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Evaluating Tetraazamacrocycle Ligands as ^{134}Ce Chelators

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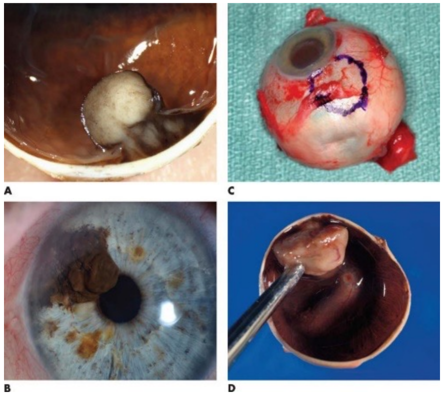
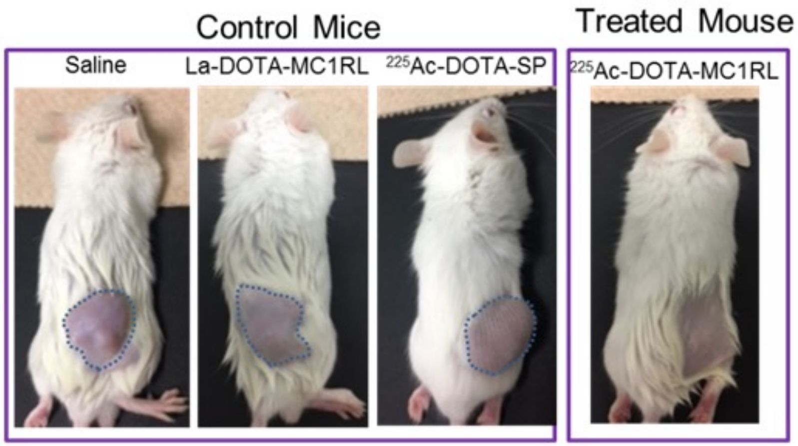
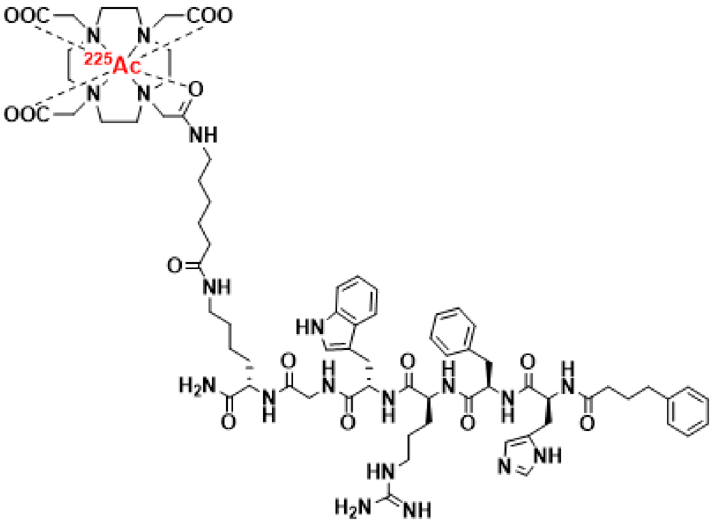
University of Iowa
September 19, 2022

NIDC Meeting on Ce-134

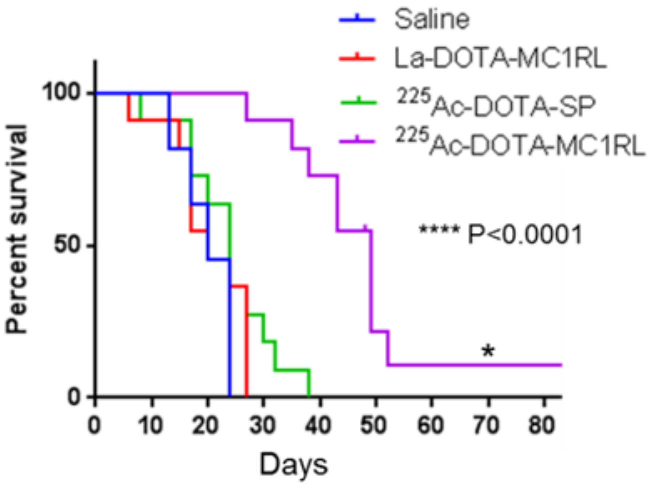
^{225}Ac-TAT is an Expanding Research Area





