Thesis for the degree of doctor of philosophy (PhD)

Equilibrium and kinetic studies of hydroxy- and halogeno-mixed ligand complexes of Al(III), Ga(III) and Tl(III) aminopolycarboxylates

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Introduction and objectives

^{18}F-fluorodeoxy glucose (FDG) is the most commonly used formulation today in Positron Emission Tomography (PET), although other radiolabelled formulations, e.g. ^{11}C-methionine, ^{15}O-butanol and ^{13}N-ammonia are also in use. The ^{18}F isotope ($t_{½}$ = 109 min, E(β^+)=635 keV) can be obtained from the cyclotron and transported to the PET centers near the cyclotron, thus being accessible in relatively few places. Labeling of particular molecules with isotopes requires complex organic chemical reactions, which, due to their short half-lives, reduce their widespread use in *in vivo* studies. In the past 10 years, radiopharmaceuticals have also been developed, which utilize simple complexation by incorporating the radioisotope present as fluoride anion. These formulations utilize the strong interaction between Al (III) and F^- to get the ^{18}F isotope to the target. Al(III) is bonded to an organic ligand and the ^{18}F isotope is non-covalently binding to Al(III). Modification of the organic ligands by coupling with a suitable bio-vector also renders the composition selective. (D'Souza, et al. *Bioconjugate Chemistry* **2011**, *22* (9), 1793–1803. https://doi.org/10.1021/bc200175c.)

Nowadays, isotopes that are easy to produce with generators have come to the forefront of research, such as ^{68}Ga. ^{68}Ga ($t_{½}$ = 67.71 minutes, E(β^+)=1900 keV) can easily be obtained from the ^{68}Ge/^{68}Ga generator, and in the case of rapid complexation, the signaling process can be shortened and the activity loss reduced.

In addition to diagnostics radiopharmaceuticals, such as the ^{131}I isotope for radiation treatment of thyroid tumors, are also widely used in therapy. The radioactive ^{131}I isotope ($t_{½}$ = 8 days, E(β^-)=606 keV), due to the "soft" nature of the iodide ion, forms a stable complex with "soft" metal ions, such as the Tl(III)-ion. The Tl(III)-I^- system may function in a similar way to the Al(III)-F^- system, but of course an organic ligand is required, which "wraps" the metal ion and also

gets it to the target with the radioisotope. In principle, ^{131}I would not only be applicable in the iodide anion form and not only in the thyroid.

In my work I investigated the complexes of three metal ions, Al(III), Ga(III) and Tl(III) aminopolycarboxylates (APC, simplified L), which could potentially be used in medical applications, with special attention to their M(L)X X=OH^-, F^-, I^-). The stability of the mixed complexes is determined by the hard-soft character and size (coordination number) of the metal ion, the number (denticity) and nature of the donor atoms of the ligand and the structure of the molecule. The investigated metal ions are particularly keen to hydrolysis, so the competition of the hydroxide and halide ligands plays an important role. The formation of M(L)OH can be the deprotonation, hydrolysis of $ML(H_2O)_x$ (the hydrated core complex), but M(L)X can also be formed by replacing water molecules in the parent complex or displacing a donor atom of the L ligand by OH^-. Mixed complex formation always causes a change in the structure of the complex relative to the parent complex, which may affect the inertness and decomposition of the metal complex. (Baranyai, Zs.; et al. *Chemistry - A European Journal* **2012**, *18* (51), 16426–16435. https://doi.org/10.1002/chem.201202930., Baranyai, Zs.; et al. *Chemistry - A European Journal* **2015**, *21* (12), 4789–4799. https://doi.org/10.1002/chem.201405967.) This kinetic effect is similar to the protonation of complexes, which is well known in the literature as an acid-assisted process, but the role of the hydroxide ion has been much less studied. My work is related to these areas the following specific objectives were set:

- Equilibrium characterization of the Al(III)-NOTA-F^- system and investigation of its inertness.
- Selection of APC organic ligands that undergo rapid formation of the AlL main complex as well as the Al(L)F mixed complex and are sufficiently stable and inert for medical diagnostic use.

