Metal-based radiopharmaceuticals: how to choose your chelator?

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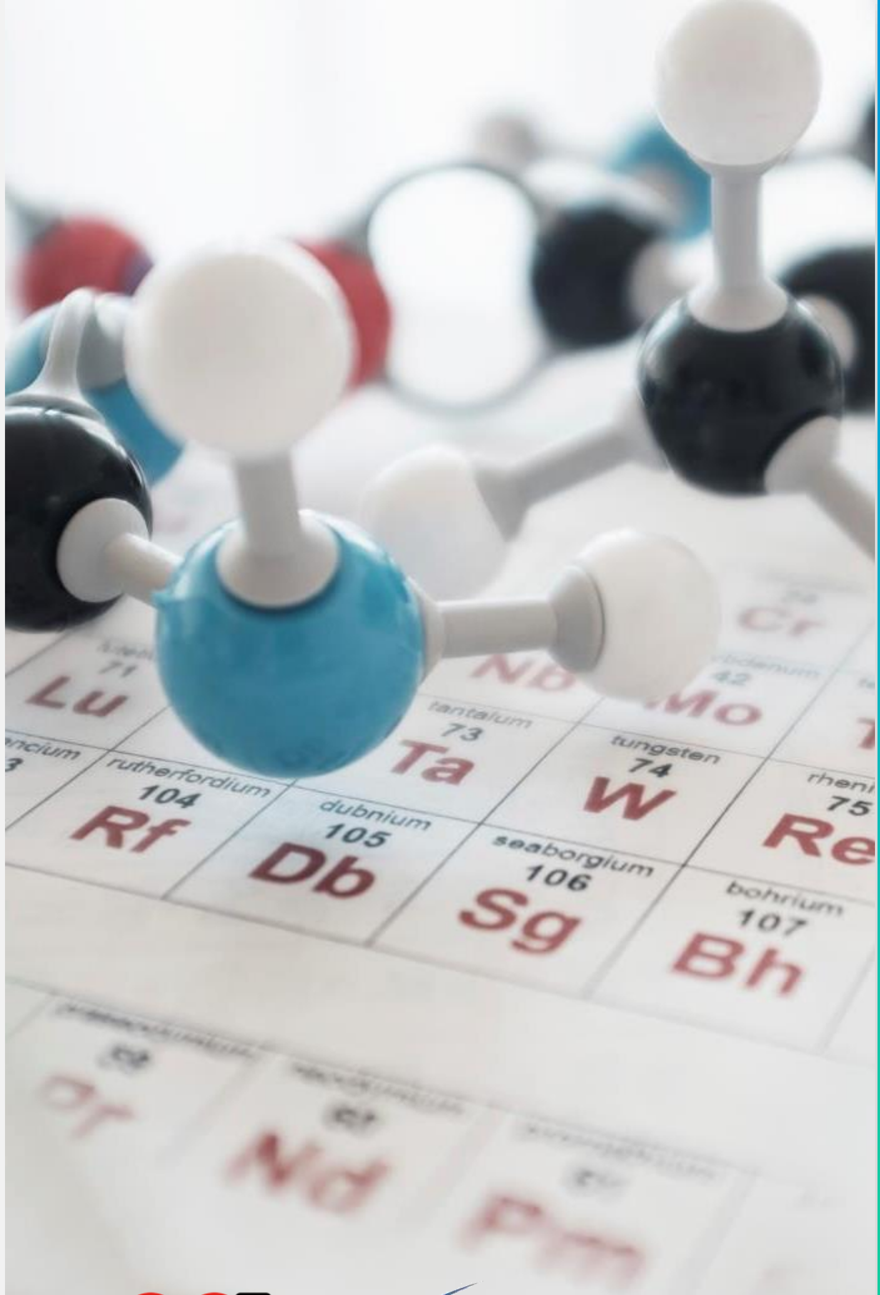
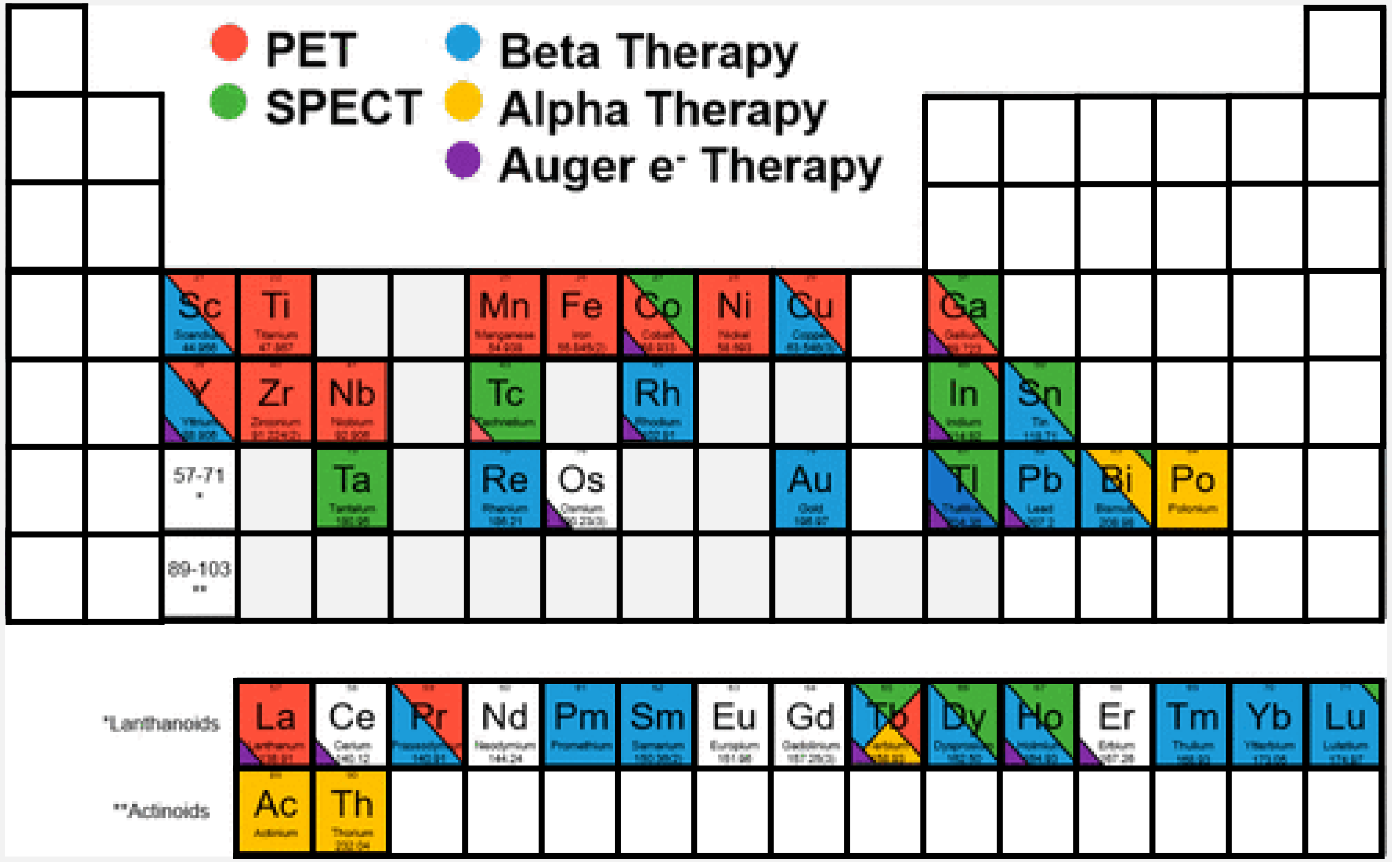
Workshop RIV, Montpellier, 14-16/03/2022



Metallic isotopes

A tool box for imaging (PET, SPECT)

and radiotherapy

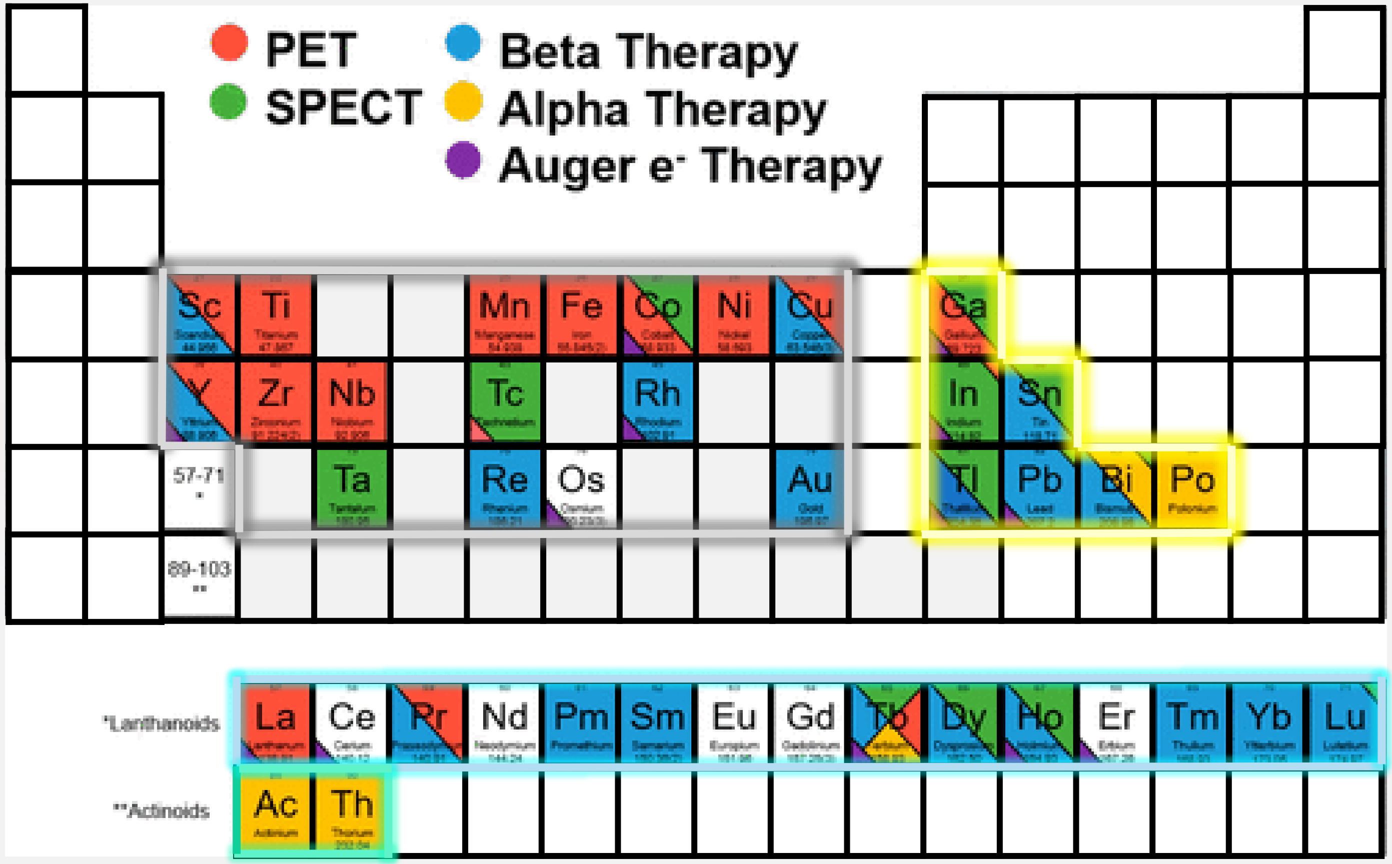


T. I. Kostelnik, C. Orvig, *Chem. Rev.* **2019**, *119*, 902

Metallic isotopes

Different chemistries

- Lanthanides (4*f*)
- Actinides (5*f*)
- Transition metals (*d*)
- Post-transition metals (*p*)



