Synthesis and complexation properties of some diamino-polycarboxilate type ligands having „in-chain" phosphinate and alcoholic OH groups

PhD Thesis Abstract

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I. Introduction and aim of the work

Ligand design for biomedical applications is steadily gaining importance for applications ranging from Gd(III) complexes used in MRI to Eu^{3+} complexes used as luminescent probes. For over two decades, there has been a continuous interest in the study of lanthanide(III) complexes formed with open-chain and macrocyclic polyamino-polycarboxylate and -polyphosphonate chelating ligands. The interest in these studies were largely driven by advances in magnetic resonance imaging (MRI) contrast agents (mostly Gd^{3+} complexes), nuclear medicine diagnostic agents (complexes of isotopes used in positron emission tomography and γ emitters such as $^{67}Ga^{3+}$, $^{111}In^{3+}$, or $^{169}Yb^{3+}$), and therapeutic radiopharmaceuticals (β emitters such as chelates of $^{90}Y^{3+}$, $^{149}Pm^{3+}$, $^{153}Sm^{3+}$, $^{166}Ho^{3+}$ or $^{177}Lu^{3+}$). In sharp contrast to the traditional MRI contrast agents, a new technique for generating image contrast has recently been proposed, known as chemical exchange saturation transfer (CEST). The CEST technique requires substantially slower water exchange and the presence of exchangeable protons (–N*H* and –O*H* or coordinated H_2O) in the contrast agent. Lanthanide complexes are also widely used in the field of optical imaging. The earliest use of lanthanide ions in imaging arose from the need to provide high sensitivity probes for use in bioassay. With the use of the fluorescent properties of Eu^{3+} and Tb^{3+} ions which have much longer luminescence lifetimes than conventional fluorescent probes, it is possible to determine qualitatively or even quantitatively antigens and other biologically important compounds.

Depending upon the field or application where the complexes will be used, the demands for the complexes are different. To meet these requirements synthesis, equilibrium, structural and kinetics studies of the complexes involving new ligands are necessary. In the Department of Inorganic and Analytical Chemistry of the University of Debrecen the research area of the lanthanide(III) complexes with open-chain and macrocyclic polyamino-polycarboxylate and -polyphosphonate ligands has been studied for a long time. In consequence of their biological activities, a few aminophosphinate ligands have been synthesized and studied recently. The coordination properties of the phosphinate and carboxylate groups have been found to be similar, though the stability constants of the aminophosphinate complexes are lower than those of the corresponding aminocarboxylate complexes and the phosphinic acid is more

acidic than the carboxylic acid. Since the lanthanide(III) ions prefer the hard donor atoms, the phosphinate moiety may be a promising donor group for the lanthanides.

Multidentate ligands containing in-chain phosphinate groups exhibit biological activity and strong coordination ability: they act as inhibitors of a number of bacterial enzymes, and symmetric phosphinic acids have been found to be powerful inhibitors of Human Immunodeficiency Virus (HIV) protease. Additionally, some bis-(aminomethyl)-phosphinic acid derivatives have been shown to have plant growth-regulating properties. It is quite interesting that only a few studies have been published about the coordination properties of the bis-(aminomethyl)-phosphinic acid derivatives.

The primary goal of our work was to synthesize bis-(aminomethyl)-phosphinic acid derivatives with different number of acetates substituents on the N atoms and to determine the stability of the complexes formed with some endogenous (Mg^{2+}, Ca^{2+}, Cu^{2+} and Zn^{2+}), highly toxic heavy metal (Ni^{2+}, Cd^{2+} and Pb^{2+}) and Ln(III) ions. We were curious about how the coordination chemical properties of the phosphinic moiety will be influenced by the increasing number and the position of acetate arms on the amine N atoms. We were also interested in the changes of the structure and solution speciation of the complexes brought about by the presence of the phosphinic moiety in the bis-(aminomethyl)-phosphinic acid ligands in comparison to the diamino-polycarboxylates.

In order to assess the benefit or the drawback of the presence (or the absence) of a particular moiety in a ligand from the point of view of the coordination chemistry it is important to have an appropriate reference ligand. The 2-hydroxy-1,3-diaminopropane derivatives may act as such a reference for the phosphitates but it is important to highlight the large difference in the basicity of these groups. Our literature search indicated that the lanthanide complexes formed with 1,3-diamino-propane-2-ol-*N,N,N',N'*-tetraacetate (dpta-OH) ligand had already been studied previously, but the literature data were contradictory about the dissociation and/or coordination of the alcoholic OH-group in these complexes. According to these observations our secondary goal was to investigate the complexation of Ca^{2+} and Ln(III) ions by the commercially available 1,3-diamino-propane-2-ol-*N,N,N',N'*-tetraacetate.

II. Experimental methods

The **pH-potentiometry** is the one of the most commonly used experimental methods for the investigation of the complex formation processes in aqueous solution. However, it can only be used when the metal ion coordination has an effect on the protonation equilibrium of the ligand. The aim of the pH-potentiometric measurements is to determine the composition and the stability constants of the complexes formed. In this work the pH-potentiometric titrations were performed in thermostated vessels at 25 ± 0.2 °C, with a Radiometer PHM 93 Reference pH-meter, Radiometer ABU 80 autoburette, PHG 211 glass and K401 calomel electrodes. 1.0 M Me_4NCl (KCl NaCl or KNO_3) were used to maintain constant ionic strength in the samples. The titrated samples were stirred and N_2 (or Ar) gas bubbled through to prevent CO_2 entry. For the calibration of the pH meter, KH-phtalate (pH=4.005) and borax (pH=9.180) buffers were used. For the calculation of $[H^+]$ from the measured pH values, the method proposed by Irving et al. was used. The stability constants from the experimental data were calculated by PSEQUAD computational program.

