Theses of the doctoral dissertation

Smart MRI contrast agents: synthesis and chemical characterization

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Introduction and the aim of the work

Magnetic resonance imaging (MRI) has become one of the most powerful diagnostic technique in medicine, as it provides high-resolution anatomical images of soft tissues. Shortening the examination times and increasing the diagnostic accuracy (differences in contrast enhancement between normal and pathologic tissues) require administration of contrast agents (CAs).

A significant part of the CAs available on the market is the complexes of Gd^{3+}-ion formed with linear or more preferably macrocyclic ligands, which possess a water molecule (q) in their inner coordination sphere responsible for the relaxation effect. In light of nephrogenic systemic fibrosis (NSF), a devastating disease associated with the toxicity of the free Gd^{3+} produced *in vivo* as a result of the decomplexation of CAs, there is a definite need to improve the dissociation kinetic parameters of Gd^{3+} based CAs. Furthermore, the CA or the free Gd^{3+} can accumulate in bones, tissues or in the brain causes increased background intensity.

In addition, after excretion from the human body, the Gd^{3+} complexes enter the surface water mostly by the effluents of sewage treatment plants. Most of the applied complexes are very stable over at least 6 months under natural conditions. Nowadays, it is not considered as a major problem to be solved, but this should also be addressed in the future.

In 2017 the European Medicine Agency recommended the suspension of three commercialized products based on open-chain ligand platforms. Finding a plausible alternative to Gd^{3+}-based CAs has received considerable attention in the past decade. The most promising candidates are the complexes of the essential Mn^{2+} ion because it has acceptable relaxation enhancement properties and its homeostasis guarantee very efficient elimination form the living systems.

Novel generation CAs that can report specific biomarkers or biochemical processes associated with certain diseases have also been developed. Anatomical images can be filled with functional information by using the so-called responsive/intelligent/smart contrast agent (SCA) candidates, the demand for this type of CAs has increased significantly in the past few years. SCAs are probes that can respond to the biological stimuli appearing in the local environment of the agent mostly related to the fluctuations in the concentration of biologically relevant metal ions, bioligands, pH or specific molecules.

For tracking neural activity, several possible markers that are responsive to the concentration of certain ions, neurotransmitters or transmembrane potential might be envisaged. Significant research efforts have been devoted to the fluorescence imaging of intracellular Ca^{2+} fluctuations in recent years. Ca^{2+} ion is indeed crucial in several steps in neuronal signaling, and their intra- and extracellular concentrations change dramatically during brain activity. For MRI applications, Angelovski and co-workers investigated several Gd^{3+}-based Ca^{2+} responsive SCA candidates with EGTA derivative moiety as sensor function which links two macrocyclic unit as well, for the complexation of Gd^{3+}. **To this aim we prepared Gd^{3+} complexes formed with DO3A-derivative ligands (DO3A-EAMA and DO3A-PAMA, Figure 1.) to mimic the behavior of the given SCAs. The physico-chemical characterization of the ligands and their Gd^{3+} complex has been carried out** focusing on the thermodynamic stability (pH-potentiometry supplemented with ^1H relaxometry) and the inertness of the Gd^{3+} complexes (accessed by studying metal exchange reactions). In addition, the complex formation processes with some divalent (essential) metal ions were also investigated in detail.

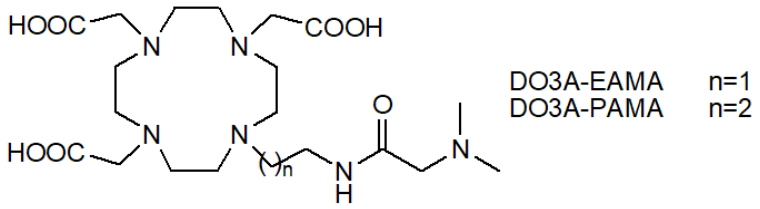

Figure 1. Structures of the examined DO3A-EAMA and DO3A-PAMA ligands

The other main field of these studies was the examination of Mn^{2+} based SCA candidate complexes. Based on the wide research experience of our group, a macrocyclic platform, the 3,9-PC2A, was selected which can carry the sensor moiety and bears acceptable physico-chemical properties in the aspects of *in vivo* application. The Mn^{2+}-complex of 3,9-PC2A ligand has high thermodynamic stability and appropriate inertness, moreover, possesses an inner-sphere water molecule and a substitutable *N*-atom in the macrocyclic ring.

