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# Complexes of tetraazacycles bearing methylphosphinic/phosphonic acid pendant arms with copper(II), zinc(II) and lanthanides(III). A comparison with their acetic acid analogues

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**Contents**



**Abstract**

A comparison of complexing properties of cyclen and cyclam derivatives containing acetic acid pendant arms on one hand and their methylphosphonic or methylphosphinic acid

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analogues on the other is made mainly with complexes of copper and lanthanides due to their applications in medicine. The stability constant values of Cu(II) complexes are determined mainly by the basicity of amine groups. The influence of other possible effects, such as the macrocyclic effect in tetraazacycle in contrast to linear amines or the number of additional donor atoms in or outside of pendant arms and their basicity, seems to be very small. The stability constants for Gd(III), in addition to the basicity of amines, are also influenced by the basicity of the pendants and their number. The values of cyclam derivatives are lower than those of cyclen and it corresponds to the ring size effect as was found for zinc(II) complexes. In contrast to Cu(II), the Gd(III) stability constants of the phosphonic acid ligands are also lower than those with $H_4$dota derivatives. A comparison of co-ordination polyhedra of the carboxylic and phosphonic or phosphinic derivatives shows similar motifs that are more determined by the macrocyclic effect than by the kind of donor groups in pendant arms. The differences between the polyhedra observed result from longer C–P(O) bond in the phosphorus derivatives than that C–C(O) in the acetate pendants. Consequently, the lanthanide(III) complexes with phosphorus acid derivatives are more sterically hindered; oxygen atoms in the $O_4$ plane are close to one another and there is insufficient room for co-ordination of a water molecule, which is crucial in MRI applications. 

*Keywords:* Tetraazacycles; Amino acid analogues; Cyclen and cyclam derivatives; Phosphonic acid; Phosphinic acid; Solution properties; X-ray structure comparison

## 1. Introduction

Polyazacycles with co-ordinating pendant arms are superior ligands for transition metal as well as for lanthanide ions [1,2]. They form thermodynamically very stable complexes showing high selectivities to metal ions [1–3]. Polydentate ligands, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid ($H_4$dota) and 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid ($H_4$teta) (Fig. 1), form thermodynamically and kinetically stable complexes even with labile metal ions such as the first row-transition metal divalent ions or trivalent lanthanides [2]. Properties of such ligands have been investigated when designing magnetic resonance imaging (MRI) contrast agents [4] based on $Gd^{3+}$ and diagnostic/ therapeutic radiopharmaceuticals utilising metal radionuclides such as $^{90}Y$, $^{64,67}Cu$, $^{111}In$, etc. [5]. In addition, azacyclic sequestering agents for toxic heavy metals such as lead, cadmium and mercury were synthesised [6]. In search for other ligands with similar or better properties than common acetate derivatives, research has also been focused on synthesis and investigation of azamacrocycles with phosphonic [7] or phosphinic [8] acids groups on pendant arms. Complexes with the phosphorus ligands exhibit higher selectivity in complexation and sufficient thermodynamic stability [9].

This paper is focused on a comparison of complexing properties of cyclen and cyclam derivatives containing acetic acid pendant arms on one hand and their methylphosphonic or methylphosphinic acid analogues on the other. For illustration of differences in their properties, the simplest ligands, glycine and its phosphorus analogues, and their complexing properties are also included in consideration.

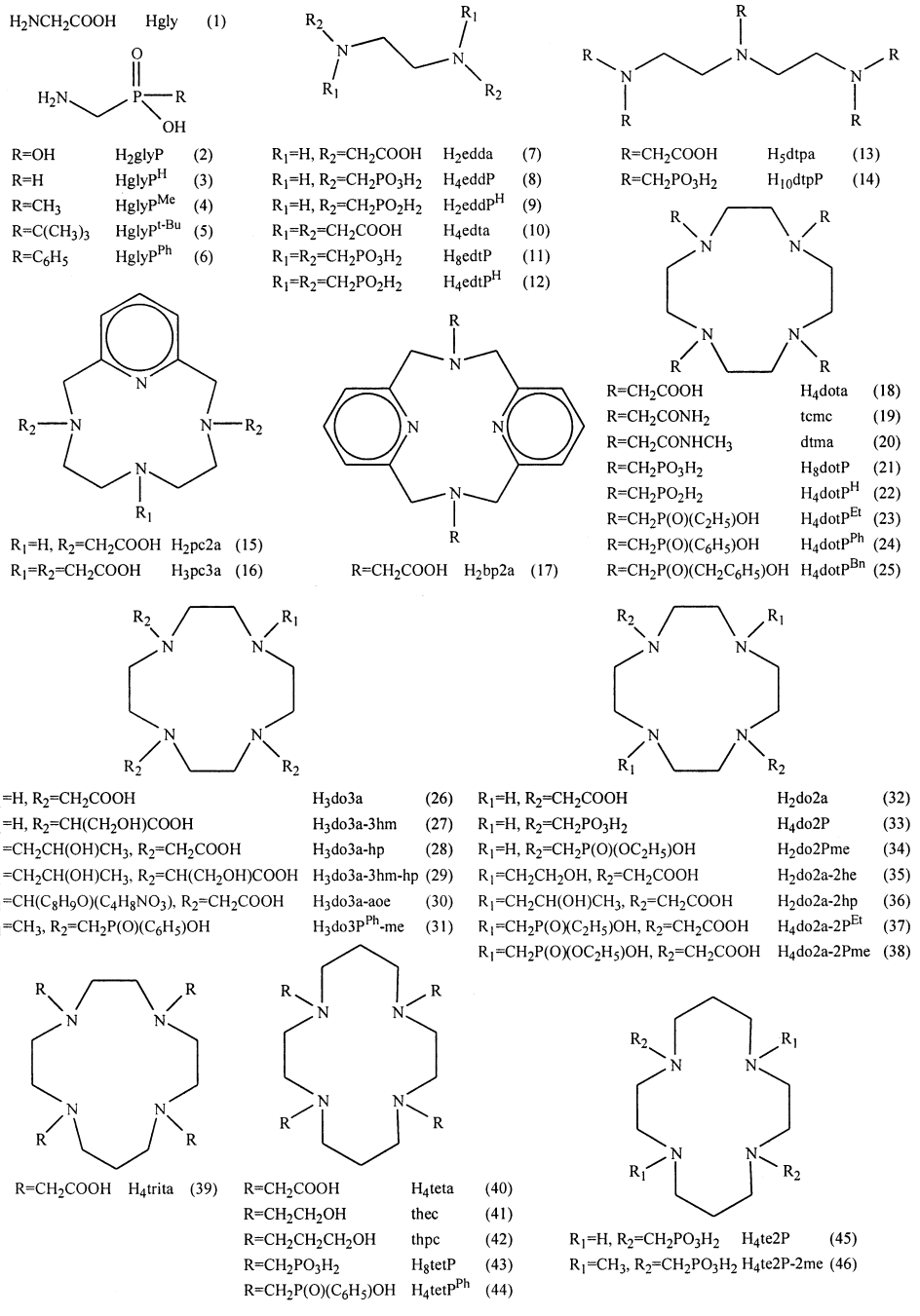



Fig. 1. Formulae of the ligands with their abbreviations and numbers. The numbers are also used for identification of the ligands in the following figures.

The comparison will be made mainly with complexes of copper and lanthanides due to their applications mentioned above.

## 2. Solution properties

### 2.1. Comparison of dissociation constants.

Dissociation constants of glycine and its phosphonic acid analogues $NH_2CH_2PO(OH)_2$ ($H_2$glyP) and phosphinic acid $NH_2CH_2PO(R)OH$ (HglyP$^R$) where R = H, Me, *tert*-Bu and Ph are listed in Table 1.

From Table 1, it is evident that the basicity increases in the order aminophosphinic < aminocarboxylic < aminophosphonic acids. This trend is well known [12] and the higher basicity of amine in phoshonic acids is explained by repulsion of the negative charge (2–) of three oxygen atoms of the phosphonate which predominates over electron withdrawing. On the other hand, the phosphinates show lower negative charge (1–), the repulsion being lower than that in the phosphonate groups and thus the lower basicity observed corresponds with the electron withdrawing effect of the phosphinate moiety. In addition, basicity of aminomethylphosphinic acids bearing hydrogen, phenyl, methyl or *tert*-butyl substituents increases in that order. This order follows the simple carboxylic acids series [10] from trimethylacetic to acetic, benzoic and formic acid.

Acid–base properties of cyclen, cyclam and their acetic, methylphosphonic and methylphosphinic acid derivatives were widely studied and their p$K_A$ values are known. Their comparison is shown in Table 2 and formulae together with abbreviations used throughout the paper are shown in Fig. 1.

From the comparison, it is evident that the protonation schemes of the compounds are similar. The first two protonations occur in the alkaline region and reflect protonations of two opposite nitrogen atoms of the ring. On the basis of protonation of $H_4$dota·HCl [19], $H_4$dotP$^{Ph}$·4$H_2O$ and $(AdNH_3)_2(H_2dotP^{Ph})$·6$H_2O$ (where $AdNH_2$ = 1-adamantylamine) [14], $H_4$dotP$^{Bn}$·HCl [20], $H_4$teta [21] and $H_8$dotP [22] in the solid state and comparison of the constants in Table 2, it is widely accepted that further protonations occur on pendant arms. Except for p$K_1$ of $H_4$dotP$^{Ph}$, the other p$K_A$ values indicate that the $-P(R)O_2^-$ group is more electron-withdrawing than $-CO_2^-$ and $-PO_3^{2-}$ and this order follows the well-

Table 1
Comparison of the protonation constants of glycine and its phosphorus acid derivatives

| | | Hgly | $H_2$glyP | HglyP$^{t\text{-Bu}}$ | HglyP$^{Me}$ | HglyP$^{Ph}$ | HglyP$^{H}$ |
|---|---|---|---|---|---|---|---|
| Ref. | | [10] | [10] | [11] | [11] | [11] | [11] |
| Log $\beta_1$ | p$K_1$ | 9.57 | 10.00 | 8.427 | 8.403 | 8.082 | 8.066 |
| Log $\beta_2$ − log $\beta_1$ | p$K_2$ | 2.36 | 5.38 | 1.204 | 0.89 | ~0.4 | <0.5 |
| Log $\beta_3$ − log $\beta_2$ | p$K_3$ | | ~0.5 | | | | |

Table 2
Comparison of the protonation constants of cyclen and cyclam and their derivatives

| | | Cyclen | $H_4$dota | $H_4$dotP$^{Ph}$ | $H_4$dotP$^{H}$ | $H_4$dotP$^{Et}$ | $H_8$dotP |
|---|---|---|---|---|---|---|---|
| Ref. | | [10] | [13] | [14] | [15] | [16] | [17] |
| Log $\beta_1$ | p$K_1$ | 10.6 | 11.74 | 11.44 | 10.41 | 10.94 | 13.7 |
| Log $\beta_2 - \log \beta_1$ | p$K_2$ | 9.6 | 9.76 | 7.27 | 6.84 | 8.24 | 12.2 |
| Log $\beta_3 - \log \beta_2$ | p$K_3$ | (1.5) | 4.68 | 2.75 | 1.97 | 3.71 | 9.28 |
| Log $\beta_4 - \log \beta_3$ | p$K_4$ | (0.7) | 4.11 | 1.45 | | | 8.09 |
| Log $\beta_5 - \log \beta_4$ | p$K_5$ | | 2.37 | | | | 6.12 |
| Log $\beta_6 - \log \beta_5$ | p$K_6$ | | | | | | 5.22 |
| | | Cyclam | $H_4$teta | $H_4$tetP$^{Ph}$ | $H_8$tetP | | |
| Ref. | | [10] | [18] | [14] | [17] | | |
| Log $\beta_1$ | p$K_1$ | 11.29 | 10.52 | 9.85 | 13.4 | | |
| Log $\beta_2 - \log \beta_1$ | p$K_2$ | 10.19 | 10.17 | 9.94 | 12.8 | | |
| Log $\beta_3 - \log \beta_2$ | p$K_3$ | 1.61 | 4.09 | 1.85 | 8.82 | | |
| Log $\beta_4 - \log \beta_3$ | p$K_4$ | 1.91 | 3.35 | | 7.75 | | |
| Log $\beta_5 - \log \beta_4$ | p$K_5$ | | | | 6.25 | | |
| Log $\beta_6 - \log \beta 5$ | p$K_6$ | | | | 5.42 | | |

known order observed for the simple aminophosphinic, phosphonic and carboxylic acids mentioned above. The last dissociation constant p$K_1$ of $H_4$dotP$^{Ph}$ is unexpectedly higher than the values for $H_4$dotP$^{H}$ and $H_4$dotP$^{Et}$, probably due to steric hindrance and hydrophobic interactions as was discussed on the basis of NMR results [14]. By comparison the phosphinic acid derivatives of cyclen, we can also observe an influence of the substituent on the phosphorus atom. The values of the other p$K_A$ increase in the expected order, $H_4$dotP$^{H}$ < $H_4$dotP$^{Ph}$ < $H_4$dotP$^{Et}$, i.e. from H to phenyl and ethyl substituents.

