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# Hybrid hydroxypyridinone-macrocyclic chelators for coordination of lanthanide and actinide radionuclides

*Michelle Ma*

**King's College London**



# Acknowledgements

## Paul Scherrer Institute

Cristina Muller  
Nicholas van der Meulen  
Christian Vaccarin  
Pascal Grundler

## King's College London

Alex Rigby  
Charlotte Rivas  
Rory Kenrick

### *Current group*

Natasha Patel  
Rory Kenrick  
Jung Sik Shin  
Dr Truc Pham  
Dr Rachel Nuttall  
Dr Ollie Carter

### *Past members*

Dr Ingebjorg Hungnes  
Dr Alex Rigby  
Dr Charlotte Rivas  
Dr Jessica Jackson  
Dr Matt Farleigh  
Dr Ruslan Cusnir



Dr Alex  
Rigby

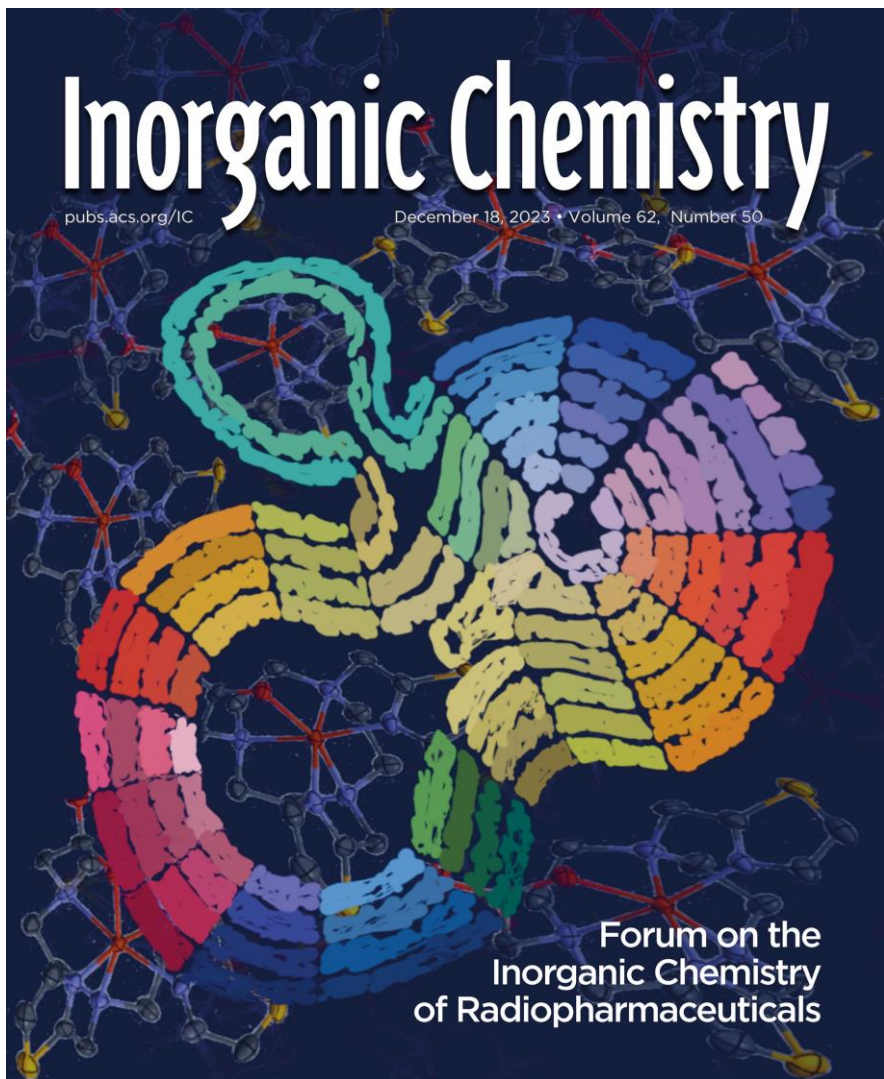


Dr Charlotte  
Rivas





# Inorganic Chemistry of Radiopharmaceuticals



*Inorg. Chem.* 2023, volume 62, issue 50

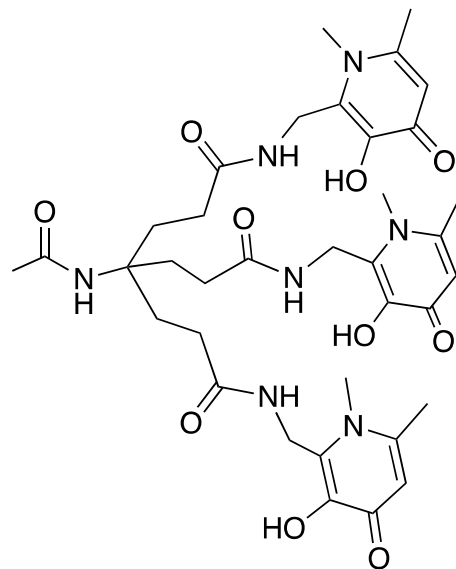
Eszter Boros, Michelle Ma, Justin Wilson

Coordination chemistry for Ln and An is  
alive and well

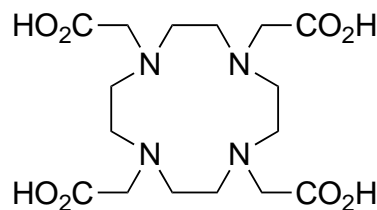


# Hydroxypyridinone derivatives of macrocycles

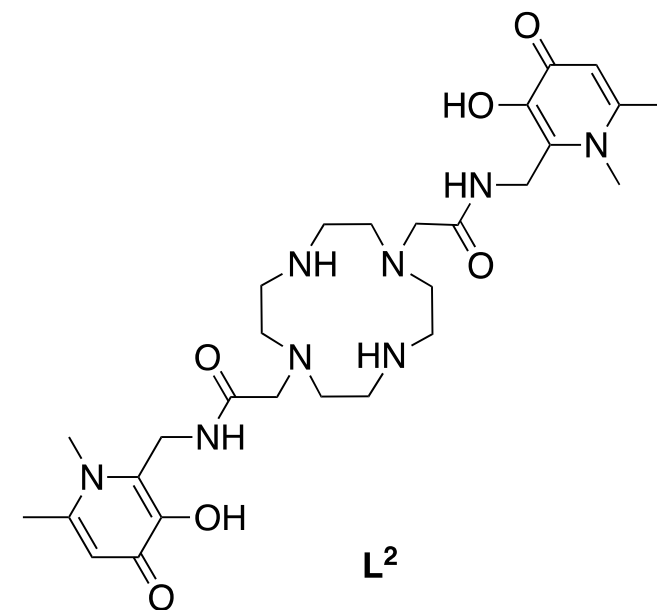
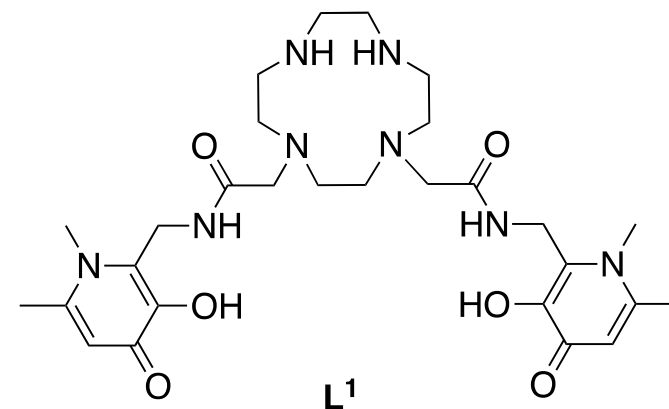
- Hydroxypyridinones have exceptionally high affinity for hard metal ions