- The equilibrium characterization, determination of kinetic inertness and mapping of complex structures of the Ga(III) complexes of some newly synthesized hybrid (semimacrocyclic) AAZTA derivatives, Ga(DATA^{m})-, Ga(DATA^{5m})$^{-}$-, Ga(PID(A))$^{-}$- and Ga(PID(B))$^{-}$-.
- Investigation of equilibrium of Tl(III)-ligand-I^{-} systems with some open-chain and macrocyclic ligands.

Structural formulas of the investigated ligands

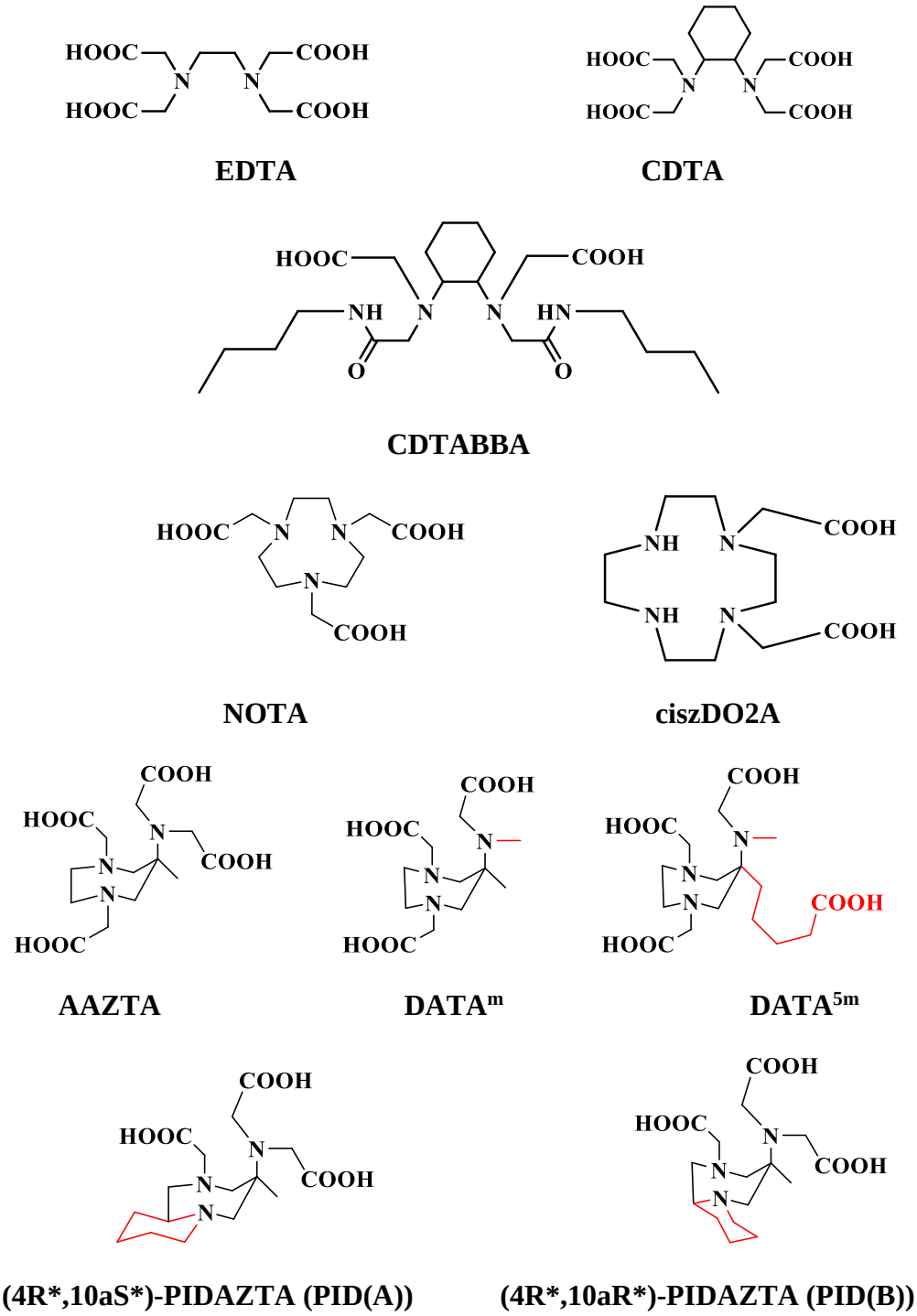


Figure 1 Structure of the investigated ligands.