### 2.2. Comparison of stability constants of Cu(II), Zn(II) and Gd(III) complexes

The complexing ability of glycine and its phosphorus acid analogues toward Cu(II) is described by a similar simple chemical model. Their stability constants (Cu:L = 1:1) increasing in order: aminophosphinic < aminophosphonic ≈ aminocarboxylic acid [11,12].

$$4.41\ (\text{HglyP}^{Ph}) < 4.60\ (\text{HglyP}^{Me}) < 4.97\ (\text{HglyP}^{H}) < 5.37\ (\text{HglyP}^{t\text{Bu}}) < 7.95\ (\text{H}_2\text{glyP}) < 8.15\ (\text{Hgly})$$

This order, roughly following the overall basicity of the acids, was observed for a number of metal ions. In the phosphinic acid series, except for HglyP$^{H}$, this order follows, as expected, the order found for p$K_A$ values. The log $K_{ML}$ and log $K_{ML2}$ values of HglyP$^{H}$ are surprisingly high, this is probably caused by the better deformability of the $-PO(H)O^-$ group and, consequently, better ability to form the chelate ring and/or by a softer character of the group in comparison with

alkyl/phenyl substituents. The stability constants with lanthanides were found only for glycine with Ce(III), Pr(III) and Eu(III) systems. The values of $\log K_{ML}$ lie in the range from 0.5 to 0.7 [10]. Systems with phosphonic/phosphinic acids have not been investigated; nevertheless, similar or even lower values of $\log K_{ML}$ are expected.

A number of azacycles bearing acetate or methylphosphonic or phosphinic acid pendant arms were studied and their stability constants with Cu(II) were determined. A plot of stability constant values versus overall basicity, i.e. the sum of $pK_A$ values should be a straight line for similar ligands [23]. Unfortunately, we could not find any fit for the Cu(II) dependence. On the other hand, if we used only the sum of the two basic $pK_A$ values corresponding to protonation of nitrogen atoms of the azacycles, a rough correlation $\log K_{ML}$ versus $pK_1 + pK_2$ was found. This correlation is plotted in Fig. 2. Stability constants for complexes (molar ratio 1:1) of Cu(II) with glycine and its phosphorus analogues are also included in the plot.

The most stable complexes are formed with cyclam and cyclen derivatives containing methylphosphonic acid arms followed by those with acetic and methylphosphinic acid arms. This order corresponds with the order observed for glycine and its phosphorus analogues. From this plot it is also evident that cyclam and cyclen derivatives together with linear amine derivatives fall into the fit and thus the effect of azacycle or the size of cavity do not substantially change the stability of the complexes. In addition, the influence of a number of pendant arms seems to be also negligible; e.g. the basicity of the two nitrogen atoms of $H_4$dota, $H_4$teta, $H_4$trita and $H_3$do3a is virtually the same and the stabilities of their copper(II) complexes fall into a very narrow range. Only three values, two for cyclam derivatives, with 3-hydroxypropyl (point 42) and methylene(phenylphosphinic) acid (point 44) pendants, and one for phosphonic analogue of $H_5$dtpa (point 14) show lower values of $\log K_{ML}$. The correlation indicates that thermodynamic stability of Cu(II) complexes is mainly influenced by basicity of the nitrogens.

We also tested similar correlations for Zn(II) and for Gd(III) and the ligands characterised both by overall basicity and basicity of the two nitrogen atoms. For zinc, a better fit was observed when only the sum of $pK_1 + pK_2$ was included in consideration. The correlation is plotted in Fig. 3.

The plot indicates that, in contrast to the Cu(II) systems, the values of the stability constants for cyclam and its derivatives differ from those observed for cyclen derivatives. This points to an influence of the ring size. In addition, the values of linear amine derivatives lie on the edge of the considered belt. However, like in the Cu(II) system, all cyclen derivatives containing acetate or methylphosphinate or methylphosphonate pendant arms fit and thus, the influence of the coordination ability of the pendant arm is small. The stability constants again follow the order phosphinic < carboxylic < phosphonic acid as basicity of nitrogen atoms increases. The values for derivatives of linear amines are close to those for the cyclen series. The values for phosphonic acid derivatives are higher than those for the acetic, however, they are too scattered to draw any conclusion.

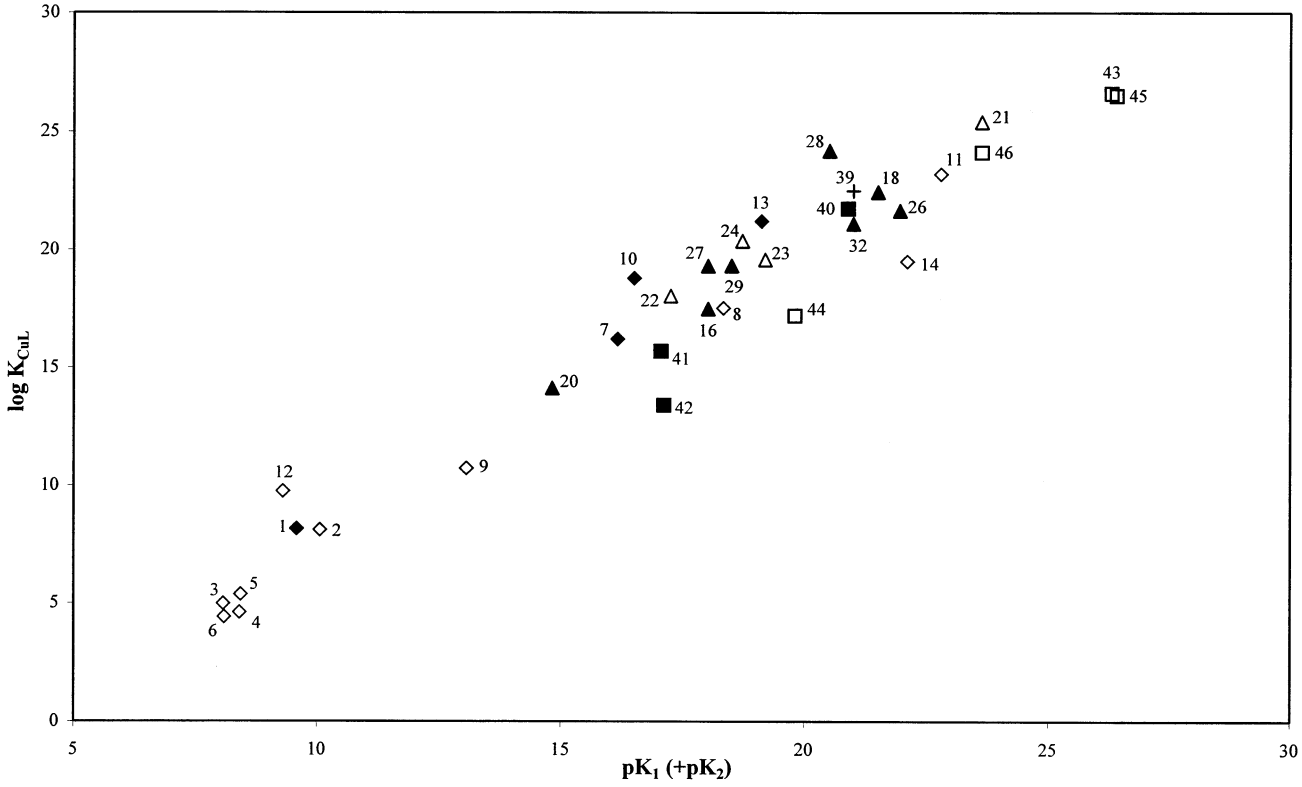



Fig. 2. Plot of stability constant of CuL vs. basicity of nitrogen atom(s) of ligand. Filled symbols — ligands with acetate and/or alcoholic pendant arms; open symbols — phosphorus acid derivatives. Numbers of ligands follow from Fig. 1. Ligands with open-chain backbone, ◆: 1 — Hgly [10]; 7 — $H_2$edda [10]; 10 — $H_4$edta [10]; 13 — $H_5$dtpa [10]; ◇: 2 — $H_2$glyP [10]; 3 — $HglyP^{H}$ [11]; 4 — $HglyP^{Me}$ [11]; 5 — $HglyP^{t\text{-}Bu}$ [11]; 6 — $HglyP^{Ph}$ [11]; 8 — $H_4$eddP [10]; 9 — $H_2eddP^{H}$ [10]; 11 — $H_8$edtP [10]; 12 — $H_4edtP^{H}$ [24]; 14 – $H_{10}$dtpP [10]. Ligands based on cyclen skeleton, ▲: 16 — $H_3$pc3a [25]; 18 — $H_4$dota [13]; 20 — dtma [13]; 26 — $H_3$do3a [13]; 27 — $H_3$do3a–3hm [13]; 28 — $H_3$do3a–hp [13]; 29 — $H_3$do3a–3hm–hp [13]; 32 — $H_2$do2a [26]; △: 21 — $H_8$dotP [17]; 22 — $H_4dotP^{H}$ [15]; 23 — $H_4dotP^{Et}$ [16]; 24 — $H_4dotP^{Ph}$ [14,29]. +: 39 — $H_4$trita [18,27,30]. Ligands based on cyclam skeleton, ■: 40 — $H_4$teta [10]; 41 — thec [31]; 42 — thpc [32]; □: 43 — $H_8$tetP [28]; 44 — $H_4tetP^{Ph}$ [14,29]; 45 — $H_4$te2P [33,34]; 46 — $H_4$te2P–2me [33,34].

