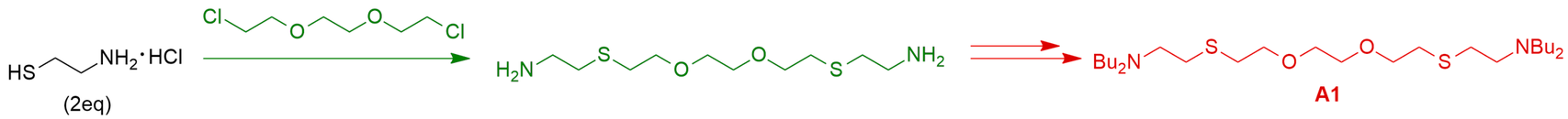


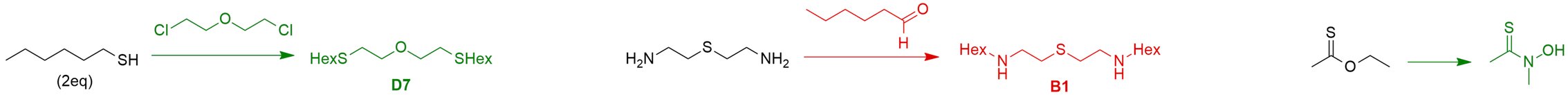


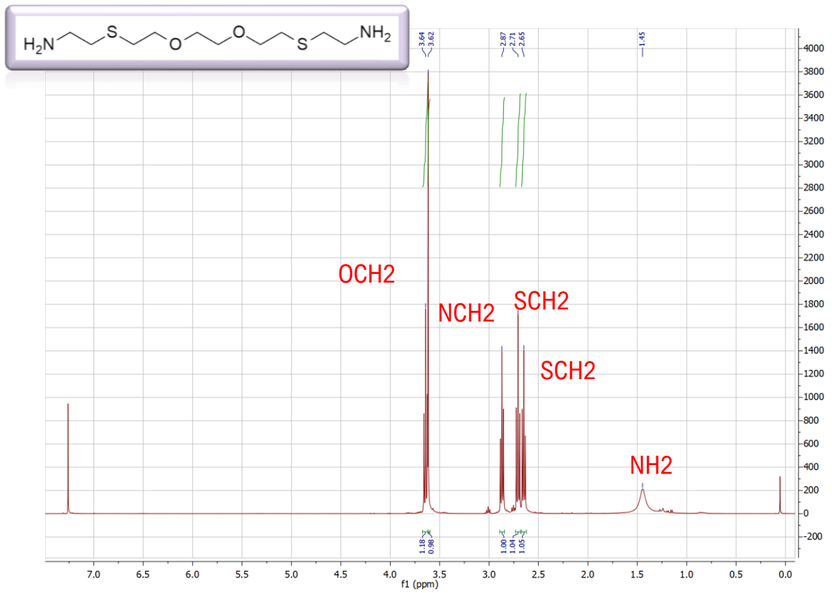
References structures for comparison to the litterature

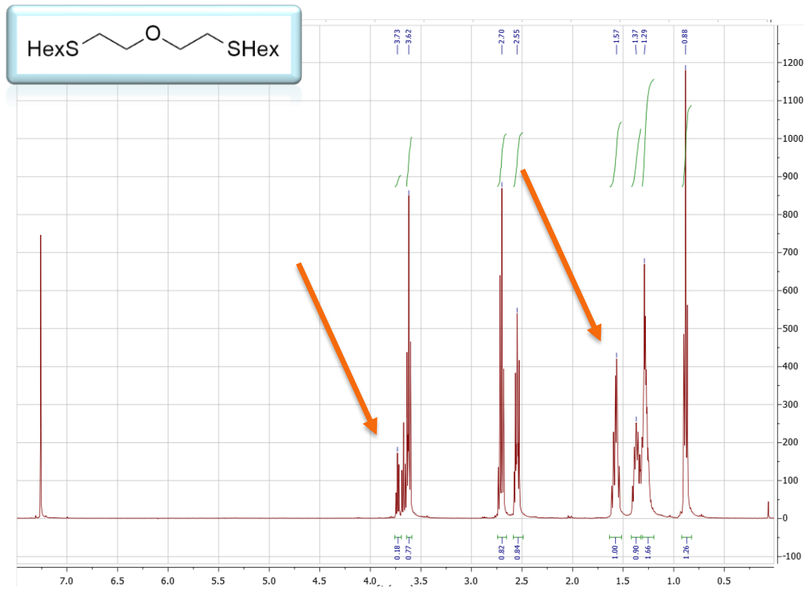
Organic synthesis summary

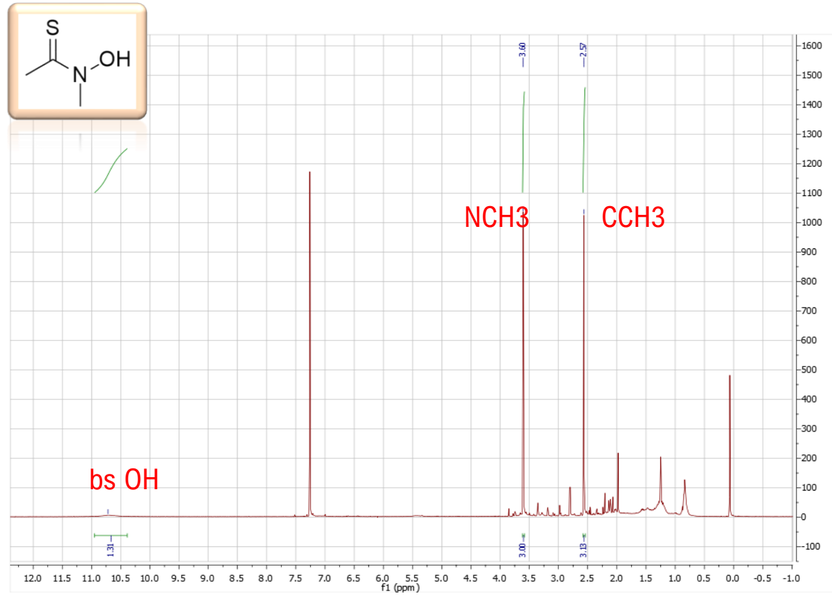
Synthesis of monodentate / reference ligands











Starting material / compound isolated or to purify / failed reaction

Evaluation of interactions with ligands

Working with trace amount of astatine

IR spectroscopy

Mass spectroscopy

NMR spectroscopy

Most spectroscopy tools are unusable at ultratraces concentrations…

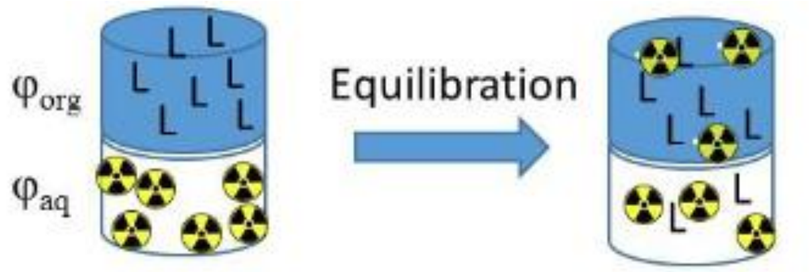
Evaluation of interactions with ligands

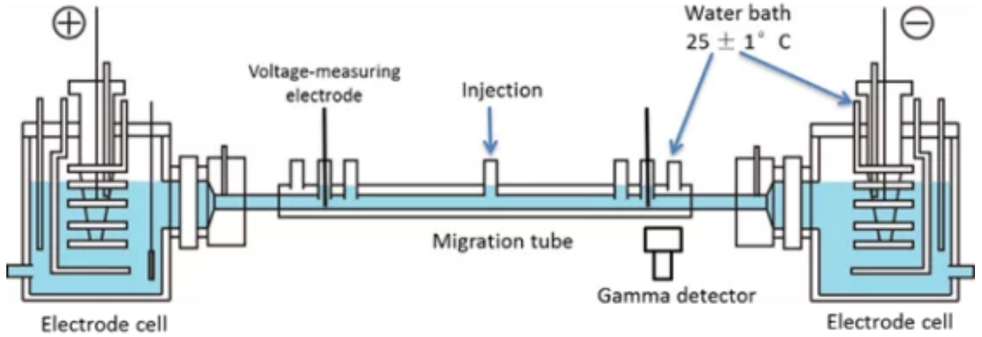
Formation of astatine complexes

How to evaluate complexation of astatine at ultra trace concentrations ?

