Theses of doctoral (PhD) dissertation

Gd^{3+} and Mn^{2+} complexes as potential MRI contrast agents: synthesis and coordination chemical properties of some rigidified aminopolicarboxylate ligands

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Introduction and the aim of the work

In recent years many problems have been described (positive Gd^{3+} anomaly, Nephrogenic Systemic Fibrosis (NSF) disease, Gd^{3+}-retention in different tissues) concerning contrast agents (CAs) used in Magnetic Resonance Imaging (MRI). In 2017 the European Medicine Agency recommended the suspension of three commercialized products based on open-chain ligand platforms (Magnevist, Optimark and Omniscan) and restricted the use of the Multihance agent.

These problems have spurred new research aiming to design and characterize safer CA candidates. One solution can be to use an essential paramagnetic metal ion instead of the toxic Gd^{3+}. Mn^{2+}, high-spin Fe^{2+} and Fe^{3+} ions and their compounds are among the first mentioned in this respect yet these metal ions also possess potential toxicity, thus they can be used as stable and inert complexes. According to literature data, the *trans*-CDTA ligand provides a suitable platform for the complexation of the Mn^{2+}, however the *cis* isomer has not been examined in detail. Therefore, one of my aims was to synthesize and study the coordination chemical properties of the *cis*-CDTA ligand and its complexes, particularly the Mn^{2+} complex.

Bifunctional ligands can be synthesized by modifying the *trans*-CDTA ligand skeleton, thus bifunctional CDTA-derivatives having reactive groups (alkyl-azide or alkyne) in their core were prepared. To model these ligands 4HET-CDTA which contains the triazole ring expected to form in the click reaction upon bioconjugation of the chelator was also investigated.

Another possible route to develop safer contrast agents is to design and prepare ligands forming Gd^{3+} complexes with exceptionally high kinetic inertness. The inertness increases with the ligand rigidity, which can be achieved by the replacement of the flexible ethylene bridging unit in the ligand backbone with a cyclohexyl (CHXDTPA) or phenylene (PhDTPA) “building” unit. The preparation of these ligands is described in the literature yet their complexation

properties have not been investigated in detail. Thus we decided to synthesize the chelators again and study the thermodynamic stability, kinetics (dissociation and water exchange) and structures of the complexes formed with some essential metal ions (Mg^{2+}, Ca^{2+}, Cu^{2+} and Zn^{2+}) and Ln^{3+} ions of large (La^{3+}), medium (Gd^{3+}) and small (Lu^{3+}) size.

Similarly to the open-chain ligands, the inertness of the complexes formed with macrocyclic ligands is expected to increase when rigidifying the backbone (cyclic entity) of the ligands, therefore our attention was devoted to the pyridine containing macrocyclic chelators (pyclen derivatives, e.g. PCTA). Literature data showed that the inertness of Ln(PCTA) complexes were higher than those of the corresponding Ln(DO3A) chelates, thus the pyclen platform could be regarded as a promising platform in design of inert (i.e. safe) Ln^{3+} complexes. The carboxylic groups of the PCTA ligand were gradually replaced by picolinate groups resulting in PC2A1PA (containing two acetates and one picolinate pendants) and the PC1A2PA (containing one acetate and two picolinate moieties) chelators. In both ligands the pendant arms could be attached to the macrocycle in symmetric and asymmetric arrangements, returning altogether four ligands. The physico-chemical parameters of the Gd^{3+} complexes formed with these four complexons, $PC2A1PA^{sym}$, $PC2A1PA^{asym}$, $PC1A2PA^{sym}$ and $PC1A2PA^{asym}$ were also investigated within the frame of my PhD research.

