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Stability Constants and Dissociation Rates of the EDTMP Complexes of Samarium(III) and Yttrium(III)

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The stability constants of Sm(EDTMP) ($\log K_{ML}$ = 20.71) and Y(EDTMP) ($\log K_{ML}$ = 19.19) were determined by a competition reaction between the Ln^{3+} ion (Ln^{3+} = Sm^{3+} or Y^{3+}) and Cu^{2+} for the EDTMP ligand by spectrophotometry at pH ≈ 10, in the presence of an excess amount of citrate (0.15 M NaCl, 25 °C). For determining the stability constants of Cu(EDTMP) ($\log K_{ML}$ = 19.36) and Ca(EDTMP) ($\log K_{ML}$ = 8.71) pH–potentiometry was used. In the pH range 4–9 the EDTMP complexes are present in the form of nonprotonated and mono-, di- and triprotonated species. The Ca^{2+} ion forms a dinuclear complex with Ln(EDTMP). In a simplified blood plasma model consisting of Sm^{3+}, Ca^{2+} and Zn^{2+} metal ions, EDTMP, citrate, cysteine and histidine ligands, Sm^{3+} is practically present in the form of $[Sm(HEDTMP)Ca]^{2-}$, whereas Zn^{2+} predominantly forms $[Zn(HEDTMP)]^{5-}$ and $[Zn(H_2EDTMP)]^{4-}$ complexes. For studying the dissociation rates of the complexes, the kinetics of the metal exchange (transmetallation) reactions between the Ln(EDTMP) complexes and Cu^{2+}–citrate were investigated in the pH range 7–9 by the stopped-flow method. The rates of the exchange reactions are independent of the Cu^{2+} concentration and increase with the H^+ concentration. The rate constants, characterizing the proton-assisted dissociation of the Ln(EDTMP) complexes, are several orders of magnitude higher than those of the similar Ln(EDTA) complexes, because the protonation constants of Ln(EDTMP) are high and the protonated Ln(HEDTMP) and Ln(H_2EDTMP) species are present in higher concentration. The half-times of dissociation of Sm(EDTMP) and Y(EDTMP) at pH = 7.4 and 25 °C are 4.9 and 7.5 s, respectively. These relatively short dissociation half-time values do not predict the deposition of Ln^{3+} ions in bones in the form of intact Ln(EDTMP) complexes. It is more probable that sorption of the EDTMP ligand and Sm^{3+} or Y^{3+} ions occurs independently after the dissociation of complexes.

Introduction

In recent years much interest has been generated in the synthesis and study of complexes formed with chelating agents containing phosphonate pendant groups. The main reason for the interest is the wide-spread application of these chelates in different fields of industry, agriculture and medicine. Medical applications are generally based on the bone-seeking properties of the phosphonate-containing ligands and complexes, which have high affinity for the sites of actively growing bones. The bone-seeking properties are particularly definite if a methylenediphosphonate group is present in the ligand, as it was found by Adzamli et al. and Kubicek et al.[1,2] Several methanediphosphonate derivative ligands are commercially produced and marketed as drugs for the treatment of osteoporosis. It is assumed that the methanediphosphonate ligands mobilize the Ca^{2+} and Mg^{2+} ions from the plasma and increase the amount of the two metal ions available for deposition on bones.[3]

In magnetic resonance imaging investigations, the Gd^{3+} complexes of DTPA and DOTA are clinically used as contrast enhancing agents (H_5DTPA = diethylenetriamine-*N*,*N*,*N*′,*N*′′,*N*′′-pentaacetic acid; H_4DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid).[4] It was demonstrated that by replacing one of the carboxylate groups of the DTPA or DOTA ligands with a methanediphosphonate-containing functionality, the Gd^{3+} complexes of the new ligands obtained are potential bone-seeking contrast agents.[1,2]

The diagnostic utility of some methylenediphosphonate derivative complexes formed with the radioactive ^{99m}Tc isotope has been demonstrated for skeletal imaging.[5] Of the phosphonate-containing ligands used in nuclear medicine, the most important is probably the EDTA analogue EDTMP [H_8EDTMP = ethylenediaminetetrakis(methylenephosphonic acid)], which forms complexes of high stability with lanthanide(III) ions (Ln^{3+}), so with the radioactive isotopes like ^{153}Sm, ^{166}Ho, ^{177}Lu and ^{90}Y (the properties of Y^{3+} are very similar to those of the lanthanides, so the symbol Ln^{3+} will be used for marking the Y^{3+}). EDTMP has a high affinity for bones and this behaviour is valid for its Ln^{3+} complexes. Some primary tumours (e.g., breast, lung and prostate tumours) frequently metastasize

