Proposition of Ph.D. thesis

Investigation of physico-chemical properties of metal complexes used in medical diagnosis and therapy

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I. INTRODUCTION AND THE AIM OF THE WORK

The polyaminopolycarboxilate complexes of lanthanides(III) have been used in different area of the medicinal diagnosis and teraphy from the 1980's. For the effective applications it is nessesary to know their phisico-chemical properties. The biological and clinical applications are based on the special magnetic and optical properties of the lanthanide ions (Ln^{3+}). The Gd^{3+}-ion with its paramagnetical portperties is used in the Magnetic Resonance Imaging to increase the sharpness of the image. Some lanthanide(III) ions (eg. Eu^{3+}, Sm^{3+}, Tb^{3+}, Nd^{3+}, Er^{3+} és Yb^{3+}) are used in optical imaging due to their luminescence properties. The ^{90}Y ^{177}Lu, ^{153}Sm and ^{166}Ho isotopes are used in the treatment of cancerous diseases and in the case of bone metastases for pain relief.

Ln^{3+} ions are toxic and hydrolyse at physiological pH, therefore their *in vivo* application is only possible in front of stable complexes. Ln^{3+} ions form complexes of high stability with aminopolycarboxylate ligands, among which the parent compounds are the open-chain DTPA and the macrocyclic DOTA, containing 8 donor atoms. From the 1990s, several derivatives of DTPA and DOTA were also synthetized and their the Ln(III) complexes are commonly used in clinical practice (Figure 1).

Nowadays, in addition to the lanthanides, many other 3+ charged metal ions have started to be used in Nuclear Medicine (eg. Sc^{3+}, Y^{3+}, which are also rare earth elements, furthermore Ga^{3+} and In^{3+}). These metal ions are generally also used in the form of aminopolycarboxylate complexes, but the development of optimal ligands for the complexation of a given metal ion are still intensively investigated.

Over the past few years the study of the equilibrium and kinetic properties of different metal complexes have become particularly important by recognizing the *in vivo* dissociation of the Gd(III) complexes and the discovery of a new disease, called Nefrogenic Systemic Fibrosis (NSF). The exact mechanism of NSF has not known yet, but it was assumed to be associated with the in vivo dissociation of Gd^{III} complexes and the toxic effect of the released Gd^{3+} ions. Therefore, nowadays there are intensive research as in progress to determine the quantity and speciation of Gd^{3+} ions released and to explore the equilibrium and kinetic behavior of various Gd^{3+} based MRI contrast agents *in vitro* but close to physiological conditions.

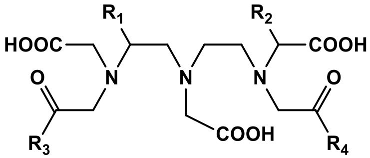
My work is related to these areas, for which we have the following generally defined aims:

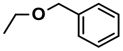
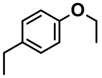
- Investigation of the equlibrium properties of CyAAZTA ligand and kinetic, relaxation, and structural characterization of its Gd(CyAAZTA) complex as a potential MRI contrast agent formed with a ligan possessing seven functional groups.

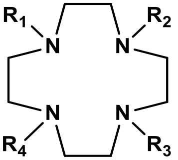
- Study of the equilibrium, kinetic and strucutal properties of the Ga(CyAAZTA) complex as a potential PET contrast agent candidate

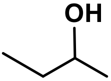
- Study of the effect of free Ca^{2+} and Mg^{2+} ions on the dissociation rates of Gd^{3+} based open-chain MRI contrast agents used in clinical practice.

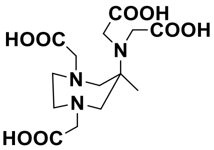
- Investigation of the interactions between the open-chain Gd(DTPA-BMA) (Omniscan), the macrocyclic Gd(HP-DO3A) (ProHance) contrast agents and bone tissues.