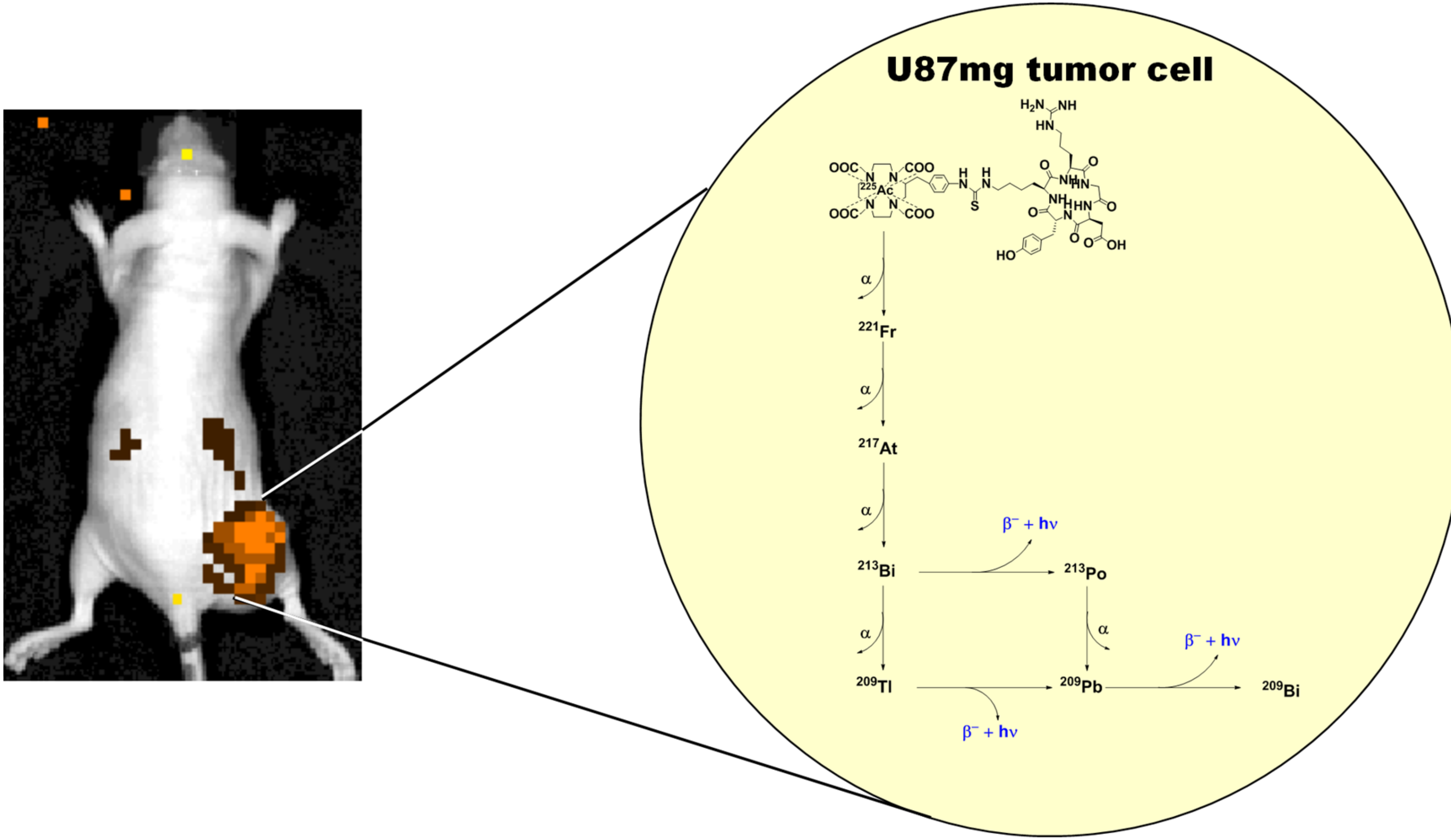


^{225}Ac-DOTA-MC1RL



Tafreshi, N., et al. J. Nucl. Med. 2019, 60(8), 1124-1133.