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to the skeleton. For the pain palliation therapy of patients having metastatic bone cancer, the ^{153}Sm(EDTMP) or ^{90}Y(EDTMP) complex is clinically used, which deposits in the bones and in a suitable dose results in pain relief for about two months.[6–9] The behaviour of a number of aminopolycarboxylate and aminopolyphosphonate complexes of radiolanthanides were investigated, but besides the skeletal uptake many compounds showed significant liver deposition and high blood activity. The ^{153}Sm(EDTMP) complex demonstrated the highest skeletal uptake and lowest blood and nonosseous tissue activity[6] (the charge of the ligands and complexes will be used only when it is absolutely necessary).

For the research and development of ligands having more favourable properties than EDTMP, we should have to understand the biodistribution and the mode of action of the Ln(EDTMP) complexes, which can be different for the complexes of different Ln^{3+} ions. The views regarding the mechanism of the uptake of the Ln^{3+} ions in the bones differ considerably. Chirby et al. assume that the ^{153}Sm and EDTMP adsorb independently after the dissociation of the complex, whereas others assume the sorption of the intact complex.[8,9] The mechanism of the sorption may depend on the kinetic behaviour of the Ln(EDTMP) complexes, namely on the rates of their dissociation. It is interesting, however, that whereas the rates of dissociation of the Ln^{3+}–aminopolycarboxylate complexes [e.g., Ln(EDTA) and Ln(DTPA), etc.] have been studied in detail, the similar properties of the Ln^{3+} complexes formed with open-chain aminopolyphosphonates have not been investigated till now.

The rates of dissociation of the Gd^{3+} complexes formed with the macrocyclic DOTA ligand and its phosphonate analogue, DOTP, are very slow [H_8DOTP = 1,4,7,10-tetraazacyclododecane-1,4,7,10-(tetrakis)methylenephosphonic acid].[10] However, the Gd^{3+} complex of the DTPA derivative ligand, prepared by replacement of the central carboxylate group of DTPA with a phosphonate group, dissociates very fast, approximately one thousand times faster than Gd(DTPA).[11] On the basis of this result it can be anticipated that the Ln^{3+} complexes of the open-chain aminopolyphosphonates are more labile than their aminopolycarboxylate analogues.

For understanding the behaviour of the Ln(EDTMP) complexes in vitro and in vivo, we should know their physicochemical properties, and first of all the stability constants. Unfortunately, the stability constants ($\log K_{ML}$) reported so far in the literature differ very considerably. The $\log K_{ML}$ values published, for example, for the Y(EDTMP) complex are 11.10,[12] 15.06[13] and 23.72.[14] The main problem in determining the stability constants is the low solubility of some protonated complexes, which results in precipitate formation at low pH values.

Recently we developed a competition method for determining the stability constant of Sm(EDTMP) and Y(EDTMP). The method is based on the competition reaction between the Ln^{3+} and Cu^{2+} ions for the EDTMP ligand at pH ≈ 10 in the presence of citrate, which prevents the hydrolysis of the Ln^{3+} and Cu^{2+} ions. For evaluation of the data, the stability constants of all the species formed in these systems were determined. For obtaining information on the dissociation rates of the complexes, the kinetics of the exchange reactions occurring between Sm(EDTMP), Y(EDTMP) and Cu^{2+}–citrate were also investigated.

Results and Discussion

Equilibrium Studies

For characterizing the complexation properties of EDTMP, the protonation constants K_i^H ($K_i^H = [H_iL]/[H_{i-1}L][H^+]$, i = 1, 2, ...6) were determined by pH–potentiometry. The $\log K_i^H$ values obtained are listed in Table 1, where the standard deviation values are given in parentheses.

Table 1. Protonation constants of $EDTMP^{8-}$.