UV-vis spectrophotometric studies were performed for Cu^{2+} (200–800 nm, l=1.0 cm), Ce^{3+} (210–330 nm, l=1.0 cm) and Nd^{3+} (420–440 nm, l=5.0 cm) complexes. The studies were performed with a Cary 1E spectrophotometer in cells thermostated at 25 °C. The ionic background in the samples was kept constant (1.0 M KCl). Analysis of the spectra may reveal the structure and the geometry of the complexes as well as the number and the quality of the coordinating ligands.

The coordination number of the Gd^{3+} aq. ions is eight, so in aqueous solution 8 H_2O molecules are coordinated to the metal ion. When a ligand coordinates to the Gd^{3+} ion the number of the coordinated water molecules decreases and as a result the longitudinal relaxation times of H_2O protons (T_1) also decreases. Based on this decrease it is possible to evaluate the number of the H_2O molecules that remained coordinated to the Gd^{3+} ion and suggest the number of the donor atoms of the ligand involved in the coordination. The **relaxivity** values were calculated from the longitudinal relaxation times of H_2O protons (T_1) measured with MS-4 NMR spectrometer (Institute Jozef Stefan, Ljubljana) at 9 MHz. The temperature of the sample holder was controlled with

thermostated air stream (25 ^{o}C). The longitudinal relaxation times were measured by the 'inversion recovery' method (180°–τ–90°) by using 6–8 different τ values.

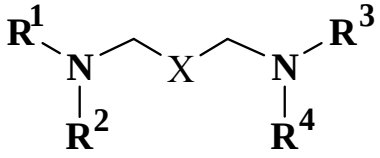
^{1}H-NMR spectroscopy was used to check the purity of the ligands synthesized in the present work. This method was also used to identify the protonation steps and to determine the protonation constants using the pD dependence of the chemical shifts of the NMR active nuclei (^{1}H and ^{31}P). Furthermore, we used the NMR technique to study and characterize the structure of Zn^{2+}, La^{3+}, Eu^{3+} Y^{3+} and Lu^{3+} complexes in solution. Bruker Avance 360 and Bruker DRX 500 spectrometers equipped with Bruker VT-1000 temperature controller unit were used for the studies. The evaluation of the spectra was performed by Bruker Winnmr® 1 and 2D software package.

The **ESI-TOF MS spectroscopy** separates the ions formed during ionization by mass/charge (m/Z). The method gives information about the molecular mass of the metal complexes confirming the assumed structures from other spectroscopic methods. ESI-TOF MS measurements were performed on a Bruker Daltonics BioTOF II instrument. The aqueous solutions with pH = 7.5 (c_{Ln} = c_L = 0.25 mM) were introduced directly into the ESI source from by a syringe pump at a flow rate of $2\cdot10^{-3}$ cm^3/min. The temperature of the drying gas (N_2) was maintained at 100˚C. The spectra were accumulated and recorded by a digitizer at a sampling rate of 2 GHz.

The **X-ray crystallography** is the best method to determine structure (the geometry of the complex, the number and the quality of the coordinating ligands, bond angles and length) of the complexes in solid state. However, the method requires single crystals, which was not possible to obtain in every case. We have managed to crystallize two of our complexes and two compounds during the synthetic work in a single crystal form. The structures of these complexes ($K[CuL^2]\cdot H^2O$ and $K_4[Nd_2(L^{12}\text{-}O)_2(H_2O)_2]\cdot 14H_2O$) and $[H_5L^4]\cdot Cl$ were determined by Dr. Attila Bényei (University of Debrecen, Department of Physical Chemistry). The structure of 6b. compound was solved by Dr. Pavel Vojtíšek (Charles University at Prague). Data were collected at 293±1 K on an Enraf Nonius MACH 3 diffractometer using monochromated Mo K_α radiation (λ=0.71073 Å), ω-2θ motion. Absorption correction was performed using psi scans. The structure was solved using a direct method with the SIR-92 software

and refined on F^2 by full matrix least square method with the program SHELX-97.