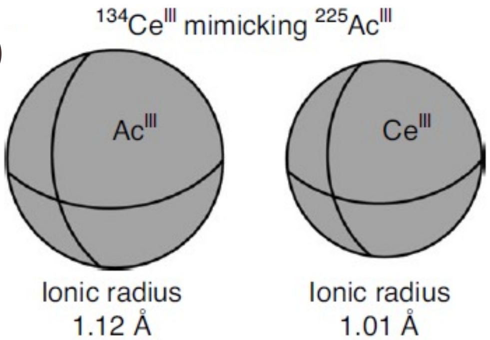
Visualizing ^{225}Ac-TAT Delivery



Pandya, D.N., et al. Theranostics. 2016, 6(5), 698-709.

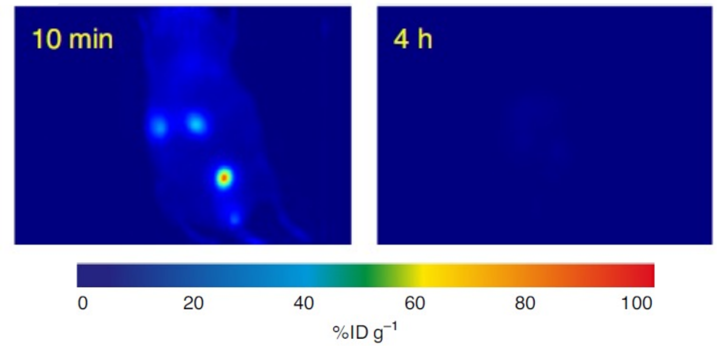
^{134}Ce as an Imaging Companion for ^{225}Ac

(A)



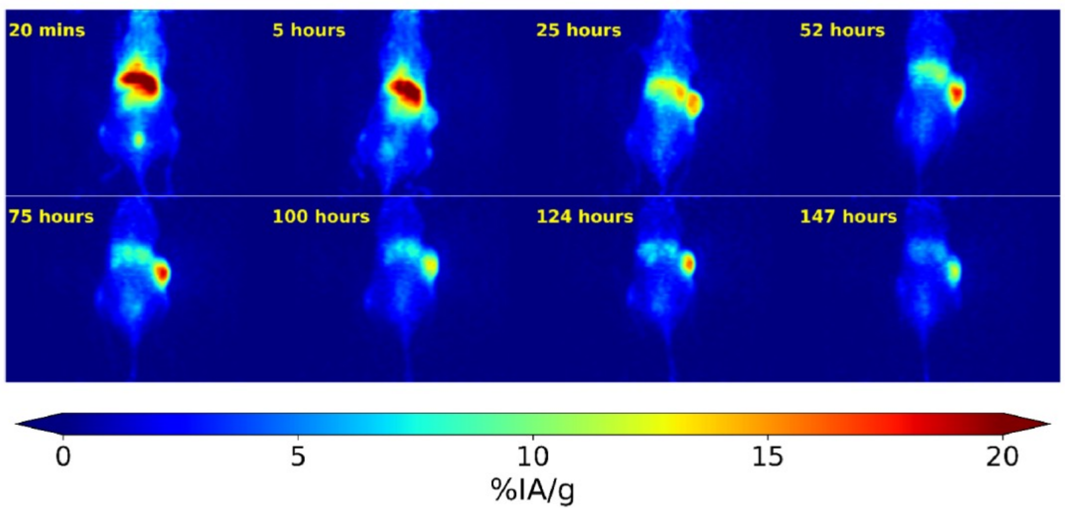
^{134}Ce-DTPA

(B)



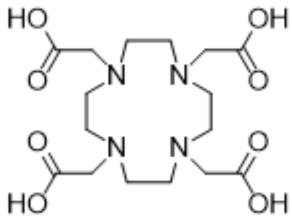
^{134}Ce-DOTA-Trastuzumab

(C)



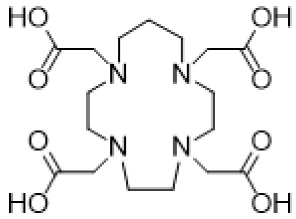
Bailey, T.A., et al. Nature Chemistry. 2021, 13, 284-289.
Bailey, T.A., et al. Nucl. Med. Biol. 2022, 110-111, 28-36.