T. I. Kostelnik, C. Orvig, *Chem. Rev*. **2019**, *119*, 902

Metallic isotopes

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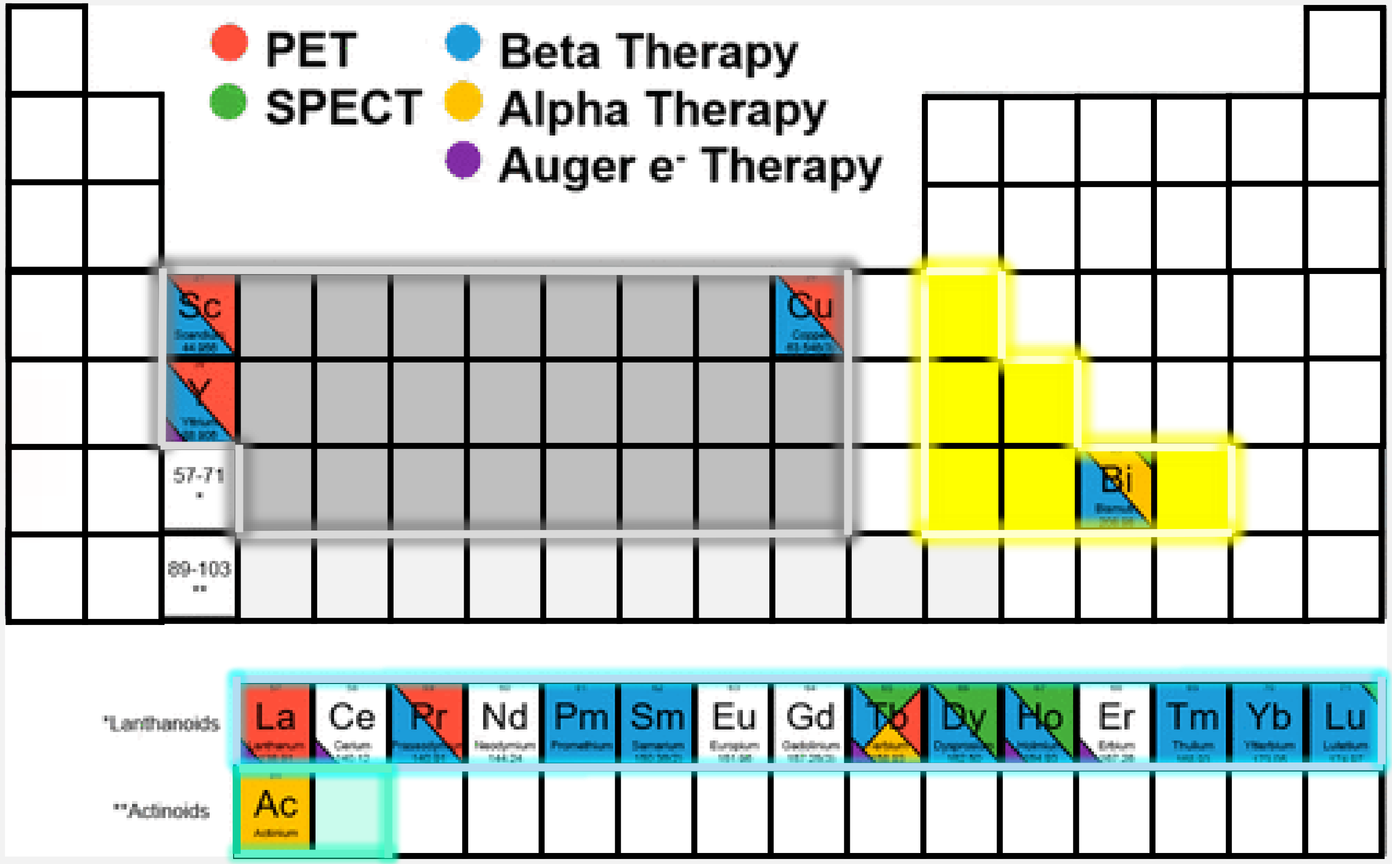
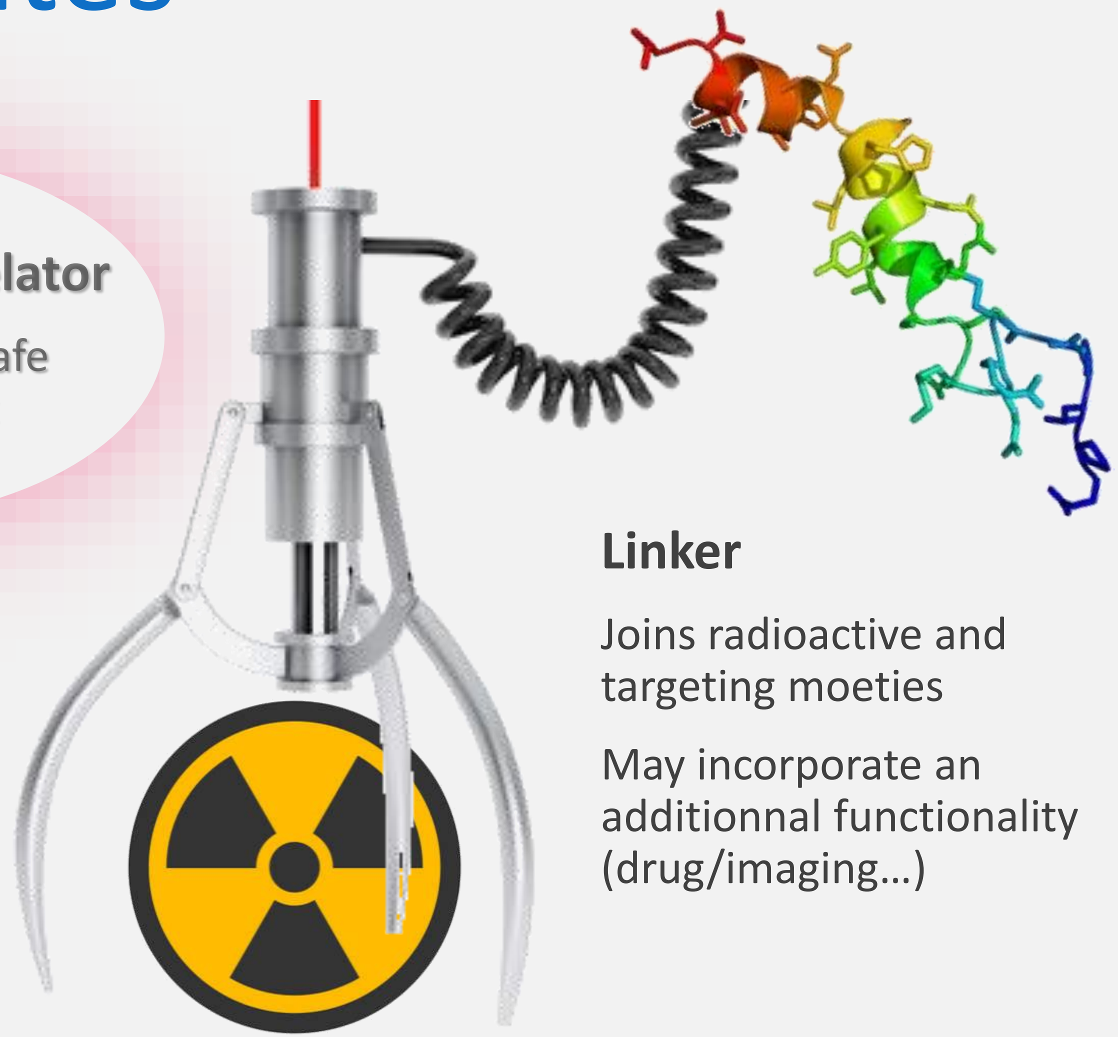


T. I. Kostelnik, C. Orvig, *Chem. Rev*. **2019**, *119*, 902

Radioconjugates

Bifunctional Chelator

Secures metal for safe biological transport



Linker

Joins radioactive and targeting moeties

May incorporate an additionnal functionality (drug/imaging…)

Bioconjugate

Ensures radioactive source accumulates at target

(small molecule, peptide, Ab and derivatives)

cf conf. Tony LAHOUTTE (VUB)

Radioactive metal ion

Source of desired radiation

cf conf. Ulli KÖSTER (ILL)

Radioconjugates

Bifunctional chelator

Cage

Fast complexation
High stability / Good selectivity
High RCY / High specific activity

Mild conditions (mAb and derivatives)

Kinetic inertness
no release
efficient targeting
↘ side-effects

Linker

Activable function
Easy/quantitative coupling
No side products/easy purification

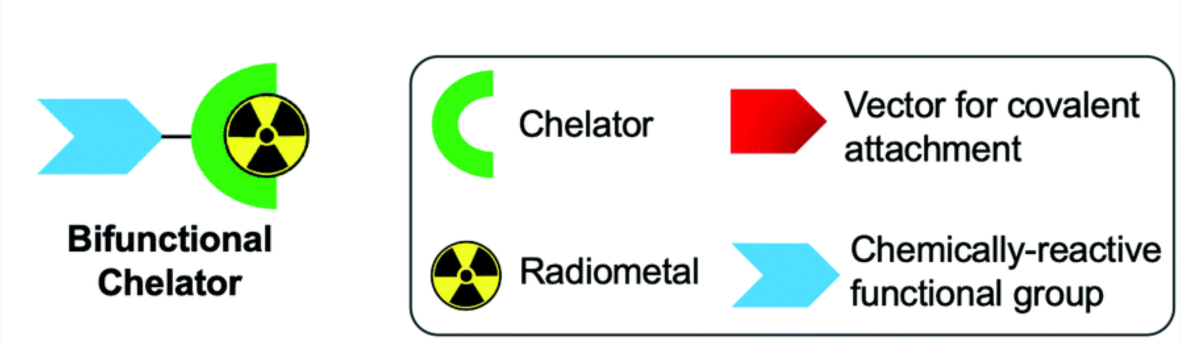
Limit the influence on the targeting
Keep affinity for the target

Possibly introduce multimodality

ADAPTED TO THE METAL OF INTEREST

ADAPTED TO THE VECTOR OF INTEREST

Activable function



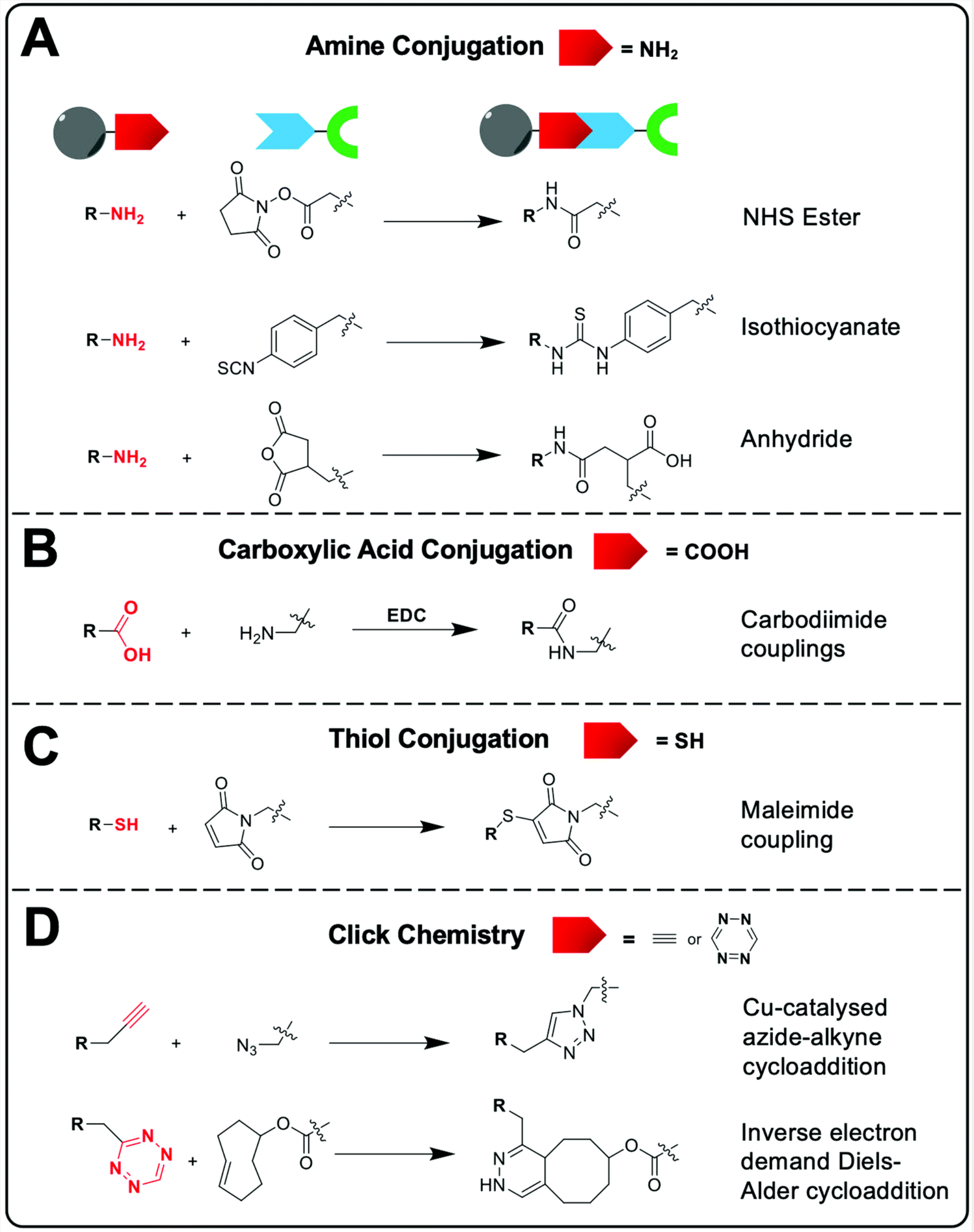
Quantitative coupling

Mild conditions (heat sensitive biovectors)

Limit side products

Site-specific ?