III. Structure of the ligands

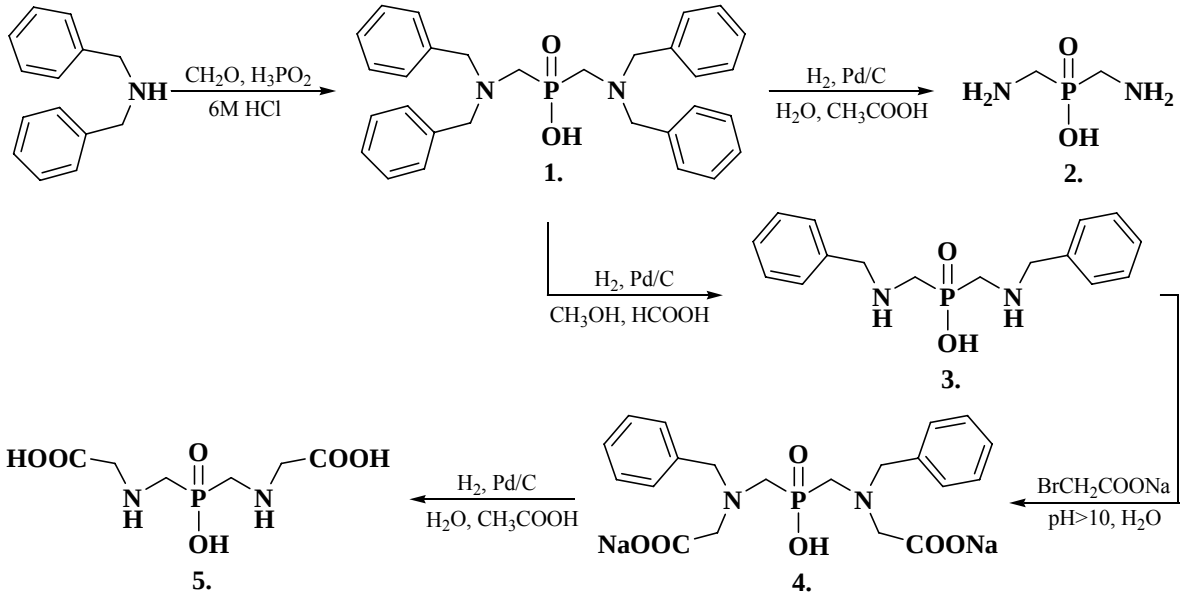


R^1	R^2	R^3	R^4	X	Ligand
H	H	H	H	>P(O)OH	HL^0
CH_2COOH	CH_2Ph	CH_2COOH	CH_2Ph	>P(O)OH	H_3L^1
CH_2COOH	H	CH_2COOH	H	>P(O)OH	H_3L^2
CH_2COOH	CH_2COOH	H	H	>P(O)OH	H_3L^3
CH_2COOH	CH_2COOH	CH_2COOH	H	>P(O)OH	H_4L^4
CH_2COOH	CH_2COOH	CH_2COOH	CH_2COOH	>P(O)OH	H_5L^5
CH_2COOH	CH_2COOH	CH_2COOH	CH_2COOH	>CH-OH	H_4L^{12}-OH

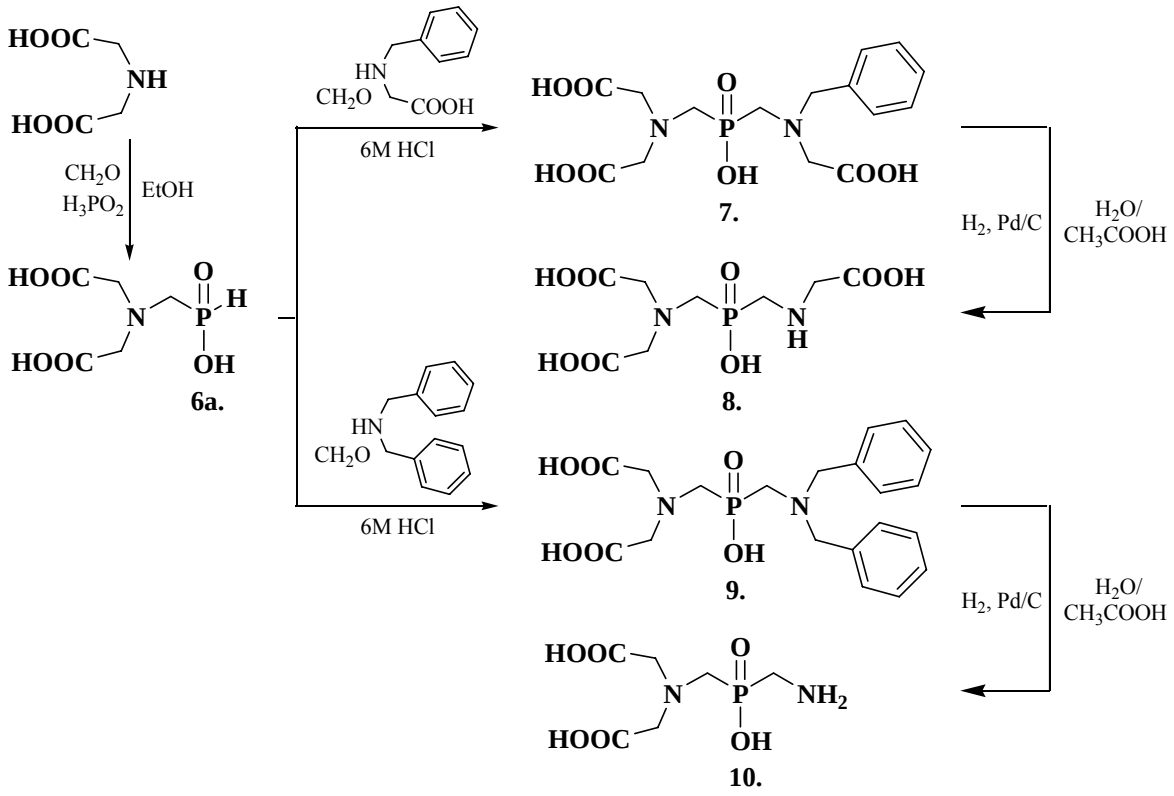
HL^0: bis-(aminomethyl)-phosphinic acid, **H_3L^1:** (benzyl-{[(benzyl-carboxymethyl-amino)-methyl]-hydroxy-phosphinoylmethyl}-amino)-acetic acid, **H_3L^2:** ({[(Carboxymethyl-amino)-methyl]-hydroxy-phosphinoylmethyl}-amino)-acetic acid, **H_3L^3:** [(Aminomethyl-hydroxy-phosphinoylmethyl)-carboxymethyl-amino]-acetic acid, **H_4L^4:** (Carboxymethyl-{[(carboxymethyl-amino)-methyl]-hydroxy-phosphinoylmethyl}-amino)-acetic acid, **H_5L^5:** ({[(Bis-carboxymethyl-amino)-methyl]-hydroxy-phosphinoylmethyl}-carboxymethyl-amino)-acetic acid, **H4L^{12}-OH:** {[3-(Bis-carboxymethyl-amino)-2-hydroxy-propyl]-carboxymethyl-amino}-acetic acid (2-hydroxy-1,3-propanediamine-*N*,*N*,*N*',*N*'-tetraacetic acid).

Synthesis of the symmetric bis(aminomethyl)phosphinic acid derivatives was achieved by a multi-step reaction starting from *N,N*-dibenzylamine according to Scheme 1. while the novel asymmetric bis(aminomethyl)phosphinic acid ligands (L^3 and L^4) were synthesized from carboxymethyl-hydroxyphosphinoylmethyl-amino)-acetic acid as shown in Scheme 2. The ligand L^5 was synthesized according to the procedure suggested by Varga[1] and recrystallized twice from hot water. The ligand 2-hydroxy-1,3-propanediamine-*N*,*N*,*N*',*N*'-tetraacetic acid was purchased from Sigma-Aldrich and was used without further purification.

[1] T. R. Varga, *Synt. Comm.* **1997,** *27,* 2899.