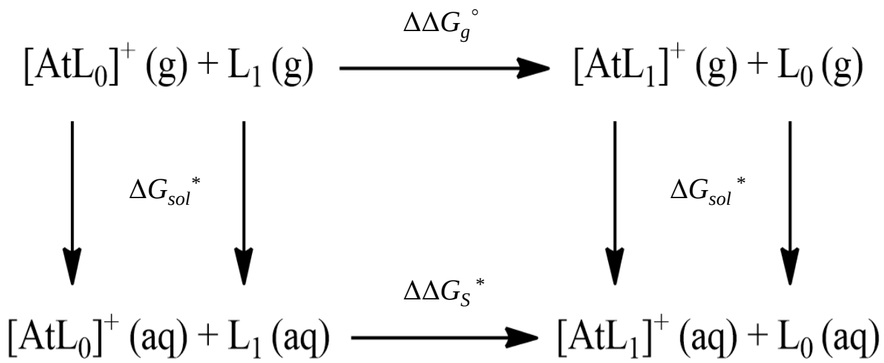
Competition methods between separate layers:

- Liquid/solid competition
- Liquid/liquid competition





Electromobility



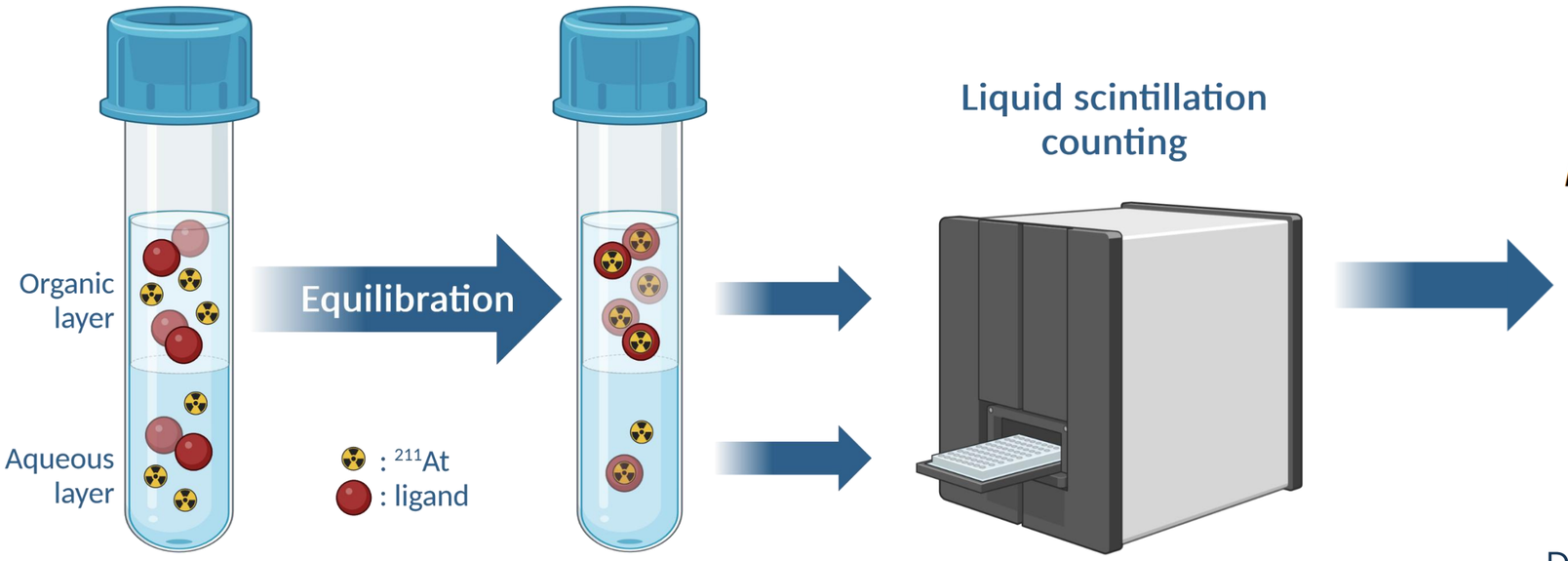
Molecular modeling

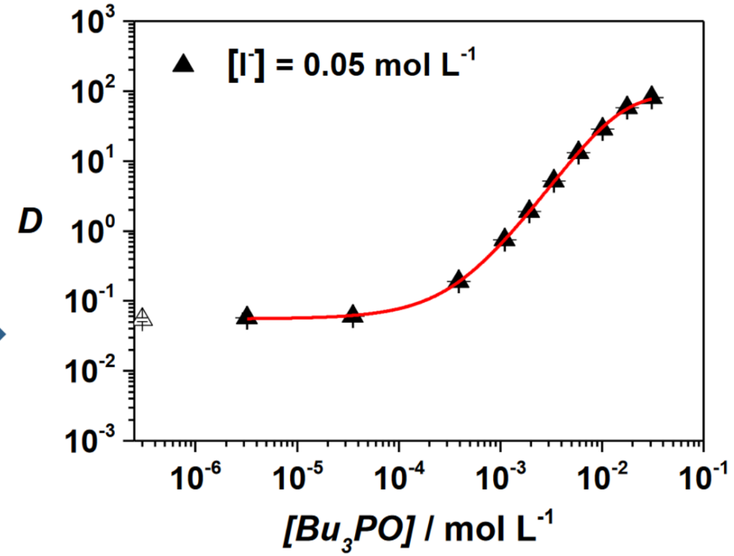
Liquid/liquid competition method

Principle

Variations of astatine distribution in biphasic immiscible system
→ Changes of astatine speciation

Distribution coefficient $D = \frac{A_{org} \times V_{aq}}{A_{aq} \times V_{org}}$





Distribution coefficient D of astatine interacting with tributylphosphine oxide Bu_3PO

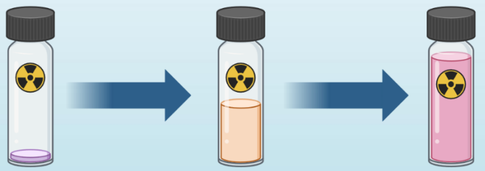
Graph : L. Liu et al., Chemistry – A European Journal, vol. 26, nº 17, p. 3713-3717, 2020, doi: 10.1002/chem.201905389.