In cancer diagnosis, mapping of tissue pH can potentially be used to recognize malignant processes at an early stage since the accelerated glucose metabolism of cancer cells results in a decrease of the extracellular pH and increase of the intracellular pH. **Using an ethylamine and a *p*-nitrophenol pH-sensing moiety, we designed heptadentate PC2A derivatives (Figure 2.), which are expected to combine the advantageous metal binding**

properties of 3,9-PC2A with the pH-responsive "on/off" (pH = 7.4 +/- 0.6) coordination feature of the pendant arms.

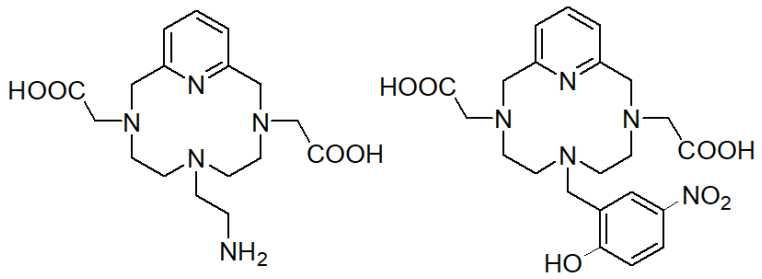

Figure 2. Structures of the examined pH-sensitive candidate ligands PC2A-EA and PC2A-NP

Owing to their widespread biological importance (structural and catalytic roles), Zn^{2+} ion responsive SCAs were among the first synthesized and studied candidates. Meanwhile, it was also realized that Zn^{2+} sensitive SCAs can bind to the human serum albumin (HSA) which interaction significantly enhances their relaxivity values when the Zn^{2+} ion is also present. Since, the zinc concentration of the cancerous prostate is considerably lower than that of the healthy one it may provide the opportunity for the early diagnosis. **Using a DPA (di-(2-picolyl)amine) sensing moiety, we designed and synthesized the PC2A-DPA ligand (Figure 3.). The thermodynamic, kinetic and relaxation properties of the [Mn(PC2A-DPA)] complex have been investigated in *in vitro* and *in vivo* experiments, respectively.**

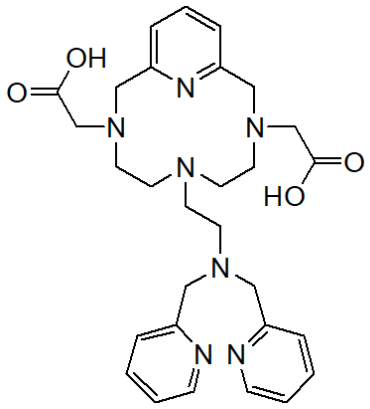

Figure 3. Structure of the examined Zn^{2+}-sensitive candidate ligand PC2A-DPA

Experimental methods

DO3A-EAMA and DO3A-PAMA ligands were synthesized in our partner laboratory and possessed analytical grade. The synthesis of PC2A-EA, PC2A-NP, PC2A-DPA ligands were carried out based on published procedures and the main products were purified by semi-preparative HPLC chromatography. ^{1}H-, ^{13}C-NMR and ESI-MS methods were applied to determine the structure and purity of the final products.

The protonation constants of the ligands and the stability and protonation constants of the metal complexes as well as the protonation constants of the Cu^{2+} complexes were also determined by pH-potentiometric titrations. The stability constant of the Gd^{3+} complexes were determined by ^{1}H-relaxometric titration (20 MHz, 25.0 °C). The determination of the stability constant of Cu^{2+} complexes was carried out by means of the UV−vis spectrophotometric method, because of the high conditional stability of the [Cu(L)] complexes. The protonation sequence of PC2A-EA ligand was determined by ^{1}H-NMR titration.