Scheme 1. Synthesis of the symmetric bis-(aminomethyl)-phosphinic acid derivatives.



Scheme 2. Synthesis of the asymmetric bis-(aminomethyl)-phosphinic acid derivatives.

IV. Results

In the present work complexation properties of seven ligands have been studied with some divalent (Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Pb^{2+}) and

Ln(III) ions in solution and in solid state. The studied ligands included six bis-(aminomethyl)-phosphinic acid derivatives (4 symmetric and 2 asymmetric) while the 7th ligand incorporated an alcoholic OH group in between the nitrogen atoms of the propane-1,3-diamine backbone.

1. A new synthetic method has been developed that utilized inexpensive starting materials and gave reasonable yields of bis-(aminomethyl)-phosphinic acid as well as derivatives with the phosphinate group in a linker position. In addition, execution of the *Mannich* reaction in two consecutive steps afforded hitherto unknown asymmetric bis-(aminomethyl)-phosphinic acids. Single crystals of (benzyl-hydroxyphosphinoylmethyl-amino)-acetic acid and the asymetric ligand (barboxymethyl-{[(carboxymethyl-amino)-methyl]hydroxyl-phosphinoyl-methyl}-amino)-acetic acid ([H_5L^4]·Cl) were isolated and the solid state structure of these compounds were determined by X-ray crystallography.

2. The basicities of the nitrogen atoms of the symmetric and asymmetric diacetate (L^1, L^2 and L^3), tri- (L^4) and tetraacetate (L^5) derivatives of bis-(aminomethyl)-phosphinic acid (L^0) are lower than those of the analogous diaminopolycarboxylates mainly due to the electron-withdrawing effect of the phosphinate group. For a given ligand, the basicity of the nitrogen atoms was found to decrease in the order of primary > secondary > tertiary.

3. The ligand L^0 does not form complexes with Mg^{2+}, Ca^{2+} and Ln(III) ions, and for the rest of the studied metal ions the ligand behaves similarly to 1,3-propilenediamine. However, the stabilities of the complexes are generally lower than those of the complexes formed with propane-1,3-diamine, which is due to the lower basicity of the N-atoms. The ligand forms ML, MLH, ML_2, ML_2H species with the metal ions. In ML and ML_2 complexes the phosphinate is not directly involved in the coordination, but the absence of ML_3 type complexes for Ni^{2+} or Cd^{2+} suggests that the phosphinate may have some role in the coordination, *i.e.* sterically hinders the coordination of 3rd ligand. In the protonated species MLH and ML_2H formed with Cu^{2+}-ions the EPR studies indicated that the phosphinate moiety may also be involved in the coordination while the amine nitrogen is being protonated.

4a. The stability constant of complexes formed between L^1, L^2, L^3, L^4 and L^5 and the metal ions Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} increase with an increasing number of carboxylate groups on the ligands. The complexes formed with L^1, L^2, L^3, and L^4 generally have lower stability constants than those of the analogous diamino-polycarboxylates indicating that the phosphinate group does not play an important role in the complexation. The existence of low stability ML, MLH, MLOH, and ML_2 type complexes were found in solution. Of the three diacetate derivatives the asymmetric L^3 forms higher stability complexes with metal ions that prefer octahedral coordination. However, metal ions that prefer square-planar coordination, like Cu^{2+}, form more stable complexes with the symmetric ligand L^2. The equatorial coordination of L^2 to Cu^{2+} in $K[CuL^2]\bullet H_2O$ has been confirmed by X-ray crystallography in the solid state. This complex exists as a polymer with hexagonal channels and the N- and O-atoms are coordinated in the equatorial plane, while one phosphinate and one acetate oxygen atom of two neighboring complexes occupy the axial positions.

4b. The coordination properties of the L^2, L^3 and L^4 ligands with Ln(III) ions are similar. The stability of the LnL complexes is comparable to that of the diamino-polycarboxylates and since these ligands are generally less basic than the diamino-di- or tri-carboxylates, it is very likely that the phosphinate group is involved in the coordination. The asymmetric L^3 and L^4 ligands form more stable LnL_2 type complexes than the L^2 suggesting that the imda type coordination is more favorable for LnL_2 complex formation. The protonation constants of the LnL_2 type complexes are as follows: $\log K_{LnL_2}^{H} = 8.33 \pm 0.28$ (L^2) and 7.86 ± 0.19 (L^3) and $\log K_{LnL_2}^{H} = 8.48 \pm 0.23$ and 7.50 ± 0.17 (L^4). These values are only slightly lower than the protonation constants of the amines in the free ligands, which indicates that the primary (L^3) and secondary amino groups of the ligands and L^2 and L^4 are not involved in coordination.

5a. The presence of the phosphinate group has a significant effect on the complexation properties of L^5. In spite of the lower basicities of the two nitrogen atoms of L^5, it forms complexes of similar or even higher stability with the smaller metal ions as the analogous 1,3-diaminopropane-*N*,*N*,*N*',*N*'-tetraacetate. L^5 also shows an unusually high selectivity for Zn^{2+} over Pb^{2+}, unlike edta or L^{13}. Its stability constants are higher probably because of the higher charge of the ligand, and there is a strong electrostatic interaction

between the phosphinate and the metal ion due to the coordination of both imda groups. Furthermore, L^5 shows a strong propensity for the formation of dinuclear M_2L complexes, which indicates that in the presence of the phosphinate group the two imda groups behave more independently than in the case of edta or L^{13}. The existence of the dinuclear complexes in equilibrium were proved by EPR (Cu^{2+}), spectrophotometry (Nd^{3+}) and ^{1}H-NMR (Lu^{3+}) spectroscopy. The stability of the dinuclear complexes is reversed, as it was found to be higher for larger Pb^{2+} ions (log K_{Pb_2L} = 6.31 vs. log K_{Zn_2L} = 1.61). The stability of the LnL^5 complexes are about 1-3 orders of magnitude higher than those of the complexes formed with structurally similar L^{13} ligand.