Interactions studies : liquid/liquid competition

Experimental conditions for distribution studies

Generation of At^+

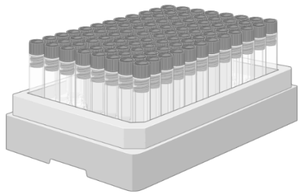
Extraction by NaOH 0.1M



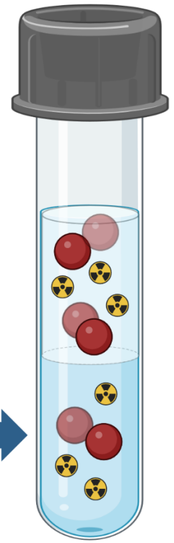
^{211}At in chloroform

Addition of $HClO_4$ 0.2M

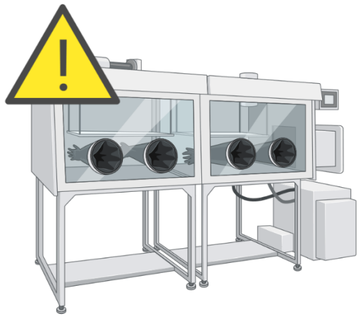
Preequilibration of biphasic system



Dilution of samples



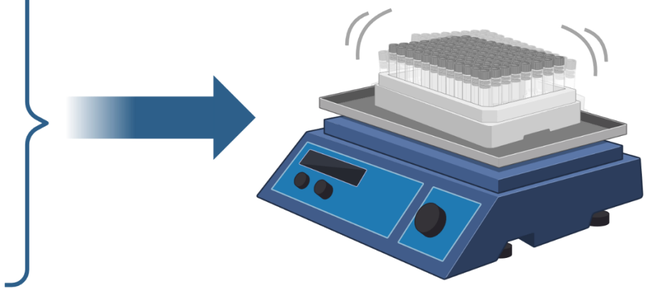
: ^{211}At
: ligand



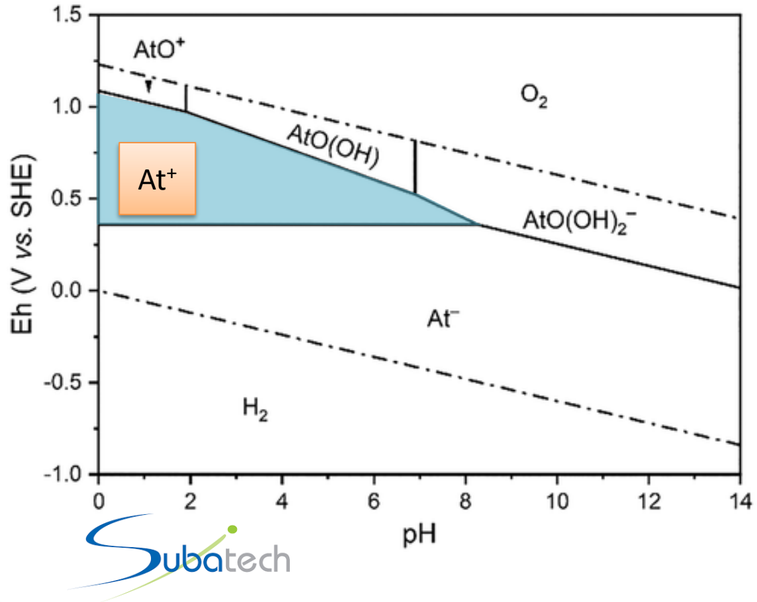
Organic layer : toluene or other solvent not miscible with water

Aqueous layer : HClO4 0.1M

- pH = 1.0 ± 0.1
- E = 0.55 ± 0.05

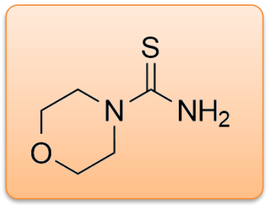


Equilibration of biphasic system with astatine + ligand

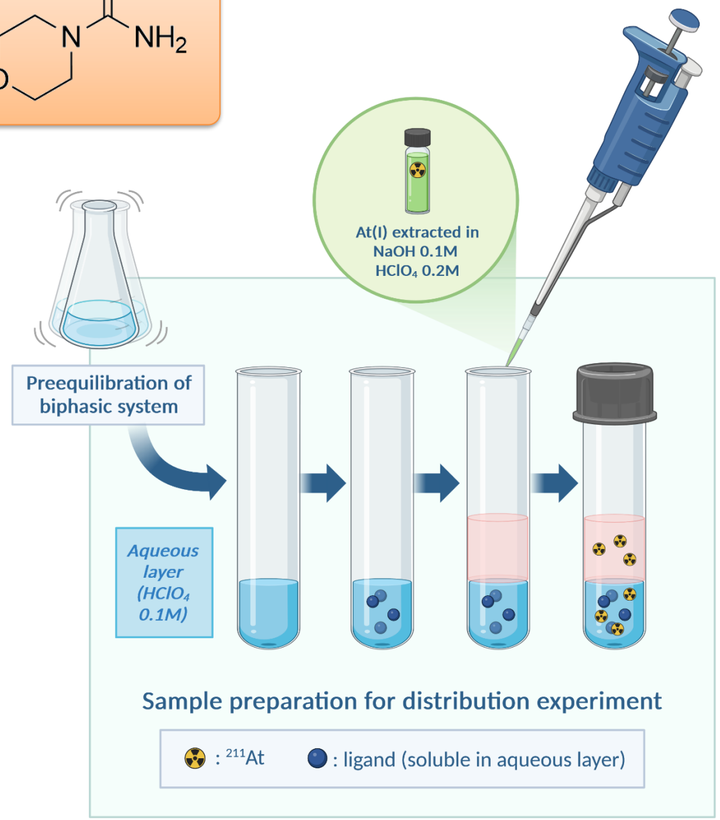


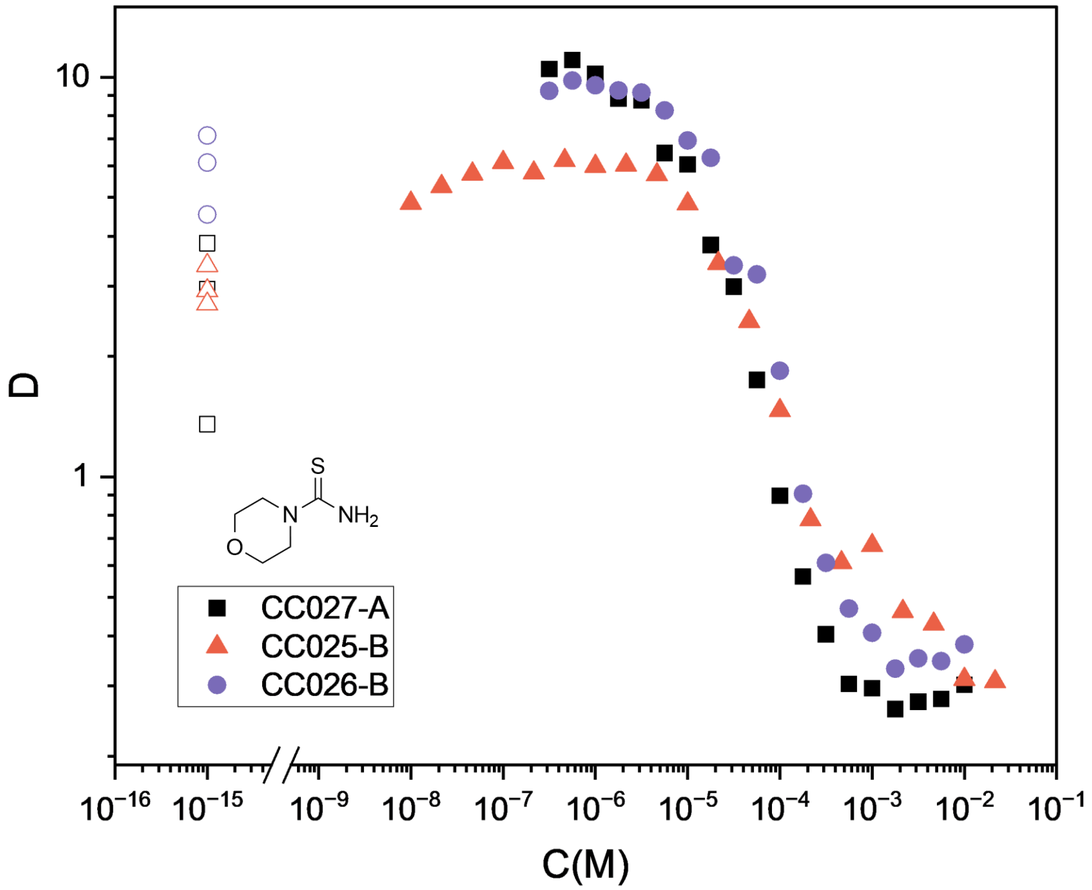
Distribution studies : preliminary results