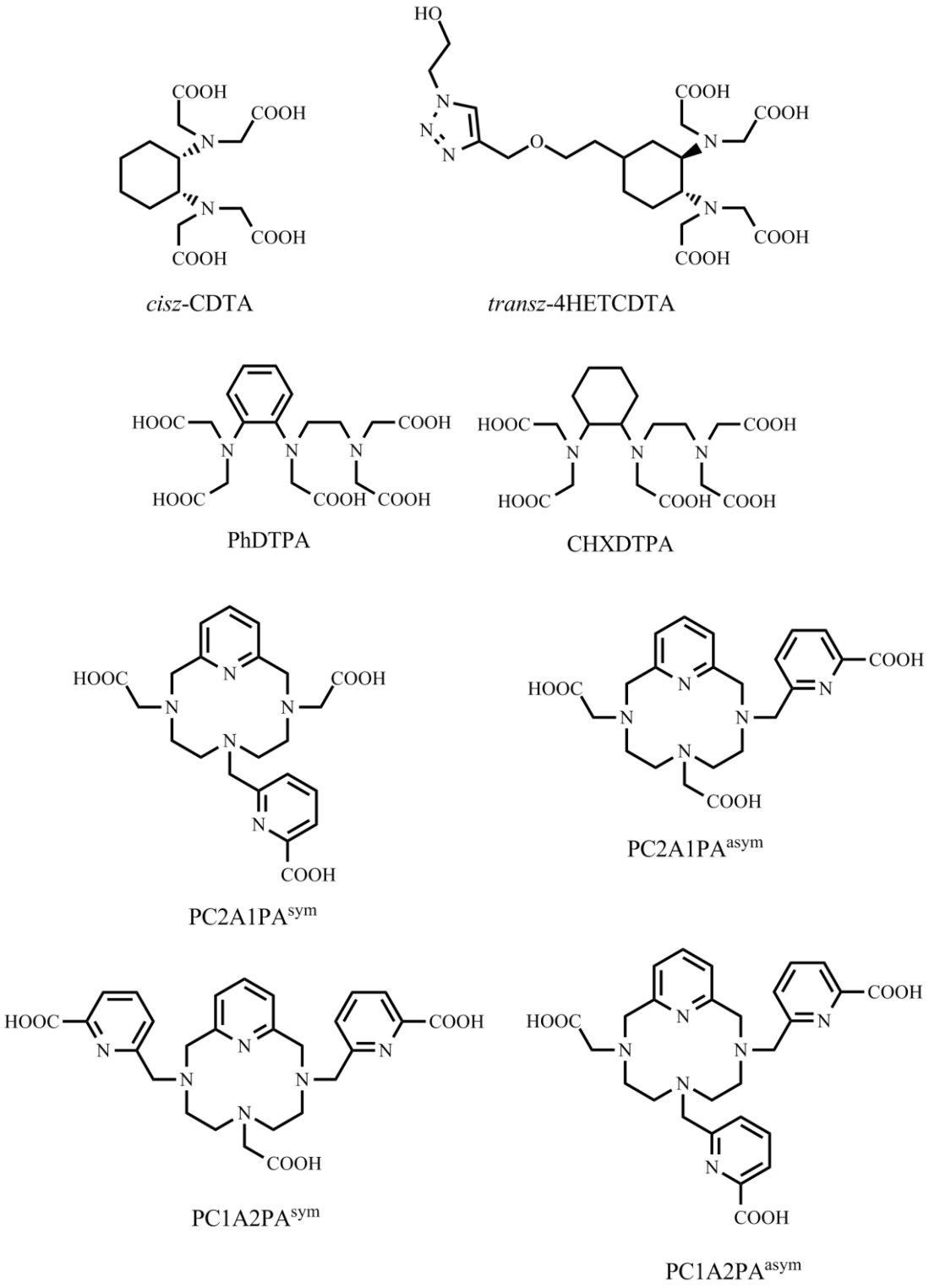

Figure 1. The formulae of the investigated ligands.

Methods

The synthesis of *cis*-CDTA, PhDTPA and CHXDTPA ligands were carried out by following published procedures and the final products applied in the analytical work were purified by preparative HPLC chromatography. During the preparative work ^{1}H, ^{13}C NMR and ESI-MS spectroscopic methods were used to determine/prove the identity/structure and purity of the products. All other ligands investigated provided by the foreign partner laboratories were of analytical purity.

The protonation constants of the ligands and the stability and protonation constants of the complexes were determined by pH-potentiometric techniques using 0.15 M NaCl as ionic strength at 25 °C. Because of the high stability of the Cu^{2+} complexes, the pH-potentiometric data were complemented with UV-VIS spectrophotometric measurements. The stability constants of the Mn^{2+} and Gd^{3+} complexes were determined by ^{1}H relaxometry (20 MHz proton Larmor frequency) and the same technique was used to confirm the equilibrium model used for the fitting of pH-potentiometric data.

The inertness of the complexes was investigated by studying metal exchange reactions occurring between the complexes and a suitable metal ion using either UV-VIS spectrophotometric (Cu^{2+}) or ^{1}H relaxometric (Zn^{2+}) technique. The dissociation kinetics of the macrocyclic complexes were also examined by spectrophotometry or ^{1}H relaxivity by following the dissociation of the complexes in acidic media.