Characterization : Advanced techniques by native Mass Spectrometry, peptide mapping

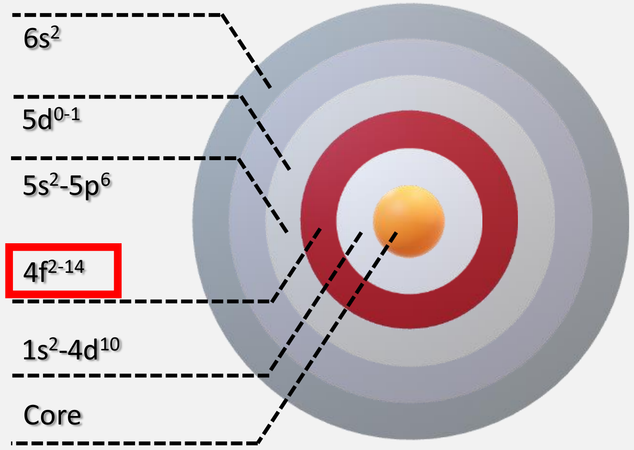


J. Pellico, P. J. Gawne, R. T. M. de Rosales, *Chem. Soc. Rev*. **2021**, *50*, 3355

Lanthanides (*4f*)

+III oxydation state

[Xe]4f^n

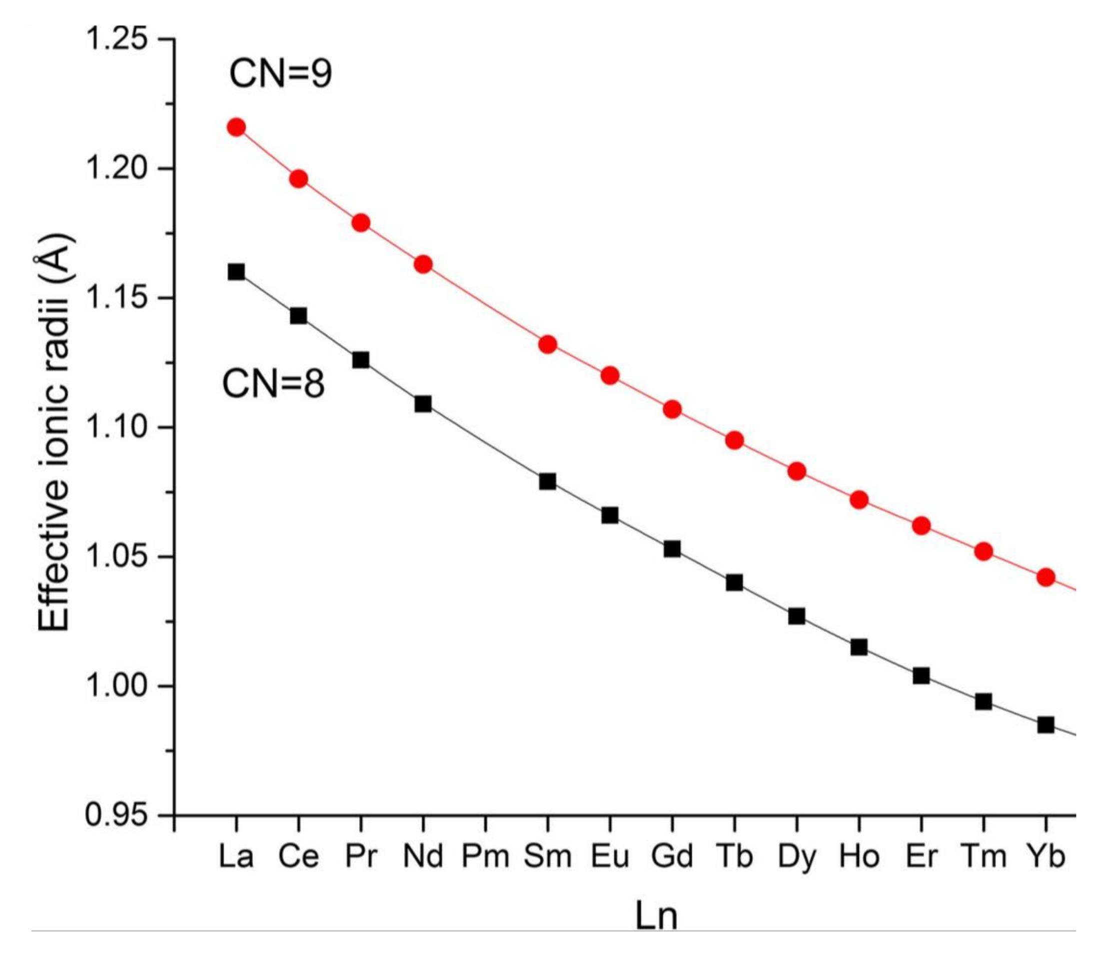


CN = 7-12, usually 9

r_{ion}

Gd^{3+} similar to Ca^{2+}

lanthanide contraction



Effective ionic radii of Ln^{3+} ions for CN = 8 and CN = 9

R.D. Shannon, *Acta Crystallogr. Sect. A*, **1976**, *32*, 751

Lanthanides (4*f*)

Hard ions: O > N

Hydroxo complexes

Hydrolysis constant:

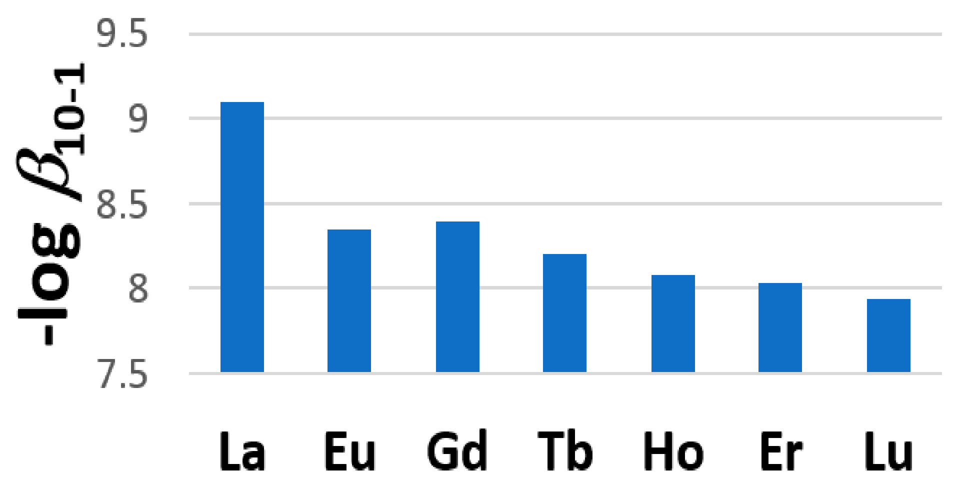
$\beta_{10\text{-}1}$: M + H_2O = M(OH) + H

$$\beta_{10-1} = \frac{[M(OH)][H]}{[M]}$$

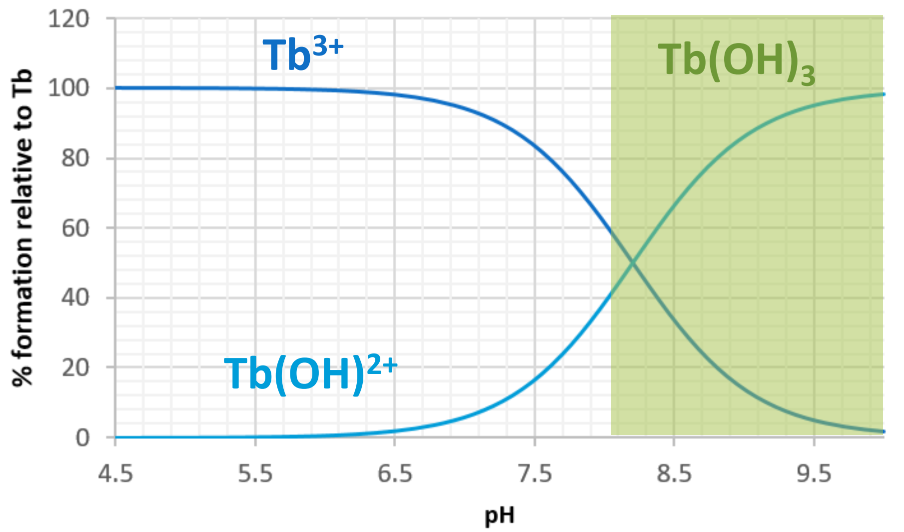
Not so problematic here

Stability governed by electrostatic interactions

Geometry governed by steric factors



Hydrolysis constants of Ln^{3+} ions in water



Distribution of Tb species in water (cTb = 1 pM, 0.1M KCl, 25°C)

P. L. Brown, R. N. Sylva, J. Ellis, *J. Chem. Soc. Dalton Trans.*, **1985**, 723

Lanthanides (*4f*)

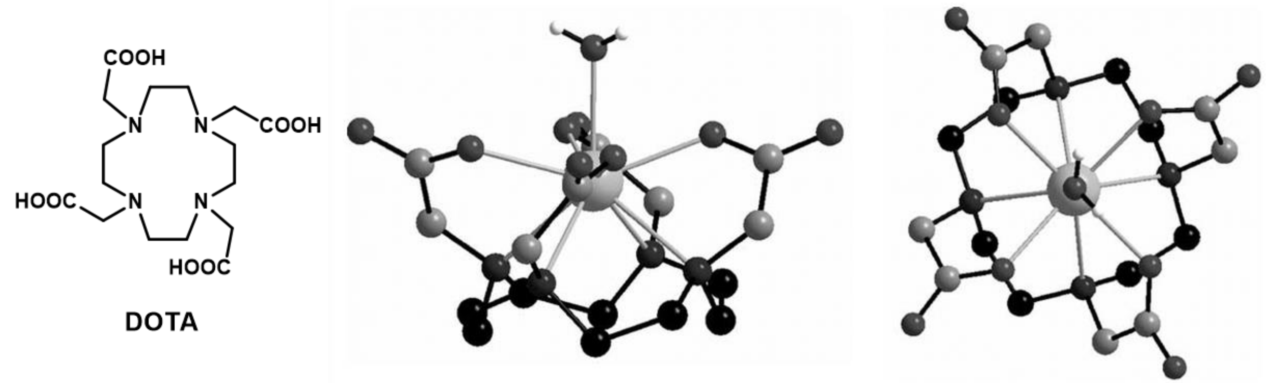
Gold standard: DOTA

$[LnDOTA(H_2O)]^-$

CN = 9

$[GdDOTA(H_2O)]^-$ = Dotarem®

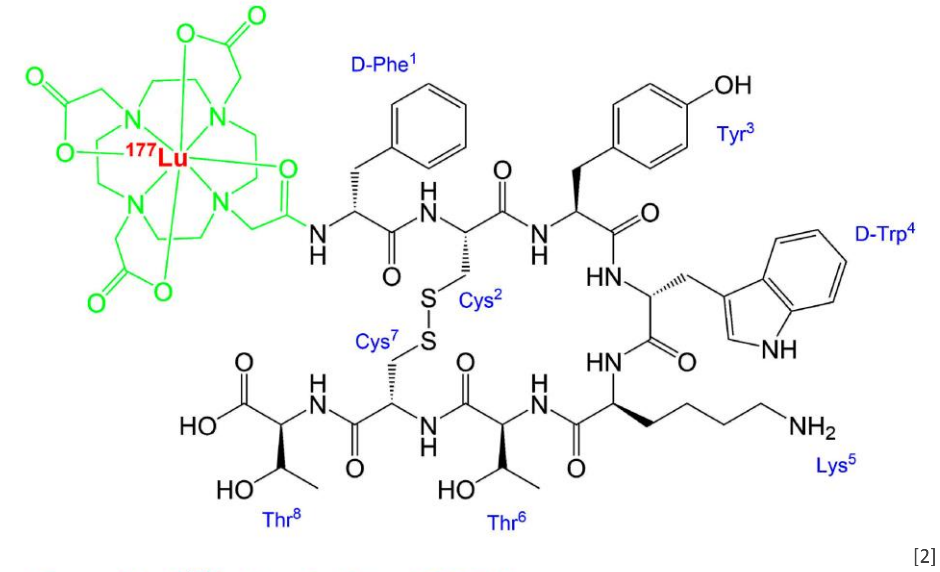
Approved MRI contrast agent since 1989 in France



X-ray structure of $[GdDOTA(H_2O)]^-$ (SAP isomer)[1]

$[^{177}Lu]$Lu-DOTA-TATE = Lutathera®

Approved since 2017 in France



radionuclide (^{177}Lu) + chelator (DOTA) + targeting peptide (octreotate)

[1]V.S. Sastri, J.R. Perumareddi, V. Ramachandra Rao, G.V.S. Rayudu, J.-C. Bünzll, *Modern Aspects of rare Earths and their complexes*, **2003**, Elsevier