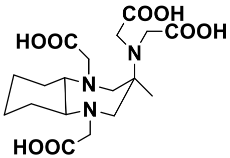
R_1	R_2	R_3 és R_4	Ligandum
-H	-H	-OH	**H$_5$DTPA**
-H	-H	-NH-Me	**H$_3$DTPA-BMA**
-H		-OH	**H$_5$BOPTA**
	-H	-OH	**H$_5$EOB-DTPA**



R_1	R_2, R_3 ésR_4	Ligandum
-CH$_2$-COOH	-CH$_2$-COOH	**H$_4$DOTA**
	-CH$_2$-COOH	**H$_3$HP-DO3A**



AAZTA



CyAAZTA

Figure 1. Structure of the studied ligands

II. EXPERIMENTAL METHODS

In this work we have studied the equilibrium behaviours of the rigid CyAAZTA ligand, the kinetic and structural properties of the Gd (CyAAZTA) and Ga(CyAAZTA) complexes, as well as the relaxation properties of Gd(CyAAZTA). Our work included examining of the effects of the free Ca^{2+} and Mg^{2+} ions on the rates of metal exchange reaction some clinically used MRI Gd^{3+}-based contrast agents was also investigated. In addition, we explored the nature of interaction between the open chain Gd(DTPA-BMA) (Omniscan), the macrocyclic Gd(HP-DO3A) (ProHance) complexes and bone tissues.

The investigated new CyAAZTA ligand was synthetised by our cooperating partners in Italy. The equilibrium studies were performed by pH-potentiometry, UV-visible spectrophotometry and multinuclear NMR spectroscopy. The protonation constants of the ligands and the stability and protonation constants of the complexes formed with metal ions (Mg^{2+}, Ca^{2+}, Sr^{3+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Ga^{3+} and Ln^{3+}) were calculated from the results of the direct pH-potentiometric titrations. In some cases, equilibrium data were obtained by UV-visible (Cu^{2+}), ^{1}H- and ^{71}Ga-NMR spectroscopic (Ga^{3+}) and ^{1}H-NMR relaxometric (Gd^{3+}) studies. The kinetic inertness of the Gd(CyAAZTA) and Ga(CyAAZTA) complexes was characterized by the rate of the exchange reactions occuring with Cu^{2+} ion or human transferrin (sTf) studied by UV-visible spectrophotometry. Those physico-chemical parameters characterizing the Gd(CyAAZTA) complex, which determine the effect on the relaxation rate of the solvent protons, were calculated from the results of ^{1}H-NMR and ^{17}O-NMR spectroscopy studies. The interaction between the $Gd(CyAAZTA)(H_2O)_2]^-$ complex containing two water molecules in the inner coordination sphere and small endogenous ligands (eg. citrate, phosphate, carbonate, lactate) as well as human serum albumin was studied by ^{1}H NMR relaxometric technique. The structure of Cu(CyAAZTA) and Ga(CyAAZTA) complexes in solution was derived from the results of UV-visible spectrophotometry and multinuclear NMR spectroscopy. The effect of the Ca^{2+} and Mg^{2+} ions on the rate of exchange reactions of Gd^{3+} -based contrast agents with Cu^{2+} ion have been studied by UV-visible spectrophotometry, ^{1}H- and ^{13}C-NMR spectroscopy and ^{1}H NMR relaxometry. The interactions between the Gd(DTPA-BMA) and Gd(HP-DO3A) complexes and the bone surface were followed by FT-IR spectroscopy by studying the changes in the vibration band of the fingerprint range.