	0.15 M NaCl[a] 25 °C	0.1 M KNO_3[b] 25 °C	0.15 M NaCl[c] 37 °C	0.1 M KCl[d] 25 °C
$\log K_1^H$	11.61 (0.02)	12.99	10.67	12.10
$\log K_2^H$	9.33 (0.02)	9.78	9.47	10.18
$\log K_3^H$	7.51 (0.03)	7.94	7.63	8.08
$\log K_4^H$	6.23 (0.03)	6.42	6.31	6.54
$\log K_5^H$	5.09 (0.03)	5.17	5.08	5.23
$\log K_6^H$	2.80 (0.04)	3.02	2.83	3.00
$\log K_7^H$	–	1.33	1.24	–

[a] This work. [b] Ref.[16] [c] Ref.[9] [d] Ref.[15]

In Table 1 some other published data are also shown for comparison.[9,15,16] The inspection of the data shows that the $\log K_1^H$ values determined in the presence of NaCl or KCl/KNO_3 differ considerably. The lower $\log K_1^H$ values obtained in NaCl solution indicate that the stability of the Na^+ complex formed with EDTMP is higher than that of the K^+ complex. The further protonation constants do not differ considerably. The set of the protonation constants reported by de Witt et al. (9.63, 7.69, 6.26, 5.04, 2.86 and 1.12, obtained in 0.15 M NaCl at 25 °C)[12] is very similar to the $\log K_2^H$, $\log K_3^H$, ···, $\log K_7^H$ values presented in Table 1. It seems as if these authors did not observe the formation of the monoprotonated ligand $HEDTMP^{7-}$.

In the protonation of $EDTMP^{8-}$ the first two protons are attached to the two nitrogen atoms, which are characterized by the $\log K_1^H$ and $\log K_2^H$ values. The further protons protonate the phosphonate oxygen atoms.[17,18]

It is known from the literature that the determination of the stability constants of the Ln(EDTMP) complexes is difficult by pH–potentiometric titration, because of the formation of precipitates of some protonated complexes at pH ≈ 2–4,[9,15–19] so the equilibrium constants obtained under such conditions are often not reliable.[19] In order to avoid these problems, we developed a competition method, which could be used at pH ≈ 10, when only deprotonated $Ln(EDTMP)^{5-}$ complexes were formed. The method is based on the competition reaction between the Ln^{3+} and Cu^{2+} ions for the EDTMP ligand in the presence of an excess amount of citrate, as it is seen in Equation (1).

$$Cu(edtmp) + Ln(cit)_2 \rightleftharpoons Ln(edtmp) + Cu(cit) + cit \quad (1)$$

The absorption spectra of Cu(EDTMP) and Cu(cit) differ considerably in the 250–340 nm wavelength range (Figure 1). Because the stability constant of Cu(EDTMP) can be determined by pH–potentiometry (Table 3), the absorbance values can be used for the calculation of the stability constants of $Sm(EDTMP)^{5-}$ and $Y(EDTMP)^{5-}$. For carrying out the calculations, the stability constants of the complexes formed in the Ln^{3+}–citrate, Cu^{2+}–citrate and Cu^{2+}–EDTMP systems and the molar absorptivities of the Cu^{2+} complexes had to be determined.

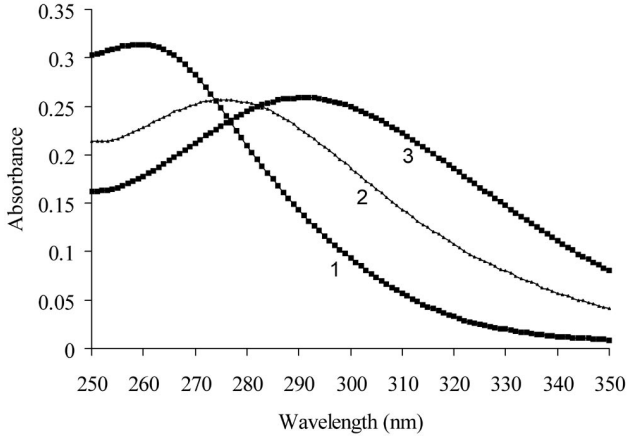

Figure 1. Absorption spectra of the Cu^{II} complexes (pH ≈ 10): (1) 1×10^{-4} M Cu^{2+}, 0.01 M citrate; (2) 1×10^{-4} M Cu^{2+}, 0.01 M citrate, 1.8×10^{-3} M Sm^{3+} and 1×10^{-4} M EDTMP; (3) 1×10^{-4} M Cu(EDTMP).