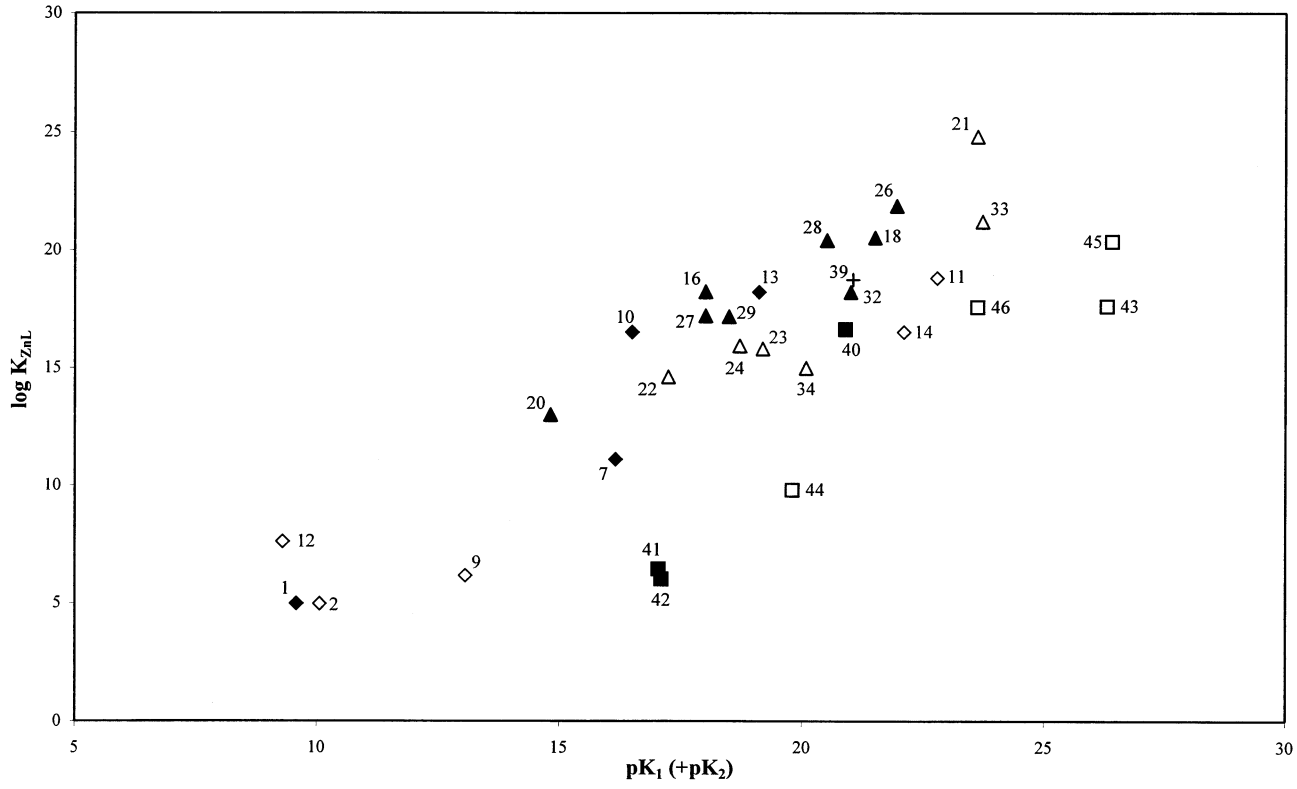



Fig. 3. Plot of stability constant of ZnL vs. basicity of nitrogen atom(s) of ligand. Filled symbols — ligands with carboxylate and/or alcoholic pendant arms; open symbols — phosphorus derivatives. Numbers of ligands follow from Fig. 1. Ligands with open-chain backbone, ◆: 1 — Hgly [10]; 7 — $H_2$edda [10]; 10 — $H_4$edta [10]; 13 — $H_5$dtpa [10]; ◇: 2 — $H_2$glyP [10]; 9 — $H_2$edd$P^H$ [10]; 11 — $H_8$edtP [10]; 14 — $H_{10}$dtpP [10]. Ligands based on cyclen skeleton, ▲: 16 — $H_3$pc3a [25a]; 18 — $H_4$dota [13,27]; 20 — dtma [13]; 26 — $H_3$do3a [13]; 27 — $H_3$do3a–3hm [13]; 28 — $H_3$do3a–hp [13]; 29 — $H_3$do3a–3hm–hp [13]; 32 — $H_2$do2a [26]; △: 21 — $H_8$dotP [28]; 22 — $H_4$dot$P^H$ [15]; 23 — $H_4$dot$P^{Et}$ [16]; 24 — $H_4$dot$P^{Ph}$ [14]; 33 — $H_4$do2P [35]; 34 — $H_2$do2Pme [35]. +: 39 — $H_4$trita [18,27,30]. Ligands based on cyclam skeleton, ■: 40 — $H_4$teta [10]; 41 — thec [31]; 42 — thpc [32]; □: 43 — $H_8$tetP [28]; 44 — $H_4$tet$P^{Ph}$ [14]; 45 — $H_4$te2P [33,34]; 46 — $H_4$te2P–2me [33,34].

Stability constants of gadolinium(III) complexes have been recently reviewed [41]. The coordination number of the Gd(III) ion is 8 or 9 and thus, it is clear that using only two $pK_A$ values corresponding to amines did not lead to any correlation. Therefore, additional $pK_A$ values had to be included in consideration. As overall basicity the sum of $pK_A$ values leading to the fully protonated electrically neutral form of each ligand is considered [23]. Thus, for $H_4$dota the sum of $pK_1 + pK_2 + pK_3 + pK_4$ was used. Testing values of the overall basicity, we found that the values from $H_4$dota and $H_3$do3a or $H_2$do2a do not fall in the fit. However, if the sum of four basic $pK_A$ values was considered for all ligands a rough correlation with $\log K_{ML}$ was observed (Fig. 4).

Some systems were studied by several authors and all the values obtained are included in the plot. In spite of large discrepancies observed in their results, the plot in Fig. 4 shows that main differences are caused by the number of donor atoms. Thus, $H_4$dota and its octadentate analogues containing phosphinic acid pendants (point 23) as well as linear polyaminocarboxylic acids correlate. As was expected, the octadentate $H_4$teta (point 40) forms weaker complexes than $H_4$dota even through their basicities are similar. This corresponds to the ring size effect as was mentioned for zinc(II) complexes. In contrast to both Cu(II) and Zn(II) ions, the stability constants of phosphonic acid ligands with Gd(III) (points 34, 33, 21) are lower than those with $H_4$dota derivatives. The points of the ligands containing both acetic and phosphonic acid pendants (points 37, 38) lie between the main belt of acetic and phosphinic acid ligands and the points corresponding to the phosphonic acid ligands. This is probably associated with high basicity of phosphonate groups and high values of $pK_3$ and $pK_4$.

The correlations indicate that stability constant values of Cu(II) complexes are determined mainly by the basicity of amine groups. The influence of other possible effects, such as the macrocyclic effect in tetraazacycle in contrast to linear amines or the number of additional donor atoms in or outside of pendant arms and their basicity, seems very small. Stability constants for Zn(II) are also influenced by the basicity of the amines and no significant differences were found for linear amines and cyclen derivatives. However, the values for cyclam are lower, especially for its phosphinic derivative. This is probably caused by preferential co-ordination through the phosphinate group, thus only a part of the azacycle participates in the co-ordination. The higher co-ordination number and hard character of Gd(III) require including additional $pK_A$ values of two pendant groups. As for zinc(II), no significant differences were found for linear amines and cyclen derivatives.

## 3. Structures of the complexes in the solid state

### *3.1. Structures of simple amino acids*

A number of glycine complexes with copper(II) have been prepared and their structures were determined. In addition to the compounds in which glycinate is non-coordinated [42] or co-ordinated only through carboxylic oxygen atoms [43],

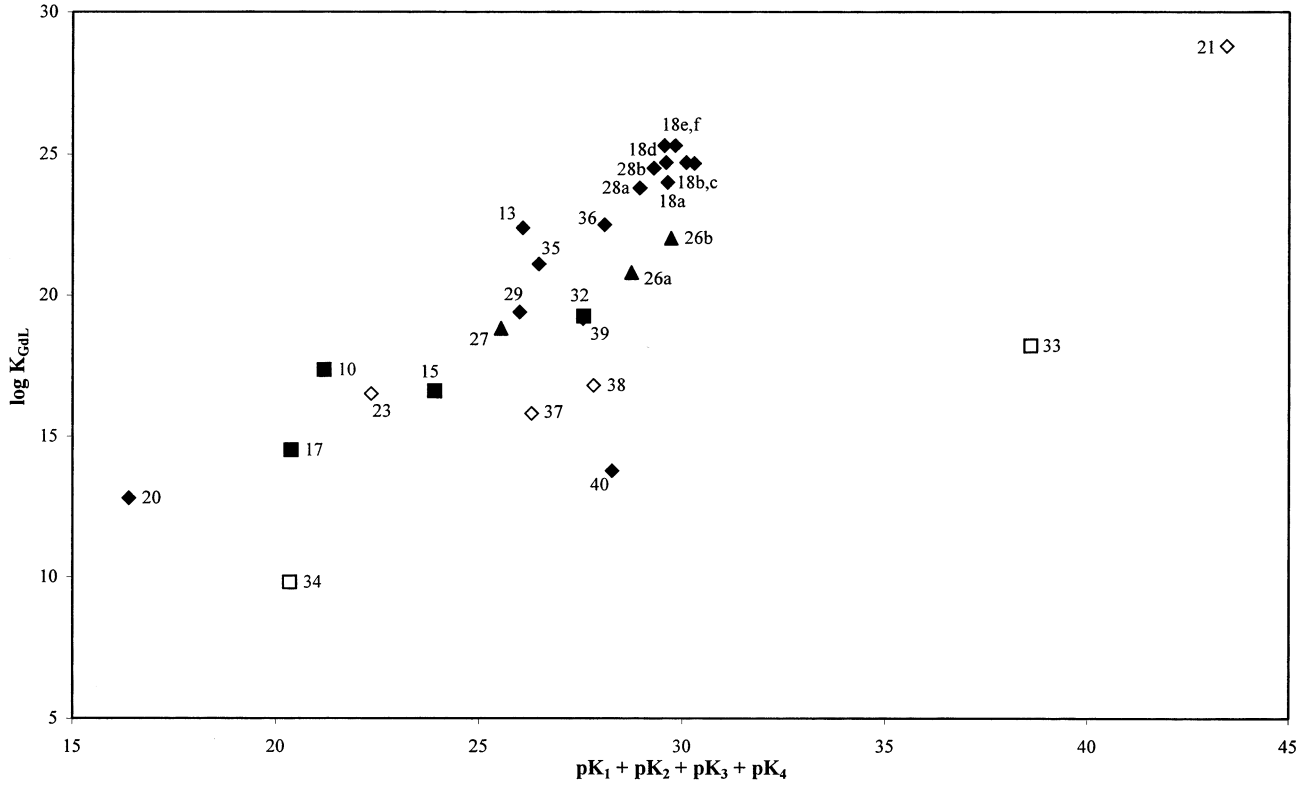



Fig. 4. Plot of stability constant of GdL vs. basicity of the ligand. Filled symbols — ligands with carboxylate and/or alcoholic pendant arms; Open symbols — phosphorus derivatives. Numbers of ligands follow from Fig. 1. Octadentate ligands, ◆: 13 — $H_5$dtpa [10]; 18a–f — $H_4$dota [10,13,36–38]; 20 — dtma [13]; 28a,b — $H_3$do3a–hp [13,38]; 29 — $H_3$do3a–3hm–hp [13]; 35 — $H_2$do2a–2he [39a]; 36 — $H_2$do2a–2hp [39a]; 39 — $H_4$trita [27,30]; 40 — $H_4$teta [10]; ◇: 21 — $H_8$dotP [40]; 23 — $H_4$dot$P^{Et}$ [16]; 37 — $H_4$do2a–$2P^{Et}$ [39a]; 38 — $H_4$do2a–2Pme [39a]. Heptadentate ligands, ▲: 26a,b — $H_3$do3a [10,13]; 27 — $H_3$do3a–3hm [13]. Hexadentate ligands, ■: 10 — $H_4$edta [10]; 15 — $H_2$pc2a [25b]; 17 — $H_2$bp2a [25b]; 32 — $H_2$do2a [39a]; □: 33 — $H_4$do2P [35]; 34 — $H_2$do2Pme [35].

glycinate is mostly bonded through amine and carboxylic group and forms a chelate. In the complexes with a molar ratio of Cu:Hgly = 1:2, the monodentate co-ordination of the carboxyl group was found [44]. In complexes with a 1:1 ratio, the carboxyl group also forms bridges between the copper atoms [45].

Several lanthanide complexes of glycine were also prepared; the results from the X-ray structure investigation have indicated that the amine group is protonated and non-coordinated [46]. The carboxyl group forms bridges between the lanthanides, their co-ordination number usually being 8 and the ratio lanthanide:Hgly = 1:3. Thus, two molecules of water complete the lanthanide co-ordination sphere; both the C–O distances in Ln–O(1)–C–O(2)–Ln are virtually the same.