For the **pH-potentiometric titrations** a *Metrohm 785 DMP Titrino* titration workstation and a *Metrohm-6.0233.100* combined glass electrode were used. Titrations were carried out at 0.1 or 1.0 M ionic strength (KCl, KNO_3), in 6 cm^3 stirred and thermostated (25°C) samples with 0.2 M KOH. The concentration was determined by titration of a KH-phthalate buffer solution of known concentration. To avoid the effect of CO_2 during the titrations, N_2 or Ar gas was bubbled through the samples. Two-point calibration of the pH meter was performed using 0.05 M KH-phthalate buffer (pH 4.005) and 0.01 M carbon-dioxide free borax buffer (N_2 atmosphere, pH = 9.180). The concentration of H^+ ions from the measured pH values was calculated by the method proposed by *Irving et al*. From the titration data (pH-ml base) the stability and protonation constants have been calculated by the PSEQUAD program

UV-visible spectrophotometric studies were performed with a *Cary 1E* spectrophotometer in a cuvette of 1 or 0.874 cm at 25 or 37 ° C using thermostated cuvette holder in the wavelenght ranges of 400-800 and 220-330 nm.

The ^{1}H, ^{13}C and ^{71}Ga NMR spectroscopy studies were performed with a *Bruker DRX 400* spectrometer (9.4 T) at 400, 100 and 122 MHz using a 5 mm BB inverse z gradient head. The temperature was kept constant with Bruker VT-1000 temperature control unit. The **^{17}O NMR** spectra were recorded by *Bruker Avance III* spectrometer with a 5 mm head and a standard temperature control unit (11.74 T) at 67.8 MHz.

Longitudinal relaxation times (T_1) were determined by *Bruker MQ-20 NMR* spectrometer at 20 MHz proton resonance frequency in 0.4 cm^3 sample volume using the magnetization inversion technique (inversion recovery pulse sequence from 180° to 90°). The signal strength of T_1 values was determined with a Stelar SmarTracer relaxometer (Proton Larmor Frequency = 0.01-10 MHz) and Stelar Relaxometer combined with *Bruker WP80 NMR* electromagnet (Proton Larmor Frequency = 15-80 MHz). The temperature was kept constant with Stelar VTC-91 thermostat and measured with a calibrated copper thermocouple (± 0.1°C).

FT-IR microspectroscopy studies were performed by Tensor 27 FT-IR spectrometer equipped with Hyperion 3000 FPA (focal plane array) detector. The spectrum of solids triturated with KBr were investigated by diffuse reflection infrared spectroscopy using an IFS 66v/S FT-IR spectrometer. After drying the liquid samples were tested with a VERTEX 80 type FT-IR spectrometer with an attenuated total reflection.

III. NEW SCIENTIFIC ACHIEVEMENTS

III.1. Compared to the analogue Ln(AAZTA) complexes the stability of Ln(CyAAZTA) complexes are lower due to the presence of the cyclohexyl group. However, the structural rigidity of complexes and, therefore the kinetic inertness of complexes are significantly higher, but the favorable relaxation properties of Gd(CyAAZTA) is unchanged.

In order to the increase in the thermodynamic stability and kinetic inertness of the previously studied $[Gd(AAZTA)(H_2O)_2]^-$ which also has good relaxation properties, the cyclohexyl-AAZTA (CyAAZTA) ligand was synthetized and the equilibrium, kinetic, relaxation and structural properties of its complex formed with the Gd^{3+} were studied. The equilibrium studies have shown that the presence of cyclohexyl ring significantly reduces the flexibility of the diazepine ring, limiting the spatial location of the 3 amino N and 4 carboxylate-O donor atoms. The size of the formed rigid coordination cavity is favorable for the metal ions in the middle of the lanthanide series (Eu^{3+} and Gd^{3+}). The structural rigidity of $Ln(CyAAZTA)^-$ complexes is confirmed by the ^1H NMR spectra of paramagnetic Eu^{3+}- and $Yb(CyAAZTA)^-$ complexes.

The rate-determining step of the metal exchange reaction of $Gd(CyAAZTA)^-$ complex is the acid catalyzed dissociation of the Gd(III) complex, surprisingly four times slower than that of the macrocyclic Gd(DO3A). The $Gd(CyAAZTA)^-$ is extremely inert complex based on its dissociation half-life ($t_{1/2}$ = 91.3 years) at physiological pH and 25°C. According to our knowledge the kinetic inertness of $Gd(CyAAZTA)^-$ is the largest among the known Gd(III) complexes, formed with open-chain ligands, containing two inner sphere water molecules.