5b. The stability of the complexes increases with the decrease of the ionic radii of Ln(III) ions. The difference in the stability constants of LnL^5 and LnL^{13} complexes are higher for the larger lanthanide ions. On the contrary, the stability of the dinuclear Ln_2L^5 complexes practically remains constant (log K_{Ln_2L} = 3.34 ± 0.24) with a little decrease at the middle of the series. In these complexes each metal is coordinated by one imda group and since the phosphinate can only coordinate to one metal ion at a time, there may be an exchange between the two metal ions. This exchange process is probably the cause of the significant broadening of the signals observed in the ^{1}H-NMR spectra of Lu_2L^5. The structure of LnL^5 complexes in solution is more rigid and asymmetric than it was found for $[La(edta)]^-$ and $[Lu(edta)]^-$ complexes since each ^{1}H and ^{13}C atoms of the ligand in LaL^5 and LuL^5 complexes give a separate signal in the NMR spectra. The ^{1}H resonances of the acetate protons are AB multiplets, which are due to the long half-life of the Ln ← N coordinative bond on the NMR time scale. In the LaL^5 complex two acetate –CH_2– resonances appear as singlets, which is probably due to some exchange processes.

6. The presence of the alcoholic OH group in the diamino-polycarboxylate ligand 2-hydroxy-1,3-diaminopropane-*N,N,N′,N′*-tetraacetate significantly changes its complexation properties in comparison to the analogous H_4dpta or H_4edta. The stability constants of the lanthanide(III) complexes formed with the heptadentate $(L^{12}\text{-}OH)^{4-}$ are somewhat lower (2-3 log *K* units) than those of the hexadentate L^{13}, probably because of the lower basicities of the nitrogen atoms of $(L^{12}\text{-}OH)^{4-}$. However, the coordination of the two iminodiacetate groups of

the ligand leads to strong interactions between the alcoholic oxygen and the Ln^{3+} ion and the alcoholic OH group dissociates at unexpectedly low pH values. The pH range of the dissociation shifts to more acidic regions (the dissociation constants of the alcoholic OH group are in the range of 5.71–2.09 (La^{3+}– Lu^{3+})) with the decrease of the size of the Ln^{3+} ions indicating the electrostatic nature of the metal-ligand interactions. The coordinated heptadentate $(L^{12}\text{-}O)^{5-}$ moiety, which contains an alkoxo oxygen, shows a strong propensity to form dinuclear dimer complex anions, $[Ln_2(L^{12}\text{-}O)_2]^{4-}$, both in solution and solid state. In the dinuclear dimers the ligands are coordinated to both Ln^{3+} with an iminodiacetate group and the alkoxo oxygens are in bridging positions. The coordination number of the Ln^{3+} ions is 9 in the complexes of the lighter elements, with a water molecule in the inner sphere of the Ln(III)ion (e.g. the solid $K_4[Nd_2(L^{12}\text{-}O)_2(H_2O)_2]\cdot 14H_2O$). The geometry of the dimer complexes of the lighter and heavier lanthanides is slightly different. Based on the literature data, in solid state there is a symmetry plane in the complexes of the heavier elements while in the Nd^{3+} dimer the only symmetry element is a center of symmetry. The probable absence of the water molecule in the inner sphere of the Gd^{3+} complex is indicated by the unusually low relaxivity value of $[Gd_2(L^{12}\text{-}O)_2]^{4-}$, which also shows the formation of dimer species with the heptadentate ligand $(L^{12}\text{-}O)^{5-}$. This is in a good agreement with the results of luminescence life-time measurements obtained for $[Eu_2(L^{12}\text{-}O)_2]^{4-}$ and with the absence of the ternary complex formation for these complexes. The ESI-TOF MS studies indicated that the complexes retain their dimeric structure even in quite dilute (0.25 mM) solutions. Based on 1D and 2D NMR spectroscopic studies, the solution structure of the complex $[La_2(L^{12}\text{-}O)_2]^{4-}$ is similar to the solid state structure of the $[Nd_2(L^{12}\text{-}O)_2]^{4-}$ complex determined by X-ray diffraction.

V. Potential use of our results

Although this work is primarily basic research, some results of this project may be valuable in medical or biological applications.

The new synthetic method developed in the present work will likely be applicable for the preparation of the parent compound bis-(aminomethyl)-phosphinic acid in a two step procedure does not require work under inert atmosphere. Bis-(aminomethyl)-phosphinic acid itself can be considered as a building block for the synthesis of C2 symmetric inhibitors of Human

Immunodeficiency Virus (HIV). Our synthetic approach may also be adapted to the synthesis of intermediates for preparation of macrocyclic ligands incorporating aminomethyl-phosphinic acid moiety.

Peptides incorporating the phosphinic moiety have been shown to have effective enzyme inhibitor properties.[2] Diamino-polycarboxylate type phosphinic acid derivatives have been shown to have plant growth-regulating properties.[3] The phosphinic acid derivatives synthesized in the recent work are diamino-polycarboxylate type phosphinic acids and thus might show enzyme inhibitor and/or plant-growth regulator activity.

The importance of double-stranded DNA cleavage in molecular biology has led to the development of lanthanide complexes that are capable of hydrolytically cleaving double-stranded DNA. Dinuclear lanthanide(III) complexes of 1,3-diamino-2-hydroxopropane-*N,N,N´,N´*-tetraacetic acid have been proposed to cleave DNA, but the formation of dinuclear $Ln_2(dpta\text{-}O)^+$ complexes solution were not observed/studied earlier. Our study may help to obtain insights into the mechanism of DNA cleavage by dinuclear $Ln_2(dpta\text{-}O)^+$ complexes and to prepare and study new dinuclear ($(Ln_2L^5)^+$) complexes for these purposes.