[2]U. Hennrich, K. Kopka, *Pharmaceuticals* **2019**, *12*, 114

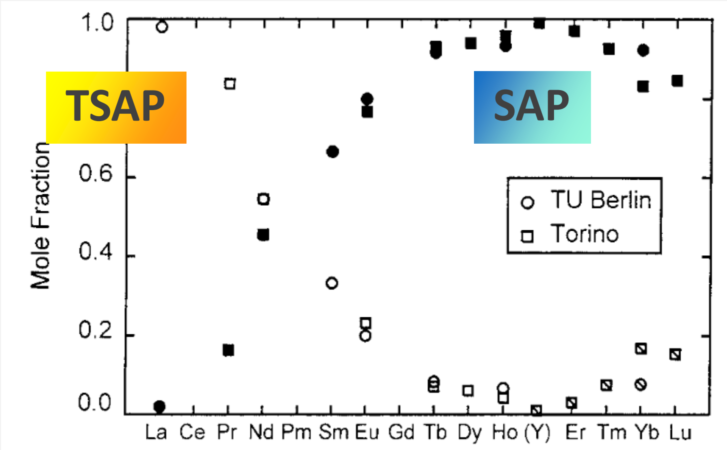
Lanthanides (*4f*)

$[LnDOTA(H_2O)]^-$

A pair of conformational isomers

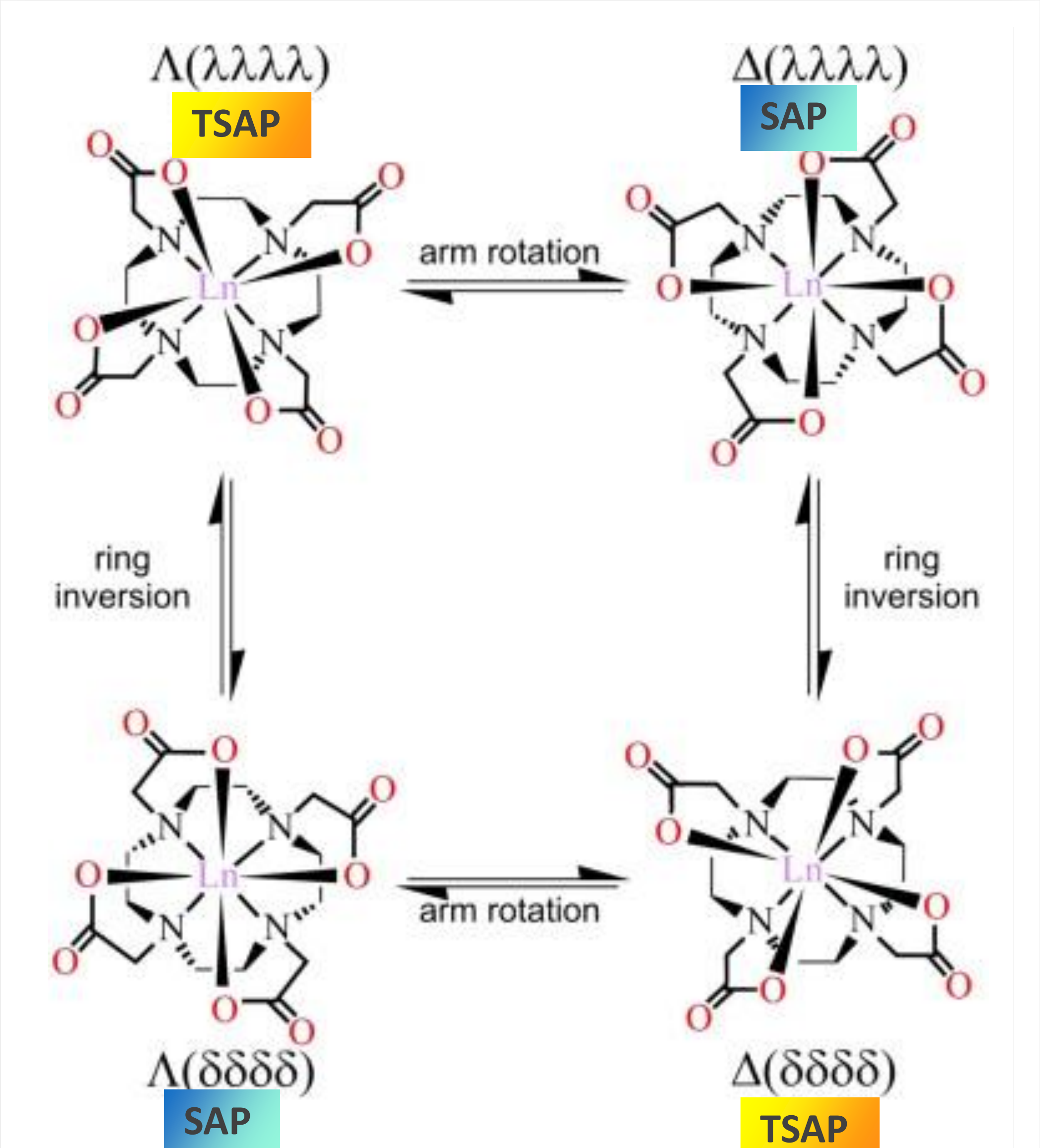
Square-anti-prismatic (SAP)

Twisted-square-anti-prismatic (TSAP)



Proportion of the two SAP/TSAP isomers as a function of Ln3+ (0.15 M, pH 7.0, 25°C)

S. Aime, M. Botta, M. Fasano, M.P.M. Marques, C.F.G.C. Geraldes, D. Pubanz, A.E. Merbach, *Inorg. Chem.*, **1997**, *36*, 2059



Molecular dynamics in Ln-DOTA system

Lanthanides (*4f*)

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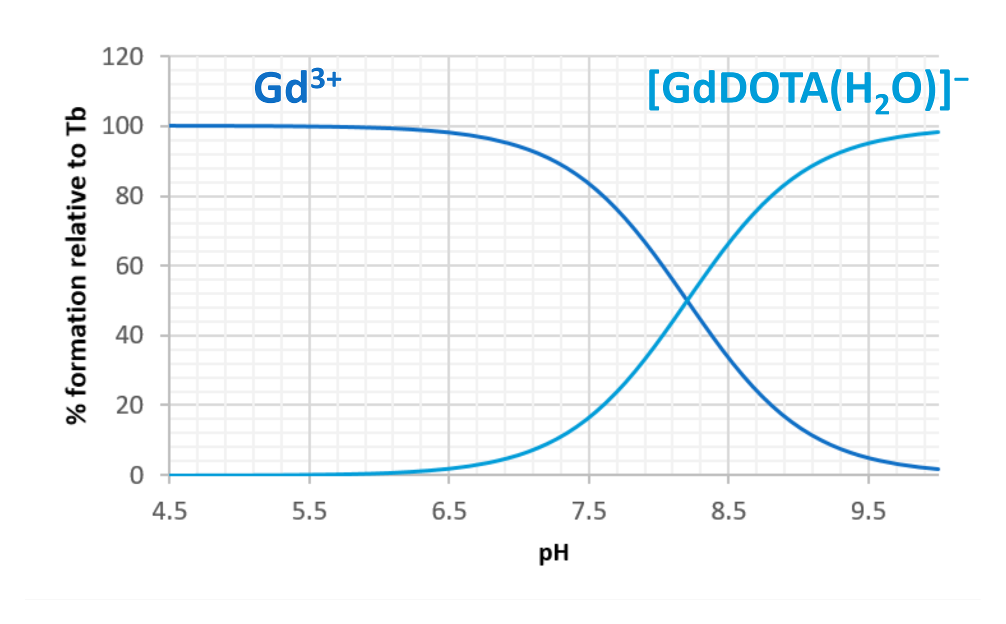

Distribution of the species of a Gd : DOTA 1: 1 in water
(c = 1 pM, 0.1M KCl, 25°C)

W. P. Cacheris, S. K. Nickle and A. D. Sherry, *Inorg. Chem*, **1987**, *26*, 958

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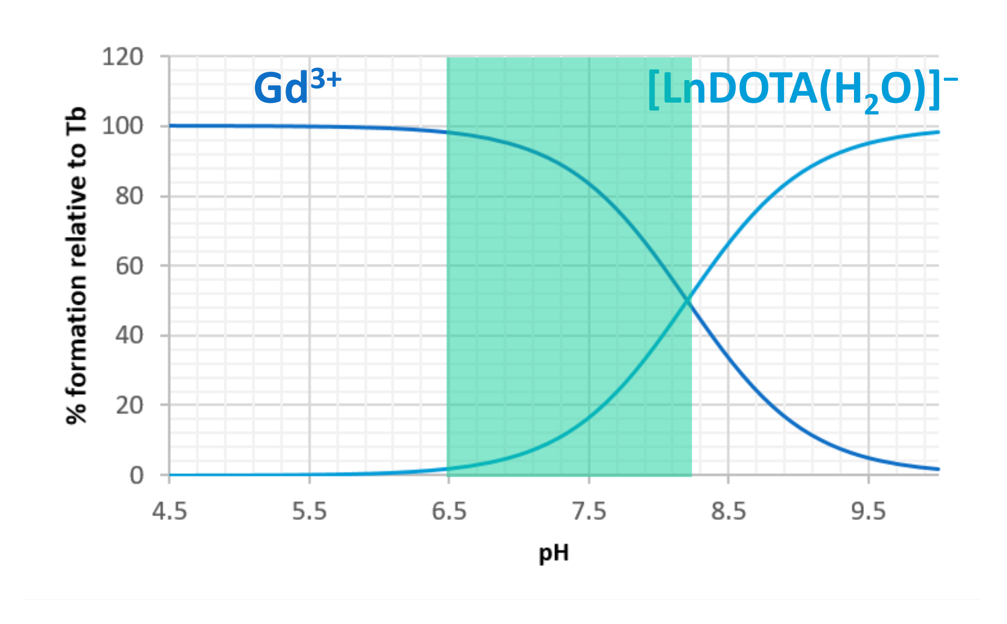

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(c = 1 pM, 0.1M KCl, 25°C)

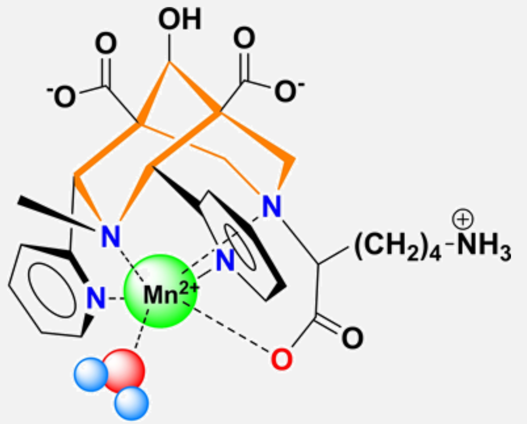
Excess of ligand

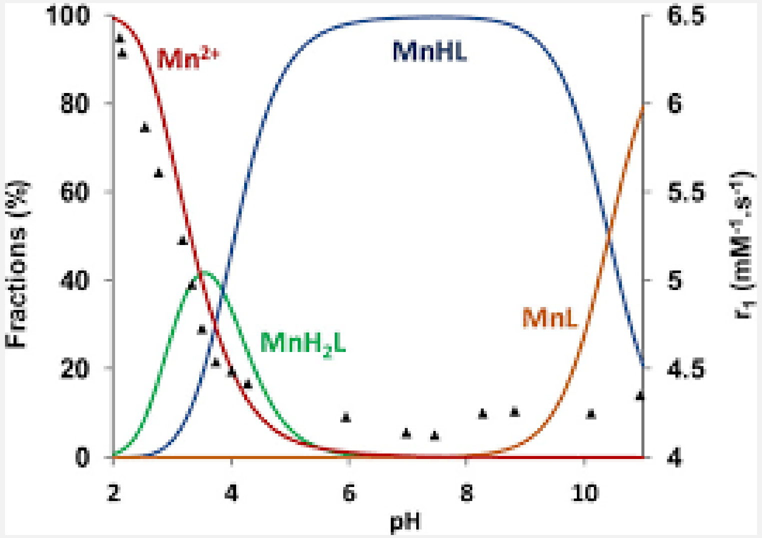
Important role of kinetic parameters

W. P. Cacheris, S. K. Nickle and A. D. Sherry, *Inorg. Chem*, **1987**, *26*, 958

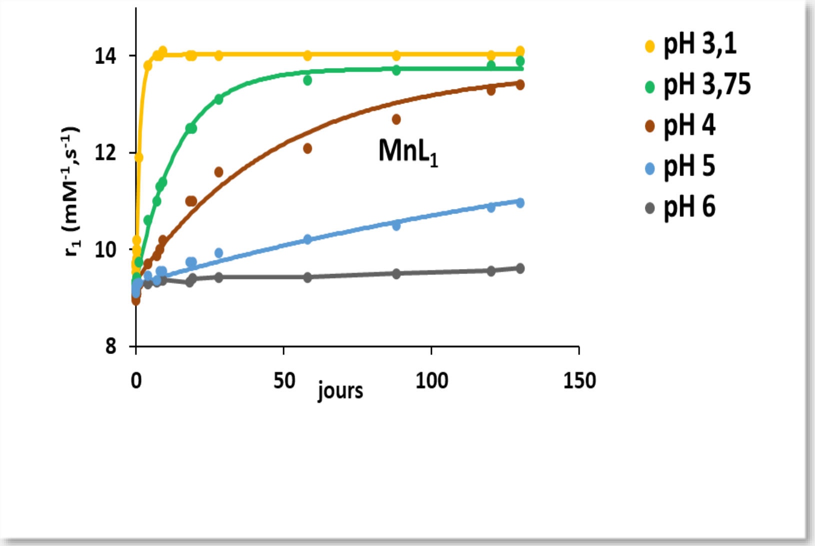
Parenthesis on kinetic inertness

Example of a extremely inert bispidine-Mn^{2+} complex





Species distribution curves calculated for MnL1 (1 mM) and pH-dependent relaxivity values (▲) measured at 258C, 60 MHz