In the study of relaxation properties, we have demonstrated that two inner sphere water molecules in the $[Gd(CyAAZTA)(H_2O)_2]^-$ complex take part in rapid exchange processes with solvent water molecules and are not substitutable with endogenous ligands (lactate, citrate and phosphate) since do not occupy neighboring positions. The proton relaxation rate of the $[Gd(CyAAZTA)(H_2O)_2]^-$ complex in Seronorm ™ does not change in time, which clearly demonstrates the high stability of the Gd(III) complex under the physiological conditions.

Due to the listed advantages, the Gd(CyAAZTA) complex is suitable for applying as an MRI contrast agent.

III.2. We have found that although $Ga(CyAAZTA)^-$ is formed much more rapidly than the macrocyclic Ga(NOTA) and $Ga(DOTA)^-$ complexes used in PET, but the stability and kinetic inertness of $Ga(CyAAZTA)^-$ is significantly lower than those of the macrocyclic complexes.

By studying the equilibrium and structural properties of the Ga(CyAAZTA)$^-$ complex, we demonstrated the formation of a stable mixed hydroxo [Ga(CyAAZTA)OH]$^{2-}$ complex that appears at pH>6.0. The hydroxide ion is directly cooerdinated to the metal ion replacing a carboxylate-O donor atom in the [Ga(CyAAZTA)OH]$^{2-}$ species. The ^{71}Ga NMR signal of Ga(CyAAZTA)$^-$ is very broad at room temperature because of the the asymmetric environment of the Ga^{3+} ion which refers to the rigidity of the CyAAZTA ligand and to the distorted geometry of the complex.

The k_d rate constant characterizing the transmetallation reaction of Ga(CyAAZTA)$^-$ complex with Cu^{2+} ion in the presence of citrate and the kd values of the transchelation reactions occuring with sTf were found to be very similar, and we concluded that neither Cu^{2+} ions nor sTf are involved in the rate determining step of the dissociation of Ga(CyAAZTA)$^-$. The rate-determining step of these exchange reactions is the spontaneous and OH-catalyzed dissociation of [Ga(CyAAZTA)OH]$^{2-}$ complex, following by the rapid reaction between the released Ga^{3+} ion and sTf or the CyAAZTA ligand with Cu^{2+}.

Based on the physico-chemical properties of Ga(CyAAZTA)$^-$, the Ga^{III} complex is formed more quickly, but its stability and kinetic inertness is much lower than those of the Ga(NOTA) and Gd(DOTA)$^-$ complexes. However, the rate of dissociation of Ga(CyAAZTA)$^-$ complex under physiological conditions ($t_{1/2}$ = 8.5 hours) is still about 7 times lower than the decay rate of ^{68}Ga isotope (^{68}Ga, $t_{1/2}$ = 67.71 min), thus ^{68}Ga(CyAAZTA)$^-$ is a good candidate for using *in vivo* PET examinations and for the development of further ^{68}Ga^{3+} based radiodiagnostics.

III.3 Free Ca^{2+} and Mg^{2+} ions significantly increase the rate of dissociation of Gd(DTPA)$^{2-}$, Gd(BOPTA)$^{2-}$ and Gd(EOB-DTPA)$^{2-}$ complexes, while they have no influence on the rate of dissociation of the Gd(DTPA-BMA) complex.

In the past years, the identification of NSF disease and the accumulation of the gadolinium in living organisms require the detailed study of the *in vivo* equilibrium and kinetic properties of Gd^{3+} based MRI contrast agents. Based on previous studies, the Cu^{2+} and Zn^{2+} ions have no effect on the rate of dissociation of the Gd(III) complexes, as these endogenous metal ions do not occur in free form under physiological conditions. The *in vivo* concentration of free Ca^{2+} and Mg^{2+} ions are significant ([Ca^{2+}] = 1.25 mM, [Mg^{2+}] = 0.5 mM), but their effect of which on the kinetic inertness of Gd(III)-based MRI contrast agent has not been studied. Therefore I have studied the transmetallation reactions of the four open-chain Gd(III) complexes with Cu^{2+} ions in the presence of citrate, Ca^{2+} and Mg^{2+} ions (0.15 M NaCl, 25 and 37°C).