Relaxation properties of the complexes (water-exchange rate constants, relaxivity) were determined by ^{1}H-relaxometry and temperature dependent ^{17}O NMR measurements (9.4 T). *In vitro* (phantom) imaging was carried out using clinical MRI scanners at 1.5 and 3 T magnetic field strengths, while the *in vivo* (mouse) experiments were performed by using a preclinical (Mediso nanoScan PET/MRI 3T system) scanner at a 3 T magnetic field strength. All the MRI scanners were validated. Animal experiments were authorized by the National Scientific Ethical Committee on Animal Experimentation (authorization number # 10/2019/DEMÁB).

The metal exchange reactions of the complexes were monitored by UV−Vis spectrophotometry or ^{1}H-relaxometry. The exchanging metal ions (Cu^{2+} or Zn^{2+}) were used in at least 10 times excess (10 − 40-fold) to ensure pseudo-first-order conditions.

New scientific results

1. [Gd(DO3A-EAMA)]-complex possesses higher stability and inertness than [Gd(DO3A-PAMA)] complex, although its relaxivity is lower with ~1.5 $mM^{-1}s^{-1}$ at pH = 7.4. Observed relaxivity values are decreasing with the increasing of pH.

The protonation constants of the DO3A-PAMA and DO3A-EAMA, and the protonation and stability constants of their complexes formed with some essential metal ions (Ca^{2+}; Mg^{2+}; Zn^{2+}; Cu^{2+}) and Gd^{3+}-ion were determined. The basicity of the macrocyclic backbone of DO3A-PAMA ligand is somewhat higher than that was found for DO3A-EAMA which is the result of the longer distance between the N donor and the amide functional group in the DO3A-PAMA where the electron withdrawing effect of the amide group is weaker. The stability constants of the Gd^{3+} complexes are lower than the corresponding values obtained for DO3A and DOTA chelates (Table 1.).

The [Gd(DO3A-EAMA)] complex possesses higher thermodynamic stability than [Gd(DO3A-PAMA)] complex, since the larger chelate-ring (6 → 7) formed with the amide oxygen coordination in the PAMA complex. Similar protonation constants of the side-chain amine group were determined for the ligand and its Gd^{3+} complex indicating that the pendant does not take part in the coordination of the metal ion. In sum, the stability constants of the investigated complexes are lower than those of DO3A and DOTA complexes, due to the substitution of acetate pendants with alkylamide moieties.

At pH = 6, where the monoprotonated species of the Gd^{3+}-complexes are dominant, the relaxivity values show bishydrated complexes in solution in which 2 water molecules are coordinated in the inner-sphere of the complex. At high pH values, the relaxivity of the complexes is decreasing continuously due to the coordination of amide oxygen.

The inertness of [Gd(DO3A-PAMA)] complex is 6 times lower than that of [Gd(DO3A-EAMA)] which is most probably due to the higher flexibility of the longer side-chain where the proton transfer between the amine nitrogen of the side chain and the acetate group becomes more favorable. However, the calculated $t_{1/2}$ values (pH = 6.0) are significantly lower than those were gained for the comparative complexes, those are high enough for biological investigations.

The characterization of the complexes delivered valuable results for further design of Ca^{2+}-responsive probes.

Table 1. Main physico-chemical properties of the DO3A-PAMA and DO3A-EAMA ligands and their Gd^{3+}-complexes compared with DO3A and DOTA ligands and their complexes (25.0 °C)

	DO3A-PAMA	DO3A-EAMA	DO3A	DOTA[a]
$\sum_{i=1}^{2} \log K_i^{H}$	18.96	18.26	20.20	21.24
$\log K_{GdL}$	13.89(4)	14.59(5)	19.06	24.70
k_1 ($M^{-1}s^{-1}$)	3.2±0.1	0.53±0.02	0.023	$1.8x10^{-6}$
$t_{1/2}$ (hours) pH=7.4	1490	9125	8400	$1.07x10^{8}$

[a] 0.1 M KCl

2. PC2A-EA and PC2A-NP-ligands were synthesized, where the ethylamine and *p*-nitrophenol moieties carry the pH-sensitive function. The Mn^{2+}-complexes endowed with high thermodynamic stability and kinetic inertness, and the relaxivity of [Mn(PC2A-EA)] complex changes in the physiological pH range.