Morpholine-4-carbothioamide



- Dilution in $HClO_4$ 0.1M



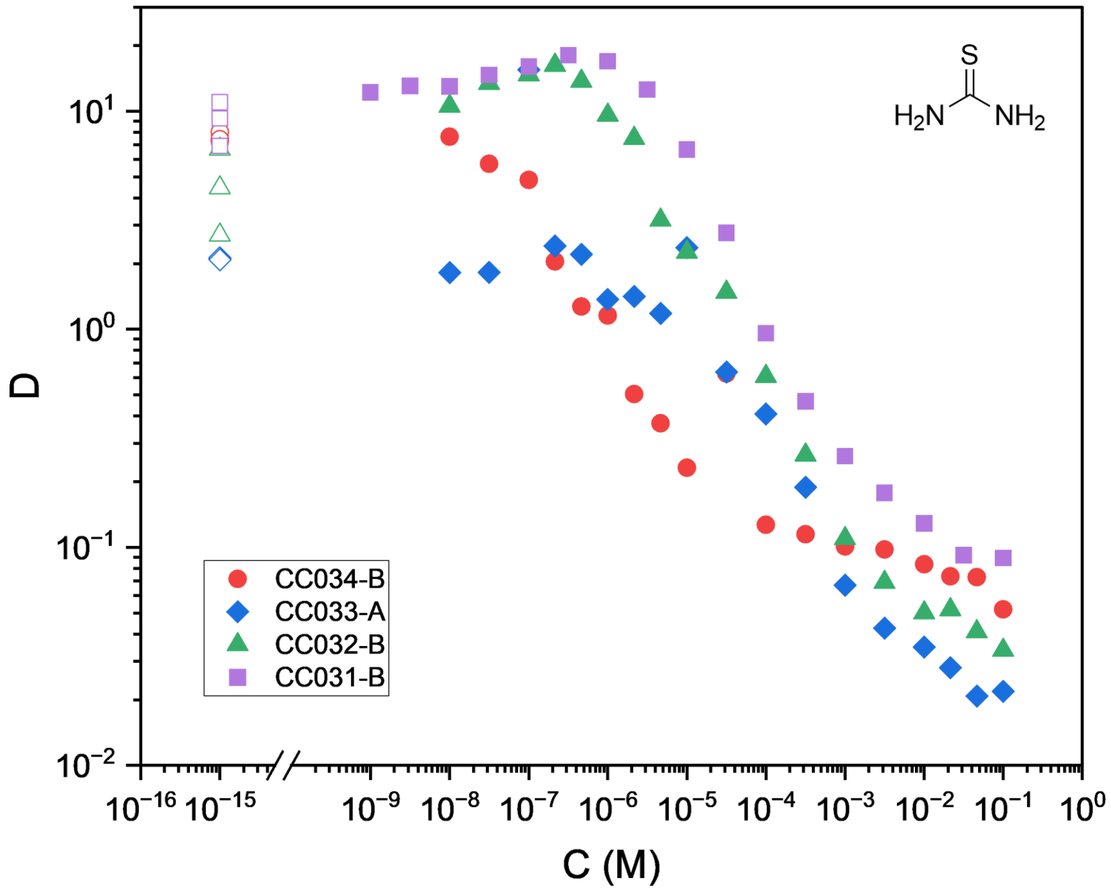


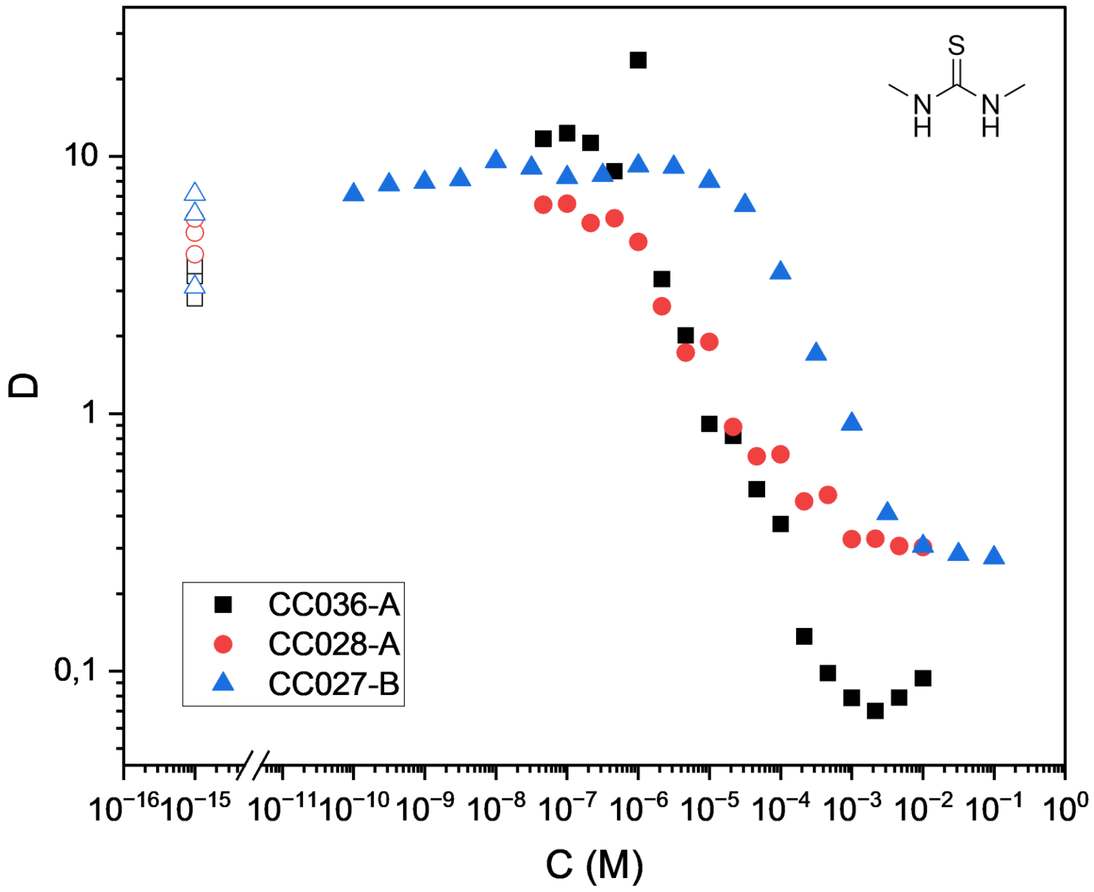
Variation of ^{211}At distribution ratio D between toluene / 1M $HClO_4$ in presence of ligand

Hollow data points indicate distribution ratio without ligand (0M).

Distribution studies : preliminary results

Interactions with thiourea and dimethylthiourea



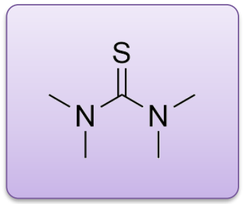


Variation of ^{211}At distribution ratio D between toluene / 1M $HClO_4$ in presence of ligand

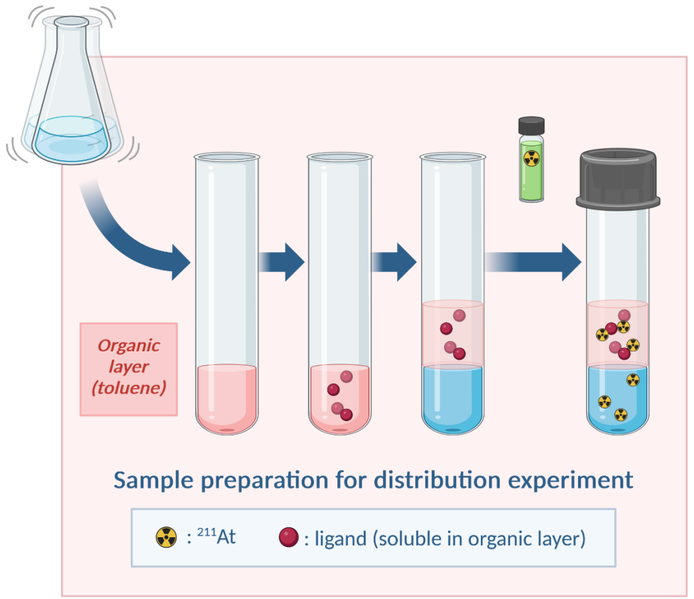
Hollow data points indicate distribution ratio without ligand (0M).