Experimental methods

NOTA ligand was produced and made available by Gyula Tircsó, EDTA and CDTA ligands were obtained from the company of Sigma-Aldrich. The CDTABBA ligand was prepared by Zoltán Garda, while the cDO2A ligand was made by Tamás Fodor in our group.

The $DATA^{m}$ and $DATA^{5m}$ ligands were prepared and made available by Prof. Frank Rösch and Dr. Johannes Nagel at the Institute of Radiopharmacology, University of Mainz, the PID(A) and PID(B) ligands were synthetiszed by Prof. Giovanni Battista Giovenzana at the Department of Pharmacy of the University of Amedeo Avogadro, Novara.

The protonation constants of the ligands and the stability and protonation constants of their complexes formed with various metal ions were determined by pH potentiometry. The titration of the Al(III) and Ga(III) systems was carried out by 0.2 M NaOH using 0.15 M NaCl as ionic strength. The Tl(III) systems were titrated in 1.0 M $NaClO_4$ with 0.2 M NaOH. In the case of Cu (II) complexes, the data obtained by pH potentiometry were supplemented with UV-visible spectrophotometric measurements, which was necessary because of the high stability of the complexes.

For the equilibrium study of the Al(NOTA) complex, „out of cell" samples were prepared due to the slow formation of the complex. After equilibration, the pH of the samples and their ^{1}H and ^{27}Al NMR spectra were measured. In the case of $Ga(DATA^{m})$-, $Ga(DATA^{5m})^{-}$, $Ga(PID(A))^{-}$ and $Ga(PID(B))^{-}$ complexes (0.15 M NaCl, 298 K) pH titration from alkaline to acidic pH was performed to determine the deprotonation constants. The stability constants of the $Ga(PID(A))^{-}$ and $Ga(PID(B))^{-}$ complexes were also determined by ^{1}H and ^{71}Ga NMR spectroscopy by „out of cell" sample technique.

For TlL complexes, the stability constants of the Tl(L)OH and Tl(L)I (L=EDTA, CDTA, CDTABBA, cDO2A) mixed complexes were determined by ^{205}Tl NMR spectroscopy in addition to pH potentiometry.

The dissociation kinetics of the Al(NOTA) complex in both acidic and alkaline media were followed by ^{27}Al NMR spectroscopy. The kinetic behavior of Ga(III) complexes was investigated by metal ion exchange and ligand exchange reactions using UV-visible spectrophotometry.

New scientific results

1. The equilibrium constant of Al(NOTA) and the kinetic equation of its decomposition were determined.

Out of cell, pH-potentiometric, ^{1}H and ^{27}Al NMR methods were used to determine the equilibrium constant of the slowly formed Al(NOTA) complex, log*K*=17.9 (1). Dissociation kinetics of the complex were investigated in both acidic and alkaline conditions. The complex barely dissociates in 1 M HCl solution even after 16 days. In the alkaline pH range, the dissociation occurs at a measurable speed, the extrapolated half-life of the dissociation reaction at physiological conditions (pH of blood serum is 7.4), is $t_{½}$=94 hours. Our attempts to prepare $Al(NOTA)F^{-}$ mixed complex in a controlled equilibrium reaction were unsuccessful.

2. The stability constant of the $Al(CDTABBA)^{+}$ complex was measured, $\log K_{A1L}$=7.2 (1).

Based on pH-potentiometric titration, the stability constant of $Al(CDTABBA)^{+}$ is 9 to 10 orders lower than the stability constants of $Al(CDTA)^{-}$ and $Al(EDTA)^{-}$. Protonated and hydroxo complexes of $Al(CDTA)^{-}$ were also detected, while in the $Al(CDTABBA)^{+}$ system such complexes could not be identified.