The complexes of aminophosphonic acids crystallise very poorly and thus, only a limited number of the structures have been determined. The anion $[Cu(HglyP)]^-$, was isolated from slight acid medium. In the polymeric structure, the formation was observed of an eight-membered ring through two copper atoms bridged with two phosphonate groups, the motif well-known from other phosphonates [47]. Amines remain protonated and non-coordinated. The motif with eight-membered ring formed by phosphinates with protonated amine groups was observed for complex $[Cu(HglyP^{Me})(H_2O)Cl_2]$ [48]. Co-ordination of an amino group and formation of the chelate ring was observed for a complex of the same acid $[Cu_2(glyP^{Me})_2Cl_2]$, but isolated from neutral solution [49]. In addition to the chloro bridges, one phosphinate group links two copper atoms. In $[Cu_3(glyP^{Me})_4](ClO_4)_2$ [11] amines are co-ordinated to form the Cu–N–C–P–O chelate ring and phosphinate moieties also bridge copper atoms yielding polymeric layers. Formation of a chelate ring and an eight-membered ring was also found in dimer $[Cu(glyP^{Ph})_2]$ [11].

Unfortunately, no structure for complexes of a lanthanide ion with phosphorus analogues of glycine was found. Nevertheless, a similar motif to that for $gly^-$ is expected for phosphorus analogues.

From correlation of complexes of both simple amino acids and azacycles with pendant arms in solution, some relationships in the solid state seem to be evident. However, their structures are entirely different and the macrocyclic effect and the size of cavity dominate in formation of the solids.

### *3.2. Structures of copper(II) complexes with macrocyclic ligands*

Copper(II) forms $H_4$dota complexes with distorted octahedral arrangement and with *cis* orientation of the oxygen donor atoms as is drawn in Fig. 5. Two pendant arms remain un-coordinated. All nitrogen atoms are co-ordinated, however; Cu(II) ion is too large to be placed inside the plane formed by nitrogen atoms [50,51]. The similar structure motif was found for $H_3$do3a [52]. The structure of the Cu(II) complex with cyclen itself [53] also points to the same co-ordination mode as for the tetraazacyclododecane derivatives. The size of cyclam and its derivatives is larger and thus, Cu(II) usually lies in the centre of the $N_4$ plane and two oxygen donor atoms are in *trans* position. The remaining pendant arms are protonated [54] or bonded to counter-ion such as Ba(II) [55]. Both the ligands form dinuclear complexes of different structure [51,54].

No structures for Cu(II) complexes with phosphorus analogues $H_4$dota and $H_4$teta were found. We studied the complexes with $H_4$te2p and in their structures, both the co-ordination modes of Cu(II) placed in the $N_4$ plane and Cu(II) surrounded by four nitrogen atoms were observed [34]. By reaction of Cu(II) ion with the ligand at room temperature, the trigonally bipyramidal complex **A** forms as is shown in Fig. 6. Isomerisation takes place on heating of aqueous solution of **A** for several hours and **B** crystallised from the solution and in its structure *trans*-octahedral co-ordination sphere was observed.

### *3.3. Structures of lanthanide(III) complexes with macrocyclic ligands*

A number of lanthanide complexes with $H_4$dota [56–63] and its phosphinic acid analogues [20,64,65] were prepared and their structures were determined. The structural motif, shown in Fig. 7, is the same for both the acetic and phosphinic acid derivatives. The ligand anions are co-ordinated to the lanthanide ion by four nitrogen atoms and four oxygen atoms. The nitrogen atoms as well as oxygen atoms form bases $N_4$ and $O_4$ which are planar and parallel within experimental error. The distance between the planes does not depend on the lanthanide, it lies in the range 2.32–2.37 Å for $H_4$dota and 2.60–2.73 Å for phosphinic acid derivatives. The lanthanide lies between the planes, closer to the $O_4$ base. The twist angle of the bases around the local four-fold axis is about 30–40° for $H_4$dota and 24–38° for phosphinic derivatives, ranging between those in ideal prism (0°) and anti-prism (45°), a little closer to the latter. Thus, the arrangement should be termed the square antiprism or twisted square antiprism depending on the sign of the twist angle. The molecule of water capping the $O_4$ base of the antiprism mostly completes the co-ordination sphere of the lanthanide. The average bond length of lanthanide(III) ion and oxygen donor atoms of the ligand is a little longer for phosphinic acid derivatives than that for acetic derivatives as will be shown below.

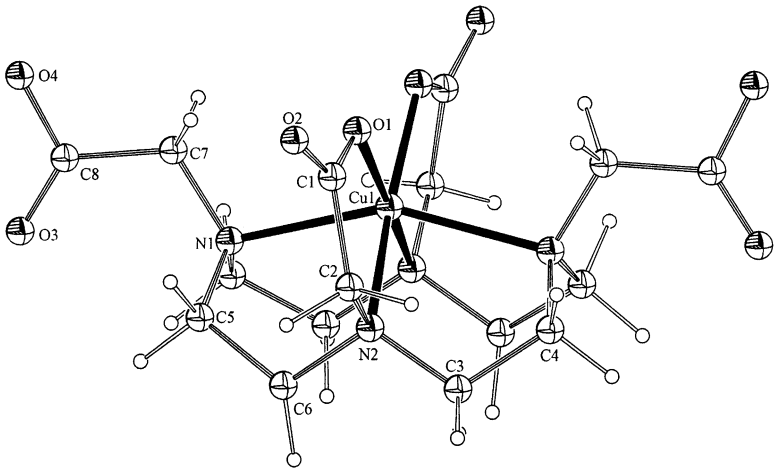
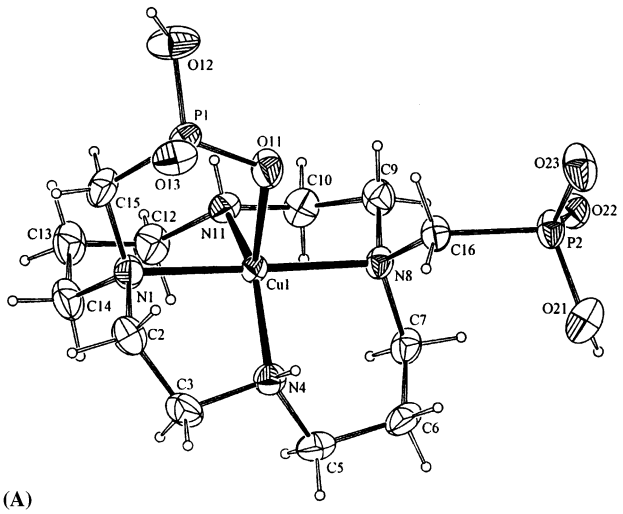
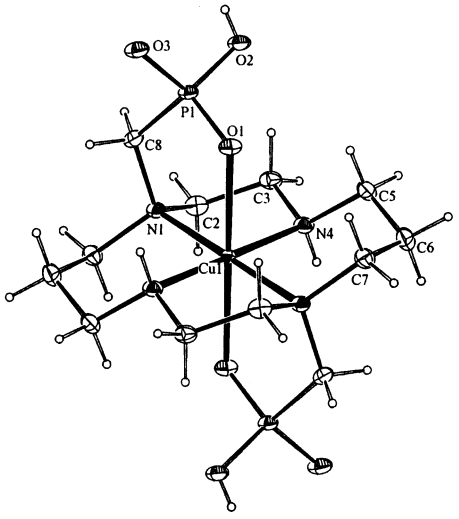



Fig. 5. Structure of $[Cu(dota)]^{2-}$, according to Ref. [50].




(A)




(B)

Fig. 6. Structures of two isomers **A** and **B** of [Cu($H_2$te2P)], according to Ref. [34].

A comparison of the co-ordination polyhedra of the acetic and phosphinic acid derivatives shows that the $N_4$ square remains virtually the same with the common square (3,3,3,3) conformation of the 12-$N_4$ ring. The conformation of the tetraaza rings of the coordination polyhedra is Λ or Δ and the difference is not influenced by the kind of pendant group. The unit cell is often formed by both enantiomeric arrangements. The phosphorus tetrahedral moiety, after coordination, brings addi-

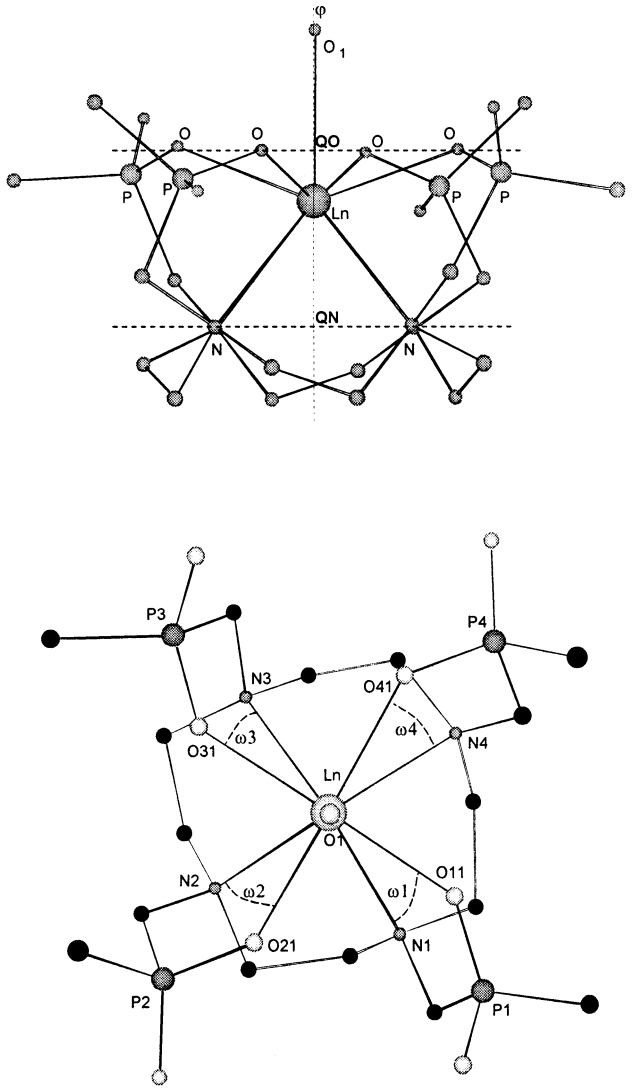



Fig. 7. Lanthanide co-ordination sphere showing the lanthanide(III) atom between the $N_4$ and $O_4$ basis and orientation of the methylphosphinic acid pendant arms with twist angles $\omega$.

tional asymmetric sites. Additional isomers due to the phosphorus substituent are formed, which were described and discussed for a number of complexes [20,64–69] and are not included in this comparison.

The cyclen derivative containing three acetate pendant arms, $H_3$do3a, forms a little different co-ordination sphere with a lanthanide(III) [58,70]. The X-ray analysis showed that [Gd(do3a)] crystallized as $Na_2[\{Gd(do3a)\}_3(CO_3)]\cdot 17H_2O$ [58] in which each gadolinium atom is co-ordinated to four nitrogen atoms of the

macrocycle and to the oxygen of each carboxylic arm as in dota complexes. However, the co-ordination sphere of Gd(III) is completed by co-ordination of two oxygens of the carbonate ion. Neither water molecule was co-ordinated to the Gd atom nor formation of the carboxylate bridges was observed. In addition, single carboxylic bridge formation was observed in the $[La(Hdota)La(dota)]^-$ complex [61].