Relaxivity, water exchange rate and other relaxation parameters were obtained by ^{1}H relaxometry and ^{17}O NMR spectroscopic methods. The structures of the complexes /existence of isomers present in solution were also studied by ^{1}H NMR spectroscopy.

New scientific results

1. The stability and inertness are smaller while the water exchange rate is higher of the Mn(*cis*-CDTA) complex compared to those of the *trans* derivative. The stability of the Mn^{2+} complex of *trans*-4HETCDTA is similar to that of the parent Mn(*trans*-CDTA), while the inertness, relaxivity and water exchange rate is slightly higher owing to the presence of the triazole ring present in the backbone of the ligand.

The protonation constants of the ligands were determined along with the stability and protonation constants of the complexes formed with some essential metal ions (Mg^{2+}, Ca^{2+}, Cu^{2+} and Zn^{2+}) and Mn^{2+}. The stability constants of the complexes of *cis*-CDTA ligand and the pMn value are lower than that of the chelate formed with the *trans*-CDTA despite the higher total basicity of the *cis*-CDTA ligand. The overall basicity and as a consequence, the stability constants of the complexes of the *trans*-4HETCDTA ligand are lower than that of the *trans*-CDTA which can be assigned to the electron withdrawing nature of the triazole ring attached to the *trans*-cyclohexane bridging unit. However, the pMn values of the Mn^{2+} complexes formed with *trans*-CDTA and *trans*-4HETCDTA ligands are very similar.

The dissociation kinetic studies showed that the inertness of the Mn(*cis*-CDTA) complex is significantly lower (comparable to that of Mn(EDTA) while it is slightly increased in the case of the Mn(*trans*-4HETCDTA) in comparison to the Mn(*trans*-CDTA).

The relaxivity of the Mn(*cis*-CDTA) and Mn(*trans*-CDTA) are very similar, while it is higher for the Mn(*trans*-4HETCDTA) which can be explained in terms of its higher rotational correlation time. The water exchange rate is the highest for the Mn(*cis*-CDTA), while it is still faster for the Mn(*trans*-4HETCDTA) than the value determined for the Mn(*trans*-CDTA) chelate.

In conclusion, the *trans*-CDTA ligand provides a better platform for the complexation of the Mn^{2+} ion, thus bifunctional ligands (BFLs) shall be prepared using the given metal binding moiety. The *trans*-4HETCDTA ligand is one of the BFLs that can be used in two different modalities such as in PET (^{52}Mn) and MRI (^{55}Mn) owing to its satisfying parameters (high thermodynamic stability, inertness, fast formation and fast water exchange necessary to achieve high relaxivities).

Table 1. The most important physico-chemical parameters of the CDTA based ligands and their Mn^{2+} complexes compared to those of the EDTA and *trans*-CDTA systems (25 °C).

	***trans*-4HETCDTA**	***cis*-CDTA**	***trans*-CDTA**	**EDTA**
$\sum_{i=1}^{5} \log K_i^H$	22.25	23.32	23.09	21.14
$\log K_{MnL}$	13.80 (3)	14.19 (2)	14.32	12.46
pMn[a]	8.62	7.82	8.68	7.83
k_1 ($M^{-1}s^{-1}$)	$(2.97\pm0.08)\times10^2$	$(1.02\pm0.09)\times10^5$	4.0×10^2	5.2×10^4
$t_{1/2}$ (h)[a]	16.2	0.47	12.1	0.076
r_1 ($mM^{-1}s^{-1}$)	4.56	3.79	3.65	3.23
k_{ex}^{298} ($x10^7$ s^{-1})	17.6±4.4	22.5±0.5	14.0	47.1

[a] pH = 7.4

2. DTPA derivatives incorporating phenylene (PhDTPA) and cyclohexyl (CHXDTPA) bridging moieties were prepared which possess lower affinity towards Gd^{3+} ion owing to their more rigid structure. Surprisingly the inertness of the Gd^{3+} complexes increased only slightly while the relaxivity and the water exchange rates increased considerably when these data compared to that of Gd(DTPA).

The protonation constants of the ligands have been determined and the total basicity of the CXHDTPA is three orders of magnitude higher, while the basicity of the PhDTPA is three orders of magnitude lower than that of the DTPA. As a result of these changes in terms of basicity, the stability constants of the CHXDTPA complexes formed with divalent (Mg^{2+}, Ca^{2+}, Cu^{2+} and Zn^{2+}) and lanthanide (La^{3+}, Gd^{3+} and Lu^{3+}) ions are the highest, while the stability constants of the complexes of PhDTPA are the lowest. When comparing the pGd values however, the highest value is obtained for the Gd(DTPA), which means that the rigidity of the ligand backbone does not have a positive impact on the conditional stability of the Gd^{3+} complexes.