- Derivatives of cyclen (e.g. DOTA) provide complexes of high kinetic stability

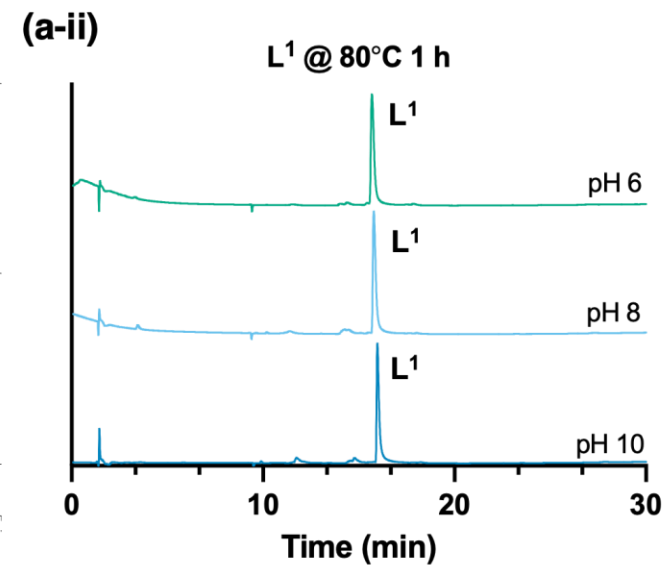
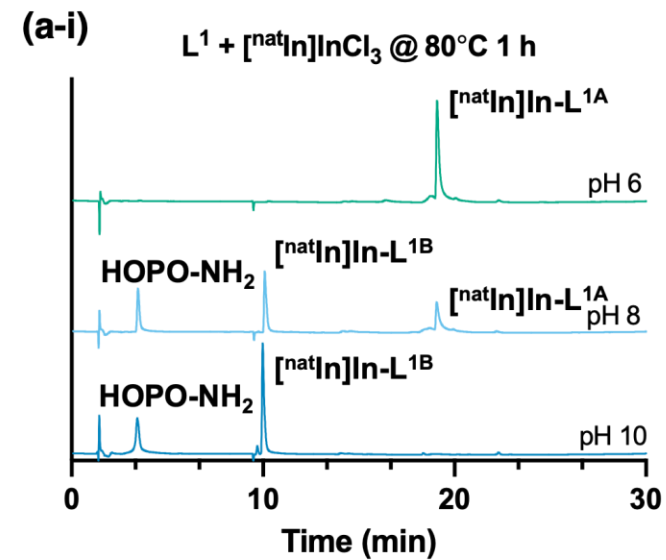
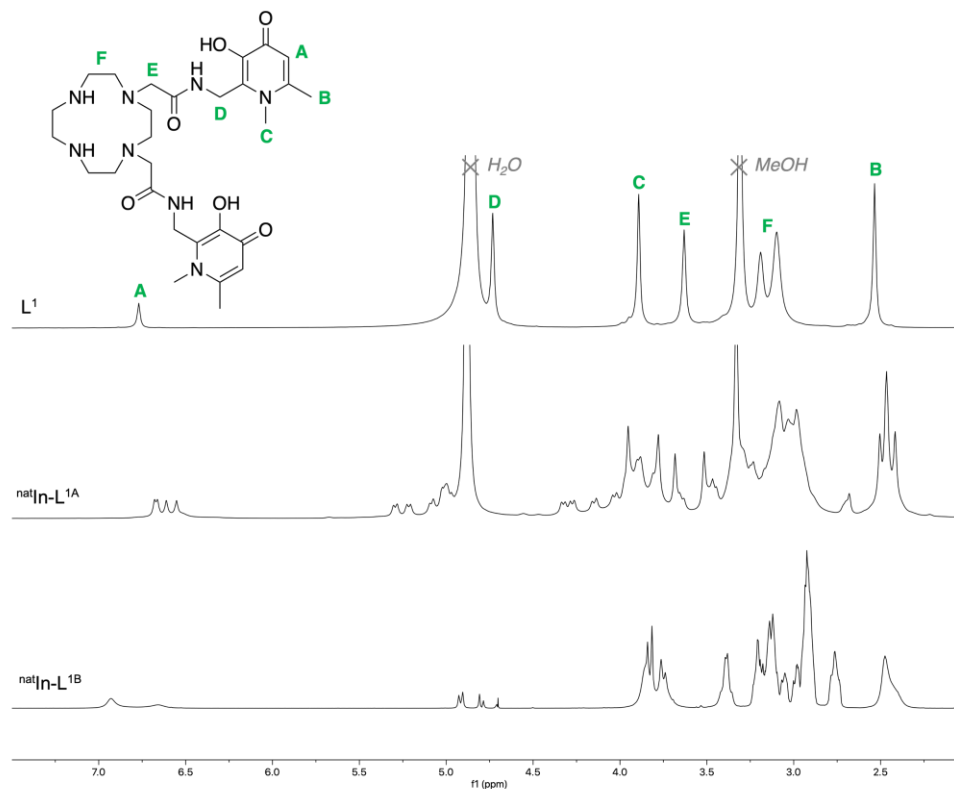
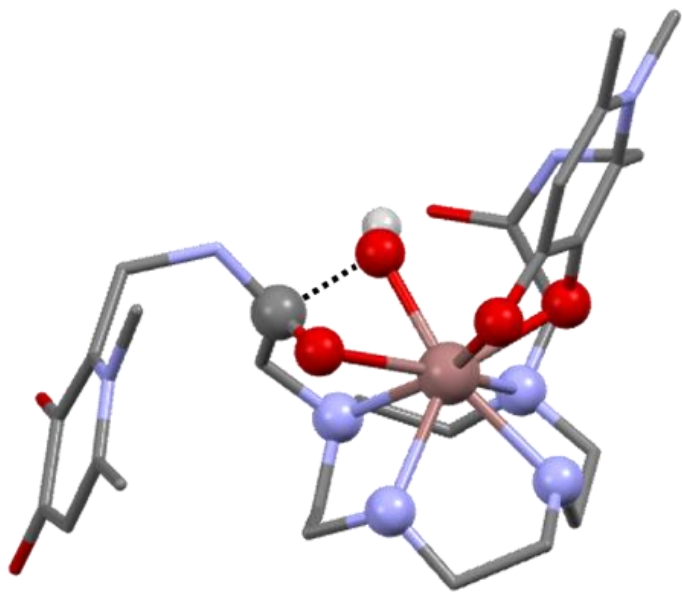
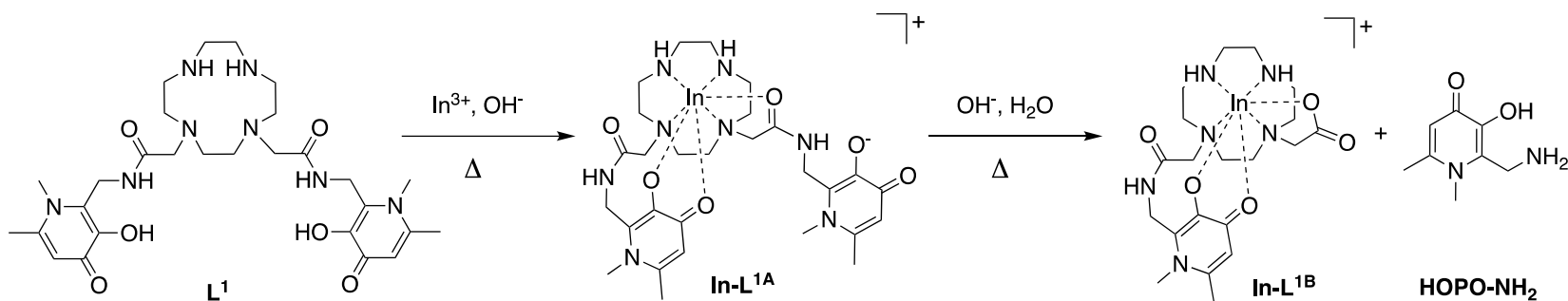


- Is there utility in combining these chelating motifs?





# Prior work on $^{111}\text{In}^{3+}$

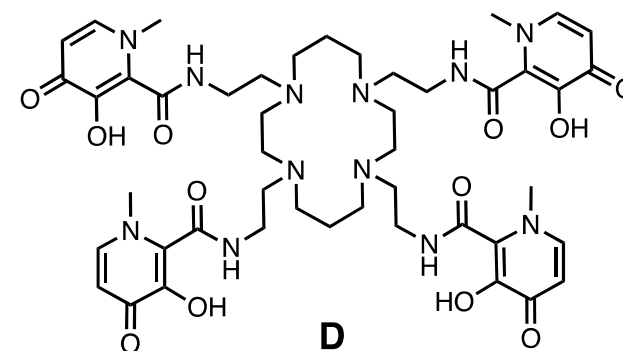
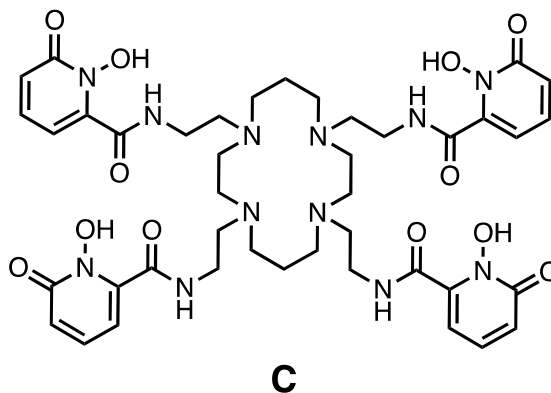
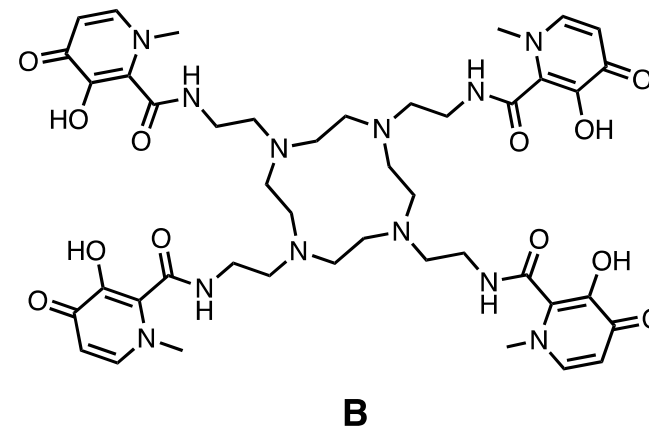
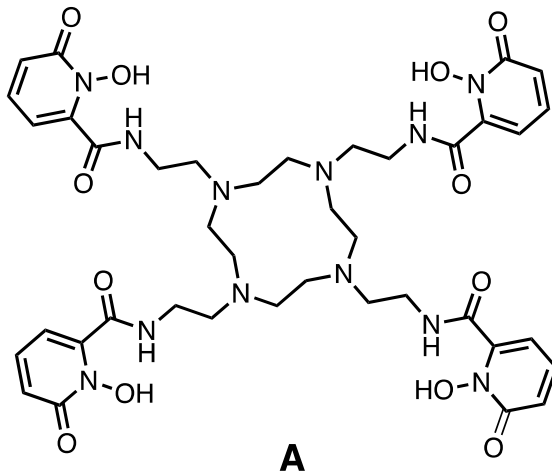






# A new library of HOPO-macrocycles

- Therefore we modified the amide bond and also looked into incorporating 4 HOPO groups
- Hydroxypyridinones exhibit high affinity for hard metal ions and can complex metal ions under mild conditions:
  - 1,2-HOPO
  - 3,4-HOPO
- Cyclen/cyclam-based chelators provide high kinetic stability