The phosphinic acid analogue of $H_3do3a$ was synthesized and X-ray analysis of its seven lanthanide complexes showed that $(do3P^{Ph}–me)^{3-}$ is co-ordinated to a lanthanide(III) ion by four nitrogen atoms, two oxygen atoms from two monodentate phosphinate groups, and two oxygen atoms from two didentate phosphinate groups [66]. The nitrogen and oxygen atoms form $N_4$ and $O_4$ bases which are planar and parallel within an experimental error. Twist angles of the bases around the local four-fold axis are in the range 28–33° the values being independent of ionic radius of the central atom. The Ln(III) ion lies between the co-planar $O_4$ and $N_4$ bases (Fig. 8) the distances between the bases being independent of the Ln(III) radius (2.67(1) Å for La and 2.65(1) Å for Yb). Thus, a difference between $H_3do3a$ and ($H_3do3P^{Ph}$–me) complexes results from the well-known better capability of the phosphinic acid group of didentate co-ordination and formation of the bridges connecting co-ordination polyhedra.

From the similarity and differences observed in the structures mentioned above we can draw the following conclusions:

1. The Ln(III) ion lies between the coplanar $O_4$ and $N_4$ bases the distances between them being independent of the Ln(III) radius (2.31–2.43 Å for acetate and 2.61–2.73 Å for methylphosphinate pendants).
2. The twist angle of the bases is not influenced by the Ln(III) radius (30–38° for acetate and 24–33° for methylphosphinate pendants).
3. In dependence on the Ln(III) radius, the distance of the lanthanide from the $N_4$ base changes and the dependence is the same for both acetic and phosphinic acid derivatives (Fig. 9).

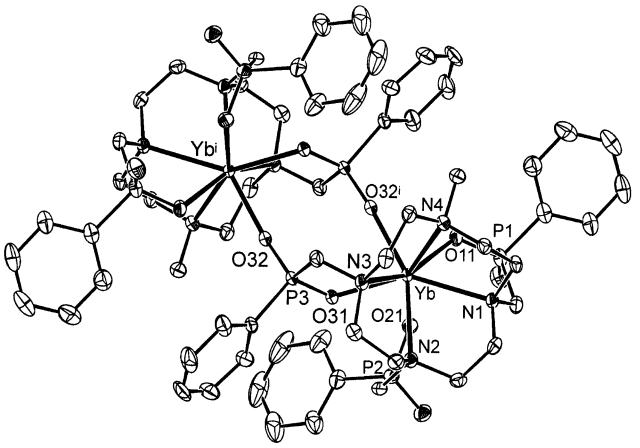



Fig. 8. View of $[Yb(do3P^{Ph}–me)]_2$, according to Ref. [66]

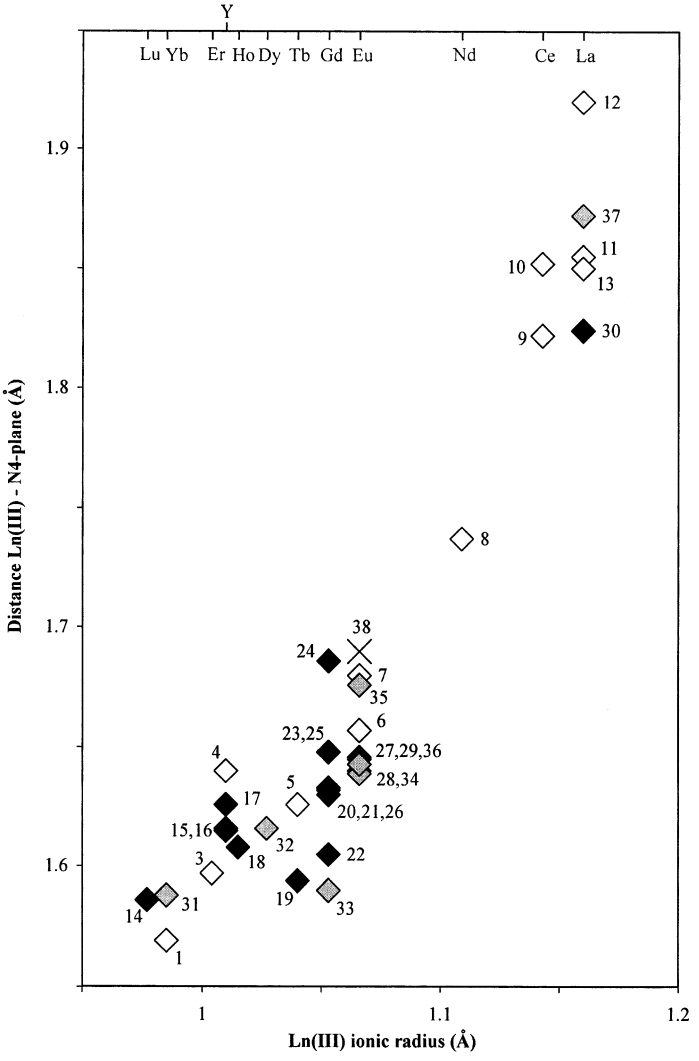



Fig. 9. Plot of the distance of Ln(III)–$N_4$ base vs. Ln(III) ionic radius (from Ref. [71]). The filled symbols — ligands with acetate pendant arms; open symbols — phosphorus acid derivatives. The symbols of the amides are grey and the cross is used for $[Eu(thp)]^{3+}$. Numbers of the compounds follow from Table 3.

4. The distance of the lanthanide from the $O_4$ base in acetate derivatives is shorter by about 0.3 Å than in phosphinate derivatives. The difference follows from different values of $C–CO_2^-$ and $C–P(R)O_2^-$ bond distances. In both the series, the distance of the lanthanide from the $O_4$ base depends on the Ln(III) radius (Fig. 10).

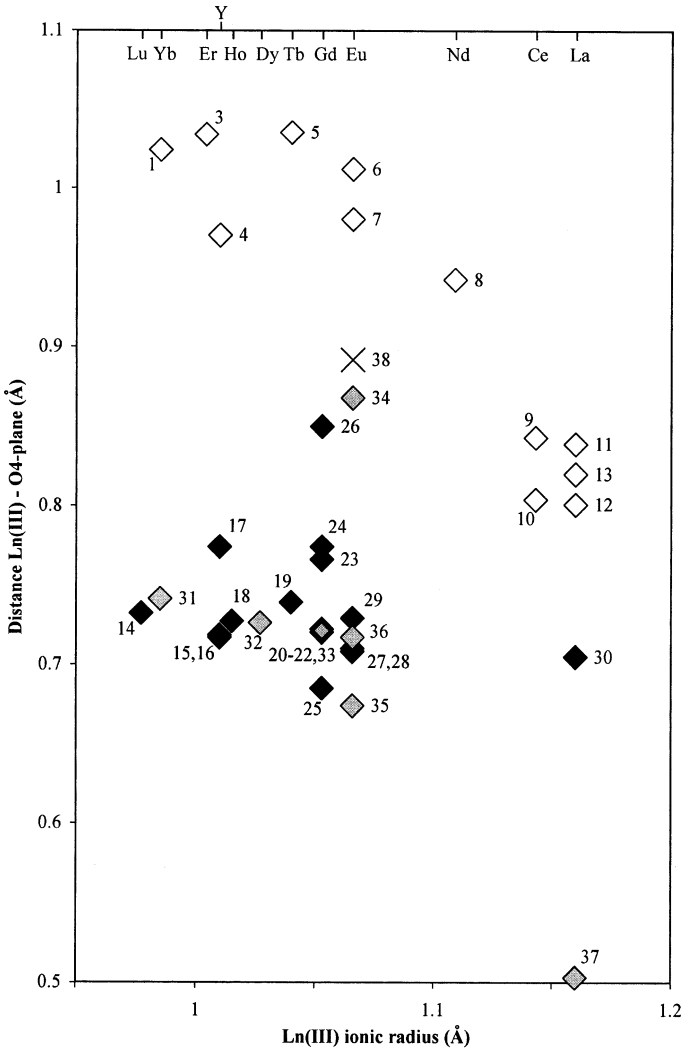



Fig. 10. Plot of the distance of Ln(III)–$O_4$ base vs. Ln(III) ionic radius (from Ref. [71]). The filled symbols — ligands with acetate pendant arms; open symbols — phosphorus acid derivatives. The symbols of the amides are grey and the cross is used for $[Eu(thp)]^{3+}$. Numbers of the compounds follow from Table 3.

5. In view of potential utilisation of the complexes as contrast agents, an important feature of these structures is the position of the water molecule. Water is mostly co-ordinated in complexes of acetic acid derivatives; in those of phosphinic acid derivatives, only for La(III) or Ce(III) central ions.

The changes in the co-ordination of water molecule in the phosphinic acid derivatives depend on the lanthanide(III) radii as follows from the [Ln(do3P$^{Ph}$–

me)]$_2$ series [66]. For all the complexes, the direction of the vector Ln–O($H_2$) is the same in all the structures studied, and thus the molecule is situated approximately in the same direction with regard to the $O_4$ plane. However, the Ln–O($H_2$) distance is strongly dependent on Ln(III) increasing in the order La (2.815 Å), Ce (2.854 Å), Nd (3.171 Å), Eu (3.745 Å), Tb (4.275 Å), Er (4.050 Å) and Yb (4.448 Å). Thus, this water molecule can be considered as co-ordinated in the La and Ce complexes and obviously uncoordinated in the complexes of Eu, Tb, Er and Yb. The distance in [Nd(do3P$^{Ph}$–me)]$_2$ is a little larger than that of the co-ordinated O atoms. From this point of view the position of the water molecule seems to be given by the space between phosphinic pendant arms above the $O_4$ base. We found that for the decision on whether water can or cannot be co-ordinated, a crucial point seems to be the O–Ln–O angle as shown in Figs. 7 and 11. Table 3 lists the angles for a number of acetic and phosphinic acid derivatives. If the value of the O–Ln–O angle is larger than 136°, co-ordination of water molecule is possible; if it is smaller, the space above the $O_4$ plane is too small for the co-ordination. The dependence of the O–Ln–O angle on the ionic radius is shown in Fig. 12. For carboxylic acid derivatives, the dependence is not significant (values in the range of about 7°), outlier 25 corresponds to [Gd(do3a(me)$_3$)($H_2O$)]. On the other hand, for the phophinic acid derivatives, the angle varies from 125 to 142°.

The crucial value of the angle would also explain the fact that complexes of the cyclen-based compounds containing two acetate and two phosphinate arms, in position 1,7 and 4,10, respectively, exhibit low thermodynamic as well as kinetic stability in aqueous solution [39a]. The oxygen base is not planar, the oxygen donor atoms of phosphinate should be farther from the lanthanide than the oxygens of the acetic groups and also the angle O–Ln–O should be lower than that of 136°. Thus, the geometry of the oxygen base hinders the access of water molecule.

In our consideration, only the cyclen derivatives with the acetic pendants were included. In addition, their amides [72–78] and ligands with mixed coordination sphere [38,79,80] were also synthesized and structures of their complexes were determined. The similar derivative, 1,4,7,10-tetrakis(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane (thp), and its complex with europium(III) was also investi-

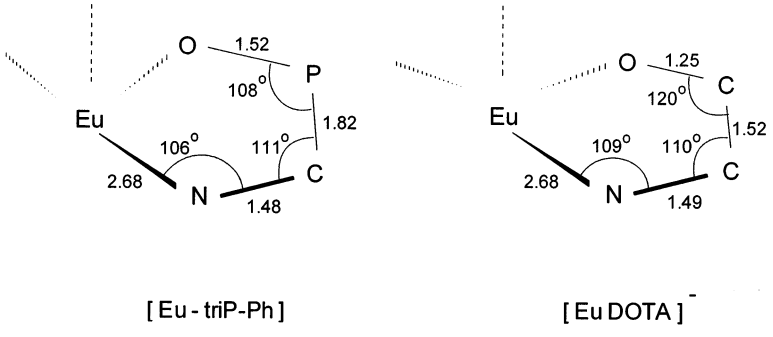



Fig. 11. Geometry of pendants arms in [Eu(dota)($H_2O$)]$^-$ and [Eu(do3P$^{Ph}$–me)]$_2$.