The calculation of the stability constants of the citrate (X^{3-} or X^{4-} if the alcoholic OH is dissociated) complexes of Sm^{3+} and Y^{3+} from the titration data resulted in the lowest-fitting parameters if the formation of the LnX, LnXH, LnX_2, LnX(HX), $LnXH_{-1}$, $LnXH_{-2}$ and LnX_2H_{-1} species was assumed. The formation of some similar species was assumed earlier by Jackson et al. and Sal′nikov et al.[20,21]

For the formation of the Ln^{3+}–citrate complexes it was assumed that in the LnX species beside a terminal and the central carboxylate group, the oxygen atom of the alcoholic OH group is coordinated, whereas the other terminal carboxylate group is free or protonated (LnXH).[20] As a result of the high coordination number of the Ln^{3+} ions, $Ln(X_2)^{3-}$ and $LnX(XH)^{2-}$ complexes can also be formed. The titration data indicate that both the LnX and $Ln(X_2)^{3-}$ complexes can be deprotonated in the pH range ca. 4.5–7, which is related to the dissociation of the alcoholic OH group when the $LnXH_{-1}$ (LnX^-) and LnX_2H_{-1} [$Ln(X_2)^{4-}$] species are formed. However, there is a further base consumption in the titration curves that can be interpreted by the coordination of an OH^- group, when the $LnXH_{-2}$ [$LnX(OH)^{2-}$] species is formed.

The pH–potentiometric titration data obtained for the Cu^{2+}–citrate system at 1:1 and 1:2 metal to ligand concentration ratios could be interpreted by assuming the predominant formation of 1:1 species, CuX^-, CuXH, $CuXH_{-1}$ (CuX^{2-}) and $CuXH_{-2}$ [$CuX(OH)^{3-}$]. By the calculation of the stability constants the fitting was better if the formation of the Cu_2XH_{-1} (Cu_2X^0) species was also considered (it was formed in the pH range 4–6).

The equilibrium constants calculated for the formation of the citrate complexes are defined in the left-hand column of Table 2. The stability constants of the complexes formed with Sm^{3+}, Y^{3+} and Cu^{2+} were calculated from the data of pH–potentiometric titration and the $\log K$ values obtained are listed in Table 2. The calculation of the species distribution for the Cu^{2+}–citrate complexes indicates that under such conditions, which were used for determining the stability constants of Sm(EDTMP) and Y(EDTMP), the Cu^{2+} was present in the form of the $CuXH_{-1}$ (CuX^{2-}) and $CuXH_{-2}$ [$CuX(OH)^{3-}$] species.

Table 2. Stability and protonation constants ($\log K$) of the citrate (X^{3-}) complexes of Sm^{3+}, Y^{3+} and Cu^{2+} (0.15 M NaCl, 25 °C).

	Sm^{3+}	Y^{3+}	Cu^{2+}
[MX]/[M][X]	7.38(0.03)	6.95(0.02)	5.58(0.03)
[MXH]/[MX][H^+]	3.38(0.02)	3.43(0.02)	3.39(0.06)
[MX_2]/[MX][X]	5.08(0.04)	4.45(0.03)	–
[MX_2H]/[MX_2][H^+]	4.21(0.05)	4.29(0.05)	–
[MX]/[MXH_{-1}][H^+]	5.82(0.07)	5.88(0.03)	3.97(0.02)
[MXH_{-1}]/[MXH_{-2}][H^+]	7.02(0.07)	8.42(0.04)	10.78(0.05)
[MX_2]/[MX_2H_{-1}][H^+]	6.85(0.07)	7.66(0.08)	–
[M_2XH_{-1}]/[MXH_{-1}][M]	–	–	3.11(0.05)

The stability constants of Sm(EDTMP) and Y(EDTMP) were calculated with the use of the absorbance values obtained for the Cu^{2+}–Ln^{3+}–EDTMP–citrate equilibrium systems by knowing the total concentrations and pH values. The $\log K_{ML}$ values calculated for $Sm(EDTMP)^{5-}$ and $Y(EDTMP)^{5-}$ are shown in Table 3. The high negative charge of the EDTMP complexes and the high basicity of the phosphonate oxygen atoms result in the formation of protonated species. The protonation constants ($K_{MH_iL} = [MH_iL]/[MH_{i-1}L][H^+]$, i = 1, 2 and 3) obtained by the titration of the complexes with acid are presented in Table 3.