Transmetallation experiment in presence of Zn^{2+} (50 eq) at various pH values

D. Ndiaye, M. Sy, A. Pallier, S. Même, I. de Silva, S. Lacerda, A. M. Nonat, L. J. Charbonnière, E. Toth, *Angew. Chem. Int. Ed.*, **2020**, *59*, 1158

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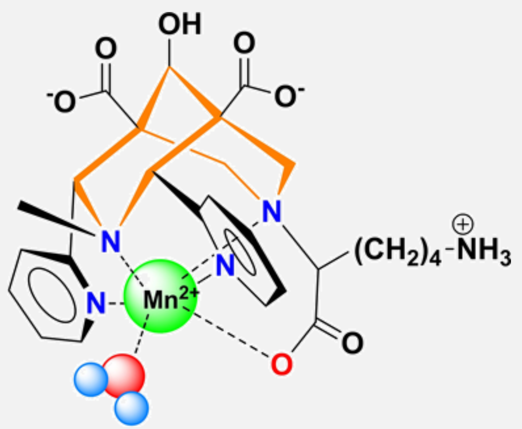

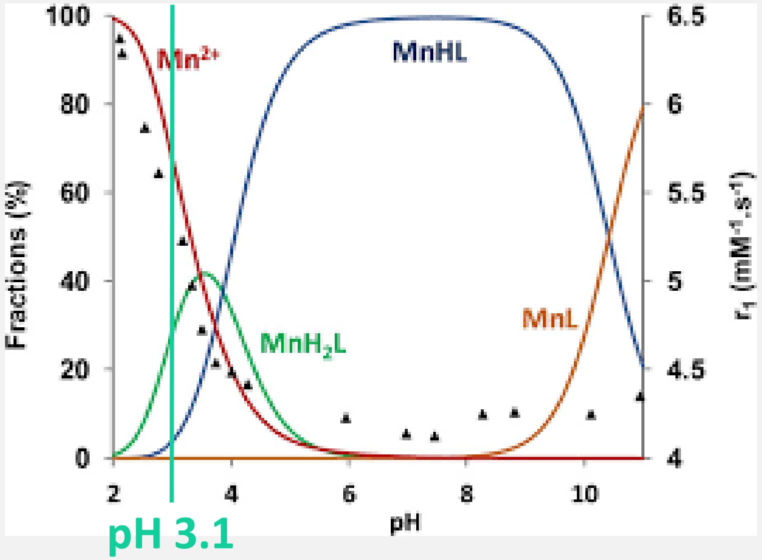

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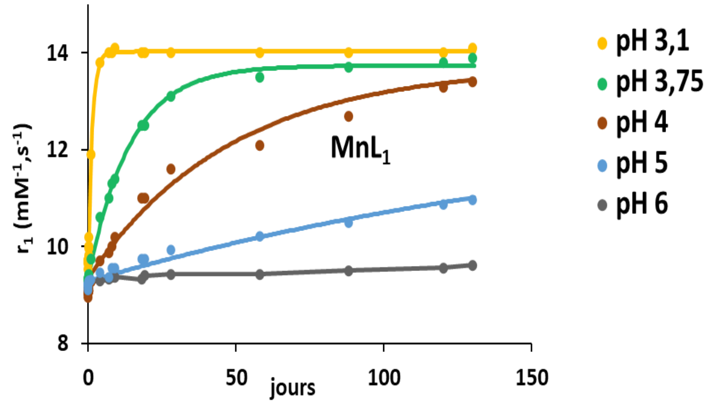


$t_{1/2}$ = 22h, pH 3.1 ($t_{1/2}$ >> 137 days, pH 6)

Transmetallation experiment in presence of Zn^{2+} (50 eq) at various pH values

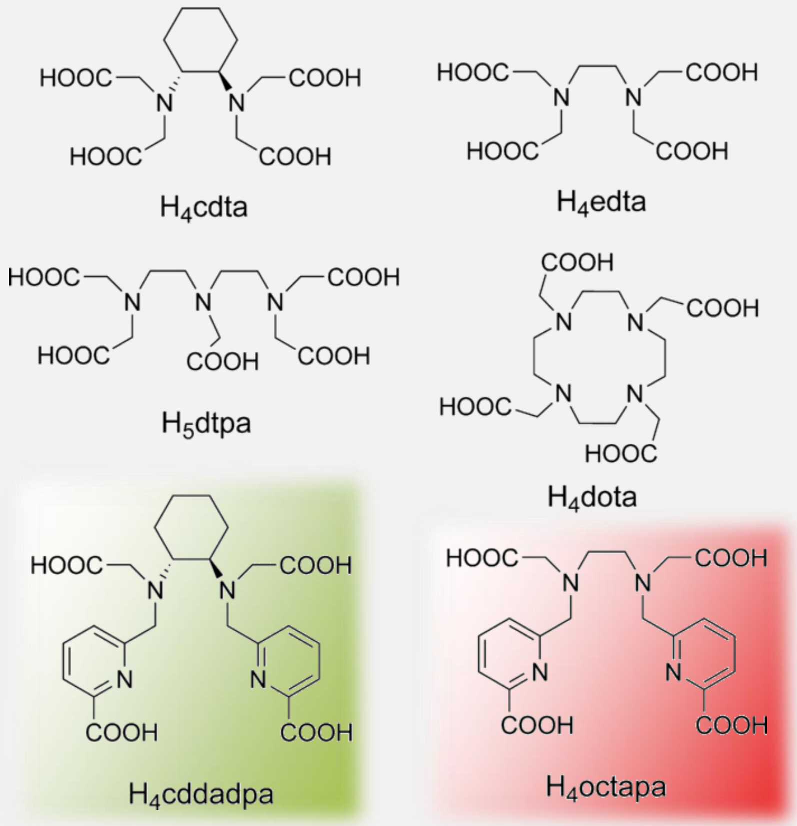
Kinetic = Determining factor

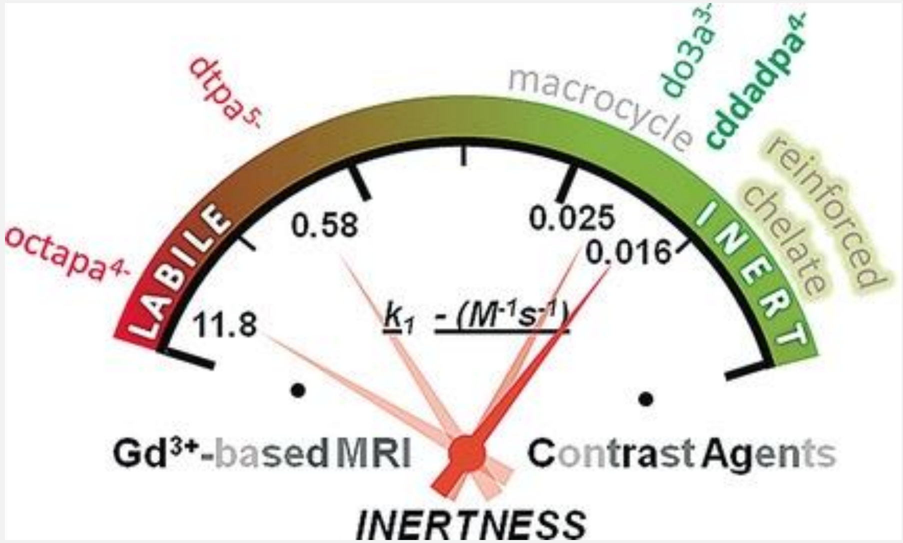
- **Rigidity**
- **Pre-organisation**

D. Ndiaye, M. Sy, A. Pallier, S. Même, I. de Silva, S. Lacerda, A. M. Nonat, L. J. Charbonnière, E. Toth, *Angew. Chem. Int. Ed.*, **2020**, *59*, 1158

Lanthanides (*4f*)

Ligand development: effect of rigidity





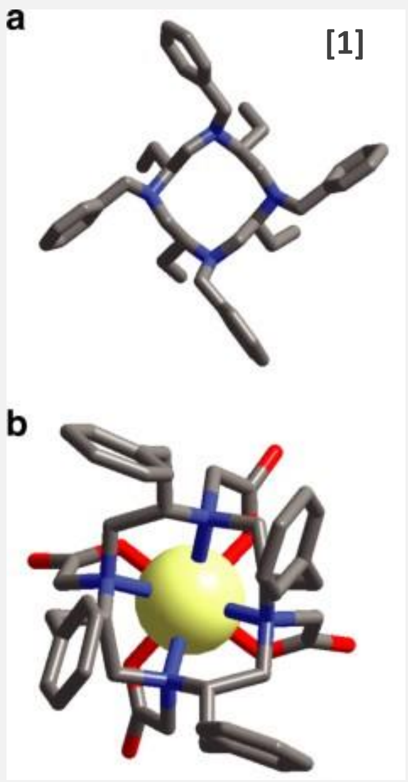
Pseudo-first-order rate in transmetallation assays with of Cu^{2+} (50 mM, 25 °C, 0.15 M NaCl, at pH 3.4 -4.9)

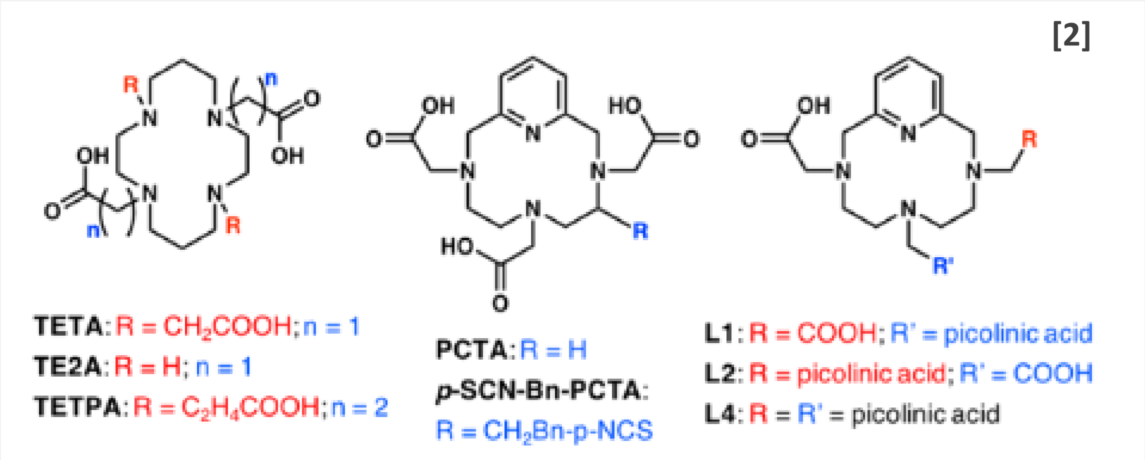
G. Ticso, M. Regueiro-Figueroa, V. Nagy, Z. Garda, T. Garai, F. K. Kalman, D. Esteban-Gomez, E. Toth, C. Platas-Iglesias, *Chem. Eur. J.*, **2020**, *59*, 11958

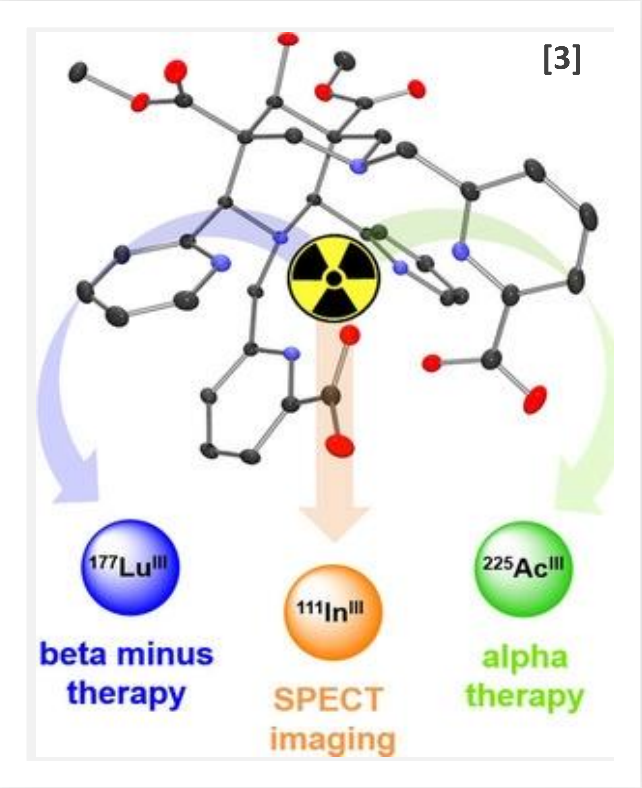
Lanthanides (*4f*)