Table 3
List of lanthanide(III) complexes with their O–Ln–O and Ln–$OH_2$ parameters

| No. | Compound | Ref. | Angle [a], O–Ln–O (°) | Distance, Ln–$OH_2$ (Å) |
|---|---|---|---|---|
| 1 | $[Yb(do3P^{Ph}–me)]_2·6H_2O$ | 66 | 125.1 | – |
| 2 | $[Yb(dotP^{Bn})]^{1-}$ | 64 | 126.6 | – |
| 3 | $[Er(do3P^{Ph}–me)]_2·5H_2O$ | 66 | 125.2 | – |
| 4 | $[Y(dotP^{Bn})]^{1-}$ | 64; 20 | 128.9 | – |
| 5 | $[Tb(do3P^{Ph}–me)]_2·6H_2O$ | 66 | 126.5 | – |
| 6 | $[Eu(do3P^{Ph}–me)]_2·5H_2O·2MeOH$ | 66 | 128.3 | – |
| 7 | $[Eu(dotP^{Bn})]^{1-}$ | 64 | 130.8 | – |
| 8 | $[Nd(do3P^{Ph}–me)]_2·7H_2O$ | 66 | 132.9 | – |
| 9 | $[Ce(do3P^{Ph}–me)]_2·5H_2O·MeOH$ | 66 | 138.6 | 2.854 |
| 10 | $Li[Ce(dotP^{Ph})(H_2O)]·10H_2O$ [b] | 65 | 141.4 | 2.618 |
| 11 | $[La(do3P^{Ph}–me)]_2·6H_2O$ | 66 | 139.1 | 2.815 |
| 12 | $Li[La(dotP^{Ph})(H_2O)]·10H_2O$ [b] | 65 | 142.3 | 2.638 |
| 13 | $[La(dotP^{Bn})(H_2O)]^{1-}$ | 64 | 141.8 | 2.66 |
| 14 | $Na[Lu(dota)(H_2O)]·4H_2O$ | 60 | 141.7 | 2.417 |
| 15 | $Na[Y(dota)(H_2O)]·4H_2O$ | 59 | 143.0 | 2.425 |
| 16 | $Na[Y(dota)(H_2O)]·4H_2O$ | 58 | 143.1 | 2.436 |
| 17 | $[Y(do3a–hp)(H_2O)]·4H_2O·C_3H_6O$ [b] | 38 | 140.3 | 2.502 |
| 18 | $Na[Ho(dota)(H_2O)]·4H_2O$ | 61 | 142.6 | 2.443 |
| 19 | $H_3O[Tb(dota(propionyl)_4)(H_2O)]·2H_2O$ | 63 | 144.0 | 2.427 |
| 20 | $Na[Gd(dota)(H_2O)]·4H_2O$ | 57 | 143.6 | 2.458 |
| 21 | $Na[Gd(dota)(H_2O)]·4H_2O$ | 58 | | 2.463 |
| 22 | $H_3O[Gd(dota(propionyl)_4)(H_2O)]·2H_2O$ | 63 | 144.5 | 2.431 |
| 23 | $[Gd(do3a–hp)(H_2O)]·1.3H_2O$ [b] | 38 | 141.7 | 2.504 |
| 24 | $[Gd(do3a–trihydroxybutyl)(H_2O)]·H_2O$ | 80 | 142.5 | 2.43 |
| 25 | $[Gd(do3a–oea)(H_2O)]·3H_2O$ | 79 | 145.1 | 2.428 |
| 26 | $[Gd(do3a(me)_3)(H_2O)]_2·4H_2O$ [b] | 70 | 143.0 | 2.56 |
| 27 | $Na[Eu(dota)(H_2O)]·4H_2O$ | 62 | 144.1 | 2.481 |
| 28 | $Na[Eu(dota)(H_2O)]·4H_2O$ | 56 | 143.1 | 2.483 |
| 29 | $H_3O[Eu(dota(propionyl)_4)(H_2O)]·2H_2O$ | 63 | 145.2 | 2.447 |
| 30 | $Na[La(dota)La(Hdota)]·10H_2O$ [c] | 61 | 146.7 | – [d] |
| 31 | $[Yb((R)\text{-tcmc(Me,Ph)})(H_2O)](CF_3SO_3)_3·3H_2O$ | 77 | 141.1 | 2.440 |
| 32 | $[Dy((S)\text{-tcmc(Me,Ph)})(H_2O)](CF_3SO_3)_3$ | 75b | 143.6 | 2.418 |
| 33 | $[Gd(dtma)(H_2O)](ClO_4)_3·NaClO_4·3H_2O$ | 76 | 142.3 | 2.461 |
| 34 | $[Eu(tcmc)(H_2O)](CF_3SO_3)_3·2MeOH$ | 74 | 141.3 | 2.442 |
| 35 | $[Eu((R)\text{-tcmc(Me,Ph)})(H_2O)](CF_3SO_3)_3$ | 75 | 144.8 | 2.425 |
| 36 | $[Eu((S)\text{-tcmc(Me,Ph)})(H_2O)](CF_3SO_3)_3$ | 75 | 144.6 | 2.438 |
| 37 | $[La(tcmc)(EtOH)](CF_3SO_3)_3$ | 73 | 146.8 | – [e] |
| 38 | $[Eu(thp)(H_2O)]_2(CF_3SO_3)_6·2EtOH·H_2O$ [b] | 81 | 137.8 | 2.507 |

[a] Minimum value from all possibilities.
[b] Mean values for two independent molecules in unit cell.
[c] Mean values for two different coordination polyhedra in dimeric structure.
[d] Co-ordination of carboxyl group from second dota molecule (Ln–O = 2.547 Å).
[e] Co-ordination of EtOH molecule (Ln–O = 2.523 Å).

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gated [81]. Parameters of these analogous complexes were added to the plots and are shown in Figs. 9, 10 and 12. The symbols of the amides are grey and the cross is used for $[Eu(thp)]^{3+}$. In Fig. 9, we can see that all these points fit and therefore, the position of the lanthanide towards the $N_4$ base is independent on a type of the pendants. The relationship of the lanthanide distances toward $O_4$ bases and O1–Ln–O3 angles for the amide derivatives mostly follows their acetic pattern

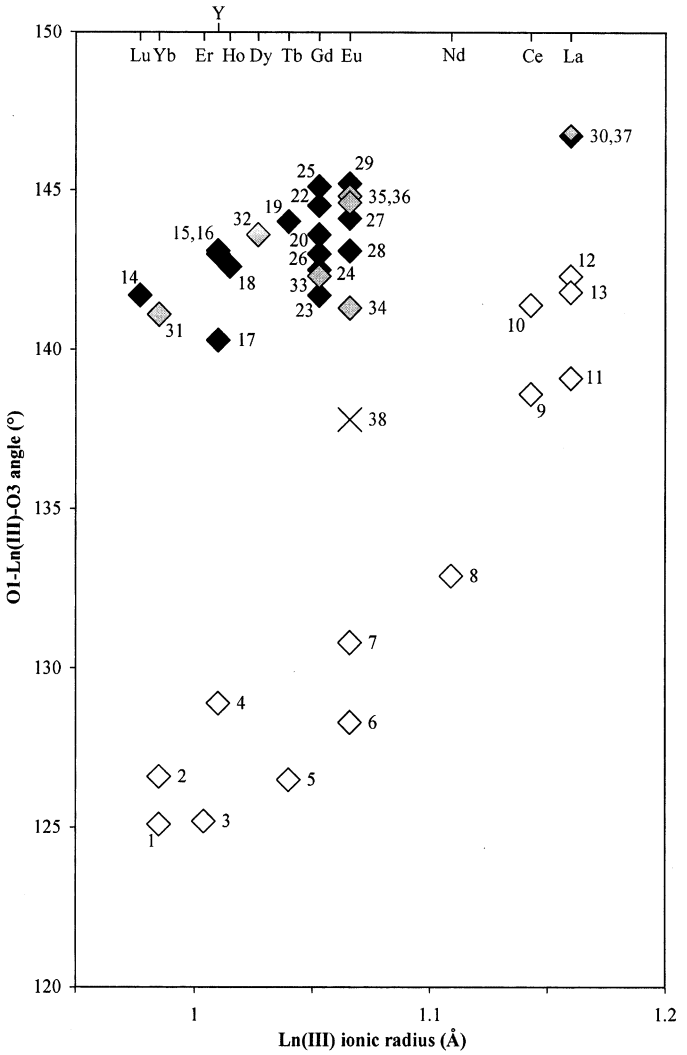


Fig. 12. Plot of the O1–Ln(III)–O3 angle vs. Ln(III) ionic radius (from Ref. [71]). The filled symbols — ligands with acetate pendant arms; open symbols — phosphorus acid derivatives. The symbols of the amides are grey and the cross is used for $[Eu(thp)]^{3+}$. Numbers of the compounds follow from Table 3.

(Figs. 10 and 12). However, the distance of the Ln–$O_4$ base in $[Eu(thp)]^{3+}$ differs and is close to the relationship for the phosphorus derivatives. It is caused by a longer C–O length in alcohol than in acetate, difference in charge and also by tetrahedral angle of the O–$CH(CH_3)$–C moiety.

Cyclam derivatives were investigated much less often than those of cyclen; their structures were determined only for $Na[Tb(teta)]\cdot 6H_2O\cdot 0.5NaCl$ [82a] and $Na[Eu(teta)]\cdot 2H_2O\cdot 4NaCl$ [82b]. Lanthanides are encapsulated between the $O_4$ and $N_4$ bases, similar to the observations in $H_4$dota complexes. However, in contrast to the $H_4$dota complexes, the bases do not form planes and their structures are described in terms of a severely distorted dodecahedron. No molecule of water is co-ordinated to the central ion. Lanthanide(III) complexes with phosphorus acid analogues of $H_4$teta have not been prepared, nevertheless, our orientation experiments showed only a weak interaction between the ion and $H_4tetP^{Ph}$.

## 4. Kinetic properties

The kinetic inertness of these complexes is an important property in view of their utilisation in medicine. The inertness should be considered as stability to substitution with additional relevant ions such as Zn(II) or Ca(II) or as stability to the reaction of the ion bonded in complex with phosphate, carbonate or metal transferring proteins [84]. However, the inertness is mostly presented as stability to acid-assisted hydrolysis. Such reactions were investigated for Cu(II) complexes with cyclen [85] and cyclam [86], with $H_3$do3a [87] and also for $H_4dotP^{Ph}$ and $H_4tetP^{Ph}$ [29]. The estimated half-lives showed that the most stable are the complexes with cyclam and with $H_3$do3a, followed by that of cyclen (45.5 min in 1 M HCl). On the other hand, $[Cu(dotP^{Ph})]^{2-}$ hydrolyses with half-life 5.46 min whereas $[Cu(tetP^{Ph})]^{2-}$ with 26.3 s. Unfortunately, we have not found analogous work dealing with $H_4$dota and $H_4$teta complexes. Nevertheless, their higher stability than that of phosphinic acid analogues can be safely assumed.

The acid-assisted dissociation was investigated for a number of lanthanides complexes with $H_4$dota and $H_4$teta and their derivatives [88]. However, the dissociation of complexes with phosphinic acid analogues was mentioned only in one paper [89]. The results confirmed that the $[Gd(dota)(H_2O)]^-$ complex is more stable than those of $[Gd(dotP^R)]^-$ where R = Ph, Me or Bn. The half-life of acid-assisted dissociation at pH 2 for $[Gd(dota)]^-$ is 3929 h and that for $[Gd(dotP^{Me})]^-$ only 171 h. Such comparisons for both Cu(II) and Gd(III) systems point to lower stability of phosphinic derivatives to acid-assisted hydrolysis. However, their stability in neutral solution is high enough for utilisation in medicine. Even though lanthanide complexes with $H_8$dotP have often been investigated [7,9,40,90,91], no dissociation kinetics were published.