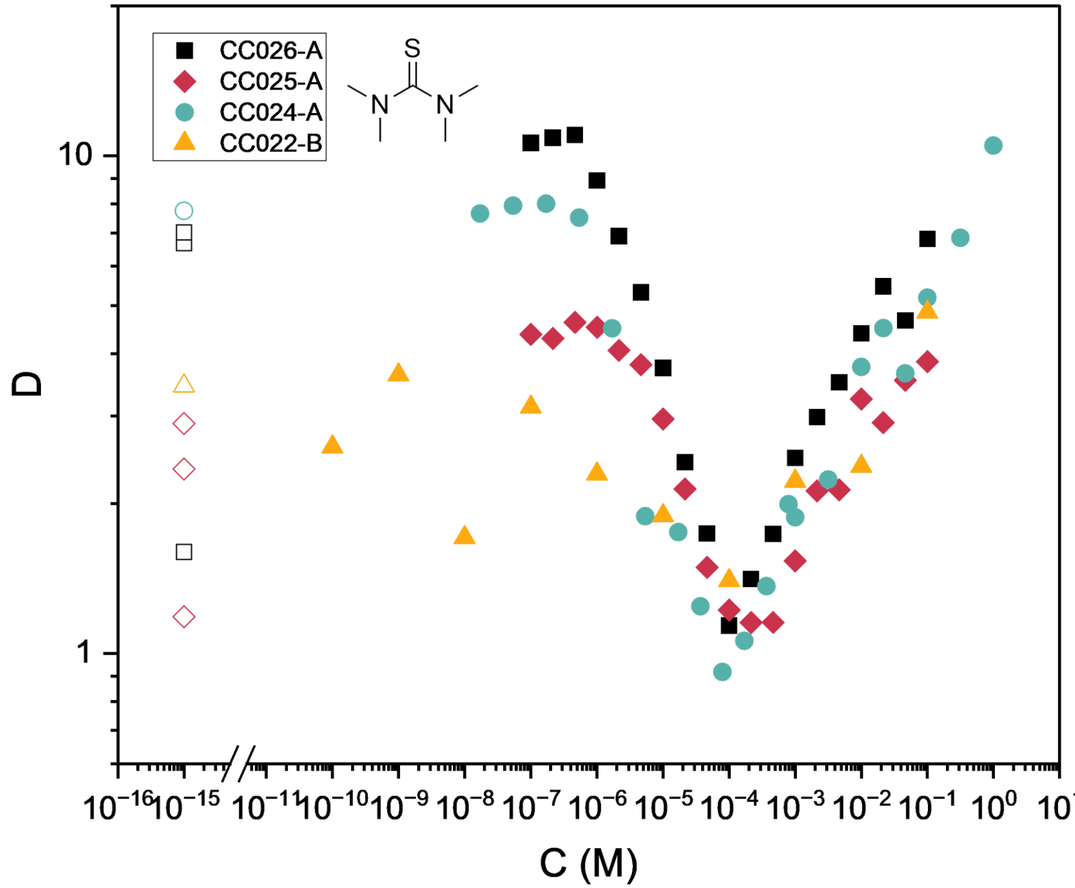
Distribution studies : preliminary results

Interactions with tetramethylthiourea



- Dilution in toluene
- Addition of 40µL of astatine: 10000-20000 CPM



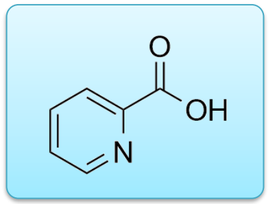


Variation of ^{211}At distribution ratio D between toluene / 1M $HClO_4$ in presence of ligand

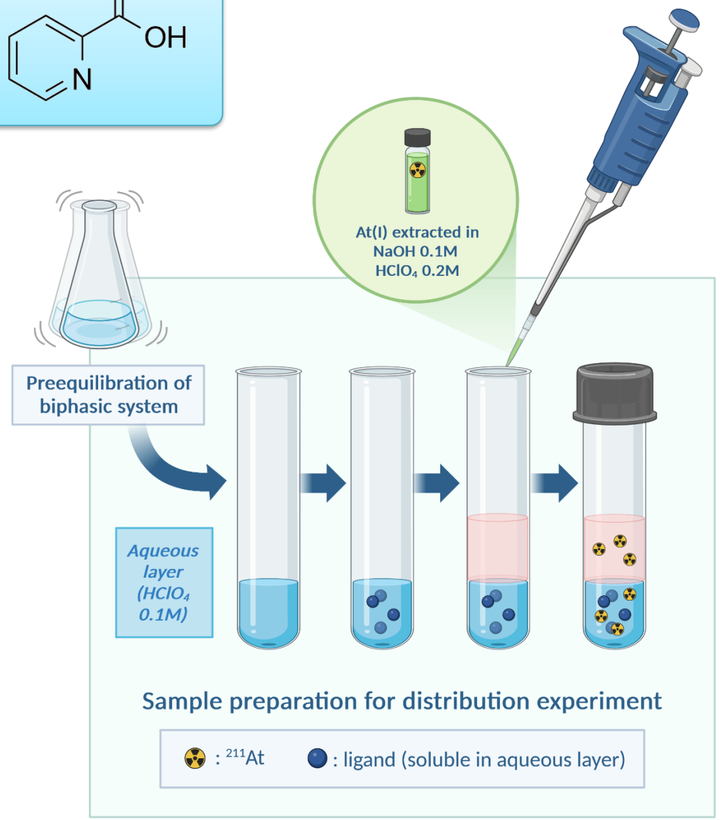
Hollow data points indicate distribution ratio without ligand (0M).

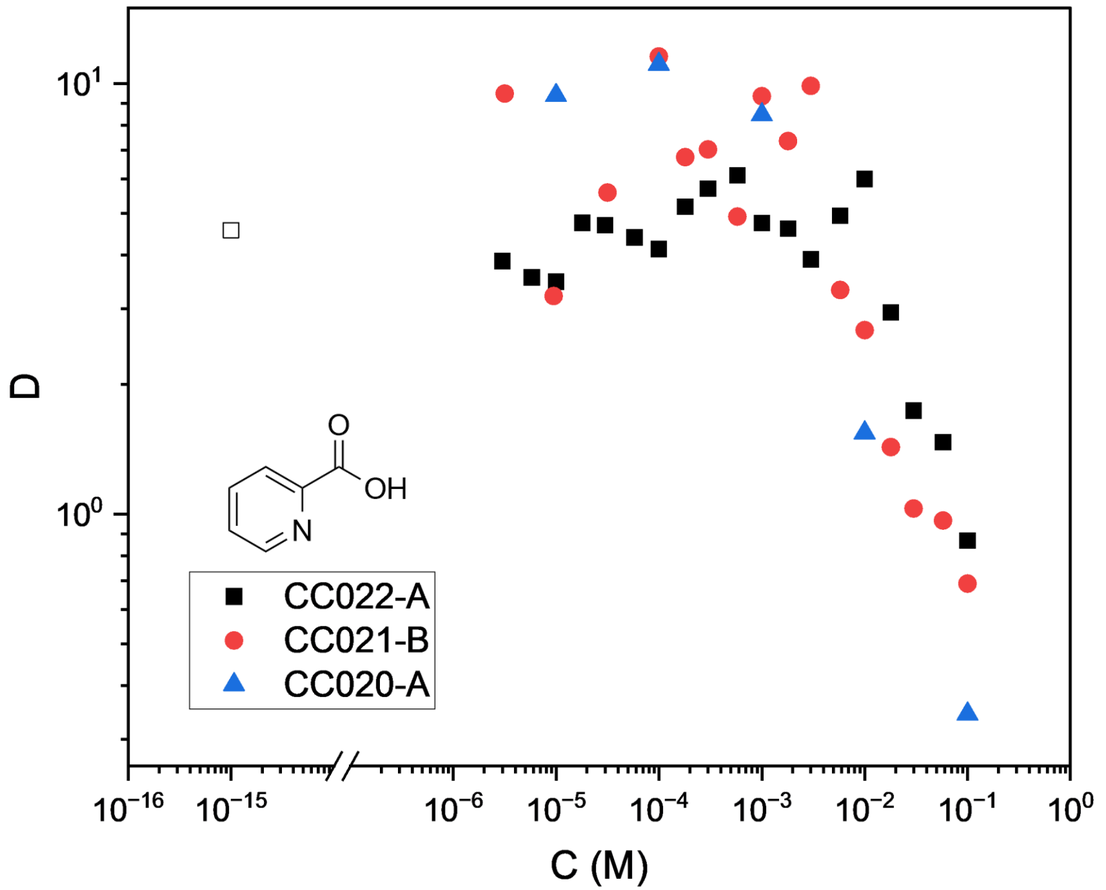
Distribution studies : preliminary results

Interactions with picolinic acid



- Dilution in $HClO_4$ 0.1M





Variation of ^{211}At distribution ratio D between toluene / 1M $HClO_4$ in presence of ligand

Hollow data points indicate distribution ratio without ligand (0M).