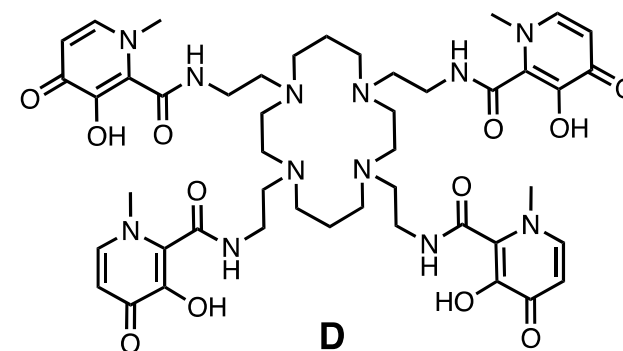
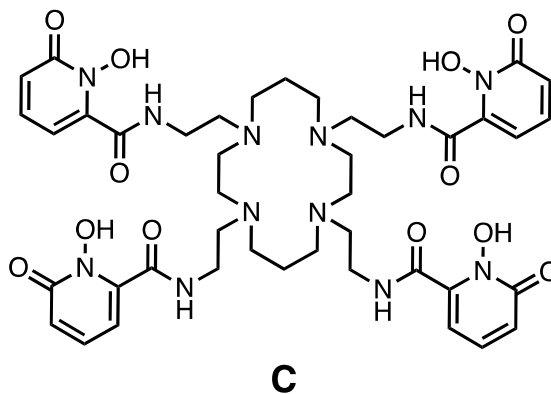
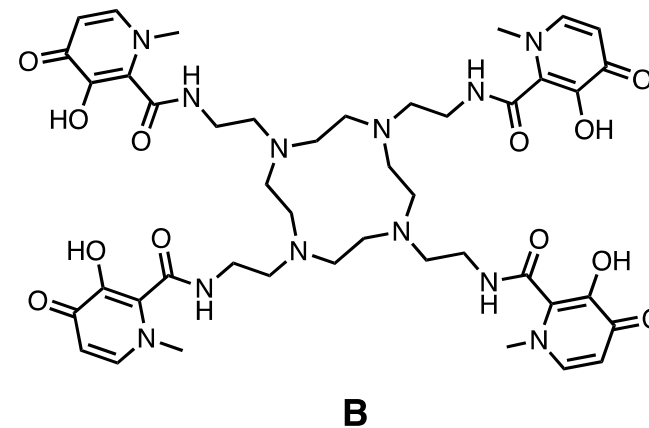
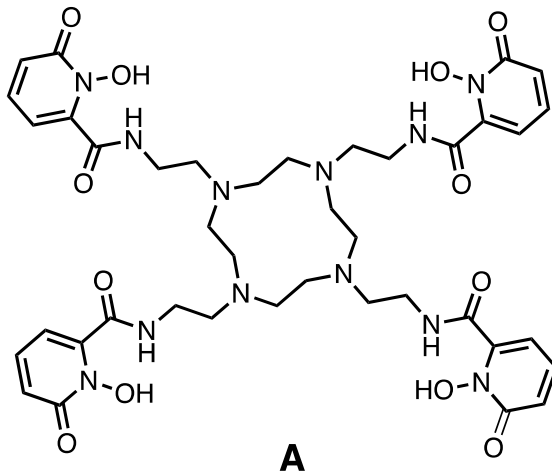


*We have synthesised a series of new chelators that coordinate Ln and An ions*



# A new library of HOPO-macrocycles

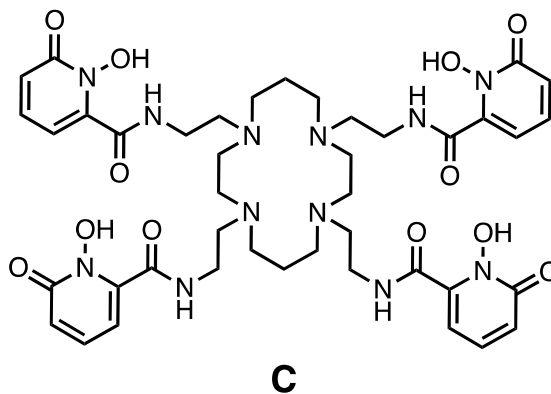
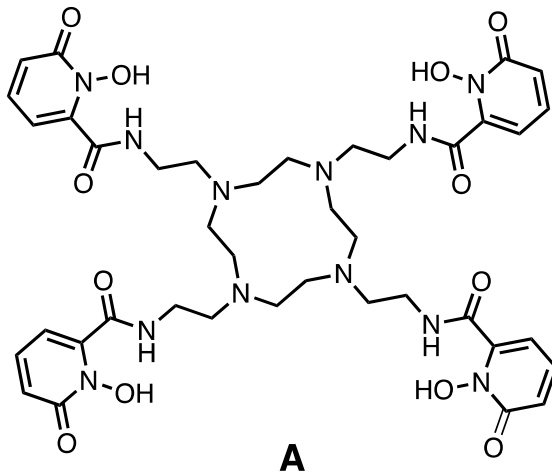
- 1,2-HOPO derivatives of cyclam and cyclen coordinate  $\text{La}^{3+}$ ,  $\text{Th}^{4+}$ ,  $\text{Tb}^{3+}$  and  $\text{Lu}^{3+}$
- 3,4-HOPO derivatives do not coordinate anything much...
- ... except  $\text{Th}^{4+}$





# A new library of HOPO-macrocycles

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# $^{161}\text{Tb}$ and $^{177}\text{Lu}$ radiolabelling

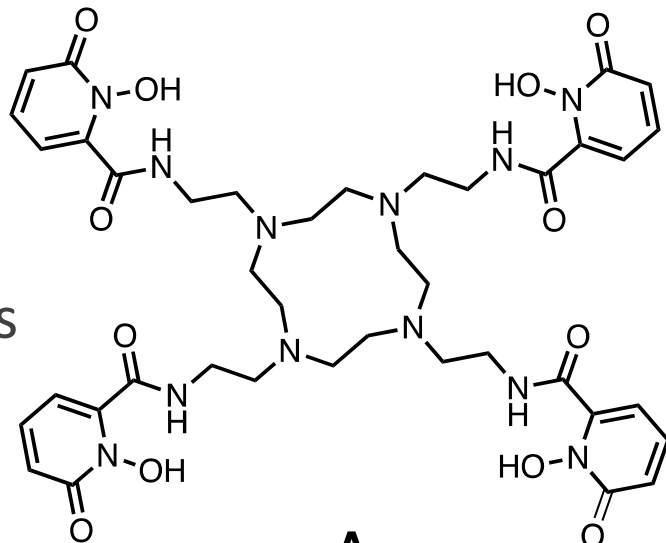
## 1,2-HOPO-cyclen

binds

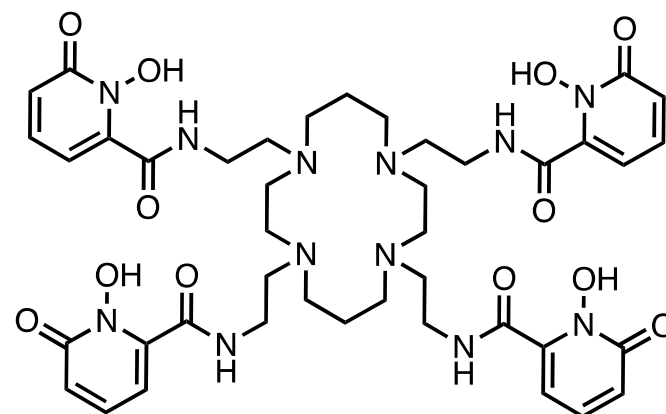
- $^{161}\text{Tb}^{3+}$
- $^{177}\text{Lu}^{3+}$

at higher specific activities than

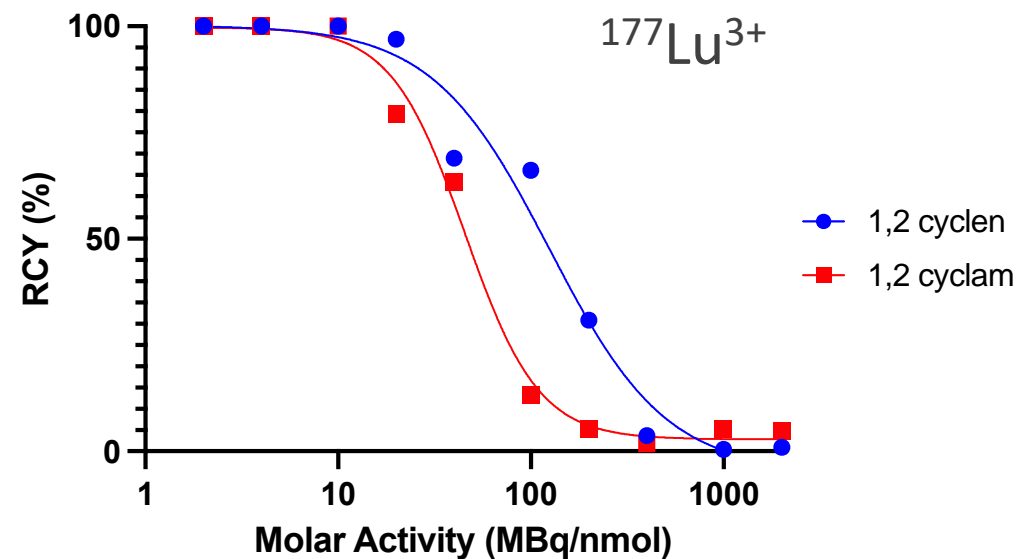
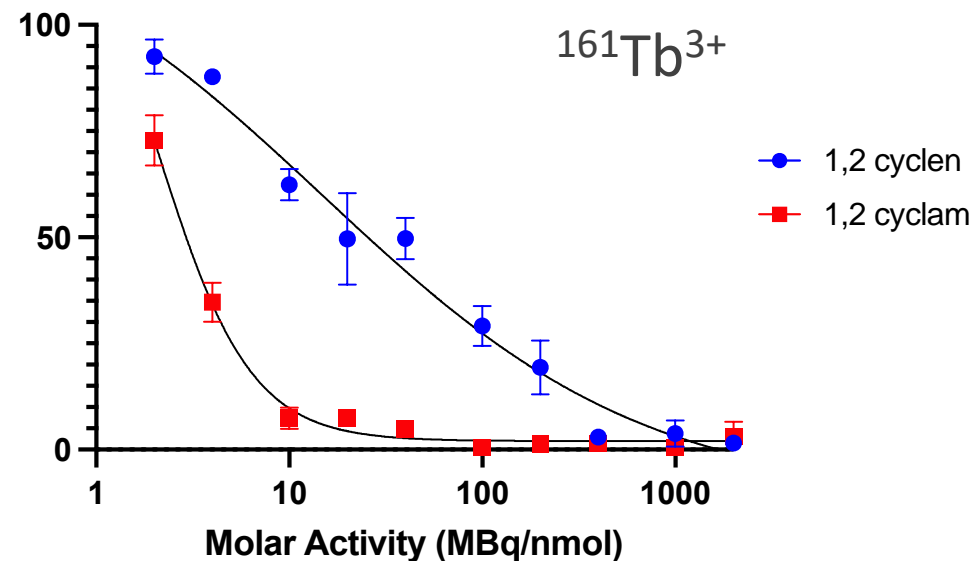
## 1,2-HOPO-cyclam