Ligand development: increased rigidity

- Chiral complexes[1]
- Reinforced structures[2]
- Macrobicycles[3]





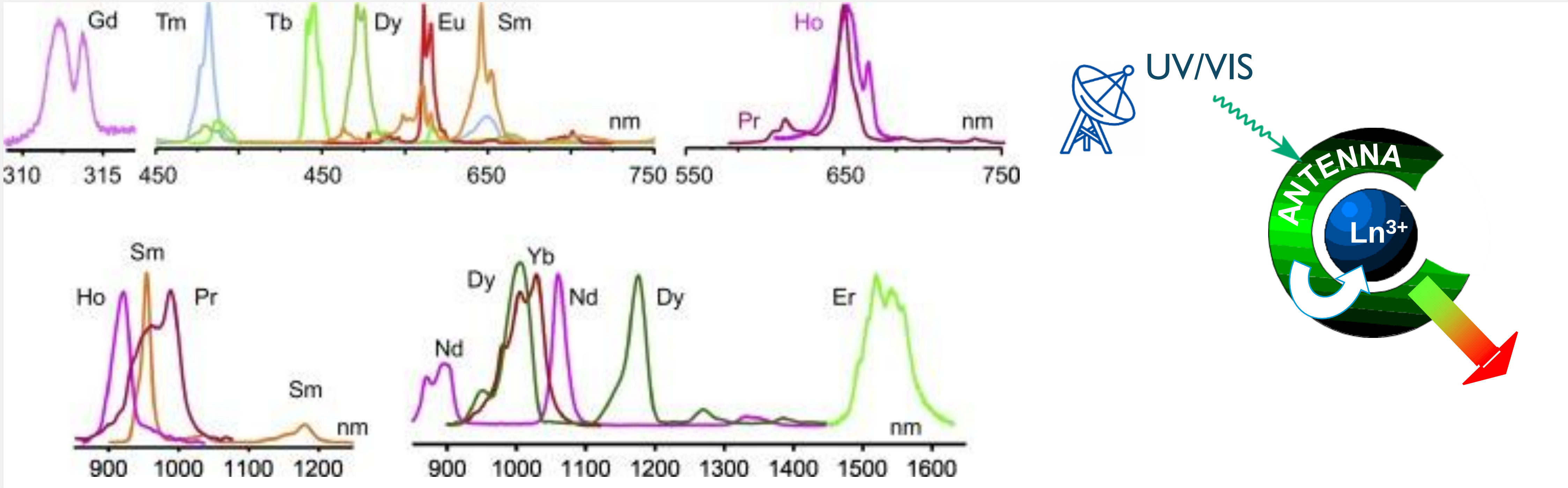


[1]L. Dai, C. M. Jones, W. T. K. Chan, T. A. Pham, X. Ling, E. M. Gale, N. J. Rotile, W. C.-S. Tai, C. J. Anderson, P. Caravan, G.-L. Law, *Nature Commun.*, **2018**, 9, 857
[2] M. Le Fur, M. Beyler, N. Lepareur, O. Fougère, C. Platas-Iglesias, O. Rousseaux, R. Tripier, *Inorg. Chem.*, **2016**, *55*, 8003
[3] P. Comba, U. Jermilova, C. Orvig, B. O. Patrick, C. F. Ramogida, K. Rück, C. Schneider, M. Starke, *Chem. - Eur. J*, **2017**, *23*, 15945

Lanthanides (*4f*)

Ligand development: luminescent complexes

Optical imaging, cell microscopy/ *in vitro* assays



Emission spectra of luminescent Ln^{3+} complexes in the UV, visible or NIR and antenna effect

M. Sy, A. Nonat, N. Hildebrandt, L. J. Charbonnière, *Chem. Commun.*, **2016**, *52*, 5080

Ac (5*f*)

+III oxydation state

High CN = 9-10

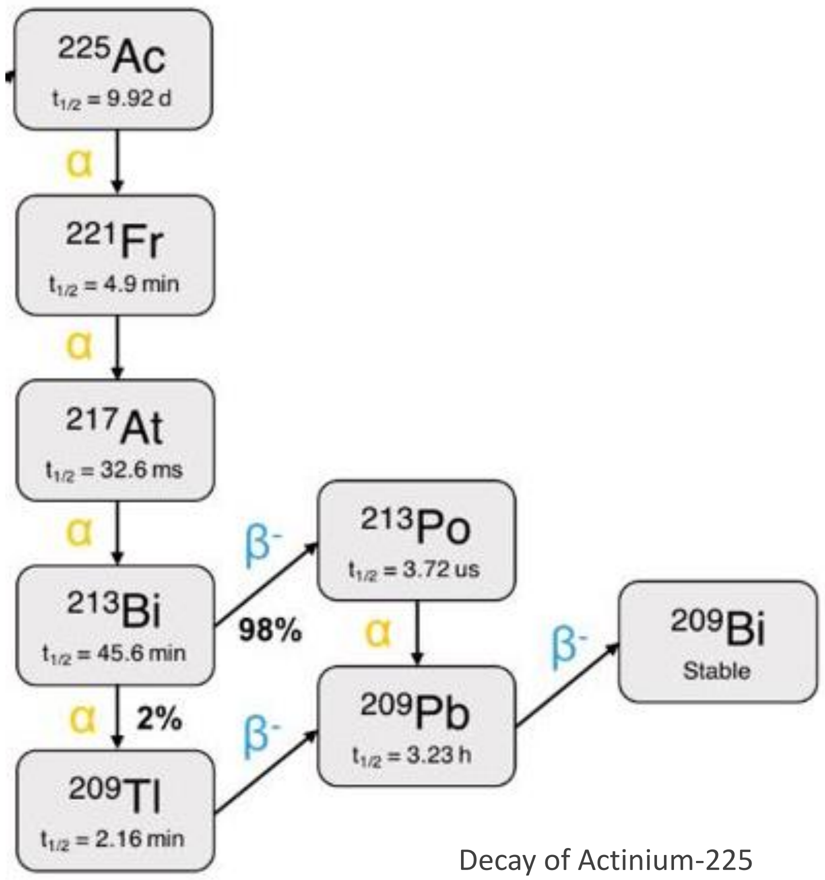
Large r_{ion} = 1.12 Å

borderline hard: N > O

Not easily hydrolysed

La(III) used as a cold surrogate

BUT Multiple isotopes with different chemistries: ***e.g.*** ^{221}Fr, ^{217}At



Decay of Actinium-225

T. I. Kostelnik, C. Orvig, *Chem. Rev*. **2019**, *119*, 902

Ac (5*f*)

Good candidate: DOTA

Quantitative radiolabelling

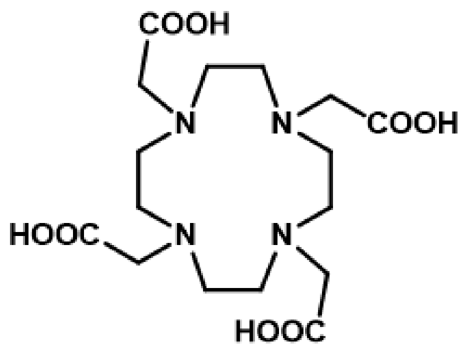
pH 5, **70°C**, 60 min

Serum stability

>75% over 50 days

Bifunctional p-SCN-Bn-DOTA

mAb, protein labeling



Interest of ligands with larger denticities

Radiolabelling in milder conditions (r.t.)

Improved stability / kinetic inertness

→ **Other polyaza derivatives**

W. F. Maguire, M. R. McDevitt, P. M. Smith-Jones, D. A. Scheinberg, *Nucl. Med.*, 2014, *55*, 1492

Ac (5*f*)

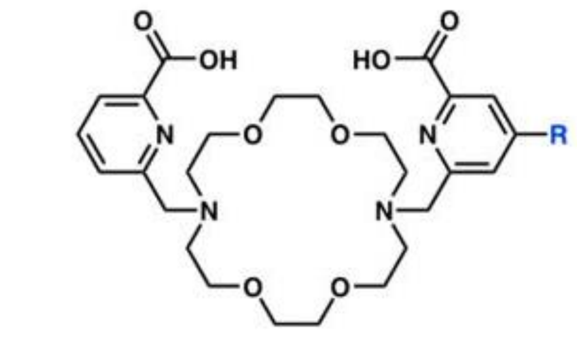
Strong candidates

H_2macropa [1]

Quantitative RCY: pH 5, **r.t**, 5 min

Serum stability > 7 days

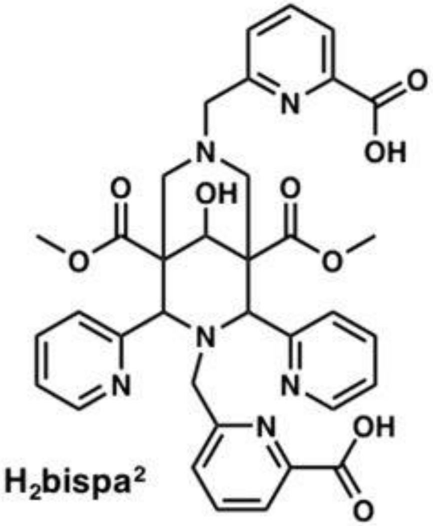
PSMA/albumin targeting conjugate with high tumor/organ uptake + renal excretion



Bispidine H_2bispa[2] [2]

98% RCY : pH 7, **r.t.**, 30 min

Serum stability: >89%, 7 days



[1] N. A. Thiele, V. Brown, J. M. Kelly, A. Amor-Coarasa, U. Jermilova, S. N. MacMillan, A. Nikolopoulou, S. Ponnala, C. F. Ramogida, A. K. H. Robertson et al. *Angew. Chem., Int. Ed.*, **2017**,*56*, 14712

[2] P. Comba, U. Jermilova, C. Orvig, B. O. Patrick, C. F. Ramogida, K. Rück, C. Schneider, M. Starke, *Chem. - Eur. J*, **2017**, *23*, 15945

Transition metals (*d*)

Yttrium

+III oxydation state

CN = 8-9

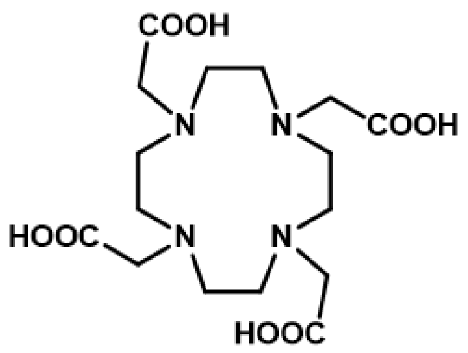
Hard

r_{ion} = 1.02 Å ~ Gd(III)

Hydrolysis constant ~ Lu(III)

Similar coordination chemistry to Ln(III)

DOTA: quantitative RCY, pH 4.5, **100°C**, 10-30 min



DOTA

Radiolabelling in milder conditions (r.t.)

→ Other polyaza derivatives

Transition metals (*d*)

Scandium

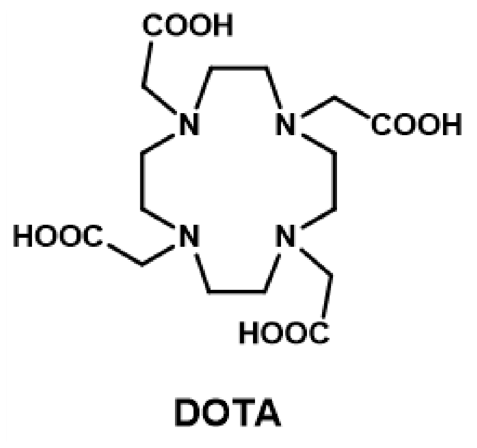
+III oxydation state

CN = 6-8

r_{ion} = 0.87 Å

Hard

Easily hydrolysed: $Sc(OH)^{2+}$ from pH =2.5 then insoluble $Sc(OH)_3$



Similar coordination chemistry to Ln(III)

DOTA: quantitative RCY, pH4, **95°C**, 10-30 min

Radiolabelling in milder conditions (r.t.)