Table 1 Stability constants of $Al(CDTA)^{-}$ and $Al(CDTABBA)^{+}$ complexes (25 °C, 0.15 M NaCl)

	H_4CDTA	**H_2CDTABBA**
$\log K_{AlL}$	16.66 (1)	7.2 (1)
$\log K_{AlL}^{H}$	1.99 (2)	-
$\log K_{AlL}^{OH}$	-7.34 (5)	-
$\log K_{AlL}^{OH2}$	-11.45 (5)	-

3. The formation of $Al(CDTA)F^{2-}$ and Al(CDTABBA)F mixed-ligand complexes in aqueous solutions was demonstrated.

The $Al(CDTA)F^{2-}$ and Al(CDTABBA)F complexes were detected by ^{19}F NMR at -49 and -55 ppm chemical shift values. In more concentrated solutions, 2 signals were found in the chemical shift region of each complex, which can be assigned to the two isomers of the complexes. Only one equivalent of fluoride is enough to partially displace the organic ligand from $Al(CDTABBA)^{+}$, forming AlF_x^{+3-x}, however only the $Al(CDTA)F^{2-}$ complex can be detected in the Al(CDTA)-F^{-} system.

4. Slow exchange reaction was detected in the $Al(CDTA)F^{2-}+OH^{-} \rightleftharpoons Al(CDTA)(OH)^{2-} + F^{-}$ equilibrium system.

The exchange reaction was followed by ^{19}F NMR. The reaction showed a decrease in $Al(CDTA)F^{2-}$ complex intensity and, at the same time increased $Al(CDTA)OH^{2-}$ complex signal intensity. The half-life of the exchange reaction was determined to be 133 minutes, slightly above the half-life of the ^{18}F isotope ($t_{½}$ = 109 minutes).

5. The Ga(III)-binding ability of four AAZTA derivative ligands (DATA^{m}, DATA^{5m} and two isomers of PIDAZTA) was determined by a detailed equilibrium analysis.

The complex Ga(PID(A)) showed the lowest stability constant (logK_{GaL}=18.84 (6)) of investigated Ga(L) complexes (by pH-metry and ^{71}Ga NMR), with the rest being similar in stability to Ga(AAZTA)$^{-}$ (logK_{GaL}=21.15), see Table 2. For each of the Ga(III) complexes investigated, Ga(L)OH is the prevalent particle at blood serum pH. The Ga(L)OH species appears in the widest pH range (pH=5.5-10) in the Ga (III)-PID(B) system.

Table 2 Stability and protonation constants of Ga(DATA^{m}), Ga(DATA^{5m})$^{-}$, Ga(PID(A))$^{-}$ and Ga(PID(B))$^{-}$ (0.15 M NaCl, 25 °C)

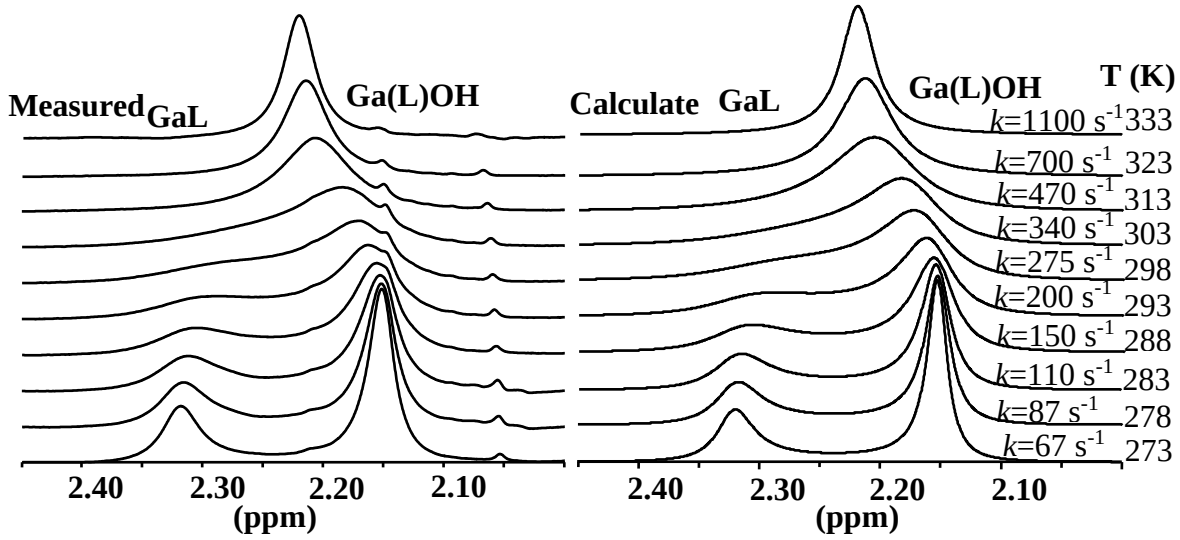
	Ga(DATA^{m})		**Ga(DATA^{5m})$^{-}$**		**Ga(PID(A))$^{-}$**		**Ga(PID(B))$^{-}$**	
I	0.15 M NaCl							
Method	**pH-pot.**	**^{1}H and ^{71}Ga NMR**	**pH-pot.**	**^{1}H and ^{71}Ga NMR**	**pH-pot.**	**^{1}H and ^{71}Ga NMR**	**pH-pot.**	**^{1}H and ^{71}Ga NMR**
pH range	12→1.7	12→1.7	12→1.7	12→1.7	1.7→12 12→1.7	0.0→2,0 12→1.7	1.7→12 12→1.7	0.0→2.0 12→1.7
logK_{GaL}	**21.78(2)**	**22.00 (4)**	**21.32(2)**	**21.45 (5)**	**18.88 (1)** **18.66 (4)**	**18.84 (6)**	**-** **21.70 (4)**	**21.56 (8)**
logK_{GaHL}	2.42 (2)	2.25 (9)	4.44 (3) -COOH	4.40 (4) -COOH	2.35 (1) 2.46 (5)	-	2.53 (5) 2.48 (1)	-
logK_{GaH2L}	–	–	2.05 (5)	–	-	-	-	-
log$K_{Ga(L)OH}$	**6.25 (2)**	**6.38 (4)**	**6.31 (4)**	**6.25 (4)**	**4.06 (2)** **4.02 (3)**	**3.88 (2)**	**3.74 (36)** **3.76 (2)**	**3.56 (9)**
log$\beta_{Ga(L)OH}$	15.52 (2)	15.62 (4)	15.02(4)	15.20(5)	14.83 (2) 14.64 (3)	14.90 (4)	- 17.94 (4)	17.84 (8)
p*Ga*$^{[a]}$	**19.58**		**19.65**		**19.23**		**22.03**	