Tetraazamacrocycles as Ce-134 Chelators



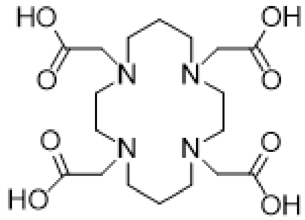
DOTA

12-member ring



TRITA

13-member ring



TETA

14-member ring

Radiochemical Synthesis of ^{134}Ce-DOTA

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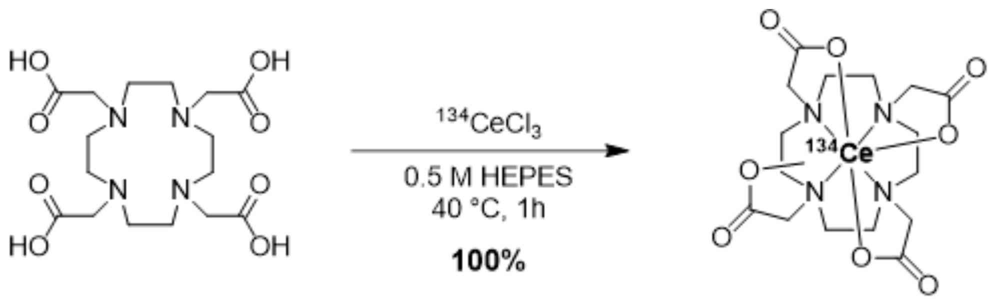
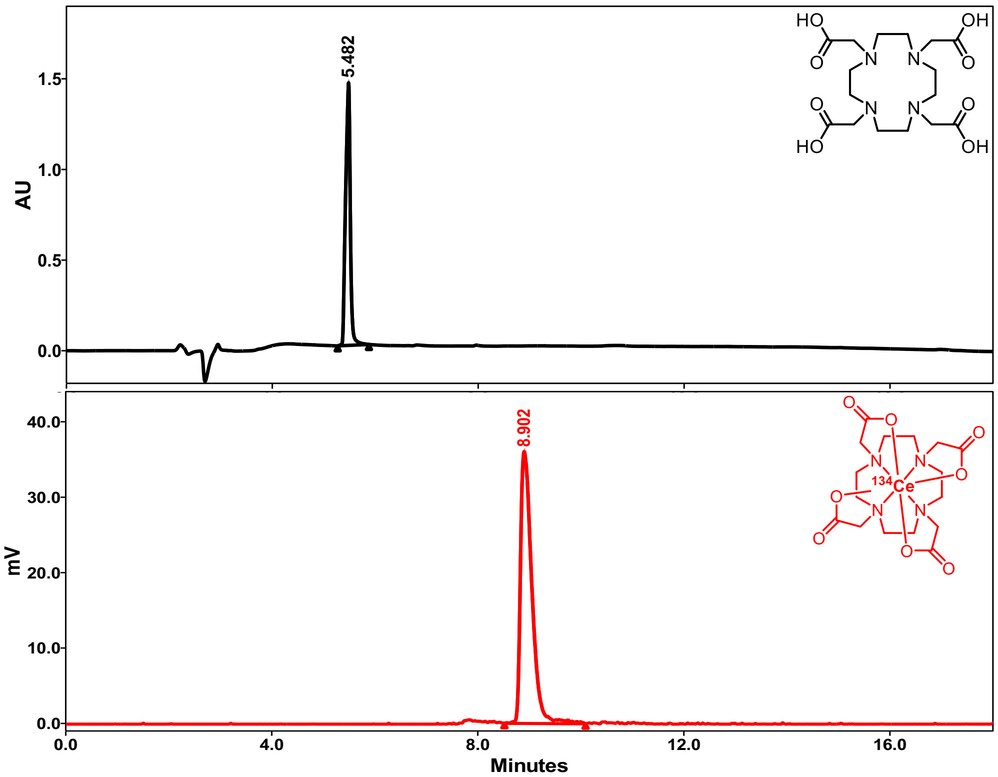
Quantity of Ligand DOTA (µg)	Reaction Buffer (pH 6.8 – 7.2)	Reaction Temperature (°C)	Reaction Time (min)	Radiochemical Yield by Radio-ITLC (%)
2	0.5 M NH_4OAc	40	60	100
1	0.5 M NH_4OAc	40	60	100
0.5	0.5 M NH_4OAc	40	60	98.8 ± 0.3
0.2	0.5 M NH_4OAc	40	60	89.5 ± 0.5
0.1	0.5 M NH_4OAc	40	60	36.3 ± 2.3
0.05	0.5 M NH_4OAc	40	60	12.1 ± 1.7
2	0.5 M HEPES	40	60	100
1	0.5 M HEPES	40	60	100
0.5	0.5 M HEPES	40	60	99.6 ± 0.3
0.2	0.5 M HEPES	40	60	98.3 ± 0.2
0.1	0.5 M HEPES	40	60	95.4 ± 0.4
0.05	0.5 M HEPES	40	60	62.3 ± 1.1
2	0.5 M NaOAc	40	60	100
1	0.5 M NaOAc	40	60	100
0.1	0.5 M NaOAc	40	60	10.8 ± 2.6