Improved stability / kinetic inertness

→ **Other polyaza derivatives**

Transition metals (*d*)

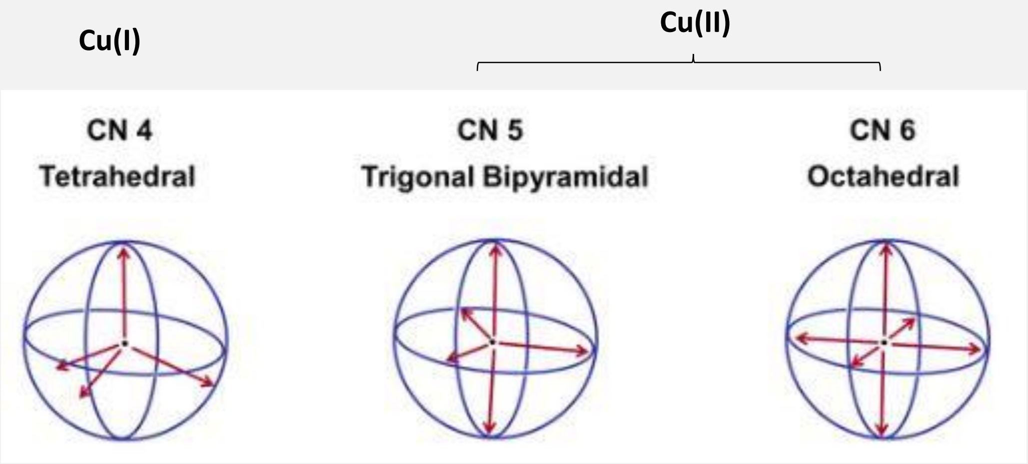
Copper

+I/+II (+III) oxydation states

CN = 5-6

Borderline : N, O, S

r_{ion} = 0.73 Å



Coordination geometry depending on CN and ligand field

Transition metals (*d*)

Copper

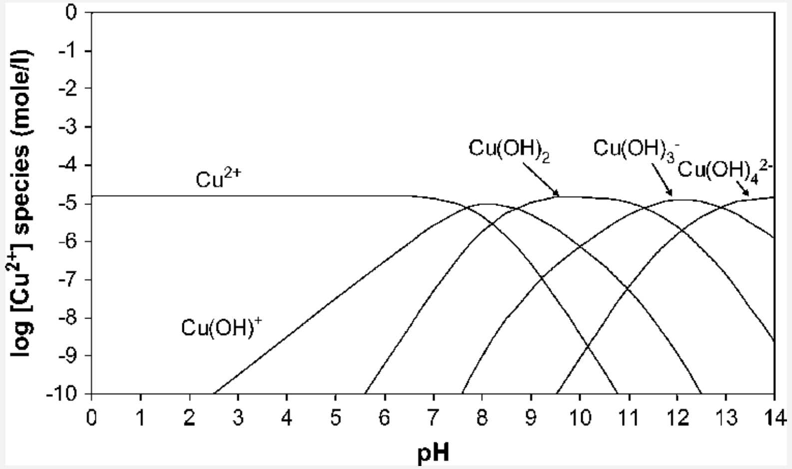
+I/+II (+III) oxydation states

CN = 5-6

Borderline : N, O, S

r_{ion} = 0.73 Å

Hydroxo complexes



Theoretical copper speciation for hydroxo complexes in pure water for a total copper concentration of 1 mg/L

Transition metals (*d*)

Copper (67-Cu /64-Cu)

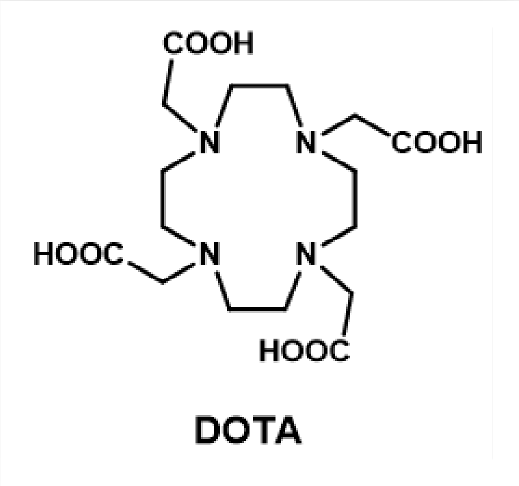
Potential ligands (^{64}Cu)

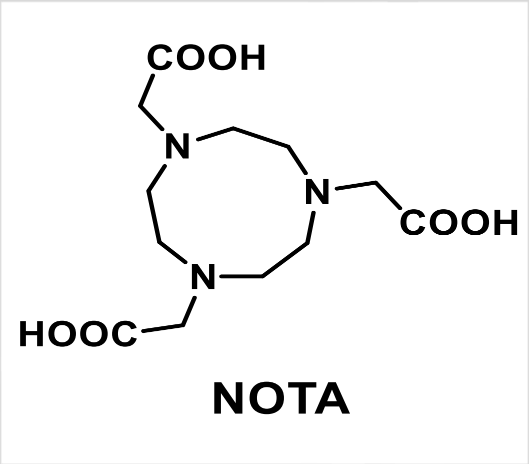
DOTA: quantitative RCY

pH 5.5-6.5, **25-90°C**, 30-60 min

NOTA: quantitative RCY

pH 5.5-6.5, **25°C**, 30-60 min





Improved stability / kinetic inertness

Stabilise both Cu(I) and Cu(II)

→ **Other polyaza derivatives**

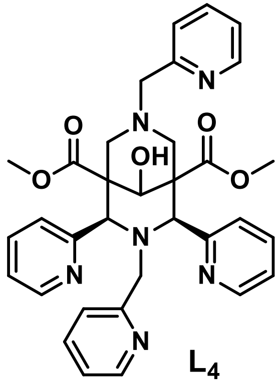
Copper (64-Cu) ligands

Radiolabeling

Kinetic

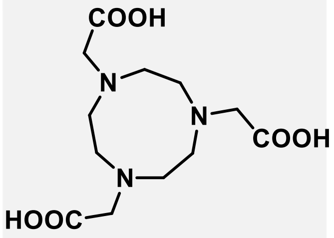
Thermodynamic

t.a., 1 min, pH 6.5



L4

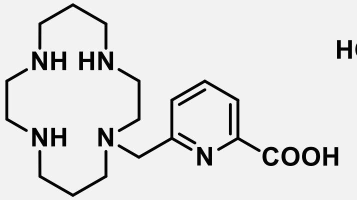
25°C 30-60 min
pH 5.5-6.5
$t_{1/2}$ < 3 min
(5M HCl, 30°C)



NOTA

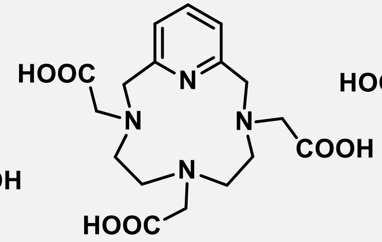
t.a., 15 min, pH 5

$t_{1/2}$ = 32 min
(1M HCl, 25°C)



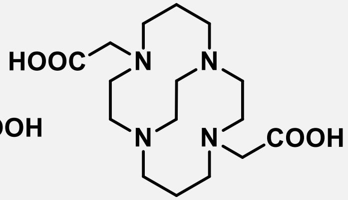
HTE1PA

25°C, 5 min,
pH 5.5



PCTA

95°C, 60 min,
pH 6-7

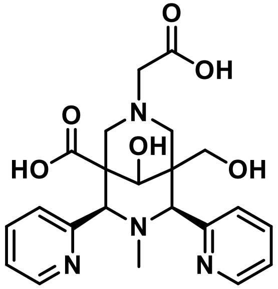


CB-TE2A

pCu

16.28 17 18.4 18.64 19.1

[1]

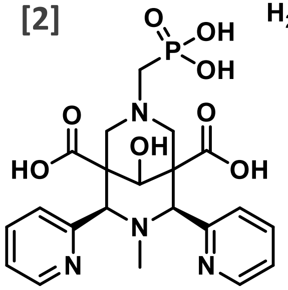


L1

t.a., 15 min, pH 2-6

$t_{1/2}$ = 110 days (5M $HClO_4$, 25°C)

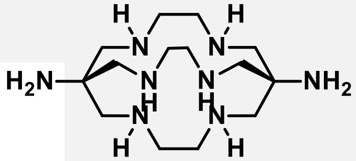
[2]



L2

t.a., 5-15 min, pH 3-6.6

$t_{1/2}$ > 20 months (5M $HClO_4$, 25°C)



DiamSar

25°C, 5-30 min,
pH 5.5

[1] A. Roux, A. M. Nonat, J. Brandel, V. Hubscher, L. J. Charbonnière, *Inorg. Chem.*, **2015**, *54*, 4431
[2] R. Gillet, A. Roux, J. brandel, S. Huclier, F. Camerel, O. Jeannin, A. M. Nonat, L. J. Charbonnière, *Inorg. Chem.*, **2017**, *56*, 11738
for other ref see D. Brasse, A. Nonat, *Dalton Trans.*, **2015**, *44*, 4845

Post-transition metals (*p*)

Bismuth

+III oxydation state (Bi(V))

CN = 8

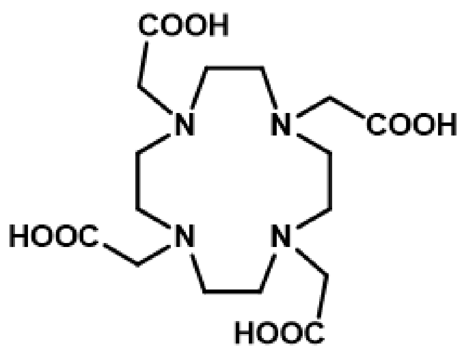
Borderline hard: N > O

r_{ion} = 1.17 Å ~ Ac(III)

Very strong hydrolysis (from pH = 0)

-> Use of weakly coordinating buffers (citrate, acetate)

High covalent bonding contribution to the M-L bond



DOTA

DOTA: pH 8.5, 95°C, 5 min

Radiolabelling in milder conditions (r.t.)

Improved stability / kinetic inertness

→ **Other polyaza-macrocyclic ligands**

Post-transition metals (*p*)

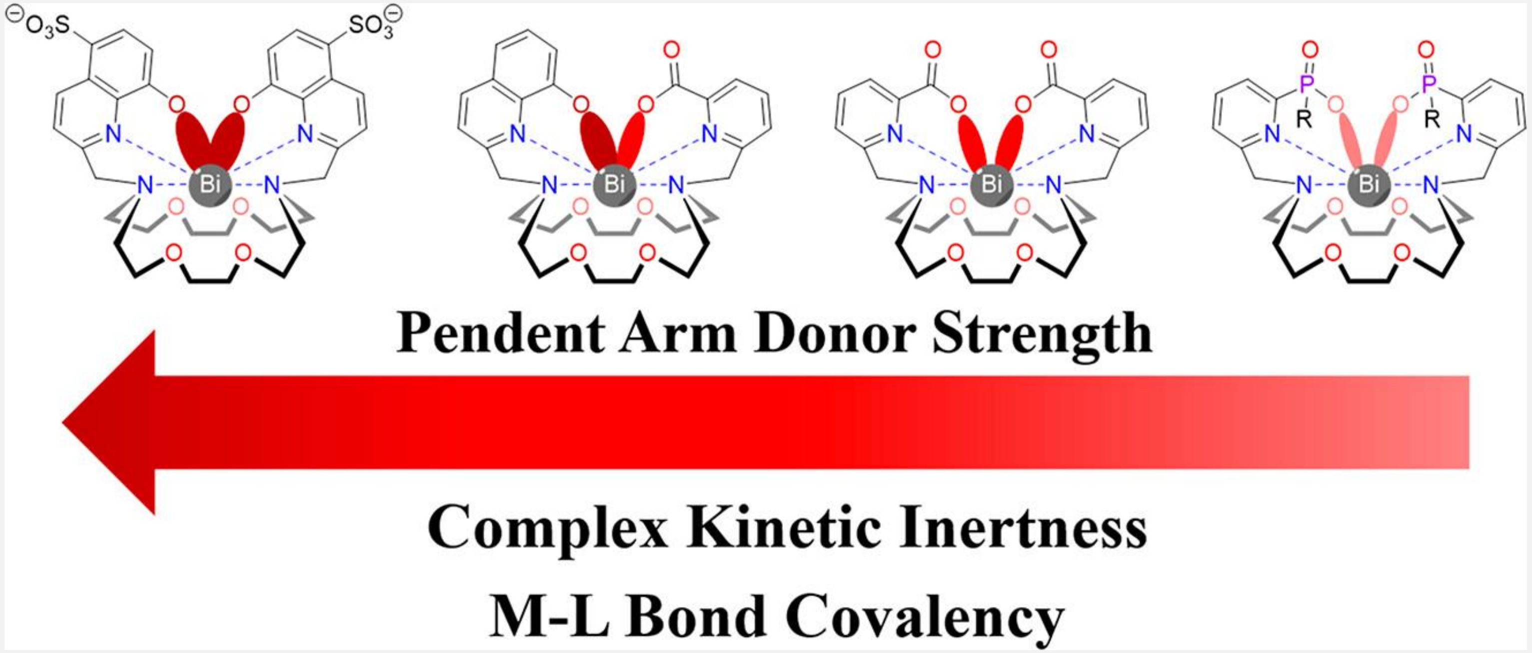
Bismuth

macropa

>99% RCY, MES buffer (0.5 M, pH 5.5–6), 8 min, **r.t**

vs **95 °C** for 5.5 min for DOTA

macropaquin-SO_3 macropaquin macropa macrophospho (R = OH) macrophosphi (R= Me)