$^{[a]}$$c_{(Ga(III))}$=1·10^{-4} M, $c_{(L)}$=1·10^{-3} M, 0.15 M NaCl, 25 °C)

6. For the Ga(DATA^{m}) and Ga(DATA^{5m})$^{-}$ complexes, a chemical exchange reaction between Ga(L) and Ga(L)OH particles were described using full ^{1}H NMR signal analyzis (Figure 2).

The activation parameters were calculated based on the temperature dependence of the rate constants using the Eyring equation. Identical reaction mechanisms are likely based on similar values. The formation of Ga(L)OH species in case of Ga(DATA^{m}) and Ga(DATA^{5m})$^{-}$ is accompanied by a (relatively slow) structural rearrangement with a relatively large $\Delta G^{\ddagger}_{298}$ (DATA^{m}: 59.0 (1), DATA^{5m}:59.3 (1)) value.

Figure 1 Band slope analysis of ^{1}H NMR signals of N-CH$_3$ Ga(DATA^{5m})$^{-}$ and Ga(DATA^{5m})OH^{2-} complexes



7. The rate equations of the decomposition of the Ga(L)OH complexes in the presence of Cu(II) and transferrin were measured, and the mechanism of the reactions was suggested: the complexes may dissociate by the disintegration of M(L)OH and assisted by hydroxide ions. Neither the concentration of the exchange metal ion nor the concentration of the ligand affects the rate of decomposition.

In the Ga(L)OH complex, the electrostatic repulsion between the donor atoms and the OH^- is stronger than in the GaL complex, so the „spontaneous" dissociation of the Ga(L)OH complex is more favorable.

Table 3 The rate, equilibrium constants and half-lives of the metal exchange reactions of Ga(DATAm), $Ga(DATA^{5m})^-$, Ga(PID(A))$^-$, és a Ga(PID(B))$^-$ complexes ($t_{½}$=ln2/k_d) (0.15M NaCl, 25 °C).