Radio-HPLC of ^{134}Ce-DOTA

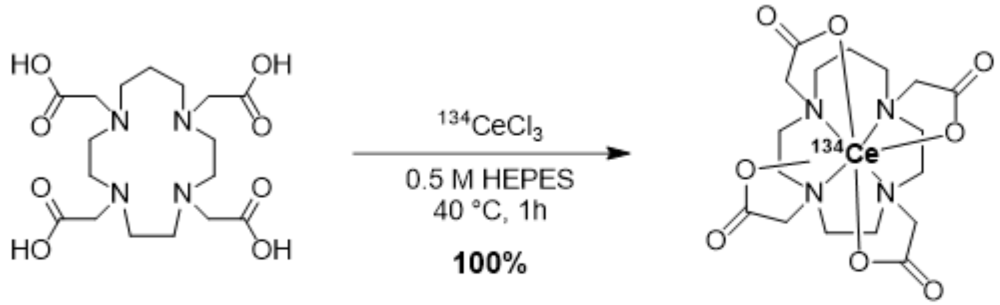


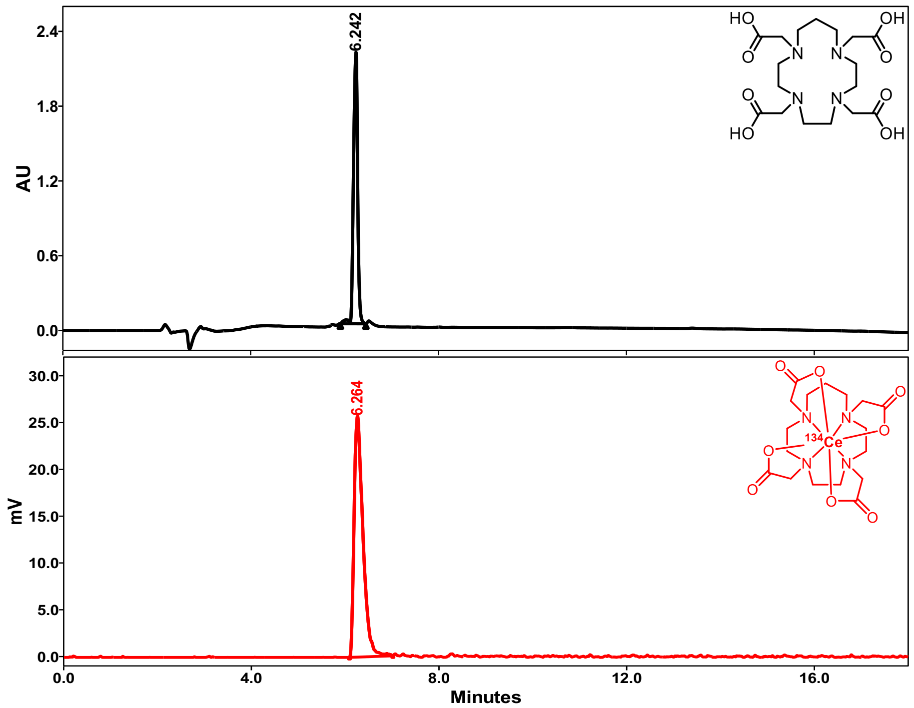


Radiochemical Synthesis of ^{134}Ce-TRITA

Quantity of Ligand TRITA (µg)	Reaction Buffer (pH 6.8 – 7.2)	Reaction Temperature (°C)	Reaction Time (min)	Radiochemical Yield by Radio-ITLC (%)
2	0.5 M NH_4OAc	40	60	100
1	0.5 M NH_4OAc	40	60	100
0.1	0.5 M NH_4OAc	40	60	99.1 ± 0.2
2	0.5 M HEPES	40	60	100
1	0.5 M HEPES	40	60	100
0.1	0.5 M HEPES	40	60	100
2	0.5 M NaOAc	40	60	100
1	0.5 M NaOAc	40	60	100
0.1	0.5 M NaOAc	40	60	34.9 ± 3.5