[2] D. J. Miller, S.M. Hammond, D. Anderluzzi, T. D. H. Bugg, *J. Chem. Soc. Perkin Trans. 1,* **1998,** 131.
[3] M.A. Dhansay, P.W. Linder, R.G. Torrington, T.A. Modro, *J. Phys. Org. Chem.*, **1990,** *3,* 248

VI. Publications

VI.1. Articles connected to the thesis

5. **Gy. Tircsó,** E. Brücher, I. Lázár:
Mannich-type condensation reactions in alcoholic media as a practical route to aminomethyl-phosphinic acid derivatives containing P–H bond
In preparation.

4. **Gy. Tircsó,** I. Bányai, E. Brücher, F. K. Kálmán, R. Király, I. Lázár, R. Pál:
Equilibrium and NMR spectroscopy studies on the complexes of lanthanides formed with di-, tri- and tetraacetate derivatives of bis-(aminomethyl)-phosphinic acid
In preparation.

3. **Gy. Tircsó,** A. Bényei, R. Király, I. Lázár, R. Pál, E. Brücher:
Complexation properties of the di-, tri- and tetraacetate derivatives of bis-(aminomethyl)-phosphinic acid
Eur. J. Inorg. Chem. **2007,** 701-713.

2. **Gy. Tircsó,** A. Bényei, E. Brücher, A. Kis, R. Király:
Equilibria and structure of the lanthanide(III)-2-hydroxy-1,3-diaminopropane-*N,N,N′,N′*-tetraacetate complexes: Formation of alkoxo-bridged dimers in solid state and solution
Inorg. Chem. **2006,** *45(13),* 4951-4962.

1. N. V. Nagy, T. Szabó-Plánka, **Gy. Tircsó,** R. Király, Zs. Árkosi, A. Rockenbauer, E. Brücher:
Copper(II) complexes of some N-substituted bis(aminomethyl)phosphinate ligands. An integrated EPR study of microspeciation and coordination modes by the two-dimensional simulation method
J. Inorg. Biochem. **2004,** *98,* 1655-1666.

VI.2. Articles not detailed in the thesis:

8. A. Pasha, **Gy. Tircsó,** E. Brücher, A. D. Sherry:
Synthesis and Characterization of some DOTA-tetra(amide) Derivatives: Equilibrium and Kinetic Behavior of Lanthanide(III) Complexes
In preparation.

7. M. M. Ali, M. Woods, E. Suh, Z. Kovács, **Gy. Tircsó,** V. Kodibagkar, A. D. Sherry:
Albumin-binding PARACEST agents
Submitted to J. Biol. Inorg. Chem.

6. F. K. Kálmán, M. Woods, P. Jurek, M. Spiller, P. Caravan, **Gy. Tircsó,** Y. Zhuo, R. Király, E. Brücher, A. D. Sherry:

Potentiometric and Relaxometric Properties of Gadolinium(III) DOTA-4AmP; a pH responsive MRI Contrast Agent
Submitted to Inorg. Chem.

5. J. Vipond, M. Woods, P. Zhao, **Gy. Tircsó,** J. Ren, S. G. Bott, D. Ogrin, G. E. Kiefer, Z. Kovács, A. D. Sherry:
A Bridge to Coordination Isomer Selection in Lanthanide(III) DOTA-tetraamide Complexes
Inorg. Chem. **2007,** DOI: 10.1021/ic062184+.

4. **Gy. Tircsó.** Z. Kovács, A. D. Sherry:
Equilibrium and Formation/Dissociation Kinetics of Some Ln^{III}PCTA Complexes
Inorg. Chem., **2006,** *45(23),* 9269-9280.

3. M. Woods, G. E. Kiefer, S. Bott, A. Castillo-Muzquiz, C. Eshelbrenner, L. Michaudet, K. McMillan, S. D. K. Mudigunda, D. Grin, **Gy. Tircsó,** S. R. Zhang, P. Zhao, A. D. Sherry:
Synthesis, Relaxometric and Photophysical Properties of a New pH-Responsive MRI Contrast Agent: The Effect of Other Ligating Groups on Dissociation of a p-nitrophenolic Pendant Arm
J. Am. Chem. Soc., **2004,** 126 (30), 9248-9256.

2. I. S. Balog, D. I. Molnar, **Yu. B. Tircho,** I. L. Mushkalo:
Selective Extraction and Spectrophotometric Determination of Cobalt(II) with Carbocyanine Dyes
Ukr. Khim. Zhurnal (in Russian), **2001,** *67(9-10),* 40-44.

1**.** I. M. Maga, I. S. Balogh, **Yu. B. Tircho:**
Analytical Problems of Spectrophotometric Determination of Different Forms of Chromium(III, VI)
Naukovij Visznik Uzhgorodszkovo Univ. (in Ukrainian), **1999,** *4,* 89-92.

VI.3. List of the presentations (E) and posters (P) connected to the thesis:

19E. R. Pál, E. Brücher, F. Kálmán, R. Király, **Gy. Tircsó:**
Az *N,N',N'*- trisz-(karboximetil-aminometil)-foszfinsav előállítása és komplexképző sajátságai (Synthesis and complexation properties of the *N,N',N'*-tris(carboxymethyl-aminomethyl)-phosphinic acid)
Young Chemist's Meeting (*Fiatal Kémikusok Előadóülése),* 25 November **2003,** Budapest, Hungary.

18P. **Gy. Tircsó,** I. Bányai, A. Bényei, E. Brücher, R. Király
Comparative multinuclear NMR studies on the solution structure of the complexes of lanthanides formed with bis(methyliminodiacetato)hydroxy-methane and bis(methyliminodiacetato)phosphinate ligands
5th International Conference on f-elements, 24-29 August **2003,** Geneva, Switzerland.

17P. R Pál, E. Brücher, **Gy. Tircsó,** Ferenc Kálmán:
Synthesis and complexation properties of the *N,N',N'*-tris(carboxymethyl-aminomethyl)-phosphinic acid
28th International Conference on Solution Chemistry, 23-28 August **2003,** Debrecen, Hungary.