Based on the equilibrium studies, one can conclude that the basicity of PC2A-EA and PC2A-NP is higher than that was found for PCTA ligand, ($\log K_1^H + \log K_3^H$). By means of NMR spectroscopy, the protonation scheme of the PC2A-EA ligand was also determined. The results also proved that the $\log K_2^H$ (8.93) protonation step belongs to the amino-group of the side-chain (Table 2.).

The stability and protonation constants of complexes formed with biologically relevant metal ions were also determined, and the [Mn(PC2A-EA)] was found to be the most stable among the investigated ones. According to the calculated pMn values all of the investigated Mn^{2+}-complex are suitable for *in vivo* application.

The protonation constant of the Mn^{2+}-complex is one of the most important parameter of a pH-responsive probe since the protonation has to occur in the physiological pH range. The [Mn(PC2A-EA)] complex fulfills this requirement, but unfortunately, the protonation process of [Mn(PC2A-NP)] takes place in acidic condition, below the desired pH range.

Not surprisingly, above pH 6 the relaxivity of [Mn(PC2A-NP)]-complex corresponds to the value characterizing the outer-sphere relaxation, when $q = 0$. On the other hand, the [Mn(PC2A-EA)] presents a significant change both in the longitudinal ($\Delta r_{1p} = 0.56$ $mM^{-1}s^{-1}$) and transvers ($\Delta r_{2p} = 1.01$ $mM^{-1}s^{-1}$) relaxivity at 20 MHz, in the pH range 6.8 – 7.4, which is even higher at the clinically applied 3 T magnetic field ($\Delta r_{1p} = 0.82$ $mM^{-1}s^{-1}$, $\Delta r_{2p} = 4.92$ $mM^{-1}s^{-1}$).

The water exchange rate constants, k_{ex}^{298}, determined for the Mn^{2+} complexes are lower than that was obtained for [Mn(PC2A)] which is the result of the incorporation of the pH-sensitive function into the ligand structure causing significant changes in the coordination environment.

The complexes are more labile than the $[Mn(PCTA)]^-$, but the calculated half-lives show that the inertness is high enough to be applied as MRI contrast agents. In summary, [Mn(PC2A-EA)] complex can be applicable *in vivo* as responsive probe.

Table 2. Main physico-chemical properties of the PC2A-EA, PC2A-NP and the compared ligands and theirs Mn^{2+}-complexes (25.0 °C)

	PC2A-EA	PC2A-NP	PC2A-SA	PCTA
$\log\beta_{mc}$[a]	18.25	17.75	18.03	16.70
$\log K_{MnL}$	19.01(4)	18.05(6)	17.96	16.83
$\log K_{MnHL}$	6.88(2)	4.58(2)	8.77	1.96
pMn	9.27	9.67	9.77	9.74
Δr_2 ($mM^{-1}s^{-1}$) pH = 6.8 – 7.4	4.92	-	-	-
r_{1p} ($mM^{-1}s^{-1}$)	2.5	1.6	4.0	-
k_{ex}^{298} ($x10^7\ s^{-1}$)	4.0±0.1	4.5±0.1	5.9	-
k_1 ($M^{-1}s^{-1}$)	0.7±0.1	0.60±0.01	4.8±0.2	8.2×10^{-2}
k_2 ($M^{-2}s^{-1}$)	$(3.2\pm0.2)\times10^4$	-	-	3.5×10^2
$t_{1/2}$ (pH = 7.4, hours)	6700	8050	1000	5.9×10^4

[a] basicity of the macrocycle

3. PC2A-DPA ligand was synthesized, where the (di-(2-picolyl)amine) moiety carries the Zn^{2+}-sensitive function. The [Mn(PC2A-DPA)] complex bears acceptable thermodynamic stability and inertness, in addition, we were able to carry out experiments *in vitro* and *in vivo*.