At(I) / ligands interaction studies

Complexation equilibrium

Equilibrium hypotheses for ***fitting*** of data with the software Origin

D_0 : distribution coefficient of astatine
D : distribution coefficient of astatine with ligand
K_1, K_2 : equilibrium constants

Model1 : interaction with 1 ligand L

$$\overset{D_0}{At^+_{aq} \leftrightharpoons At^+_{org}}$$

$$\overset{K_1}{At^+ + L^- \rightleftharpoons AtL}$$

$$D = \frac{[At_{org}]}{[At_{aq}] + [AtL]} = \frac{D_0}{1 + K_1[L]}$$

$$\Rightarrow \boxed{y = \frac{D_0}{1 + xK_1}}$$

Model 2 : interactions with 2 ligands L

$$\overset{D_0}{At^+_{aq} \leftrightharpoons At^+_{org}}$$

$$\overset{K_2}{At^+ + 2L^- \rightleftharpoons AtL_2{}^-}$$

$$D = \frac{[At_{org}]}{[At_{aq}] + [AtL_2]} = \frac{D_0}{1 + K_2[L]^2}$$

$$\Rightarrow \boxed{y = \frac{D_0}{1 + x^2K_2}}$$

Model 3 : interaction with 2 ligands → formation of 2 complexes

$$\overset{D_0}{At^+_{aq} \leftrightharpoons At^+_{org}}$$

$$\overset{K_1}{At^+ + L^- \rightleftharpoons AtL} \qquad \overset{K_2}{At^+ + 2L^- \rightleftharpoons AtL_2{}^-}$$

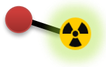
$$D = \frac{[At_{org}]}{[At_{aq}] + [AtL] + [AtL_2]} = \frac{D_0}{1 + K_1[L] + K_2[L]^2}$$

$$\Rightarrow \boxed{y = \frac{D_0}{1 + xK_1 + x^2K_2}}$$

Distribution models for At(I) distribution studies

Complexation equilibrium

Model 1



$$y = \frac{D_0}{1 + xK_1}$$

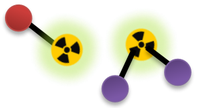
Formation of 1:1 complex

Model 3

$$y = \frac{D_0}{1 + x^2K_2}$$

Formation of 1:2 complex

Model 5



$$y = \frac{D_0}{1 + xK_1 + x^2K_2}$$

Formation of 1:1 and 1:2 complexes

Model 2

$$y = \frac{D_0 + x * D_1 * K_1}{1 + xK_1}$$

Formation of 1:1 complex considering complex distribution

Model 4

$$y = \frac{D_0 + D_2 * x^2K_2}{1 + x^2K_2}$$

Formation of 1:2 complex considering complex distribution

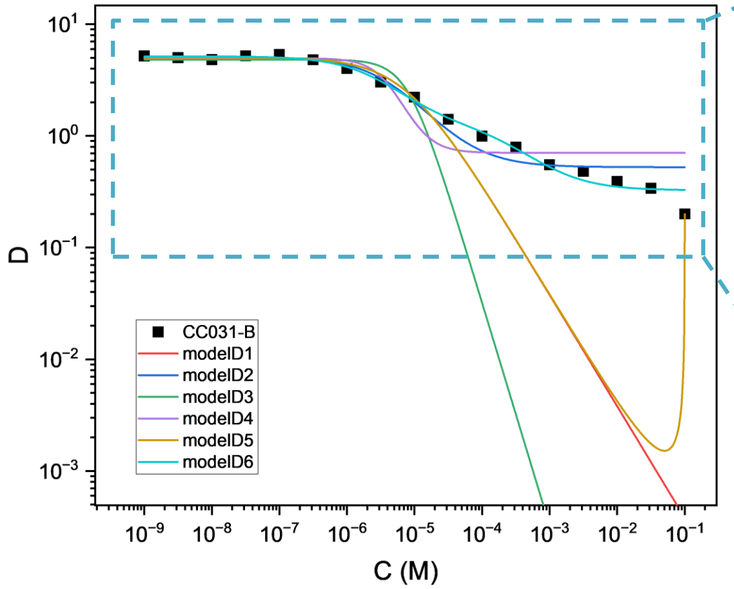
Model 6

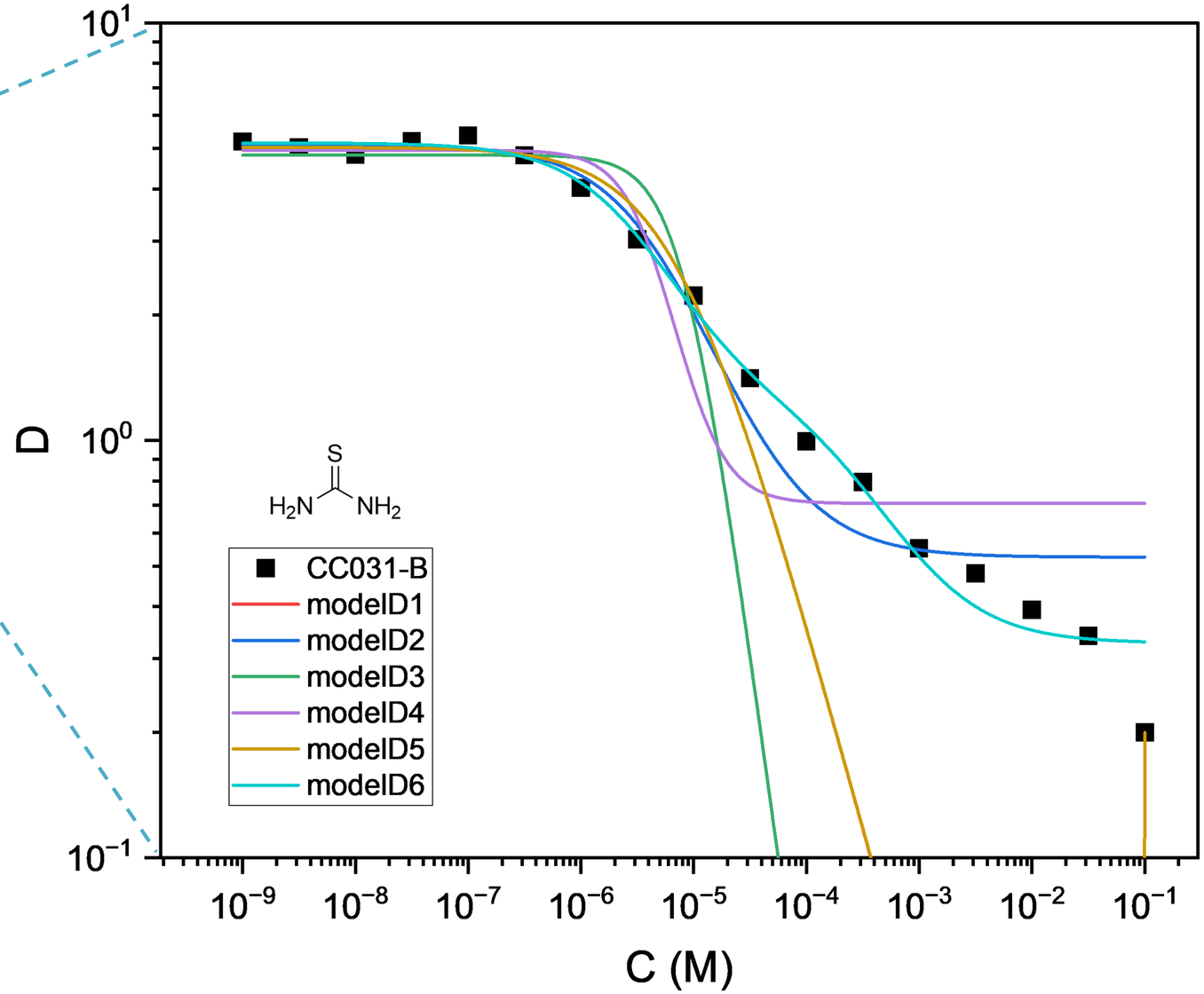
$$y = \frac{D_0 + x * D_1 * K_1 + D_2 * x^2K_2}{1 + xK_1 + x^2K_2}$$