16P. N. V. Nagy, T. Szabó-Plánka, **Gy. Tircsó,** R. Király, Zs. Árkosi, A. Rockenbauer, E. Brücher
A two-dimensional EPR study of copper(II) and some N-substituted bis-(aminomethyl)-phosphinic acids. Microspeciation and coordination modes
28th International Conference on Solution Chemistry, 23-28 August **2003,** Debrecen, Hungary.

15P. N. V. Nagy, T. Szabó-Plánka, **Gy. Tircsó,** R. Király, Zs. Árkosi, A. Rockenbauer, E. Brücher:
Microspeciation and coordination modes in solutions of copper(II) and some aminocarboxylate ligands containing in-chain phosphinate group. A two-dimensional EPR study
19th International Conference on Coordination and Bioinorganic Chemistry, Progress in Coordination and Bioinorganic Chemistry, 2-6 June **2003,** Smolenice, Slovakia.

14E. **Gy. Tircsó,** I. Bányai, A. Bényei, E. Brücher, R. Király:
A bisz(metiliminodiacetáto)-foszfinsav és a bisz(metiliminodiacetáto)-hidroxi-metán ligandumok komplexei oldatbeli szerkezetének összehasonlító tanulmányozása multinukleáris NMR spektroszkópia segítségével (Comparative multinuclear NMR studies on the solution structure of the complexes of lanthanides formed with bis(methyliminodiacetato)hydroxy-methane and bis(methyliminodiacetato)phosphinate ligands)
XXXVIIIth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium) 21-23 May **2003,** Gyula, Hungary.

13E. R. Pál, E. Brücher, F. Kálmán, R. Király, **Gy. Tircsó:**
Az *N,N',N'*-trisz-(karboximetil-aminometil)-foszfinsav előállítása és komplexképző sajátságai (Synthesis and complexation properties of the *N,N',N'*-tris(carboxymethyl-aminomethyl)-phosphinic acid)
XXXVIIIth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium) 21-23 May **2003,** Gyula, Hungary.

12P. R. Pál, E. Brücher, **Gy. Tircsó,** F. K. Kálmán:
Synthesis and complexation properties of the *N,N',N'*-tris(carboxymethyl-aminomethyl)-phosphinic acid
3rd Interdisciplinary Symposium on Biological Chirality, April 30-May 4, **2003,** Modena, Italy.

11E. **Gy. Tircsó,** I. Bányai, E. Brücher, R. Király, A. Kis, I. Lázár, T. R. Varga:
Lantanoida(III)ionok 2-hidroxi-1,3-diaminopropán-*N,N,N',N',*-tetraacetát- és bisz-(iminodiacetáto-N-metil)-foszfinsavval képződő komplexei (Lanthanide(III) complexes formed with 2-hydroxy-1,3-diaminopropane-N,N,N'N'-tetraacetic and bis(iminodicarboxymethyl-N-methyl)phosphinic acids)
VIIIth Conference of Chemistry (Vegyészkonferencia) 15-17 November **2002,** Kolozsvár, Romania.

10E. **Gy. Tircsó,** E. Brücher, R. Király, I. Lázár:
Láncközi foszfinátcsoportot tartalmazó poliamino-polikarboxilát-és polifoszfonát típusú ligandumok előállítása Mannich-reakcióval (Synthesis of some polyamino-polycarboxilate type ligands incorporation the phosphinate group „in-chain" position via Mannich type reaction)
VIIIth Conference of Chemistry (Vegyészkonferencia) 15-17 November **2002,** Kolozsvár, Romania.

9E. E. Brücher, **Gy. Tircsó,** I. Bányai, A. Bényei, F. Kálmán, R. Király, I. Lázár:
Lanthanide(III) complexes of some bis-(aminomethyl)-phosphinic acid derivative ligands
Lanthanide Chemistry for Diagnosis and Therapy, Mid Term Evaluation Workshop, July 22-25, **2002,** Heidelberg, Germany.

8P. R. Király, E. Brücher, A. Kis, **Gy. Tircsó:**
Lanthanide(III) complexes of 2-hydroxy-1,3-diaminopropane-*N,N,N',N',*-tetraacetate
Lanthanide Chemistry for Diagnosis and Therapy, Mid Term Evaluation Workshop, July 22-25, **2002,** Heidelberg, Germany.

7E.**Gy. Tircsó,** I. Bányai, A. Bényei, E. Brücher, F. Kálmán, R. Király, I. Lázár István:
A bisz(aminometil)-foszfinsav és néhany származéka komplexképző sajátságai
(Lanthanide(III) complexes of some bis-(aminomethyl)-phosphinic acid derivative ligands)
XXXVIIth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium), 29-31 May **2002,** Mátraháza, Hungary.

6E. R. Király, E. Brücher, A. Kis, **Gy. Tircsó**:
A 2-hidroxi-1,3-diaminopropán-*N,N,N',N',*-tetraacetát lantanoida(III)-komplexei
(Lanthanide(III) complexes of the 2-hydroxy-1,3-diaminopropane-*N,N,N',N',*-tetraacetic acid)
XXXVIIth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium), 29-31 May **2002,** Mátraháza, Hungary.

5E. N. V. Nagy, T. Plankáné-Szabó, A. Rockenbauer, Zs. Árkosi, L. Korecz, **Gy. Tircsó,** R. Király, E. Brücher:

Szekunder foszfinsavak Cu(II)komplexeinek egyensúlyi és szerkezetvizsgálata kétdimenziós ESR-spektroszkópiai módszerrel (A two-dimensional EPR study of copper(II) complexes formed with N-substituted bis-(aminomethyl)-phosphinic acid derivatives)
XXXVIIth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium), 29-31 May **2002,** Mátraháza, Hungary.

4E. **Gy. Tircsó,** I. Lázár, R. Király, E. Brücher Ernő:
Láncközi foszfinátcsoportot tartalmazó aminokarbonsavak komplexképző tulajdonságai (Complexation properties of some amino-polycarboxilates incorporating „in-chaine" phosphinate moiety)
VIIth Conference of Chemistry (Vegyészkonferencia) 16-18 November **2001,** Félix-fürdő, Romania.