**A**



**C**





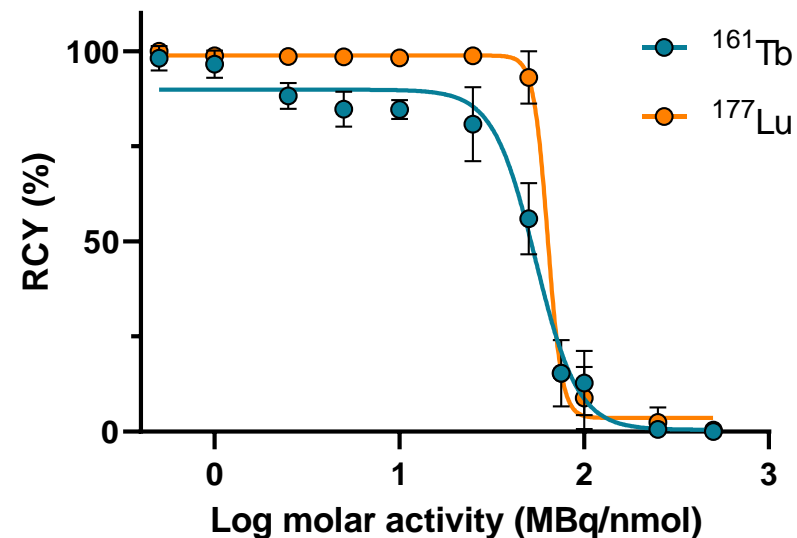
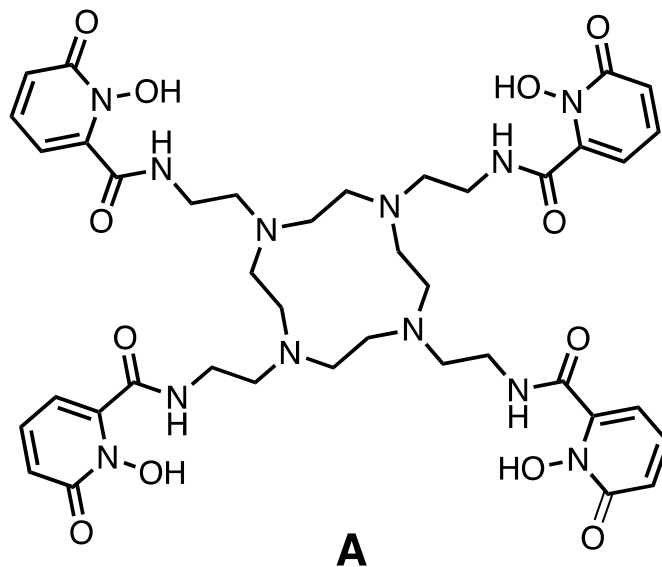
# $^{161}\text{Tb}$ and $^{177}\text{Lu}$ radiolabelling

1,2-HOPO-cyclen binds

- $^{161}\text{Tb}^{3+}$
- $^{177}\text{Lu}^{3+}$

at higher specific activities than  
1,2-HOPO-cyclam

When “fresh” batches of  
 $^{161}\text{Tb}^{3+}$  and  $^{177}\text{Lu}^{3+}$   
are compared side-by-  
side, similar specific  
activities are achieved for  
radiolabelling of  
1,2-HOPO-cyclen

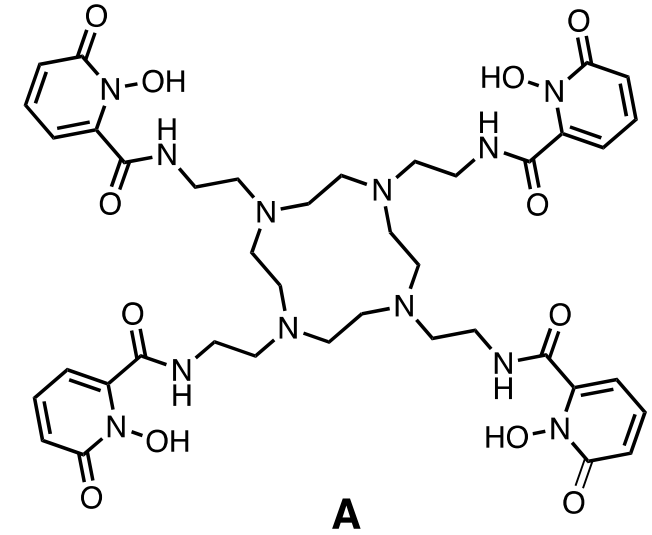




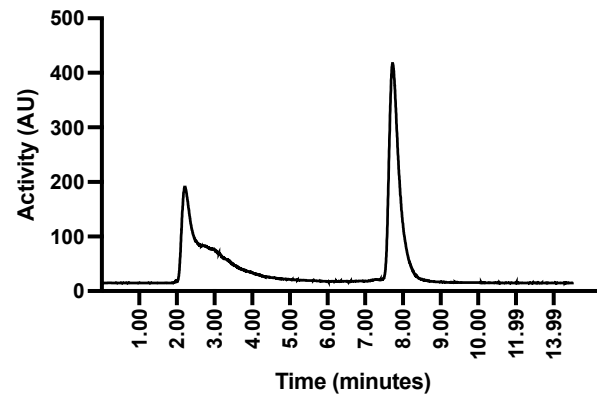
# $^{161}\text{Tb}$ and $^{177}\text{Lu}$ radiolabelling

1,2-HOPO-cyclen can be radiolabelled under mild conditions (room temperature and pH 6)

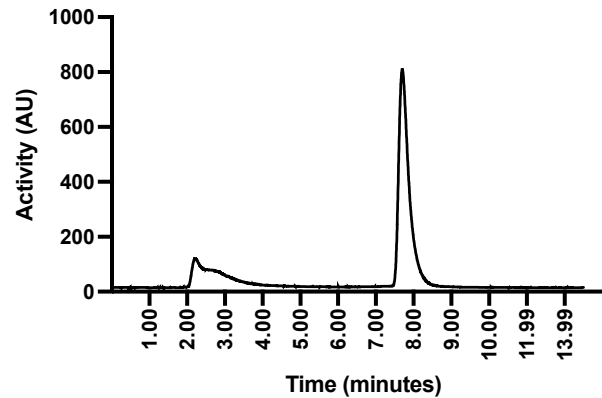
For example:  $^{161}\text{Tb}$  radiolabelling