Based on our kinetic studies we can say that the rate of exchange reactions between the charged $GD(DTPA)^{2-}$, $Gd(BOPTA)^{2-}$ and $Gd(EOB\text{-}DTPA)^{2-}$ complexes and Cu^{2+} in the presence of citrate increase with growing concentration of Mg^{2+} and Ca^{2+} ions, while the rates of transmetallation ractions of the uncharged Gd(DTPA-BMA) are not affected. Since the rate determination step of metal ion exchange reactions is the dissociation of Gd(III) complexes under physiological conditions, presumably the dissociation of the charged $Gd(DTPA)^{2-}$ derivatives take place through the formation and dissociation of a mixed binuclear [Gd(L)M] complex (M=Ca, Mg) in the presence of Ca^{2+} and Mg^{2+} ions . The binuclear Gd(L)M complexes are presumably formed by the interaction between a carboxylate group of the DTPA derivatives (coordinated to the Gd^{3+} ion) and the Ca^{2+} or Mg^{2+} ions, which has an effect on the interaction between the DTPA derivatives and the Gd^{3+} ion. The interaction of $Gd(DTPA)^{2-}$ complex with Ca^{2+} and Mg^{2+} ions has been proved by ^{1}H- and ^{13}C-NMR spectroscopy. The proton relaxation rates of the Gd(DTPA) derivatives measured in the presence of Ca^{2+} ion confirmed the formation of binuclear Gd(L)M complexes with $Gd(DTPA)^{2-}$ and $Gd(BOPTA)^{2}$. In the binuclear Gd(L)M complex, the interaction between the ligand and the Gd^{3+} ion is weaker than in the GdL complex, which makes the intramolecular rearrangements in Gd(L)M complex much faster and dissociation more probable. Connected to our kinetic resuts it is important to mention that the dissociation of $Gd(DTPA)^{2-}$ and $Gd(BOPTA)^{2-}$ complexes catalysed by Ca^{2+} and Mg^{2+} ions is significant and can exceed the contribution of citrate and phosphate ions to the dissociation rates of open-chain Gd(III) complexes under physiological conditions.

III.4. Based on the FT-IR studies of the interactions between the open-chain Gd(DTPA-BMA) and the macrocyclic Gd(HP-DO3A) complexes and bone surface, it can be concluded that the presence of Gd(DTPA-BMA) causes irreversible changes in the bone structure, while the macrocyclic Gd(HP-DO3A) has a weak interaction with the bones surface.

Previous studies have shown that the *in vivo* dissociation of open-chain Gd(III) complexes (mainly Gd (DTPA-BMA)) may take place and the free Gd^{3+} ion may contribute to the emergence of NSF. Equilibrium calculations under physiological conditions have confirmed that the released Gd^{3+} ion can form insoluble $GdPO_4$ precipitate with PO_4^{3-} ions which can accumulate in the bones due to the high similarity to $Ca_5(PO_4)_3OH$. During the infrared microscopy measurements, mouse bones were studied in the presence of open-chain Gd(DTPA-BMA) and macrocyclic Gd(HP-DO3A) complexes, which showed different behavior in the interactions with bones. In the presence of Gd(DTPA-BMA) we found radical, irreversible changes in the structure of the mineral rich portion of the bone, which may be interpreted by the integration of $GdPO_4$, formed by the released Gd^{3+} during the dissociation of the complex, into the bone surface. In the case of Gd (HP-DO3A), the accumulation of the Gd(III) complex in the organically rich portion of the bones is reversible, indicating that free Gd3+ ions are not formed, that is the macrocyclic complex does not dissociate.