Formation of 1:1 and 1:2 complexes considering complex distribution

Distribution models for At(I) distribution studies

Data analysis : Thiourea





- R^2 modelD6 = 0,99539
- R^2 modelD2 = 0,98904
- ModelD6 : D1 = 1,2408 → incoherent with observed tendency

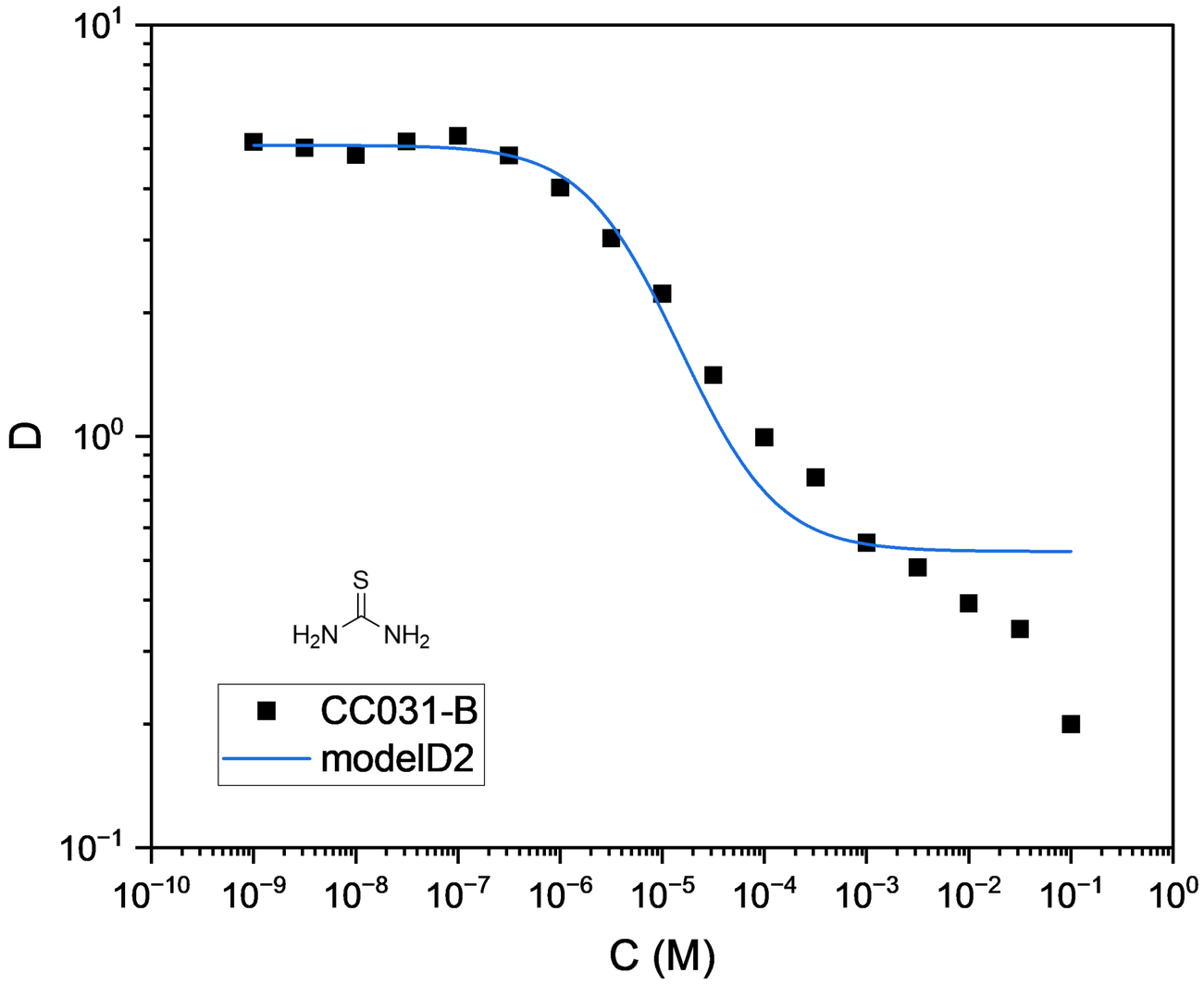
Distribution models for At(I) distribution studies

Data analysis : Thiourea

- Best fit with **modelD2**
- **Formation of 1:1 complex with distribution of said complex bewteen the 2 layers**

Model	modelD2 (User)
Equation	(D0+D1*K*x)/(1+K*x)
Plot	CC031-B
D0	5,09799 ± 0,09908
K	**208903,32628 ± 34131,76792**
D1	0,52536 ± 0,0895
Reduced Chi-Sqr	0,05557
R-Square (COD)	0,98904
Adj. R-Square	0,98747

***LogK* = 5,31994536**



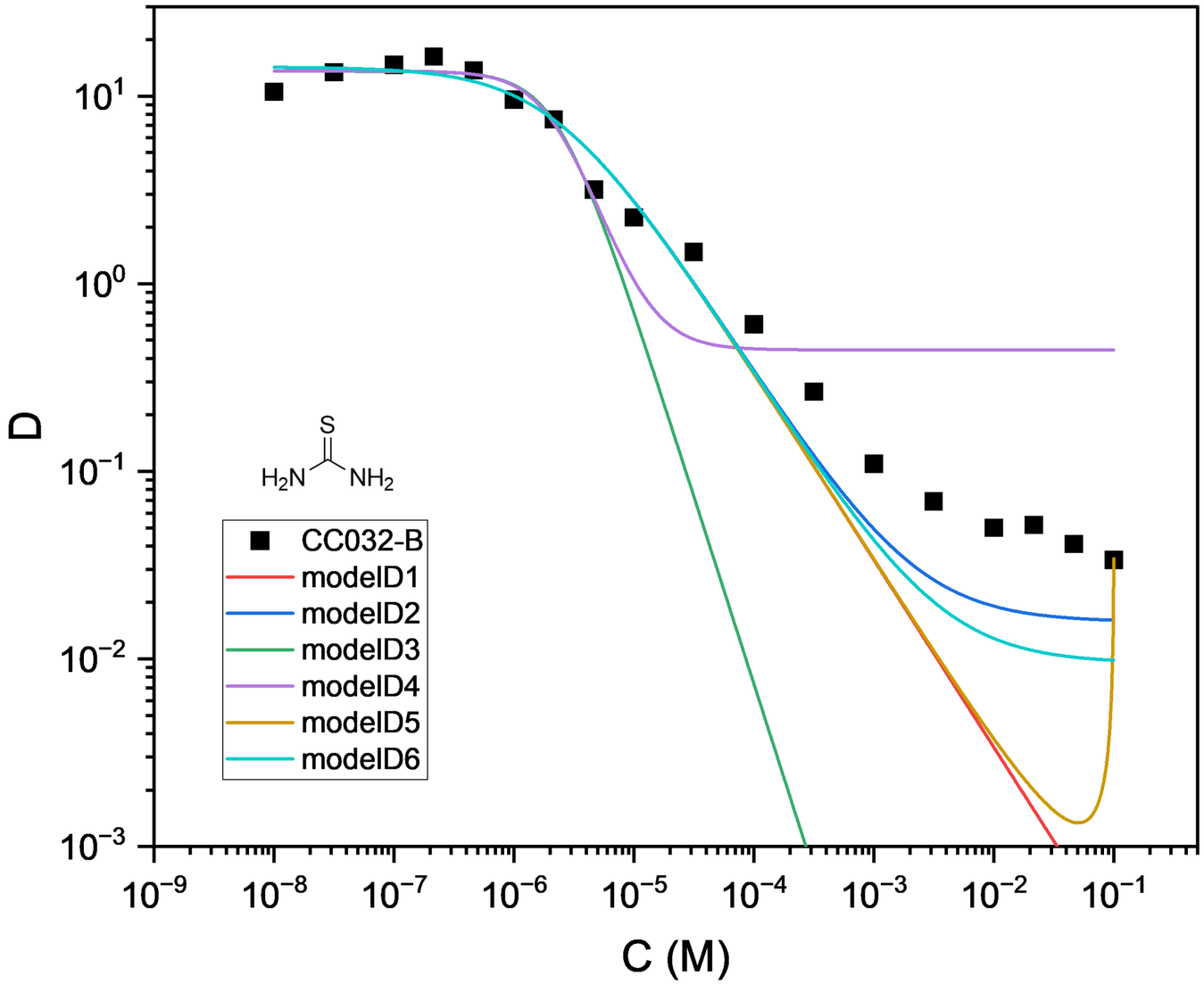
Distribution models for At(I) distribution studies