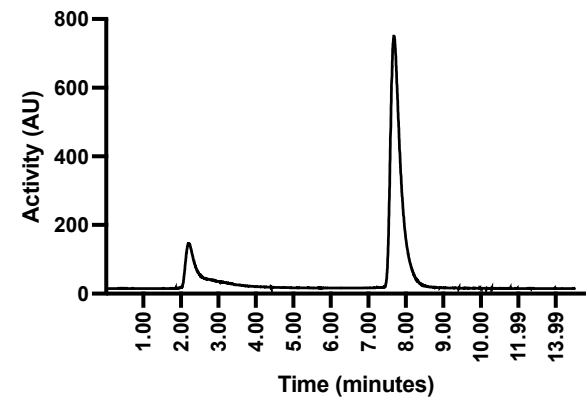
10 minutes



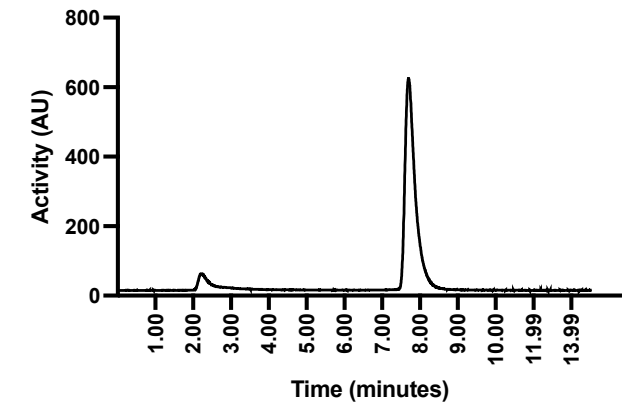
30 minutes



60 minutes



180 minutes





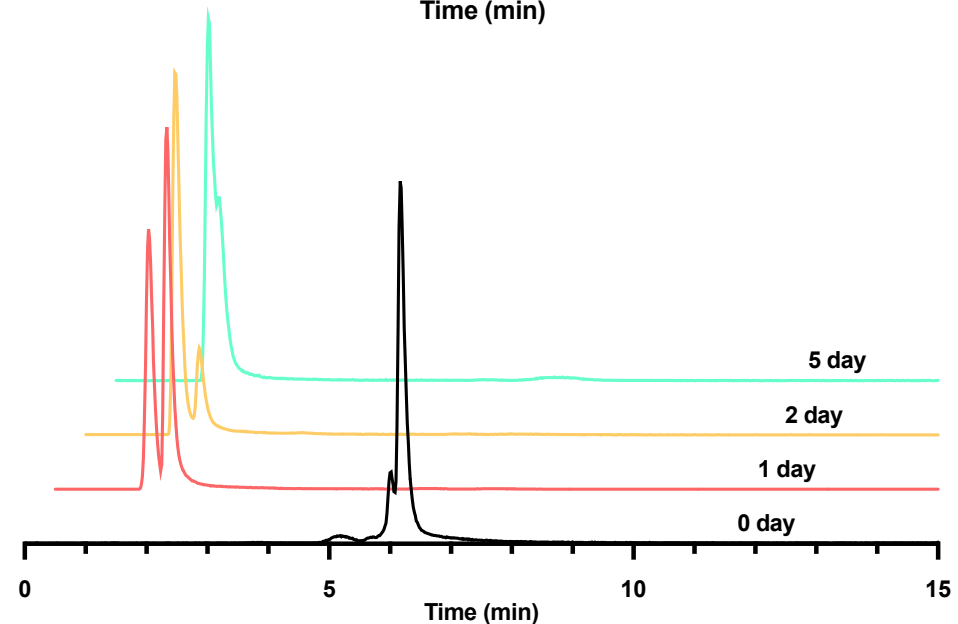
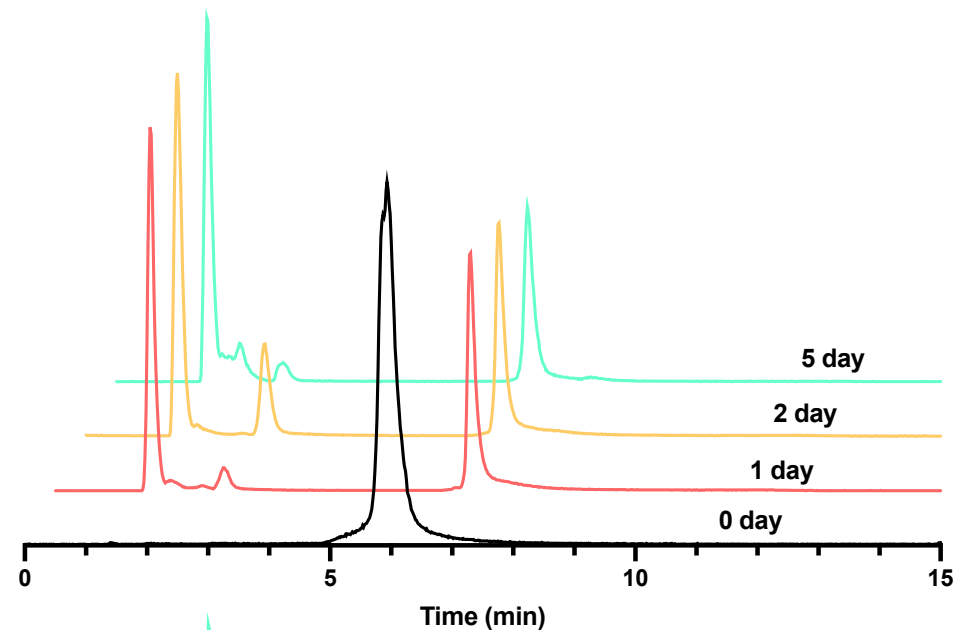
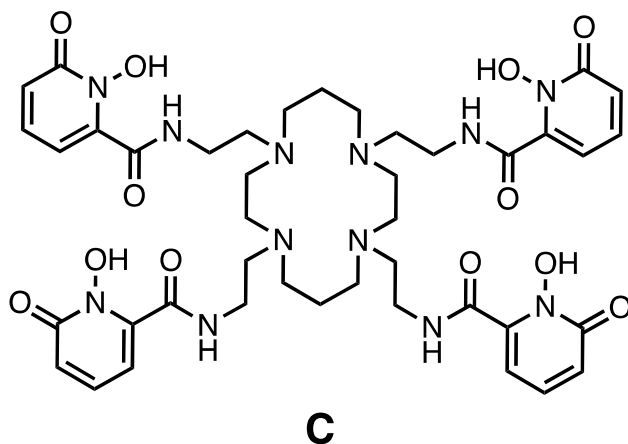
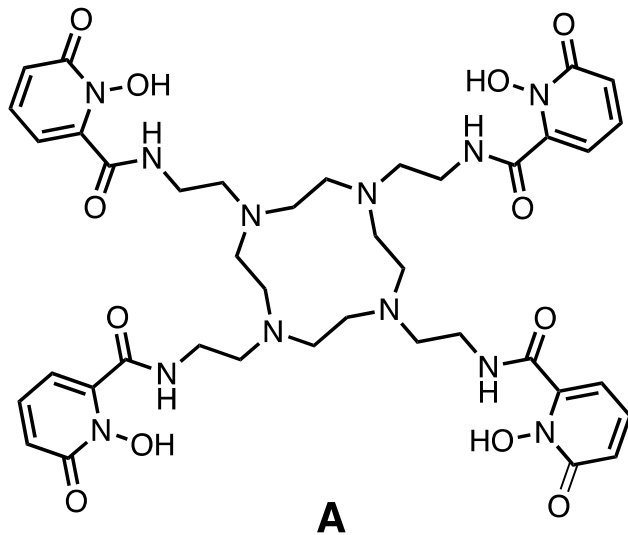
# $^{161}\text{Tb}$ and $^{177}\text{Lu}$ radiolabelling

The resulting radiolabelled complexes of 1,2-HOPO-cyclen are more stable in serum compared to those of 1,2-HOPO-cyclam

For example:

$^{177}\text{Lu}$  serum stability data

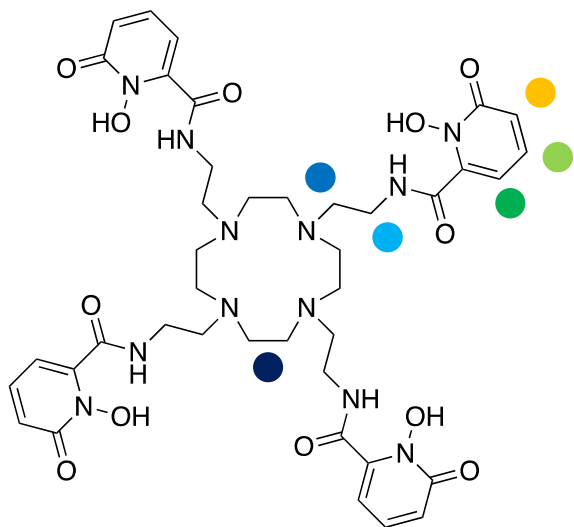
*Stability is not ideal*





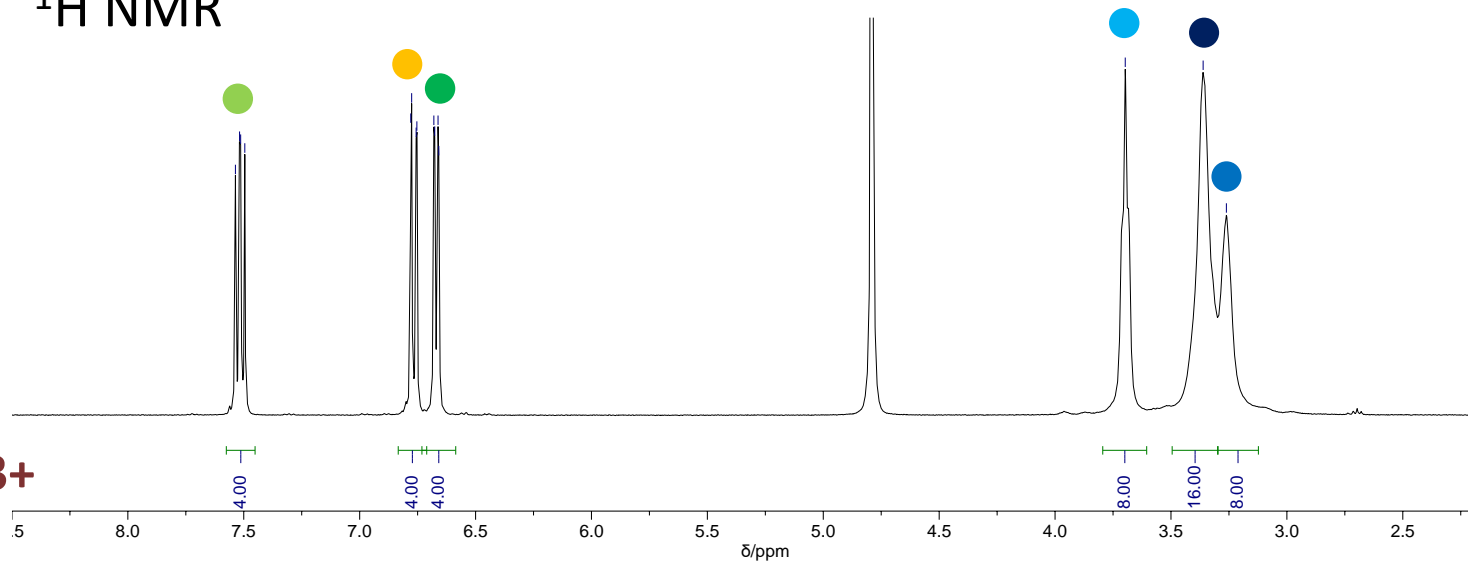
# Lu<sup>3+</sup> coordination

How does Lu<sup>3+</sup> coordinate  
1,2-HOPO-cyclen?