	Ga(DATA^m)	**Ga(DATA^{5m})$^-$**	**Ga(PID(A))$^-$**	**Ga(PID(B))$^-$**
k_0	$8.0\pm0.2\cdot10^{-6}$	$4.2\pm0.1\cdot10^{-6}$	$1.4\pm0.1\cdot10^{-4}$	$4.3\pm0.2\cdot10^{-7}$
$k_{OH}/M^{-1}s^{-1}$	31±1	1.2±0.1	–	0.6±0.1
k_d/s^{-1} (pH=7.4)	$1.7\cdot10^{-5}$	$4.3\cdot10^{-6}$	$7.2\cdot10^{-4}$	$6.5\cdot10^{-7}$
k_d/s^{-1} (sTf)[a]	$2.1\cdot10^{-5}$	$4.2\cdot10^{-6}$	$6.5\cdot10^{-4}$	$7.0\pm1\cdot10^{-7}$

[a]0.025 M $NaHCO_3$, 0.15 M NaCl, 25 °C, pH=7.4

8. The dissociation half-lives of Ga(DATA^m)OH$^-$, Ga(DATA^{5m})OH^{2-}, Ga(PID(A))OH^{2-}, Ga(PID(B))OH^{2-}, Ga(CyAAZTA)OH^{2-} and Ga(AAZTA)OH^{2-} complexes were calculated at blood serum pH. The half-lives were 11.0, 44.0, 0.3, 295.0, 8.5 and 21.0 hours, respectively.

To the best of our knowledge, Ga(PID(B))OH^{2-} is the most inert among the known non-macrocyclic Ga(III) complexes, so this complex is ideal for labeled radiopharmaceuticals.

9. Stability constants of Tl(EDTA)I^{2-}, a Tl(CDTA)I^{2-}, Tl(CDTABBA)I and Tl(cDO2A)I mixed-ligand complexes were determined by pH-potentiometry and ^{205}Tl NMR methods.

The logK_{mix} constants are respectively 5.69 (9), 5.02 (4), 6.9 (1) and 4.39 (7). The formation of halido complexes was investigated by a competitive reaction with the (Tl(L)OH) hydroxo complexes by direct pH-potentiometry. The acidic constants of the Tl(L)OH complexes (L= EDTA, CDTA, CDTABBA, cDO2A) were -6.34 (7), -6.44 (2), -5.39 (4) and -7.49 (7), respectively. The ^{205}Tl NMR chemical shift of the parent complexes ranges from 2300 to 2500 ppm, while the iodido complexes are in the 850-950 ppm range. Duplicate signals due to isomers were detected only in CDTABBA complexes. The TlL-Tl(L)I exchange system clearly falls into the "slow exchange" range on the ^{205}Tl NMR time scale, which refers to inert mixed complexes, but the inherently broad signals do not allow far-reaching conclusions. The most promising iodide carrier is the Tl(CDTABBA)$^{+}$ complex.

Table 4 Stability constants of Tl(L)I mixed complexes determined by pH potentiometry and ^{205}Tl NMR (1 M $NaClO_4$, 25 °C).

	pH-pot.	**^{205}Tl NMR**
log$K_{Tl(EDTA)-}^{I}$	5.69 (9)	5.2 (4)
log$K_{Tl(CDTA)-}^{I}$	5.02 (4)	5.1 (2)
log$K_{Tl(CDTABBA)+}^{I}$	6.9 (1)	-
log$K_{Tl(cDO2A)+}^{I}$	4.39 (7)	4.0 (3)

Possible utilization of the results

Equilibrium and kinetic studies of Al(III), Ga(III) and Tl(III) aminopolycarboxylate of hydroxy and halogeno mixed complexes have been performed. The results may be useful in medical diagnosies, especially in the development of PET contrast agents.

Based on the results of the Al(NOTA)-F^- system, our group is planning to synthesize new NO2A derivatives, replacing one acetate group with a non-coordinating group to allow the F^- ion to enter the Al(III) ion coordination sphere.

Examination of the $Al(CDTA)^-$ and $Al(CDTABBA)^+$-F^- systems has shown that open chain ligands have a much faster complexation than macrocyclic ligands, and the stability and inertness are maintained to an extent that is promising for further investigations.

Examination of Ga($DATA^m$)-, Ga($DATA^{5m}$)$^-$-, Ga(PID(A))$^-$ and Ga(PID(B))$^-$ complexes showed that although the denticity of ligands was reduced compared to the AAZTA "parent ligand", tailoring the ligands can increase the equilibrium constants of the complexes and their inertness. Among the non-macrocyclic Ga(III) complexes known to date, the Ga(PID(B))$^-$ complex is the most inert and thus can be an ideal candidate for a PET pharmacon.