The kinetic stability is caused, primarily, by convenient steric arrangement of the ligands that can fully wrap a metal ion and protect it from solvent molecules or other reagents. A comparison of the structures of lanthanide complexes indicates that the Ln(III)–O distance in the phosphinic acid complexes is longer at about 0.3

Å than that in carboxylic derivatives. Thus, the O(P)–Ln bond should be weaker than the O(C)–Ln and consequently, the bond dissociation followed by transfer of proton to the nitrogen atom would be easier for both phosphinic and phosphonic acid derivatives than for acetic derivatives. The assumption, that the kinetic stability is caused by the steric arrangement, is supported by different decomplexation properties of isomers. It is evident in the structures found for the Cu(II) complex with bis(methylphosphonic acid) derivative of cyclam $H_4$te2P. Its two isomeric forms A and B are shown in Fig. 6. At room temperature, A is formed and it changes to B after refluxing in aqueous solution for 12 h. The stability constants $\log K_{ML}$ for both compounds are similar, 25.40 for **1** and 26.5 for **2**; in contrast the stability to acid-assisted hydrolysis is completely different [34]. Complex **1** hydrolyses in 5 M $HClO_4$ at 25°C with a half-life of about 19.7 min whereas **2** hydrolyses under the same conditions with a half-life of about 0.5 year. From the published results, acetic derivatives seem to be more kinetically stable; above results on Cu(II) complexes **1** and **2** point that it is not a rule.

## 5. Conclusions

Replacement of carboxylic group in $H_4$dota and $H_4$teta by phosphonic or phosphinic acid groups results in some differences in the complexing properties of such ligands. The basicity is influenced by the pendant group and increases in the order phosphinic < carboxylic < phosphonic acid. The thermodynamic stability of the Cu(II) complexes in solution is controlled mainly by basicity of the amine groups. Therefore, the phosphonic acid derivatives, especially $H_8$tetp and $H_4$te2p, have a high thermodynamic and often kinetic stability in solution. The influence of additional effects, such as the basicity of acid pendants or size of the macrocyclic cavity is negligible. As the hard character of the central ion increases, an influence of the number and kind of pendants and the size of the cavity growths. Cyclen bearing acetate pendants forms more stable complexes with lanthanides(III) than methylphosphinic or methylphosphonic acid arms.

In the solid state, both complexes with the phosphorus acid derivatives usually follow structural motifs similar to their carboxylic patterns. However, the C–P and P–O bonds are longer than C–C and C–O in the acetic group and this results in general steric hindrance for the lanthanide(III) complexes with phosphorus acid derivatives. The co-ordinated oxygen atoms in the $O_4$ plane are close to one another and there is insufficient room for co-ordination of a water molecule, which is crucial in MRI applications. Due to the properties mentioned above, the phosphinic and phosphonic acid derivatives are less convenient for application in MRI. On the other hand, according to Aime at al. [4e,91–93], the phosphonic acid derivatives offer faster exchange of the water molecule in the Gd(III) co-ordination sphere and organise the second hydration sphere better. Both the properties would help to improve relaxivity of future contrast agents. The phosphorus acid derivatives could be also used for the design of ligands in which the lanthanide(III) ion has to be protected against direct access of water molecules, as is needed for

luminescence applications [94]. In addition, it would be possible to anchor the complexes through an ester group in phosphonic acid derivatives or through *P*-alkyl in phosphinic acid derivatives to the biological important molecules such as sugars, peptides etc. and thus, control their distribution in organisms.

## Acknowledgements

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## References

[1] (a) L.F. Lindoy, Adv. Inorg. Chem. 45 (1998) 75. (b) K.P. Wainwright, Coord. Chem. Rev. 166 (1997) 35. (c) S.F. Lincoln, Coord. Chem. Rev. 166 (1997) 255.
[2] M. Meyer, V. Dahaoui-Gindrey, C. Lecomte, R. Guilard, Coord. Chem. Rev. 178–180 (1998) 1313 and refs. therein.
[3] R.D. Hancock, H. Maumela, A.S. de Sousa, Coord. Chem. Rev. 148 (1996) 315.
[4] (a) D. Parker, in: J.-M. Lehn (Ed.), Comprehensive Supramolecular Chemistry, vol. 10, Pergamon Press, Oxford, 1996, pp. 487–536. (b) S. Aime, M. Botta, M. Fasano, E. Terreno, Chem. Soc. Rev. 27 (1998) 19. (c) P. Caravan, J.J. Ellison, T.J. Mc Murry, R.B. Laufer, Chem. Rev. 99 (1999) 2293. (d) S. Aime, M. Botta, M. Fasano, E. Terreno, Acc. Chem. Res. 32 (1999) 941. (e) M. Botta, Eur. J. Inorg. Chem. (2000) 399.
[5] (a) C.J. Anderson, M.J. Welch, Chem. Rev. 99 (1999) 2219. (b) W.A. Volkert, T.J. Hoffmann, Chem. Rev. 99 (1999) 2269. (c) D.E. Reichert, J.S. Lewis, C.J. Anderson, Coord. Chem. Rev. 184 (1999) 3.
[6] R. Hancock, in: A.F. Williams, C. Floriani, A.E. Nurbach (Eds.), Perspectives in Coordination Chemistry, Verlag Helv. Chim. Acta, Basel, 1992, p. 129.
[7] J. Ren, A.D. Sherry, Inorg. Chim. Acta 246 (1996) 331.
[8] J. Huskens, A.D. Sherry, J. Am. Chem. Soc. 118 (1996) 4396 and refs. therein.
[9] (a) A.D. Sherry, J. Alloys Comp. 249 (1997) 153. (b) F.I. Belskii, Yu.M. Polikarpov, M.I. Kabachnik, Usp. Khim. 61 (1992) 415.
[10] (a) R.M. Smith, A.E. Martell, Critical Stability Constants, vols. 1–6. Plenum Press, New York 1974–1989. (b) NIST Standard Reference Database 46 (Critically Selected Stability Constants of Metal Complexes), Version 5.0, 1994.
[11] J. Rohovec, P. Vojtíšek, I. Císarová, P. Hermann, I. Lukeš, J. Chem. Soc. Dalton Trans. (1996) 2685.
[12] (a) T. Kiss, I. Lázár, P. Kafarski, Metal-Based Drugs 1 (1994) 247. (b) T. Kiss, I. Lázár in: V.P. Kukhar, H.R. Hudson (Eds.), Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity, Wiley, New York, 2000, pp. 285–326.
[13] (a) A. Bianchi, L. Calabi, L. Ferrini, P. Losi, F. Uggeri, B. Valtancoli, Inorg. Chim. Acta 249 (1996) 13. (b) A. Bianchi, L. Calabi, C. Giorgi, P. Losi, P. Mariani, P. Paoli, P. Rossi, B. Valtancoli, M. Virtuani, J. Chem. Soc. Dalton Trans. (2000) 697.
[14] J. Rohovec, M. Kývala, P. Vojtíšek, P. Hermann, I. Lukeš, Eur. J. Inorg. Chem. (2000) 195.
[15] K. Bazakas, I. Lukeš, J. Chem. Soc. Dalton Trans. (1995) 1133.
[16] I. Lázár, A.D. Sherry, R. Ramasamy, E. Brücher, R. Király, Inorg. Chem. 30 (1991) 5016.

[17] R. Delgado, L.C. Siegfried, T.A. Kaden, Helv. Chim. Acta 73 (1990) 140.
[18] S. Chaves, R. Delgado, J.J.R. Frausto Da Silva, Talanta 39 (1992) 249.
[19] S. Aime, A. Barge, J.I. Bruce, M. Botta, J.A.K. Howard, J.M. Moloney, D. Parker, A.S. de Sousa, M. Woods, J. Am. Chem. Soc. 121 (1999) 5762.
[20] S. Aime, A.S. Batsanov, M. Botta, J.A.K. Howard, D. Parker, K. Senanayake, G. Williams, Inorg. Chem. 33 (1994) 4696.
[21] (a) M.R. Spirlet, J. Rebizant, P.D. Barthélemy, J.F. Desreux, J. Chem. Soc. Dalton Trans. (1991) 2477. (b) M.R. Maurya, E.J. Zaluzec, S.F. Pawkovic, A.W. Herlinger, Inorg. Chem. 30 (1991) 3657.
[22] I. Lázár, D.C. Hrncir, W.D. Kim, G.E. Kiefer, A.D. Sherry, Inorg. Chem. 31 (1992) 4422.
[23] (a) T.F. Gritmon, M.P. Goedken, G.R. Choppin, J. Inorg. Nucl. Chem. 39 (1977) 2021. (b) X. Wang, T. Jin, V. Comblin, A. Lopez-Mut, E. Merciny, J.F. Desreux, Inorg. Chem. 31 (1992) 1095.
[24] R.J. Motekaitis, I. Murase, A.E. Martell, J. Inorg. Nucl. Chem. 33 (1971) 3353.
[25] (a) R. Delgado, S Quintino, M. Teixeira, A. Zhang, J. Chem. Soc. Dalton Trans. (1997) 55. (b) W.D. Kim, D.C. Hrncir, G.E. Keifer, A.D. Sherry, Inorg. Chem. 34 (1995) 2225.
[26] J.M. Weeks, M.R. Taylor, K.P. Wainwright, J. Chem. Soc. Dalton Trans. (1997) 317.
[27] R. Delgado, J.J.R. Frausto de Silva, Talanta 29 (1982) 815.
[28] S.A. Pisareva, F.I. Belskii, T.Y. Medved, M.I. Kabachnik, Izv. Akad. Nauk SSSR Ser. Khim. (1987) 413.
[29] P. Lubal, M. Kývala, P. Hermann, J. Holubová, J. Rohovec, J. Havel, I. Lukeš, Polyhedron 20 (2001) 47.
[30] E.T. Clarke, A.E. Martell, Inorg. Chim. Acta 190 (1991) 27.
[31] (a) C.M. Madeyski, J.P. Michael, R.D. Hancock, Inorg. Chem. 23 (1984) 1487. (b) R.W. Hay, M.P. Pujari, W.T. Moodie, S. Craig, D.T. Richens, A. Perotti, L. Ungaretti, J. Chem. Soc. Dalton Trans. (1987) 2605.
[32] P.J. Davies, M.R. Taylor, K.P. Wainwright, Inorg. Chim. Acta 246 (1996) 1.
[33] J. Kotek, P. Vojtíšek, I. Císarová, P. Hermann, P. Jurecka, J. Rohovec, I. Lukeš, Collect. Czech. Chem. Commun. 65 (2000) 1289.
[34] J. Kotek, P. Lubal, P. Hermann, I. Císarová, I. Lukeš, J. Havel, Unpublished results.
[35] L. Burai, J. Ren, Z. Kovacs, E. Brücher, A.D. Sherry, Inorg. Chem. 37 (1998) 69.
[36] (a) W.P. Cacheris, S.K. Nickle, A.D. Sherry, Inorg. Chem. 26 (1987) 958. (b) E. Tóth, E. Brücher, Inorg. Chim. Acta 221 (1994) 165.
[37] E.T. Clarke, A.E. Martell, Inorg. Chim. Acta 190 (1991) 37.
[38] K. Kumar, C.A. Chang, L.C. Francesconi, D.D. Dischino, M.F. Malley, J.Z. Gougoutas, M.F. Tweedle, Inorg. Chem. 33 (1994) 3567.
[39] (a) J. Huskens, D.A. Torres, Z. Kovacs, J.P. André, C.F.G.C. Geraldes, A.D. Sherry, Inorg. Chem. 36 (1997) 1495. (b) C.A. Chang, Y.-H. Chen, H.-Y. Chen, F.-K. Shieh, J. Chem. Soc. Dalton Trans. (1998) 3243.
[40] A.D. Sherry, J. Ren, J. Huskens, E. Brücher, E. Tóth, C.F.C.G. Geraldes, M.M.C.A. Castro, W.P. Cacheris, Inorg. Chem. 35 (1996) 4604.
[41] A. Bianchi, L. Calabi, F. Corana, S. Fontana, P. Losi, A. Maiocchi, L. Paleari, B. Valtancoli, Coord. Chem. Rev. 204 (2000) 309.
[42] T. Glowiak, I. Podgorska, Inorg. Chim. Acta 125 (1986) 83 (from CCDC — Ref. [83]).
[43] H.O. Davies, R.D. Gillord, M.B. Hursthouse, A. Karanlov, J. Chem. Soc. Dalton Trans. (1995) 2333 (from CCDC — Ref. [83]).
[44] (a) H.C. Freeman, M.R. Snow, I. Nitta, K.Tomita, Acta Crystallogr. 17 (1964) 1463. (b) I.A. Dyakon, S.V. Donu, L.F. Chapurina, A.S. Avilov, Kristallografiya 36 (1991) 219. (c) B. Kaitner, G. Ferguson, N. Paulic, N. Raos, J. Coord. Chem. 26 (1992) 95. (d) M.A.S. Goher, L.A. Al-Shatti, F.A. Mautner, Polyhedron 16 (1997) 889. (e) T.S. Khodashova, M.A. Porai-Koshits, N.K. Davidenko, N.N. Vlasova, Koord. Khim. 10 (1984) 262 (from CCDC — Ref. [83]).
[45] (a) H.O. Davies, R.D. Gillard, M.B. Hurthouse, M.A. Mazid, P.A. Williams, Chem. Commun. (1992) 226. (b) R.E. Norman, N.J. Rose, R.E. Stenkamp, Acta Crystallogr. Sect. C 46 (1990) 1 (from CCDC — Ref. [83]).
[46] (a) V.I. Pakhomov, N.N. Bukov, V.T. Panyuskkin, Koord. Khim. 8 (1982) 402. (b) J. Legendziewicz, E. Huskowska, A. Waskowska, G. Argay, Inorg. Chim. Acta 92 (1984) 151. (c) L.