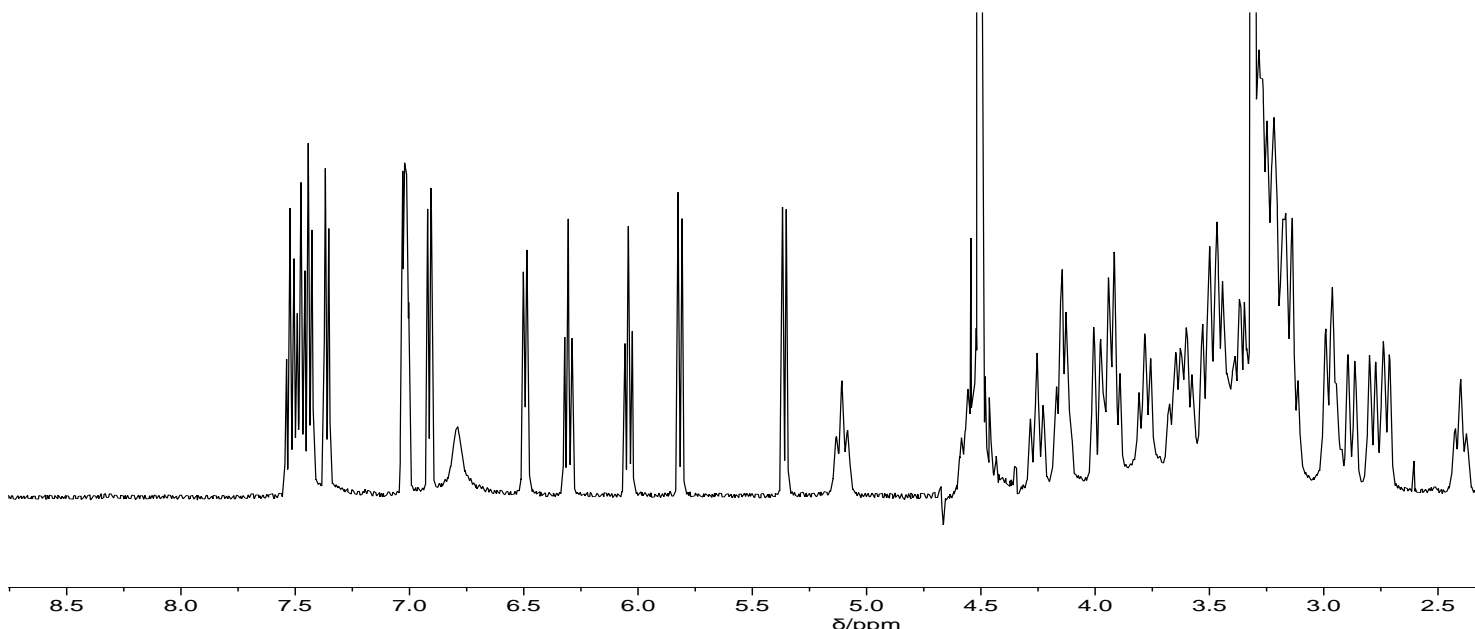


+ Lu<sup>3+</sup>

<sup>1</sup>H NMR



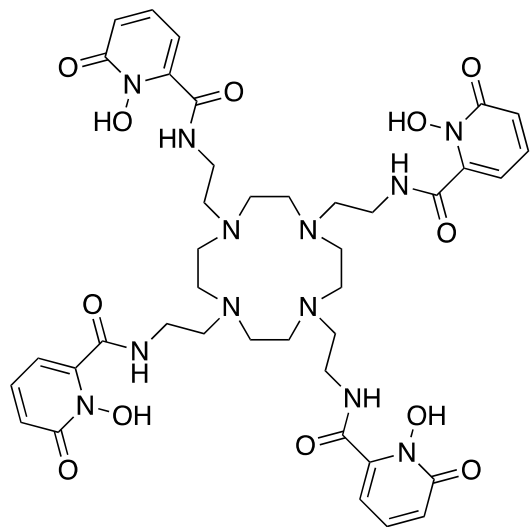
Coordination includes HOPO  
groups and amine rings of  
cyclen





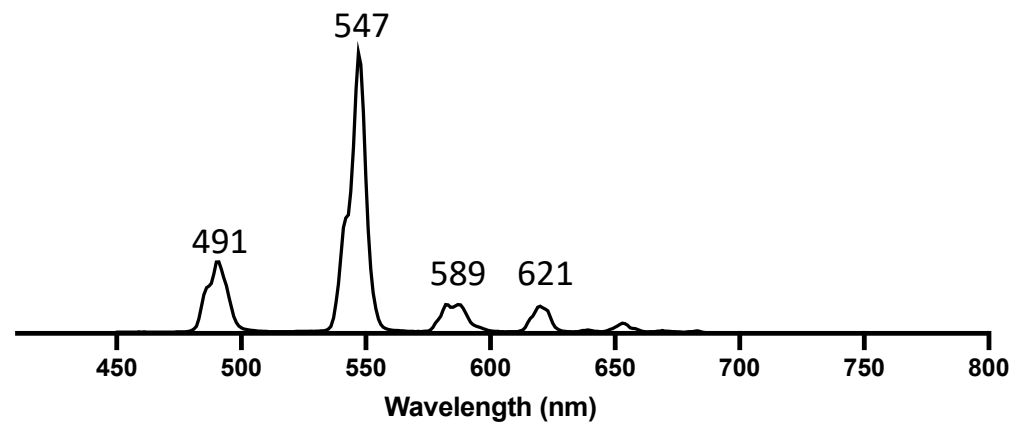
# Tb<sup>3+</sup> coordination

How does Tb<sup>3+</sup> coordinate  
1,2-HOPO-cyclen?

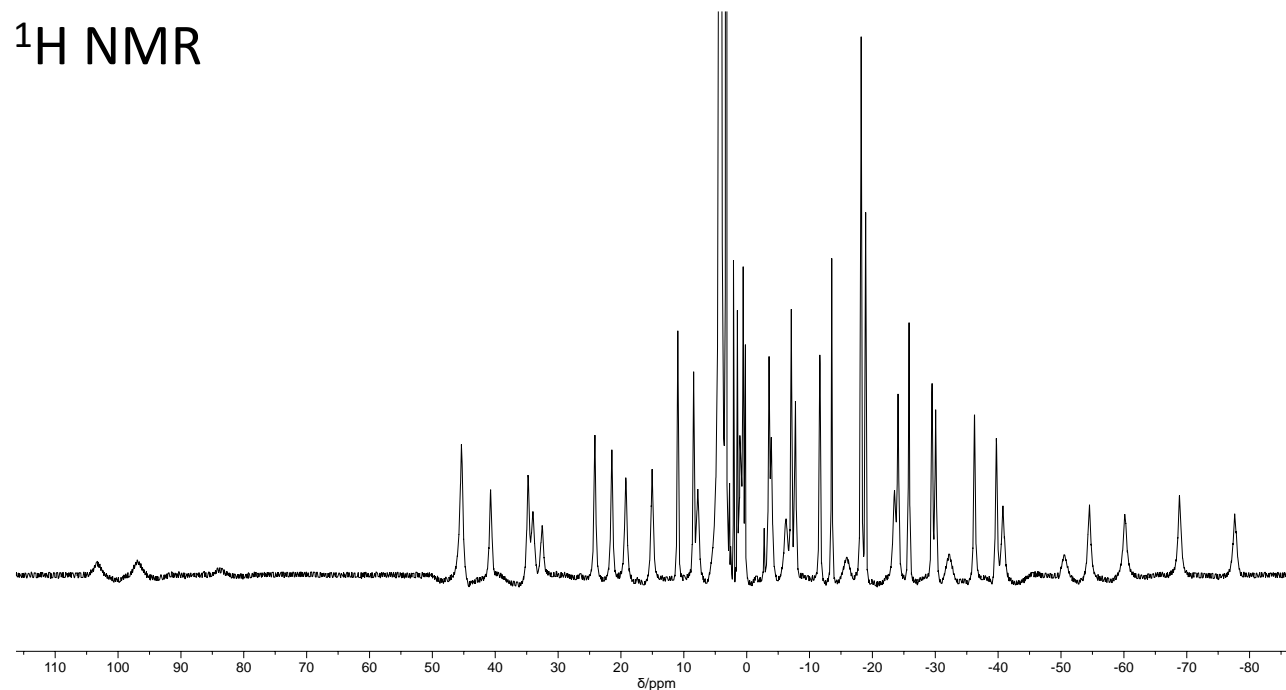


**We postulate that 1,2-HOPO-cyclen coordinates Tb<sup>3+</sup> / Lu<sup>3+</sup> via cyclen amines and at least two HOPO groups**