The results of the dissociation kinetic measurements showed that the inertness of the Gd(PhDTPA) is 2.5 times higher (based on the calculated $t_{1/2}$ values) than the inertness of the Gd(DTPA). The Gd(CHXDTPA) exists in two isomeric forms in solution which possess different inertness. One of them has an inertness similar to that of the Gd(DTPA), while the other one appears to be 18 times more inert. The existence of the isomers of the Gd(CHXDTPA) complex was proved by ^{1}H NMR spectroscopy by using Eu^{3+} and Yb^{3+} complexes, however we were not able to separate these isomers so far (by means of reversed phased HPLC and CE techniques).

The relaxivities of the Gd(PhDTPA) and Gd(CHXDTPA) complexes are higher than that of the parent Gd(DTPA) which is the consequence of their higher molecular weight. The water exchange rate of the Gd(PhDTPA) is five times

higher, while that of the Gd(CHXDTPA) is twenty times higher than it was observed for the Gd(DTPA) complex.

Our results indicate that the structural modifications applied to the parent DTPA ligand (rigidifying its backbone) did not result in considerable increase in the inertness of the corresponding complexes as it was expected. The thermodynamic stabilities, especially the pGd values are a bit lower, although the observed relaxivities get somewhat higher as compared to the parent Gd(DTPA) complex. The X-ray structures of these complexes are not known thus it is difficult to explain their behaviour, but the ^{1}H NMR spectra of these isomeric complexes differ significantly (DFT studies are in progress to identify these isomeric complexes and to find an explanation to the unusual kinetic behaviour).

Table 2. The most important physico-chemical parameters of the PhDTPA and CHXDTPA and the comparing ligand (DTPA) as well as their Gd^{3+} complexes (25 ºC).

	PhDTPA	**CHXDTPA**		**DTPA**
$\sum_{i=1}^{5} \log K_i^H$	24.06	30.40		27.19
log K_{GdL}	18.20 (1)	22.83 (3)		22.03
pGd[a]	16.37	18.81		19.44
k_1 ($M^{-1}s^{-1}$)	4.1±0.4	17.1±0.1	1.23±0.03	0.58
$t_{1/2}$ (h)[a]	530	250	3534	202
r_1 ($mM^{-1}s^{-1}$)	5.80	5.40		4.69
k_{ex}^{298} ($\times 10^6$ s^{-1})	16.4±1.0	65.6±7.8		3.3

[a] pH = 7.4

3. The investigation of pyclen derivatives containing acetate and picolinate pendant arms revealed that the coordination chemical parameters of the Gd^{3+} complexes formed with the non-symmetric ligands are more favorable due to the labile capping bond effect.

The results of thermodynamic and dissociation kinetic studies of the octadentate (PC2A1PA^{sym} and PC2A1PA^{asym}) and the nonadentate (PC1A2PA^{sym} and PC1A2PA^{asym}) ligands revealed that the stability constants and the inertness of the complexes are higher when two picolinate and one acetate groups are attached to the macrocyclic pyclen platform. The results also show that the stability of these complexes are higher than that of the Gd(PCTA). It can also be seen that the non-symmetric arrangement of the pendant arms on the pyclen platform is more favorable than the symmetric layout, which can be explained in terms of labile capping bond effect in Ln^{3+} complexes. In these complexes the capping position is occupied by the oxygen atom of the bound water molecule (as in PC2A1PA^{asym}) or oxygen atom of the acetate pendant arm (as in PC2A1PA^{sym}) resulting in more compact coordination environment around the Ln^{3+} ion.

The relaxivities of the Gd(PC2A1PA^{sym}) and Gd(PC2A1PA^{asym}) complexes are higher than those of the Gd^{3+} complexes formed with PC1A2PA ligands because they contain one water molecule bound to the metal center. The relaxivity of the other two complexes is smaller because they either do not possess an inner sphere water molecule (Gd(PC1A2PA^{asym}), or isomeric nonacoordinated (q = 0) and decacoordinated (q = 1) complexes exist in solution (Gd(PC1A2PA^{sym})). There is a significant difference in the water exchange rates of the monoaquated Gd(PC2A1PA^{sym}) and Gd(PC2A1PA^{asym}) complexes. The water exchange of the symmetric derivative is slower (20 times), while it is faster for the asymmetric derivative when compared to the parent Gd(PCTA). According to DFT calculations, carried out in the partner laboratories, the differences can be explained by the position of the bound water molecule. In the Gd(PC2A1PA^{asym})

complex the water molecule occupies one of the capping positions of the tricapped trigonal prism structure which in turn results in a longer Gd-O bond distance being responsible for the faster water exchange. In contrast, the given position is occupied by the O atom of the carboxyl group in the symmetric derivative causing smaller stability and inertness of the corresponding Ln^{3+} complexes.