Based on the equilibrium studies, the basicity of PC2A-DPA is lower than that was found for PCTA ligand, ($\log K_1^H$ + $\log K_3^H$). The stability and protonation constants of complexes formed with biologically relevant metal ions were also determined, and the [Mn(PC2A-DPA)] was found to be less stable among the investigated ones. According to the calculated pMn value, the investigated Mn^{2+}-complex is suitable for *in vivo* application (Table 3.).

The stability constant of the dinuclear complex of PC2A-DPA ($\log K_{Zn2L}$ = 6.52(3)) and the effective binding affinity to HSA (K_D= 40 μM) were determined and used to calculate the binding ratio of the complex to the HSA. The calculation shows that 60% of $[Mn(PC2A\text{-}DPA)(H_2O)Zn]^{2+}$ complex binds to HSA in the given conditions.

The relaxivity of $[Mn(PC2A\text{-}DPA)Zn]^{2+}$ complex is increasing significantly in the presence of HSA due to a relatively strong interaction between the complex and the protein making the system suitable for *in vivo* applications. Successful *in vivo* experiments were carried out on mice model, in which the glucose stimulated zinc secretion from prostate was detected in MRI.

The water exchange rate constants, k_{ex}^{298}, determined for the Mn^{2+} complex is lower than that was obtained for [Mn(PC2A)] which is the result of the modification of the ligand structure.

The inertness of the Mn^{2+} complex is higher than that of the [Mn(PC2A)] and the calculated half-life shows that its inertness is suitable for MRI applications. In summary, [Mn(PC2A-DPA)] complex is a good candidate to be used *in clinical practice* as Zn^{2+} responsive probe.

Table 3. Main physico-chemical properties of the PC2A-DPA and the compared ligands and theirs Mn^{2+}-complexes (25.0 °C)

	PC2A-DPA	PC2A	PC2A-EA
$\log\beta_{mc}$[a]	16.49	18.22	18.25
$\log K_{MnL}$	15.87(6)	17.09	19.01
$\log K_{Mn2L}$	3.0(1)	–	–
pMn	8.79	8.64	9.27
$\log K_{ZnL}$	19.05(6)	19.49	21.4(1)
$\log K_{Zn2L}$	6.52(3)	–	–
$K_{D(HSA)}$ (μM)	40±4	–	–
Δr_2 ($mM^{-1}s^{-1}$) in HSA 0 → 1 eq. Zn^{2+}	13.41 (~ 50%)	–	–
r_{1p} ($mM^{-1}s^{-1}$)	3.24	2.91	2.5
k_{ex}^{298} (x10^7 s^{-1})	7.6±0.4	12.6	4.0
k_{obs} (s^{-1}) pH = 6.00	(2.98±0.01)×10^{-6}	5.43×10^{-4}	3.54×10^{-6}
$t_{1/2}$ (pH = 6.00) (hours)	64.5	0.35	54.4

[a] basicity of the macrocycle

Possible application of the results

The coordination chemistry characterization of the investigated complexes is mostly fundamental research, however the possible application of [Mn(PC2A-EA)] and [Mn(PC2A-DPA)] has been demonstrated in *in vitro* and *in vivo* experiments. Furthermore, our results contribute to the development of further smart MRI contrast agents.

The results obtained for the DO3A-EAMA and DO3A-PAMA ligands show that the length of alkyl chain has significant effect on the inertness of Gd^{3+}-complexes. The Ca^{2+}-sensitive complex mimics have satisfying thermodynamic and relaxation properties, but their inertness has to be improved to minimize the *in vivo* dissociation.