Radio-HPLC of ^{134}Ce-TRITA





Radiochemical Synthesis of ^{134}Ce-TETA

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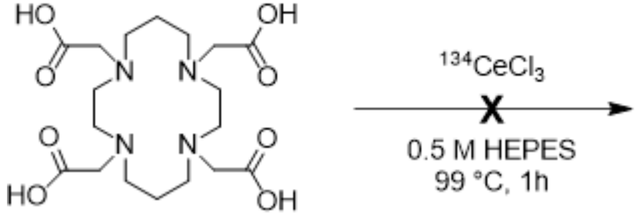
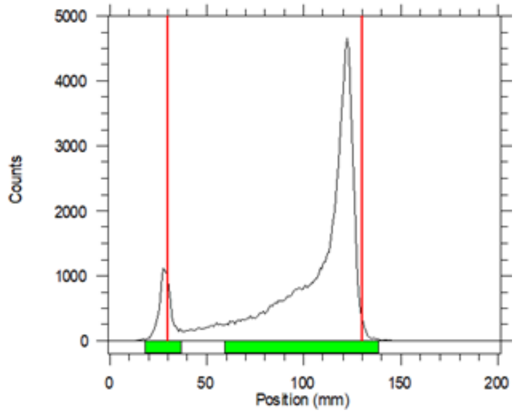
Quantity of Ligand TETA (μg)	Reaction Buffer (pH 6.8 – 7.2)	Reaction Temperature (°C)	Reaction Time (min)	Radiochemical Yield by Radio-ITLC (%)
2	0.5 M NH_4OAc	80	60	0.7 ± 0.5
2	0.5 M NH_4OAc	99	60	8.9 ± 1.2
2	0.5 M HEPES	80	60	1.2 ± 0.4
2	0.5 M HEPES	99	60	10.1 ± 0.8
2	0.5 M NaOAc	80	60	0
2	0.5 M NaOAc	99	60	7.4 ± 0.9