The results show that these macrocyclic ligands have some potential for clinical applications because of their favorable physico-chemical parameters (thermodynamic stability and kinetics (formation, dissociation and water exchange)), which are almost as good as it is found in Ln(DOTA) complexes, often referred to as the "gold standard". However for the MRI applications the Gd(PC2A1PA^{asym}) complex possesses the most attractive parameters.

Table 3. The most important physico-chemical parameters of the pyclen based ligands and their Gd^{3+} complexes (25 ºC).

	PC2A1PA^{sym}	**PC2A1PA^{asym}**	**PC1A2PA^{sym}**	**PC1A2PA^{asym}**	**PCTA**
$\sum_{i=1}^{5} \log K_i^H$	23.69	25.13	26.66	25.49	21.32
log K_{GdL}	20.49 (2)	22.37 (3)	23.56	23.44 (2)	18.48
pGd[a]	17.74	20.25	20.69	21.83	16.81
k_1 ($M^{-1}s^{-1}$)	(6.9±0,1) $\times10^{-4}$	(2.13±0.08) $\times10^{-4}$	(1.45±0.07) $\times10^{-4}$	(6.3±0.2) $\times10^{-7}$	5.08 $\times10^{-4}$
$t_{1/2}$ (min)[a]	167	542	845	75506	231
r_1 ($mM^{-1}s^{-1}$)	4.74	4.95	3.58	2.10	7.09
k_{ex}^{298} ($x10^6$ s^{-1})	1.08±0.02	22.5±2.3	-	-	14.3

[a] c_{H+} = 0.1 M

Possible utilization of the results

This research is a fundamental research in the field of coordination chemistry of aminopolicarboxylate ligands, which can be utilized in the development of more efficient MRI CAs or in other diagnostic complexes (e.g. chelates for Positron Emission Tomography, PET) as well as in the development new complexes for therapeutic applications.

Results obtained concerning the *cis*-CDTA and *trans*-4HETCDTA have already been used in the literature since the (±)-*trans*-1,2-diaminocyclohexane is selected mostly as a platform when it comes to the ligand design for the complexation of the Mn^{2+} ion. Recent articles describing the synthesis and investigation of new BFLs based on the *trans*-4HETCDTA are suggested for dual PET-MRI imaging. Research aimed at the synthesis of new *trans*-CDTA derivatives is expected to become more prevalent in the near future, because the advantageous properties of their Mn^{2+} complexes satisfy even the strict requirements necessary for the *in vivo* applications.

However, the results obtained for the pyclen based macrocyclic ligands are even more interesting. These results showed that the physico-chemical parameters can be tuned by the position of the pendant arms (offering a new tool for tuning the physico-chemical parameters of the complexes). Guerbet owns the patent for the synthesis and production of diagnostic and therapeutic complexes based on the PC2A1PA and PC1A2PA ligands therefore there is a chance for their real application as MRI contrast agents (Gd^{3+} complexes), luminescence probes (Eu^{3+} or Tb^{3+} complexes) or radiopharmaceuticals (based on various diagnostic and therapeutic Ln^{3+} isotopes).

Publications

Publications related to the dissertation

1. Le Fur, M.; **Molnár, E.**; Beyler, M.; Fougère, O.; Esteban-Gómez, D.; Rousseaux, O;. Tripier, R.; Tircsó, G.; Platas-Iglesias, C. Expanding the Family of Pyclen-Based Ligands Bearing Pendant Picolinate Arms for Lanthanide Complexation INORGANIC CHEMISTRY 57: 12 pp. 6932-6945. 14 p. (2018)

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List of publications related to the dissertation

Foreign language scientific articles in international journals (4)

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List of other publications

Foreign language scientific articles in international journals (4)

5. Garda, Z., **Molnár, E.**, Kálmán, F. K., Botár, R., Nagy, V., Baranyai, Z., Brücher, E., Kovács, Z., Tóth, I., Tircsó, G.: Effect of the Nature of Donor Atoms on the Thermodynamic, Kinetic and Relaxation Properties of Mn(II) Complexes Formed With Some Trisubstituted 12-Membered Macrocyclic Ligands.
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