3E. **Gy. Tircsó,** I. Lázár, R. Király, E. Brücher:
A bisz-(*N*-foszfonometil)-amin és aminokarbonsav-származékainak előállítása, protonálódási viszonyaik és komplexképzésük (Synthesis, protonation and complexation properties of the bis(N-phosphinomethyl)-amine and its acetate derivatives)
10th Science Meeting of MTA Szabolcs-Szatmár-Bereg County (A *MTA* Szabolcs-Szatmár-Bereg Megyei Tudományos Testülete 10.-közgyűléssel egybekötött *Tudományos Ülése),* 28-29 September **2001,** Nyíregyháza, Hungary.

2P. **Gy. Tircsó,** I. Lázár, E. Brücher,
Láncközi foszfinátcsoportot, és kiralitáscentrumot tartalmazó poliamino-polikarboxilát típusú ligandumok előállítása és protonálódási viszonyaik vizsgálata (Synthesis and protonation of some chiral polyamino-polycarboxylates incorporating phosphinic acid moiety "in-chaine" position)
Conference of Chemistry (Vegyészkonferencia), 27-29 July **2001,** Hajdúszoboszló, Hungary.

1E. **Gy. Tircsó,** I. Lázár, R. Király, I. Bányai, E. Brücher:
Láncközi foszfinátcsoportot tartalmazó poliamino-polikarboxilát típusú ligandumok előállítása, protonálódási viszonyaik és komplexképzésük (Synthesis, protonation and complexation properties of some polyamino-polycarboxylates incorporating phosphinic acid moiety "in-chaine" position)
XXXVIth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium), 26-28 May **2001,** Pécs, Hungary.

VI. 4. List of the presentations (E) and posters (P) not connected to the thesis:

9P. **Gy. Tircsó,** E. Tircsóné Benyó, A. D. Sherry:
Equilibrium, Formation and Dissociation kinetics of some Lanthanide(III) DOTA-bis(amide) Complexes

Abstracts of *232nd Amercian Chemical Society National Meeting,* September 10-14, **2006,** San Francisco, CA, USA, (p. 83, Inor-730).

8E. **Gy. Tircsó,** A. D. Sherry:
Effect of Macrocyclic Ligand Preorganiztion on the Formation and Dissociation Kinetics of Lanthanide(III) Complexes
Multi-face coordination chemistry: Forty-five years of rare earth chemistry with Ernő Brücher, Special symposia, August 27, **2005,** Debrecen, Hungary.

7P. Z. Kovács, **Gy. Tircsó,** A. D. Sherry:
Chelation Properties of Pyclen Based Macrocyclic Ligands
16th International Symposium on Radiopharmacrutical Chemistry, June 24-28, **2005,** Iowa City, Iowa, USA (S311).

6P. **Gy. Tircsó,** Z. Kovács, A. D. Sherry:
Synthesis, Equilibrium and Kinetics Studies on the Lanthanide Complexes of some Pyridine Containing Macrocyclic Ligands
Abstracts of *229th Amercian Chemical Society National Meeting,* March 13-17, **2005,** San Diego, CA, USA (p. 74, Inor-734).

5E. F. Kálmán, E. Brücher, R. Király, R. Pál Róbert, **Gy. Tircsó**:
Az 1,3-diaminopropán-*N,N,N′,N′*-tetraacetát (H_4PDTA) és származékai lantanoida(III)-komplexei kinetikai stabilitása (Kinetics stability of the lanthanide complexes formed with 1,3-diaminopropane-*N,N,N′,N′*-tetraacetate and its derivatives)
XXXIXth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium), 26-28 May **2004,** Gárdony, Hungary.

4E. F. Kálmán, E. Brücher, R. Pál, **Gy. Tircsó:**
A bisz(metiliminodiacetáto)-foszfinsav, a bisz(metiliminodiacetáto)-hidroxi-metán és a metiliminodiacetáto-glicináto-foszfinát lantanoida(III)-komplexei fémioncsere reakcióinak kinetikája (Metal exchange reactions of lanthanide complexes formed with structurally related ligands incorporating phosphinate and alcoholic OH groups)
Young Chemist's Meeting (*Fiatal Kémikusok Előadóülése),* 25 November **2003,** Budapest, Hungary.

3E. F. Kálmán, E. Brücher, R. Pál, **Gy. Tircsó:**
A bisz(metiliminodiacetáto)-foszfinsav, a bisz(metiliminodiacetáto)-hidroxi-metán és a metiliminodiacetáto-glicináto-foszfinát lantanoida(III)-komplexei fémioncsere reakcióinak kinetikája (Metal exchange reactions of lanthanide complexes formed with structurally related ligands incorporating phosphinate and alcoholic OH groups)
XXXVIIIth Colloqium on Coordination Chemistry (Komplexkémiai Kollokvium), 21-23 May **2003,** Gyula, Hungary.

2E. F. Kálmán, E. Brücher, R. Király, **Gy. Tircsó:**
Lantanoida(III)-bisz(iminodiacetátó-N-metil)-foszfinát komplex fémioncsere reakcióinak kinetikája (Kinetics of metal exchange reactions of lanthanide complexes formed with bis(iminodicarboxymethyl-N-methyl)phosphinic acid)
VIIIth *Conference of Chemistry (Vegyészkonferencia),* 15-17 November **2002,** Kolozsvár, Romania.

1E. **Gy. Tircsó,** J. Balogh, Á. H. Tóth, I. Maga:
A króm (III, VI) módosulatok analitikai problémái (Analytical problems of spectrophotometric determination different forms of chromium(III, VI))
8th *Science Meeting* of MTA Szabolcs-Szatmár-Bereg (A *MTA* Szabolcs-Szatmár-Bereg Megyei Tudományos Testülete 8.-közgyűléssel egybekötött *Tudományos Ülése),* 24-25 Szeptember **1999,** Nyíregyháza, Hungary.