The [Mn(PC2A-EA)] presents a significant change both in the longitudinal and transvers relaxivity in the pH range 6.8 – 7.4, so it is desirable to examine the complex behavior *in vivo*. Using ^{52}Mn radioisotope the concentration of the injected [Mn(PC2A-EA)] complex can be determined properly which can help us to determine the pH in tissues. Unfortunately, the protonation of the [Mn(PC2A-NP)] chelate falls out of the range of the physiological range, therefore it cannot be applied *in vivo*. The results can be used during the fine tuning of pH-responsive side chains.

Finally, the [Mn(PC2A-DPA)] is suitable to follow the Zn^{2+} fluctuations in the prostate due to the strong interaction between the complex and the blood proteins resulting significant increase of the relaxivity. As a result of the successful *in vivo* experiments in mice model, the complex should also be tested in different animal models.

Acknowledgement

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List of publications related to the dissertation

Foreign language scientific articles in international journals (3)

1. **Botár, R.**, Molnár, E., Garda, Z., Madarasi, E., Trencsényi, G., Kiss, J., Kálmán, F. K., Tircsó, G.: Synthesis and characterization of a stable and inert Mn-II-based Zn-II responsive MRI probe for molecular imaging of glucose stimulated zinc secretion (GSZS).
Inorg. Chem. Front. 9 (3), 577-583, 2022. ISSN: 2052-1553.
DOI: http://dx.doi.org/10.1039/D1QI00501D
IF: 7

2. **Botár, R.**, Molnár, E., Trencsényi, G., Kiss, J., Kálmán, F. K., Tircsó, G.: Stable and inert Mn(II)-based and pH responsive contrast agents.
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DOI: http://dx.doi.org/10.1021/jacs.9b09407
IF: 15.419

3. Gündüz, S., Vibhute, S., **Botár, R.**, Kálmán, F. K., Tóth, I., Tircsó, G., Regueiro-Figueroa, M., Esteban-Gómez, D., Platas-Iglesias, C., Angelovski, G.: Coordination Properties of GdDO3A-Based Model Compounds of Bioresponsive MRI Contrast Agents.
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DOI: http://dx.doi.org/10.1021/acs.inorgchem.8b00473
IF: 4.85

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List of other publications

Foreign language international book chapters (1)

4. Tircsó, G., Molnár, E., Csupász, T., Garda, Z., **Botár, R.**, Kálmán, F. K., Kovács, Z., Brücher, E., Tóth, I.: Gadolinium(III)-Based Contrast Agents for Magnetic Resonance Imaging. A Re-Appraisal.
In: Metal Ions in Bio-Imaging Techniques. Ed.: Astrid Sigel, Eva Freisinger and Roland K.O. Sigel, De Gruyter, Berlin, 39-70, 2021, (Metal Ions in Life Sciences, ISSN 1559-0836 ; 22)
ISBN: 9783110685701

Foreign language scientific articles in international journals (3)

5. Csupász, T., Lihi, N., Fekete, Z., Nagy, A., **Botár, R.**, Forgács, V., Szikra, D. P., May, N. V., Tircsó, G., Kálmán, F. K.: Exceptionally fast formation of stable rigidified cross-bridged complexes formed with Cu(II) isotopes for Molecular Imaging.
Inorg. Chem. Front. 9 (6), 1217-1223, 2022. ISSN: 2052-1553.
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IF: 7

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8. Csupász, T., Lihi, N., Fekete, Z., Nagy, A., **Botár, R.**, Forgács, V., Szikra, D. P., Tircsó, G., Kálmán, F. K.: Új típusú Cu(II)-komplexek radioteranosztikai alkalmazásokhoz.
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Foreign language abstracts (1)

9. Garda, Z., Fodor, T., Molnár, E., **Botár, R.**, Kálmán, F. K., Tóth, I., Tircsó, G., Kovács, Z.: Thermodynamic and kinetic properties of Mn2+cyclododecane derivative complexes: fine-tuning by the nature of donor atoms.
J. Biol. Inorg. Chem. 19 (S1), S686, 2014. ISSN: 0949-8257.
DOI: http://dx.doi.org/10.1007/s00775-014-1095-8

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