D. J.Fiszbein, V. Brown, N. A. Thiele, J. J. Woods, L. Wharton, S. N. MacMillan, V. Radchenko, C. F. Ramogida, J. J. Wilson, *Inorg. Chem.*, **2021**, *60*, 9199

Post-transition metals (*p*)

Bismuth

Me-DO2PA [1]

Quantitative RCY: pH 5, **r.t**, 5 min

Serum stability > 7 days

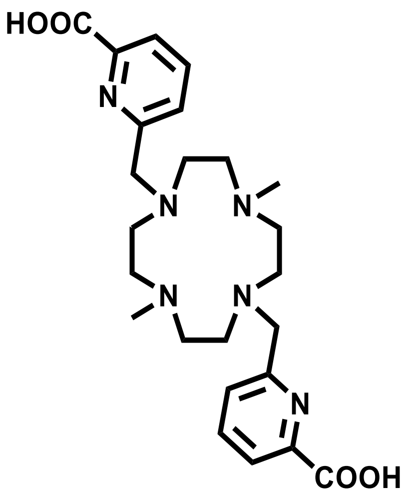
PSMA/albumin targeting conjugate with high tumor/organ uptake + renal excretion

DEPA [2]

98% RCY : pH 7, **r.t.**, 30 min

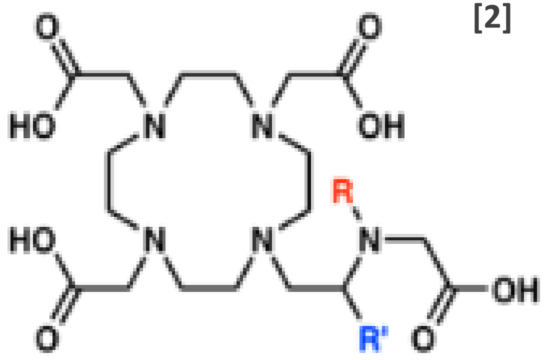
Serum stability: >89%, 7 days

[1]



Me-DO2PA: R = picolinic acid; R' = CH_3

[2]



DEPA: R = CH_2COOH; R' = H

[1] L. M. P. Lima, M. Beyler, R. Delgado, C. Platas-Iglesias, R. Tripier, *Inorg. Chem*., **2015** ,*54*, 7045
[2] H. A. Song, C. S. Kang, K. E. Baidoo, D. E. Milenic, Y. Chen, A. Dai, M. W. Brechbiel, H. S. Chong, *Bioconj. Chem*., **2011**, *22*, 1128

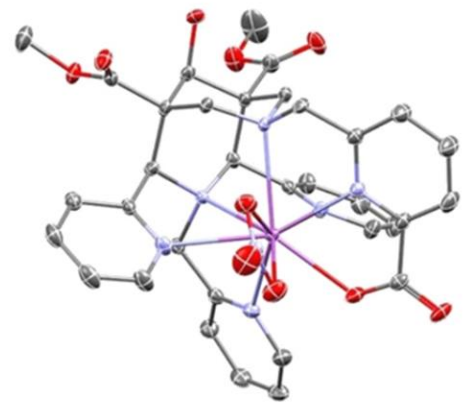
Post-transition metals (*p*)

Bismuth

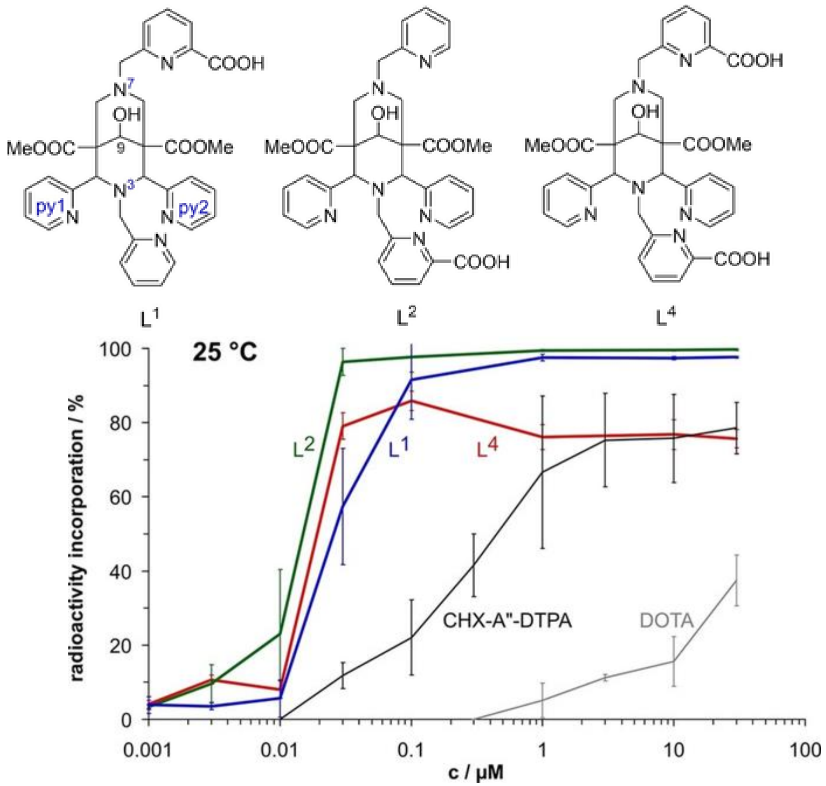
Bispidines

Efficient radiolabeling
MES buffer (0.5 M, pH 5), **5 min**, 25°C

Kineticaly stable in ligand-challenge displacement assays (EDTA)



$[Bi^{III}(L^1)(NO_3)](NO_3)\cdot MeOH$



Radiolabelling of bispidine L^1, L^2, L^4 and DOTA with $^{213}Bi^{III}$ at 25°C by as a function of ligand concentration

F.Bruchertseifer, P. Comba, B. Martin, A. Morgenstern, J. Notni, M. Starke, H. Wadepohl, *ChemMedChem*, **2020**, *15*, 1591

Take home message

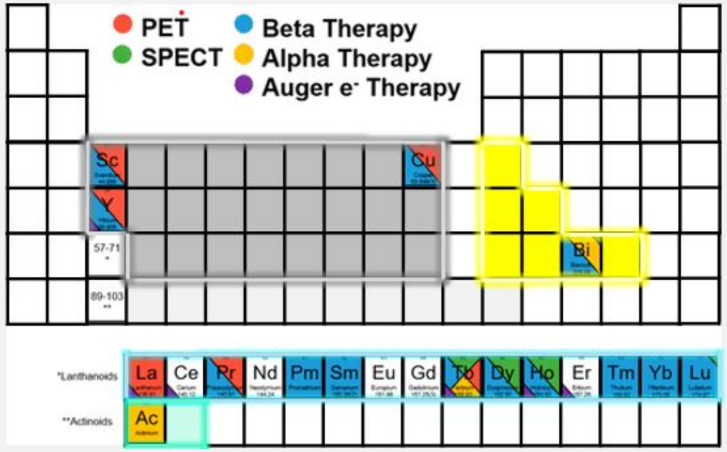
AIM : Radiolabelling + *in vivo* stability

Thermodynamic

KINETIC

→ **Rigidity**

→ **Preorganisation**



Chemical particularities

Take home message

AIM : Radiolabelling + *in vivo* stability

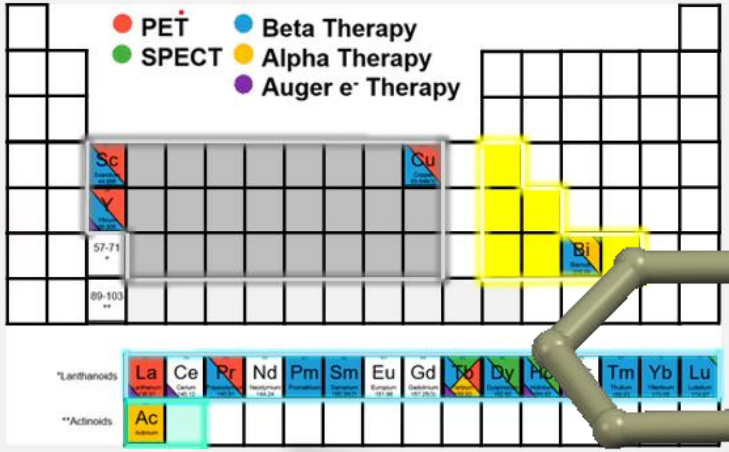
Funtionalization -> Targeting

Thermodynamic

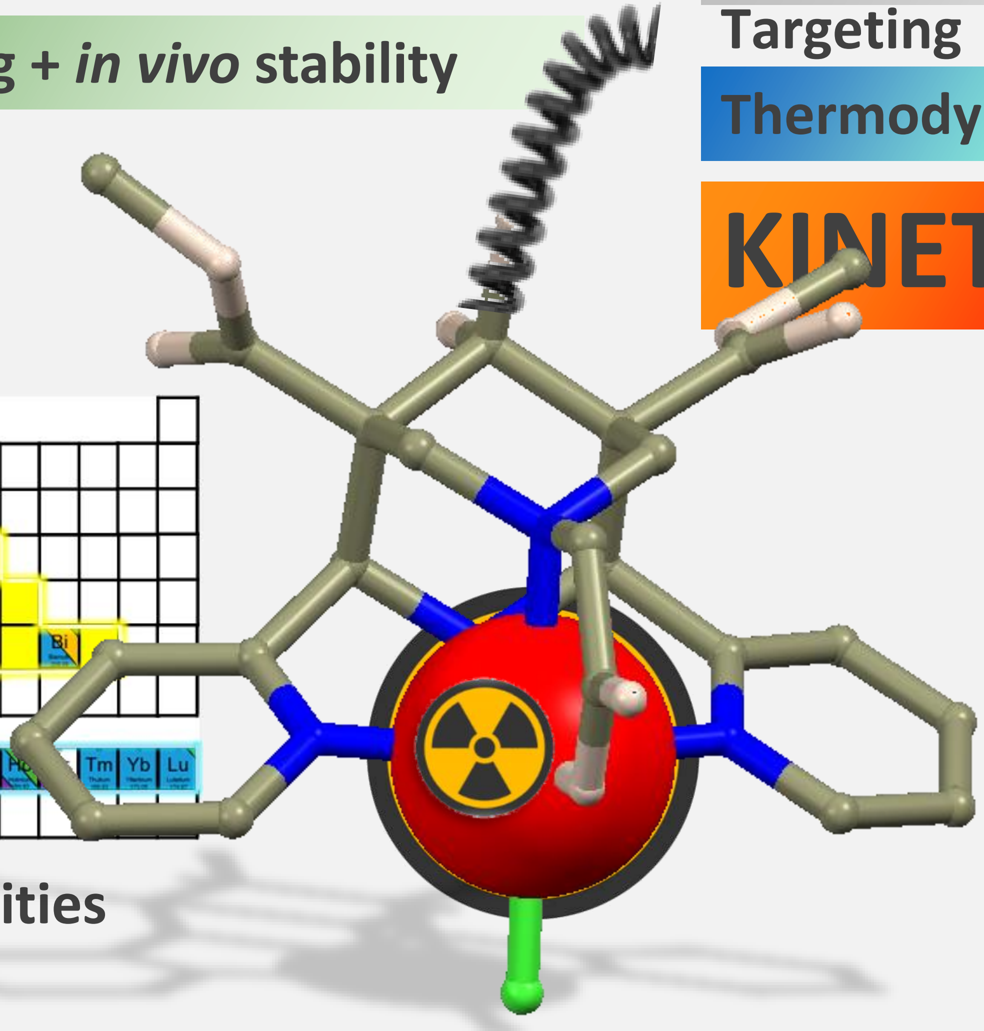
KINETIC

→ **Rigidity**

→ **Preorganisation**



Chemical particularities



^{225}Ac

^{64}Cu (^{67}Cu)

^{213}Bi

^{52}Mn, ^{68}Ga, ^{111}In, ^{177}Lu…

Bispidine for medical imaging

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Zouhair ASFARI
Clémence CHEIGNON
Câline CHRISTINE
Alex LECOINTRE
Alex DETAPPE (ICANS)

Lucas PETITPOISSON
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Tristan MARTIN
Maryame SY
Raphaël GILLET
Marie-Julie TILLY

Amandine ROUX
Anli MAHAMOUD
Tarik LEGDALI

+ all the team !!!

Bispidine for medical imaging

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Arronax/Subatech
Sandrine HUCLIER
Ferid HADDAD


Lu
71
tantalum
73
Ta
tungsten
74
W
42
Mo
Cr
Nb
rutherfordium
104
Rf
dubnium
105
Db
seaborgium
106
Sg
bohrium
107
Bh
75
Re
Nd
Pm

Merci

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