According to the $Tl(EDTA)^-$-, $Tl(CDTA)^-$-, $Tl(CDTABBA)^+$- and $Tl(DO2A)^+$- I^- systems, the Tl(CDTABBA)I mixed-ligand complex appears to be the most inert. Further modifications of the CDTABBA ligand can be converted to more stable and inert carrier, which can be a good teragnostic agent.

Publications

Publications related to the dissertation

1. Farkas, E ; Vágner, A ; Negri ,R ; Lattuada, L ; Tóth, I ;Colombo. V ; Esteban-Gómez D ; Platas-Iglesias, C ; Notni, J ; Baranyai, Zs ; Battista Giovenzana, G; *PIDAZTA: Structurally Constrained Chelators for Efficient Formation of Stable Gallium-68 Complexes at Physiological pH*
CHEMISTRY-A EUROPEAN JOURNAL
https://doi.org/10.1002/chem.201901512 (**2019**)

2. Farkas, E ; Nagel, J ; Waldron, B ; Parker, D ; Toth, I ; Brücher, E ; Rösch, F, Baranyai, Zs*; Equilibrium, kinetic and structural properties of gallium(III)- and some divalent metal complexes formed with the new DATA^{m} and DATA^{5m} ligands.*
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3. Farkas, E ; Fodor, T ; Kálmán, F K ; Tircsó, G ; Tóth, I *Equilibrium and dissociation kinetics of the [Al(NOTA)] complex (NOTA = 1,4,7-triazacyclononane-1,4,7-triacetate)*
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Other publication:

4. Ayass, W. W ; Fodor, T ; **Farkas, E** ; Lin, Z ; Qasim, H M ; Bhattacharya, S ; Mougharbel, A S ; Abdallah, K ; Ullrich, M S ; Zaib, S et al.
Dithallium(III)-Containing 30-Tungsto-4-phosphate, $[Tl_2Na_2(H_2O)_2(P_2W_{15}O_{56})_2]^{16-}$: Synthesis, Structural Characterization, and Biological Studies
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List of publications related to the dissertation

Foreign language scientific articles in international journals (3)

1. **Farkas, E.**, Vágner, A., Negri, R., Lattuada, L., Tóth, I., Colombo, V., Esteban-Gómez, D., Platas-Iglesias, C., Notni, J., Baranyai, Z., Giovenzana, G. B.: PIDAZTA: Structurally Constrained Chelators for the Efficient Formation of Stable Gallium-68 Complexes at Physiological pH. *Chem.-Eur. J. 25*, 1-13, 2019. ISSN: 0947-6539.
   DOI: http://dx.doi.org/10.1002/chem.201901512
   IF: 5.16 (2018)
2. **Farkas, E.**, Nagel, J., Waldron, B. P., Parker, D., Tóth, I., Brücher, E., Rösch, F., Baranyai, Z.: Equilibrium, Kinetic and Structural Properties of Gallium(III) and Some Divalent Metal Complexes Formed with the New DATAm and DATA5m Ligands. *Chem.-Eur. J. 23* (43), 10358-10371, 2017. ISSN: 0947-6539.
   DOI: http://dx.doi.org/10.1002/chem.201701508
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   DOI: http://dx.doi.org/10.1007/s11144-015-0892-6
   IF: 1.265

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List of other publications

Foreign language scientific articles in international journals (1)

4. Ayass, W. W., Fodor, T., **Farkas, E.**, Lin, Z., Qasim, H. M., Bhattacharya, S., Mougharbel, A. S., Abdallah, K., Ullrich, M. S., Zaib, S., Iqbal, J., Harangi, S., Szalontai, G., Bányai, I., Zékány, L., Tóth, I., Kortz, U.: Dithallium(III)-Containing 30-Tungsto-4-phosphate, [Tl2Na2(H2O)2(P2W15O56)2]16-: Synthesis, Structural Characterization, and Biological Studies.
Inorg. Chem. 57 (12), 7168-7179, 2018. ISSN: 0020-1669.
DOI: http://dx.doi.org/10.1021/acs.inorgchem.8b00878
IF: 4.85

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