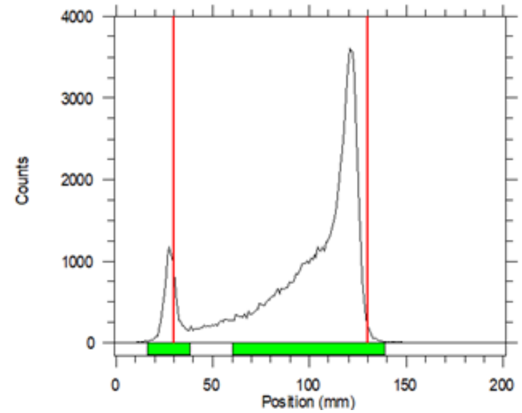
Radio-ITLC of ^{134}Ce-TETA



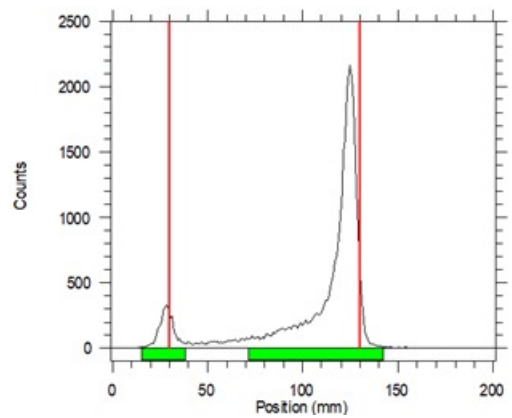
0.5 M NH_4OAc



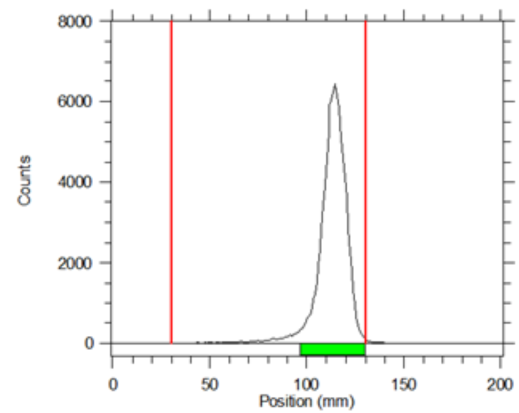
0.5 M HEPES



0.5 M NaOAc



$^{134}CeCl_3$



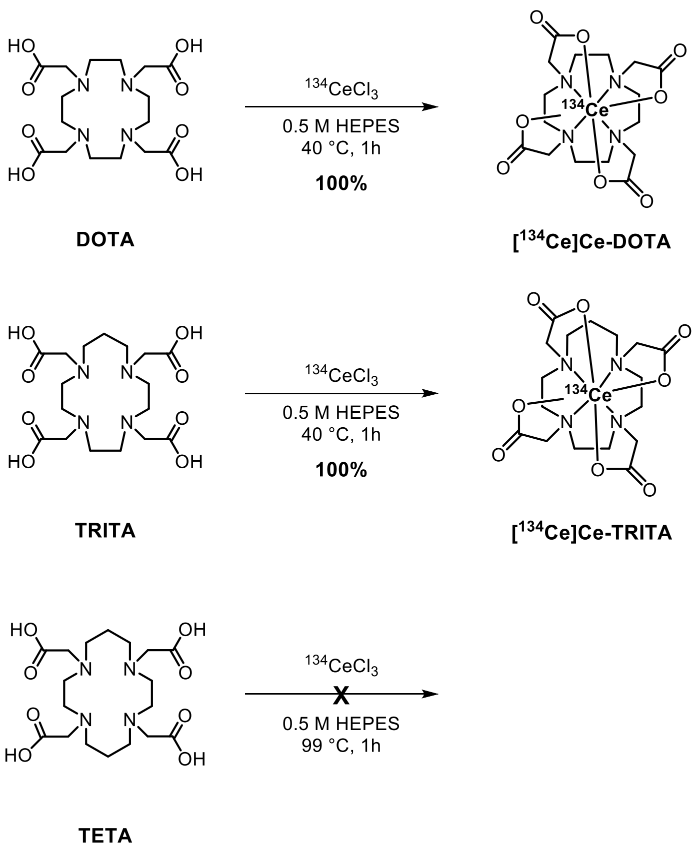
ITLC-SA / 50 mM EDTA

Unchelated ^{134}Ce

^{134}Ce-EDTA ($R_f \sim 1$)

^{134}Ce-TETA ($R_f \sim 0$)

^{134}Ce-Tetraazamacrocycle Radiochemistry and Behavior Rationale



- Ln^{3+} reactivity decreases as ring size increases
  - DOTA ≥ TRITA >> TETA
- Preorganization may influence reactivity
  - DOTA ≥ TRITA >> TETA
- Enthalpic effects

Pandya, D.N., et al. Inorg. Chem. 2020, 59, 23, 17473-17487.
Hancock, R.D. J. Chem. Ed. 1992, 69, 615-621.

Conclusions

- ^{225}Ac-TAT is an active area of research.
- ^{134}Ce has the potential to improve the development of ^{225}Ac-TAT.
- Understanding how chelating ligands interact with ^{134}Ce is important to developing ^{225}Ac/^{134}Ce theranostics.
- Tetraazamacrocycles are worthy of exploration as chelates for ^{134}Ce.
- Reactivity was investigated using different buffers, temperatures and ligand concentrations.
  - DOTA ≥ TRITA >> TETA
  - Ln^{3+} solution behavior
  - Pre-organization
  - Enthalpy

Acknowledgements

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University of Iowa - Chemistry

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NIDC/LANL

Ce-134