Data analysis : Thiourea

- Good fit with modelD2 and modelD6
- Best fit with modelD2
- **Formation of 1:1 complex with distribution of said complex**

Model	modelD2 (User)
Equation	(D0+D1*K*x)/(1+K*x)
Plot	CC032-B
D0	14,30952 ± 0,78171
K	**424668,75384 ± 125737,14054**
D1	0,01572 ± 0,49538
Reduced Chi-Sqr	2,10772
R-Square (COD)	0,95034
Adj. R-Square	0,94372

***LogK* = 5,62805031**



Distribution models for At(I) distribution studies

Data analysis : Thiourea

- Good fit with modelD2 and modelD6
- Best fit with modelD2
- **Formation of 1:1 complex with distribution of said complex**

Model	modelD2 (User)
Equation	(D0+D1*K*x)/(1+K*x)
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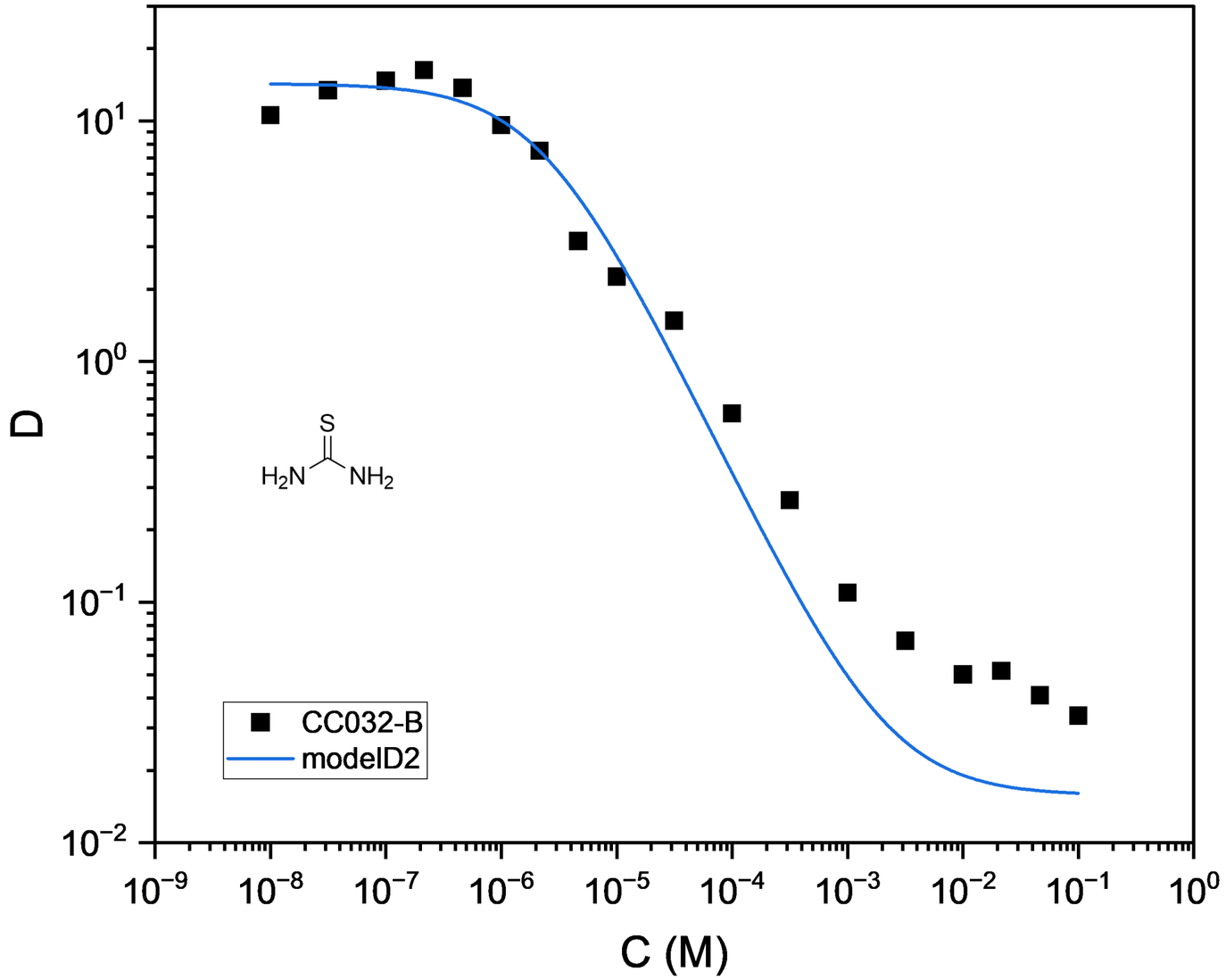
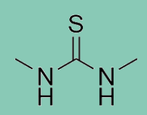
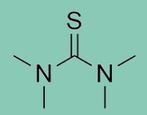
***LogK* = 5,62805031**



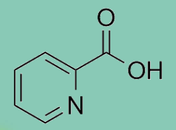
Ligand library for distribution studies



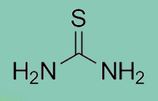
Dimethylthiourea



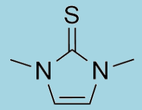
Tetramethylthiourea



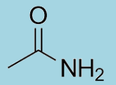
Picolinic acid



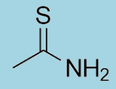
Thiourea



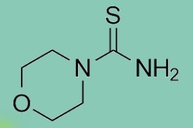
1,3-dimethyl-imidazol -2-ylidene thione



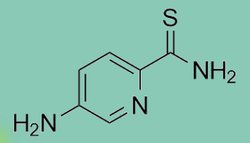
Acetamide



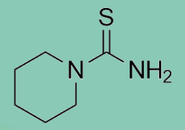
Thioacetamide



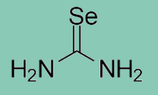
Morpholine-4-carbothioamide



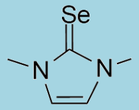
5-aminopyridine-2-carbothioamide



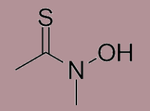
1-Piperidine carbothioamide



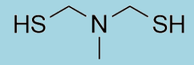
Selenourea



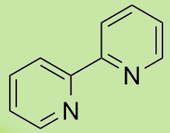
1,3-dimethyl-imidazol -2-ylidene selone



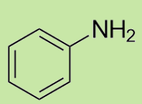
N-hydroxy-N-methylthioacetamide



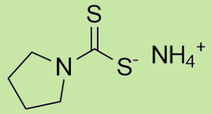
N-dimethanethiol-methylamine



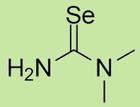
2,2'-Bipyridine



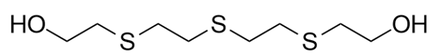
Aniline



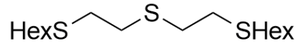
Pyrrolidine-1-dithicarboxylic acid (ammonium salt)



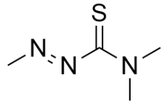
1,1-dimethyl -2-selenourea



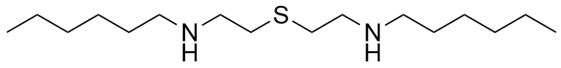
D1



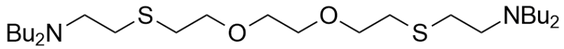
D2



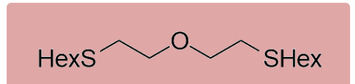
(E)-N,N,2-trimethyl diazenecarbothioamide



B1



A1



D7

Tested with ^{211}At

Available

Modeled

Synthesis in progress

R. Ludwig, et al., Polyhedron, vol. 10, nº 1, p. 11-17, janv. 1991, doi: 10.1016/S0277-5387(00)83540-8.

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Lu Liu

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