The different behavior of Gd(DTPA-BMA) and Gd(HP-DO3A) complexes can be interpreted their different kinetic inertness. The significantly faster dissociation processes of Gd(DTPA-BMA) ($t_{1/2}$ = 9.3 hours) cause the release of substantially larger amount of Gd^{3+} ions, thus the $GdPO_4$ formed can bind to the bone surface. In contrast to this the significantly higher kinetic inertness of Gd(HP-DO3A) does not allow the dissociation of the Gd^{3+} ions, so that, the interactions with bones can be formed only with intact complexes, probably through the hydroxypropyl side chain.

IV. POSSIBLE APPLICATIONS OF RESULTS

Our studies are mainly aimed to study the coordination chemistry behavior of the ligands and their metal complexes for basic research, but the results can be important in the case of their practical relevance and possible medical or biological applications mainly for the development of MRI and PET contrast agents.

Based on the equilibrium, kinetic, relaxation and structural studies of $Gd(CyAAZTA)^-$, it can be concluded that the thermodynamic stability and especially kinetic inertness of the complex are sufficiently high for biological and *in vivo* medical application as a safe and effective MRI contrast agents. The equilibrium and kinetic investigation of $Ga(CyAAZTA)^-$ complex shows that the presence of the cyclohexyl group reduces the stability and kinetic inertness of the mixed-hydroxid Ga(L)OH complex. The kinetic inertness of the $Ga(CyAAZTA)^-$ complex significantly increases in comparison to $Ga(AAZTA)^-$ because of the rigidity of the strucure of seven-membered ring, which is promising to the develope a $^{68}Ga^{3+}$ based radiopharmacon for *in vivo* PET studies.

The exploration of the role of Ca^{2+} and Mg^{2+} ions in the dissociation process of open-chain Gd(III) complexes is very remarkable, since earlier the kinetic effects of the Ca^{2+} and Mg^{2+} ions were neglected. Based on our results, the extent of dissociation of $Gd(DTPA)^{2-}$ derivatives catalyzed by the free Ca^{2+} and Mg^{2+}

ions in the in vivo release of Gd^{3+} ions is more than the contribution of the endogenous citrate and phosphate assisted dissociation. Our knowledge about the impact of Ca^{2+} and Mg^{2+} ions on the kinetic behavior of MRI contrast agents, and the interaction between the contrast agents and bone tissues can be a significant step toward the understanding of the *in vivo* behavior of Gd(III) complexes, including the exploration of the biospecification and the accumulation of the potentially released Gd^{3+} ion.

TUDOMÁNYOS PUBLIKÁCIÓK (PUBLICATIONS)

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Candidate: Adrienn Vágner
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List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. **Vágner, A.**, D'Alessandria,, C., Gambino, G., Schwaiger, M., Aime, S., Maiocchi, A., Tóth, I., Baranyai, Z., Tei, L.: A rigidified AAZTA-like ligand as efficient chelator for 68Ga radiopharmaceuticals.
   ChemistrySelect. 1 (2), 163-171, 2016. ISSN: 2365-6549.
   DOI: http://dx.doi.org/10.1002/slct.201500051
2. **Vágner, A.**, Gianolio, E., Aime, S., Maiocchi, A., Tóth, I., Baranyai, Z., Tei, L.: High kinetic inertness of a bis-hydrated Gd-complex with a constrained AAZTA-like ligand.
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List of other publications

Foreign language scientific articles in international journals (4)

3. Giani, A. M., **Vágner, A.**, Negri, R., Baranyai, Z., Giovenzana, G. B.: cis-IPDTA: an original polyaminopolycarboxylic chelating agent from isophoronediamine: Synthesis and thermodynamic characterization of metal complexes.
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Inorg. Chem. 53 (23), 12499-12511, 2014. ISSN: 0020-1669.
DOI: http://dx.doi.org/10.1021/ic5020225
IF: 4.762

Total IF of journals (all publications): 21,791
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The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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