Luminescence spectrum



<sup>1</sup>H NMR

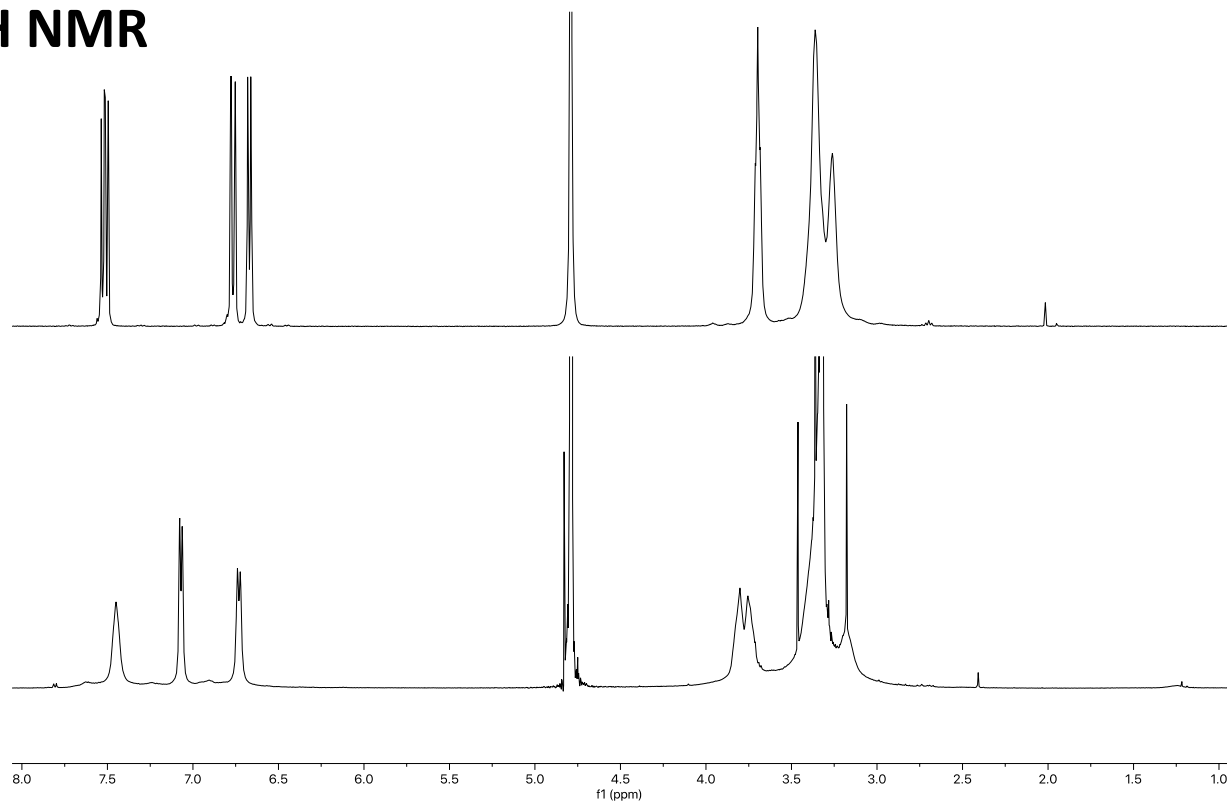




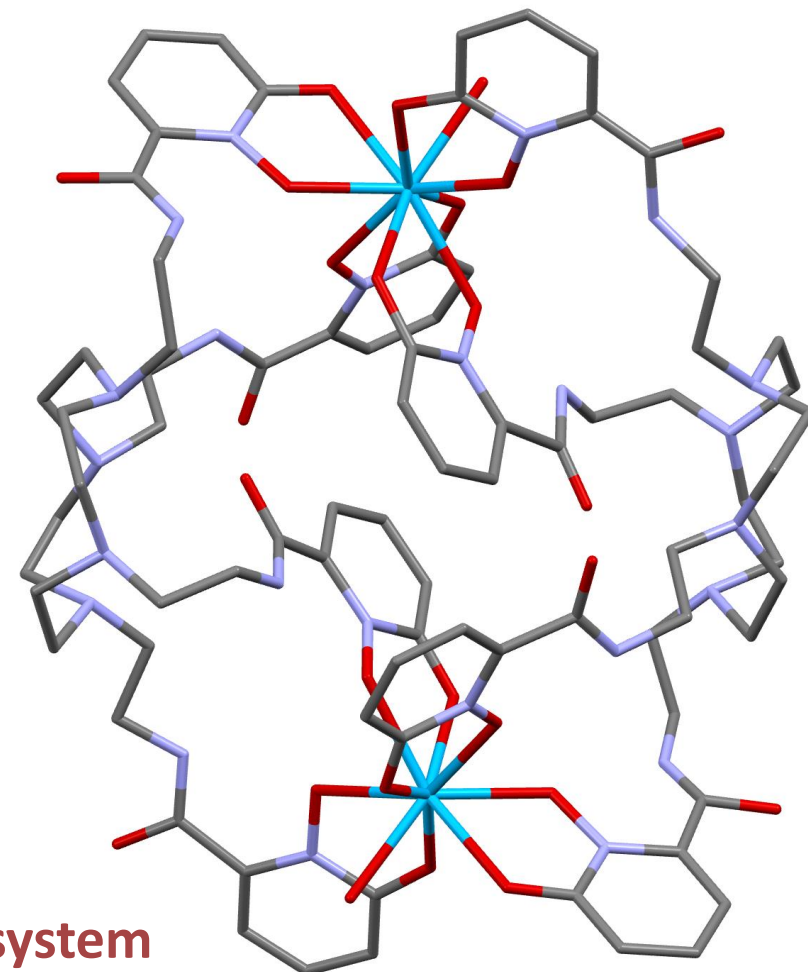


# 1,2-HOPO-cyclen binds $\text{Th}^{4+}$

$^1\text{H}$  NMR



Single XRD structure



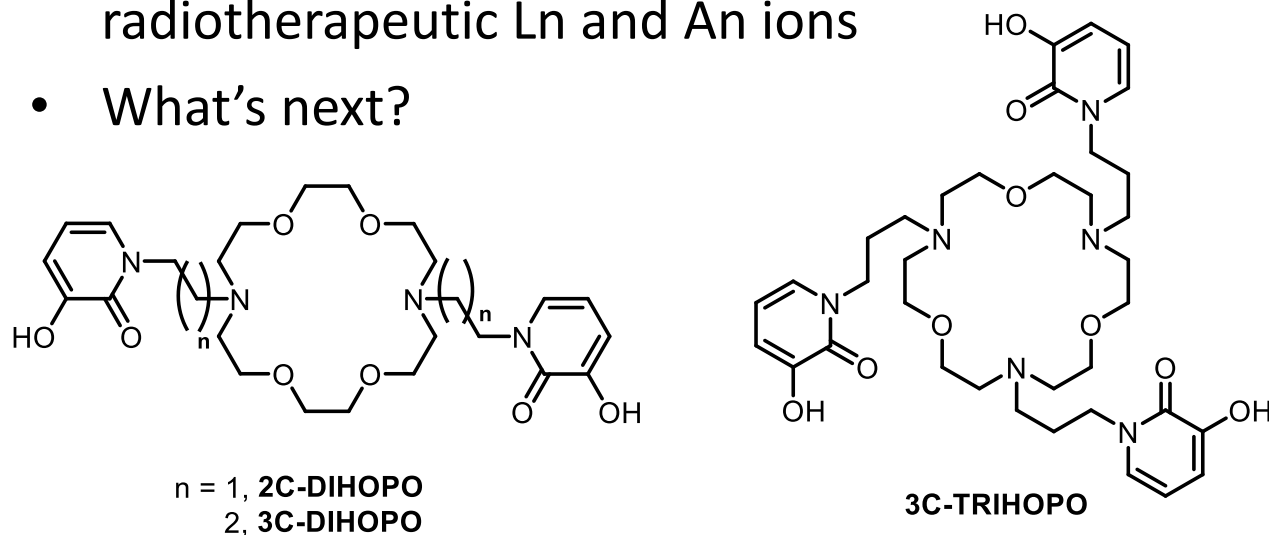
	1,2 cyclen	1,2 cyclen with Th
Diffusion coefficient ( $\text{m}^2/\text{s}$ )	$3.96 \times 10^{-10}$	$3.52 \times 10^{-10}$
Hydrodynamic radius ( $\text{\AA}$ )	9.93	11.34

**1,2-HOPO-cyclen coordinates  $\text{Th}^{4+}$  through HOPO groups only, the system is likely dynamic and the topology of the complex is entirely different**

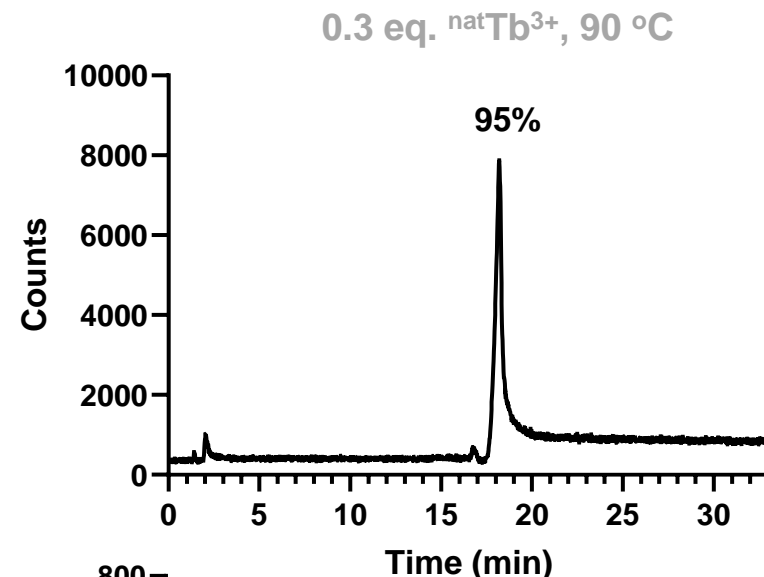


# Hydroxypyridinone derivatives

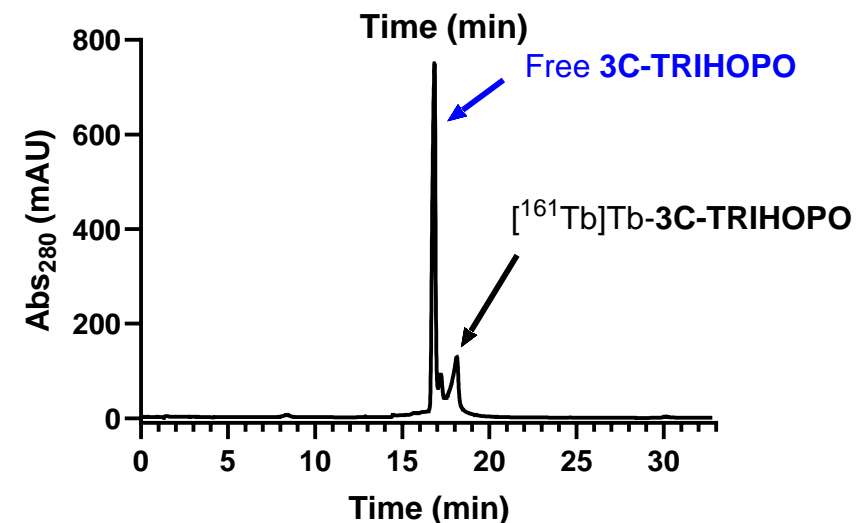
- Hydroxypyridinone derivatives of cyclen and cyclam exhibit tremendously rich chemistry, even if we (me) are still trying to properly figure it out...
- We (me) need to make sure we understand subtle and not-so-subtle intricacies at the coordination chemistry level
- Our derivatives bind a range of radiotherapeutic Ln and An ions
- What's next?