Xuye, P. Kezhen, Siegon Huaxue (J. Struct. Chem.) 4 (1985) 56. (d) Z. Yifan, P. Kezhen, Siegon Huaxue (J. Struct. Chem.) 7 (1988) 9. (e) J.-J. Zhao, T.-Z. Jin, Gaodeng Xuexiao Huaxue Xuebao (Chem. J. Chin. Univ.) 17 (1996) 519. (f) J. Legendziewicz, E. Huskowska, G. Argay, A. Waskowska, J. Less-Common Met. 146 (1989) 33. (g) J. Tianzhu, Y. Changqing, Y. Qingchnan, W. Jinguang, X. Guangxian, Gaodeng Xuexiao Huaxue Xuebao (Chem. J. Chin. Univ.) 10 (1989) 118. (h) M. Aizeng, L. Laiming, L. Yonghua, X. Shiquan, J. Inorg. Chem. (Wuji Huaxue Xuebao) 9 (1993) 401. (i) M. Aizeng, L. Laiming, L. Yonghua, X. Shiquan, J. Coord. Chem. 33 (1994) 59 (from CCDC — Ref. [83]).

[47] T. Glowiak, W. Sawka-Dobrowolska, B. Jezowska-Trzebiatowska, J. Cryst. Mol. Struct. 10 (1980) 1.

[48] W. Sawka-Dobrowolska, T. Glowiak, Acta Crystallogr. Sect. C 39 (1983) 345.

[49] T. Glowiak, Acta Crystallogr. Sect. C 42 (1986) 62.

[50] A. Riesen, M. Zehnder, T.A. Kaden, Helv. Chim. Acta 69 (1986) 2067.

[51] (a) A. Riesen, M. Zehnder, T.A. Kaden, J. Chem. Soc. Chem. Commun. (1985) 1336. (b) A. Riesen. M. Zehnder, T.A. Kaden, Helv. Chim. Acta 69 (1986) 2074.

[52] K. Kumar, M.F. Tweedle, M.F. Malley, K. Gongontas, Inorg. Chem. 34 (1995) 6472.

[53] P. Murray-Rust, J. Murray-Rust, Acta Crystallogr. Sect. B 35 (1979) 1894.

[54] H.K. Moi, M. Yamek, S.V. Deshpande, H. Hope, S.J. DeNardo, C.F. Meares, Inorg. Chem. 26 (1987) 3458.

[55] A. Riesen, M. Zehnder, T.A. Kaden, Acta Crystallogr. Sect. C 44 (1998) 1740.

[56] M.-R. Spirlet, J. Rebizaut, J.F. Desreux, M.-F. Lousin, Inorg. Chem. 23 (1984) 359.

[57] J.-P. Dubost, J.-M. Leger, M.-H. Langlois, D. Meyer, M. Schaefer, CR Acad. Sci. Paris Ser. II 312 (1991) 349.

[58] C.A. Chong, L.C. Francesconi, M.F. Malley, K. Kumar, J.Z. Gongontas, M.F. Tweedle, D.W. Lee, L.J. Wilson, Inorg. Chem. 32 (1993) 3501.

[59] D. Parker, K. Pulukkody, F.C. Smith, A. Batsanov, J.A.K. Howard, J. Chem. Soc. Dalton Trans. (1994) 689.

[60] S. Aime, A. Barge, M. Botta, M. Fasano, J.D. Ayala, G. Bombieri, Inorg. Chim. Acta 246 (1996) 423.

[61] S. Aime, A. Barge, F. Benetollo, G. Bombieri, M. Botta, F. Uggeri, Inorg. Chem. 36 (1997) 4287.

[62] F. Benetollo, G. Bombieri, S. Aime, M. Botta, Acta Crystallogr. Sect. C 55 (1999) 353.

[63] M. Woods, S. Aime, M. Botta, J.A.K. Howard, J.M. Moloney, M. Navet, D. Parker, M. Port, O. Rousseaux, J. Am. Chem. Soc. 122 (2000) 9781.

[64] S. Aime, A.S. Batsanov, M. Botta, R.S. Dickins, S. Faulkner, C.E. Foster, A. Harrison, J.A.K. Howard, J.M. Moloney, T.J. Norman, D. Parker, L. Royle, J.A.G. Williams, J. Chem. Soc. Dalton Trans. (1997) 3623.

[65] J. Rohovec, P. Vojtíšek, P. Hermann, J. Mosinger, Z. Zák, I. Lukeš, J. Chem. Soc. Dalton Trans. (1999) 3585.

[66] J. Rohovec, P. Vojtíšek, P. Hermann, J. Ludvík, I. Lukeš, J. Chem. Soc. Dalton Trans. (2000) 141.

[67] S. Aime, M. Botta, D. Parker, J.A.G. Williams, J. Chem. Soc. Dalton Trans. (1995) 2259.

[68] S. Aime, M. Botta, D. Parker, J.A.G. Williams, J. Chem. Soc. Dalton Trans. (1996) 17.

[69] W.D. Kim, G.E. Kiefer, J. Huskens, A.D. Sherry, Inorg. Chem. 36 (1997) 4128.

[70] S.I. Kang, R.S. Ranganathan, J.E. Emswiler, K. Kumar, J.Z. Gougoutas, M.F. Malley, M.F. Tweedle, Inorg. Chem. 32 (1993) 2912.

[71] R.D. Shannon, Acta Crystallogr. Sect. A 32 (1976) 752.

[72] J.R. Morrow, S. Amin, C.H. Lake, M.R. Churchill, Inorg. Chem. 32 (1993) 4566.

[73] S. Amin, J.R. Morrow, C.H. Lake, M.R. Churchill, Angew. Chem. Int. Ed. Engl. 33 (1994) 773.

[74] S. Amin, D.A. Voss Jr, W. DeW. Horrocks Jr, C.H. Lake, M.R. Churchill, J.R. Morrow, Inorg. Chem. 34 (1995) 3294.

[75] (a) R.S. Dickins, J.A.K. Howard, C.W. Lehmann, J. Moloney, D. Parker, R.D. Peacock, Angew. Chem. Int. Ed. Engl. 36 (1997) 521. (b) R.S. Dickins, J.A.K. Howard, C.L. Maupin, J.M. Moloney, D. Parker, J.P. Riehl G. Siligardi, J.A.G. Williams, Chem. Eur. J. 5 (1999) 1095.

[76] L. Alderighi, A. Bianchi, L. Calabi, P. Dapporto, C. Giorgi, P. Losi, L. Paleari, P. Paoli, P. Rossi, B. Valtancoli, M. Virtuani, Eur. J. Inorg. Chem. (1998) 1581.

[77] A.S. Batsanov, A. Beeby, J.I. Bruce, J.A.K. Howard, A.M. Kenwright, D. Parker, Chem. Commun. (1999) 1011.
[78] S. Aime, A. Barge, J.I. Bruce, M. Botta, J.A.K. Howard, J.M. Moloney, D. Parker, A.S. de Sousa, M. Woods, J. Am. Chem. Soc. 121 (1999) 5762.
[79] S. Aime, P.L. Anelli, M. Botta, F. Fedeli, M. Grandi, P. Paoli, F. Uggeri, Inorg. Chem. 31 (1992) 2422.
[80] J. Platzek, P. Blaszkiewicz, H. Gries, P. Luger, G. Michl, A. Müller-Fahrnow, B. Radüchel, D. Sülzle, Inorg. Chem. 36 (1997) 6086.
[81] K.O.A. Chin, J.R. Morrow, C.H. Lake, M.R. Churchill, Inorg. Chem. 33 (1994) 656.
[82] (a) M.-R. Spirlet, J. Rebizant, M.-F. Loncin, J.F. Desreux, Inorg. Chem. 23 (1984) 4278. (b) J.-G. Kang, M.-K. Na, S.-K. Yoon, Y. Sohn, Y.-D. Kim, I.-H. Suh, Inorg. Chim. Acta 310 (2000) 56.
[83] F.H. Allen, O. Kennard, Chem. Des. Autom. News 8 (1993) 1.
[84] L. Burai, V. Hietapelto, R. Király, E. Tóth, E. Brücher, Magn. Reson. Chem. 38 (1997) 146.
[85] R.B. Hay, M.P. Pujari, Inorg. Chim. Acta 100 (1985) L1.
[86] L.-H. Chen, C.-S. Chung, Inorg. Chem. 27 (1988) 1880.
[87] H.-Z. Cai, T.A. Kaden, Helv. Chim. Acta 77 (1994) 383.
[88] (a) K. Kumar, C.A. Chang, M.F. Tweedle, Inorg. Chem. 32 (1993) 587. (b) K.-Y. Choi, J.C. Kim, D.W. Kim, J. Coord. Chem. 30 (1993) 1. (c) K. Kumar, T. Jin, X. Wang, J.F. Desreux, M.F. Tweedle, Inorg. Chem. 33 (1994) 3823. (d) E. Tóth, E. Brücher, I. Lázár, I. Tóth, Inorg. Chem. 33 (1994) 4070.
[89] K.P. Pulukkody, T.J. Norman, D. Parker, L. Royle, C.J. Broan, J. Chem. Soc. Perkin Trans. 2 (1993) 605.
[90] S. Aime, M. Botta, S.G. Crich, G.B. Giovenzana, R. Pagliarin, M. Piccinini, M. Sisti, E. Terreno, J. Biol. Inorg. Chem. 2 (1997) 470.
[91] S. Aime, M. Botta, S.G. Crich, G. Giovenzana, R. Pagliarin, M. Sisti, E. Terreno, Magn. Reson. Chem. 36 (1998) S200.
[92] S. Aime, M. Botta, L. Frullano, S.G. Crich, G. Giovenzana, R. Pagliarin, G. Palmisano, F.R. Sirtori, M. Sisti, J. Med. Chem. 43 (2000) 4017.
[93] S. Aime, M. Botta, E. Garino, S.G. Crich, G. Giovenzana, R. Pagliarin, G. Palmisano, M. Sisti, Chem. Eur. J. 6 (2000) 2609.
[94] (a) D. Parker, J.A.G. Williams, J. Chem. Soc. Dalton Trans. (1996) 3613. (b) D. Parker, Coord. Chem. Rev. 205 (2000) 109.