Radio-HPLC



UV trace  
(280 nm)





# Acknowledgements

## Paul Scherrer Institute

Cristina Muller

Nicholas van der Meulen

Christian Vaccarin

Pascal Grundler

## King's College London

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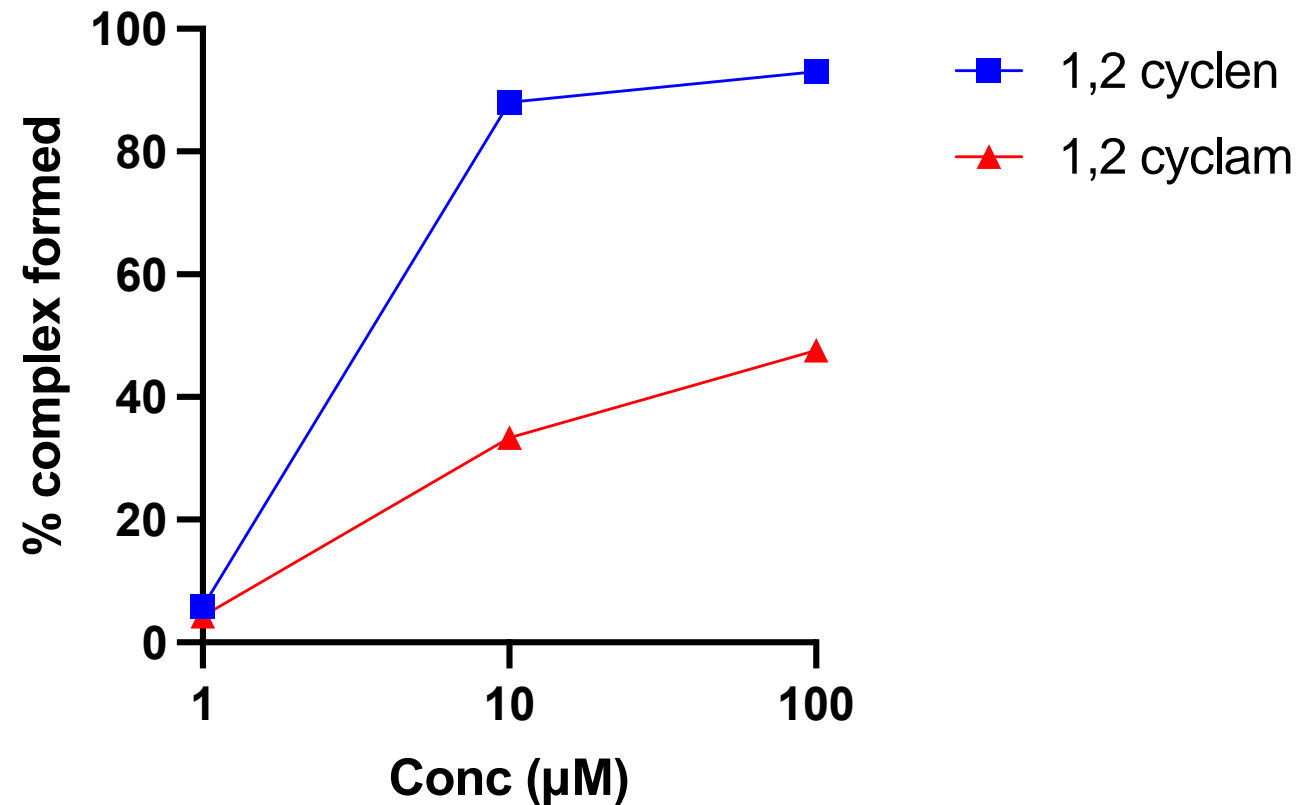
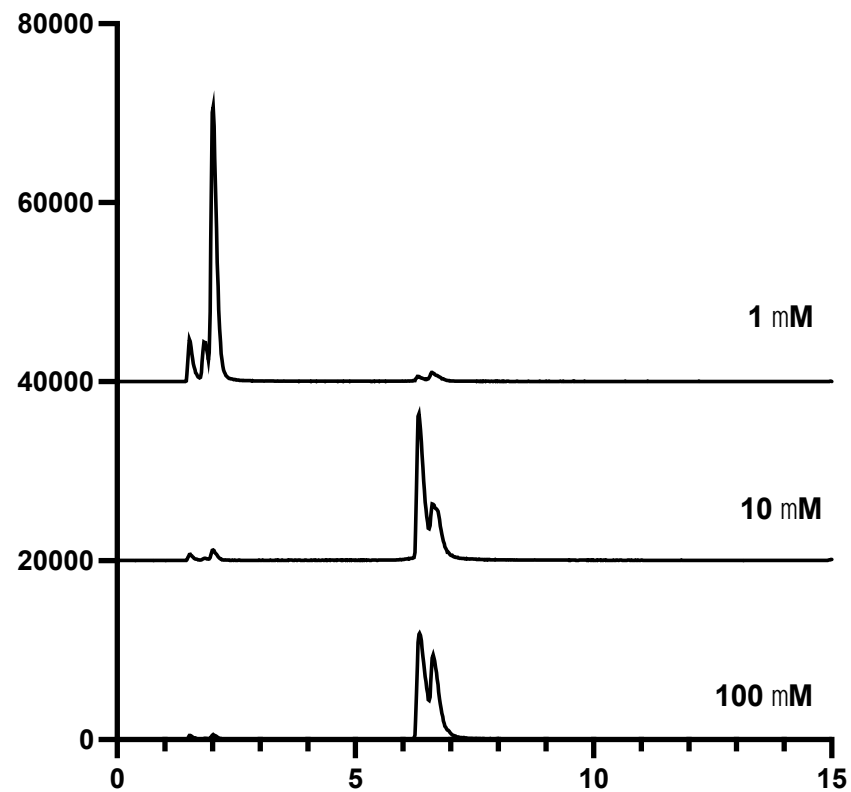
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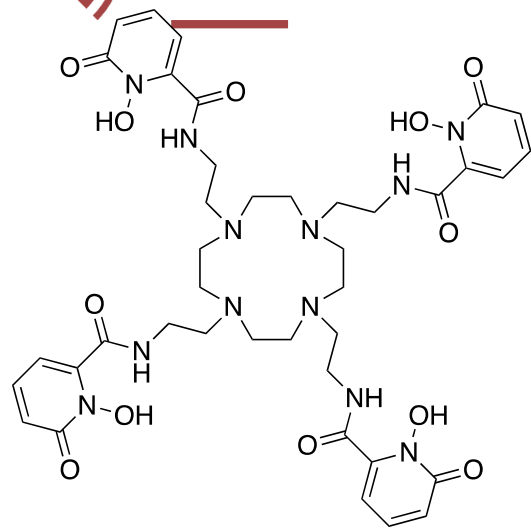
$^{177}\text{Lu}$ , pH 6.5 NaOAc, RT, 10 min



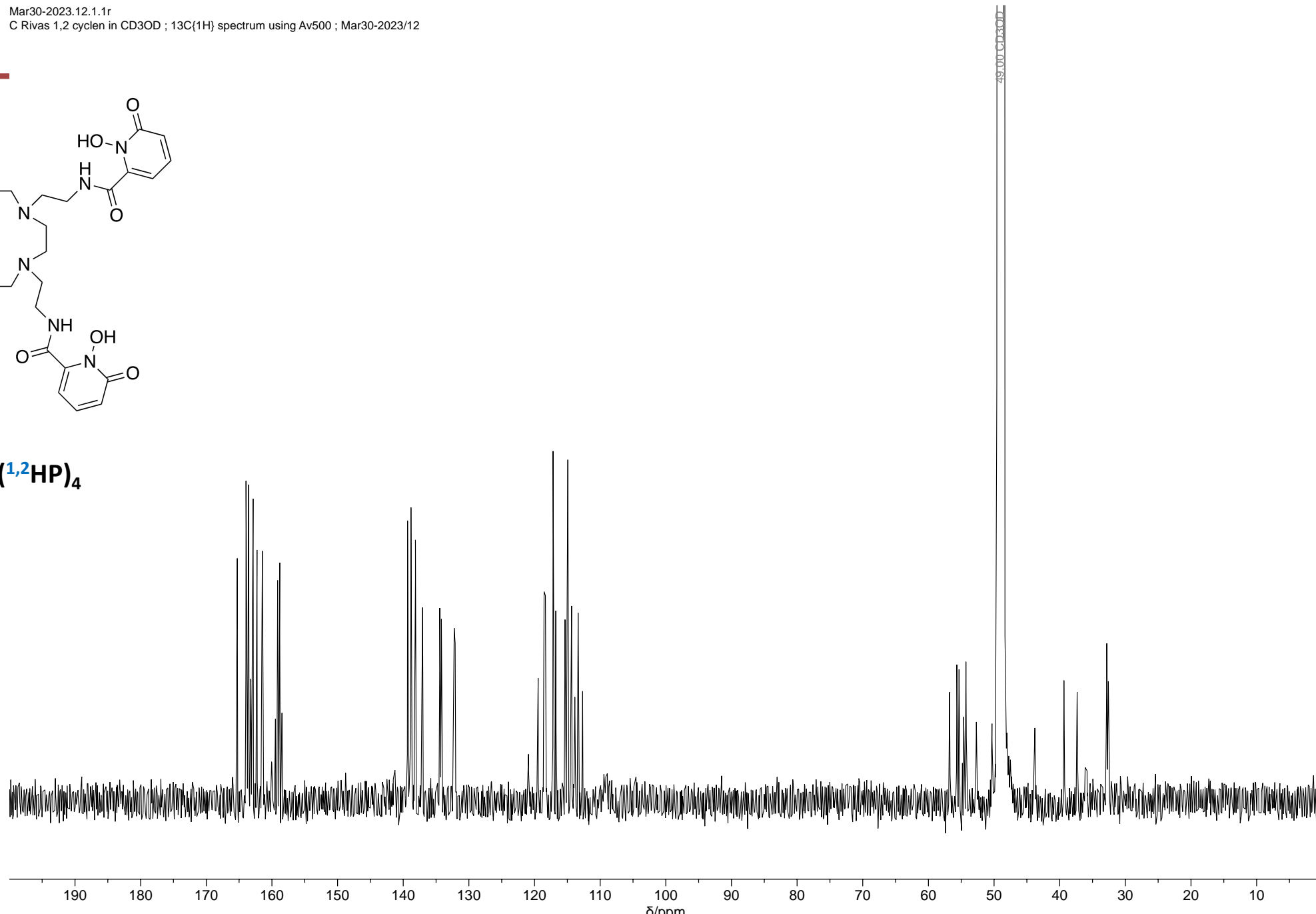
Room temperature reactions show two Lu complex species – correlating with NMR



Mar30-2023.12.1.1r  
C Rivas 1,2 cyclen in CD3OD ; 13C{1H} spectrum using Av500 ; Mar30-2023/12

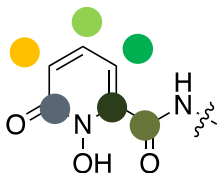


cyclen-(<sup>1,2</sup>HP)<sub>4</sub>  
Lu





Nov08-2022.32.11r  
1,2-cyclen\_D2O  
221108  
<sup>13</sup>C{<sup>1</sup>H}



Jul24-2023.14.11r  
C Rivas CR1,2 en Th in D2O ; <sup>13</sup>C{<sup>1</sup>H} spectrum using Av500 ; Jul24-2023/14