The complexes formed in the Cu^{2+}–citrate system were found to be ESR silent at about pH > 4.5, which indicates the formation of spin-coupled Cu^{II} dimers. Kiss et al. interpreted the ESR and pH–potentiometric data by assuming the formation of the CuXH, Cu_2X_2, $Cu_2X_2H_{-1}$ and $Cu_2X_2H_{-2}$ species.[22] At pH ≈ 10, the $Cu_2X_2H_{-2}$ species predominates, which is formed from the monomer $CuXH_{-1}$ without any change in the pH. With the use of the stability constants reported by Kiss et al. for the Cu^{2+}–citrate complexes, the $\log K_{ML}$ values calculated for SmL^{5-} and YL^{5-} are approximately $0.5 \log K$ units higher than the $\log K_{ML}$ values obtained by us (Table 3; by these calculations the formation of the $CuXH_{-2}$ species, which is present in 10% at about pH 10, was taken into account). These small differences can be interpreted by considering the different conditions used by Kiss et al. (0.2 M KCl)[22] and in this work (0.15 M NaCl).

Table 3. Stability and protonation constants ($\log K$) of the complexes of EDTMP formed with Sm^{3+}, Y^{3+}, Ca^{2+} and Cu^{2+}.

	0.15 M NaCl[a] 25 °C	0.15 M NaCl[c] 37 °C	0.1 M KCl[d] 25 °C	0.1 M KNO_3[f] 25 °C
$Sm^{3+} + L$	20.71 (0.08)	14.44	22.39	–
$SmL + H^+$	6.98 (0.03)	7.13	7.27	7.34
$SmHL + H^+$	5.91 (0.03)	6.00	6.30	6.20
$SmH_2L + H^+$	4.80 (0.03)	–	5.12	–
$Y^{3+} + L$	19.19 (0.08)	–	11.11[e]	–
$YL + H^+$	7.23 (0.02)	–	5.89	7.17
$YHL + H^+$	6.18 (0.02)	–	5.81	5.9
$YH_2L + H^+$	5.16 (0.02)	–	–	–
$Ca^{2+} + L$	8.71 (0.05)	6.41	9.36[b]	–
$CaL + H^+$	8.41 (0.02)	8.94	9.42	–
$CaHL + H^+$	7.36 (0.02)	8.06	8.44	–
$CaH_2L + H^+$	7.31 (0.03)	–	6.59	–
$CaL + Ca^{2+}$	5.15 (0.03)	–	–	–
$Ca_2L + H^+$	7.56 (0.03)	–	–	–
$Cu^{2+} + L$	19.36 (0.05)	16.20	23.21[b]	–
$CuL + H^+$	7.48 (0.04)	7.91	7.56	–
$CuHL + H^+$	6.06 (0.03)	6.34	5.99	–
$CuH_2L + H^+$	4.66 (0.03)	4.89	4.62	–
$CuH_3L + H^+$	3.88 (0.02)	4.15	3.74	–
$CuL + Cu^{2+}$	6.66 (0.06)	–	–	–
$Cu_2L + H^+$	6.18 (0.04)	–	–	–
$Cu_2HL + H^+$	4.57 (0.04)	–	–	–

[a] This work. [b] Ref.[16] [c] Ref.[9] [d] Ref.[15] [e] Ref.[12] [f] Ref.[24]

The stability and protonation constants characterizing the formation of Sm(EDTMP) complexes obtained in this work and by Kabachnik et al.[15] are similar if we take into account the different media used in these investigations. In 0.1 M KNO_3 the value of $\log K_1^H$ is larger, which leads to the larger value of the stability constant of Sm(EDTMP). The higher temperature (37 °C) results in a lower $\log K_1^H$ protonation constant and lower stability constant for Sm(EDTMP), but in spite of this the $\log K_{ML}$ value reported by Jarvis et al.[9] seems to be too low. As it was indicated by these authors, the data points used for the calculations were obtained at pH > 5, where the concentration of the free Sm^{3+} is very low.[9] The stability constant of Y(EDTMP) published by de Witt et al. is even lower. This value seems to be unreliable, as the purity of the ligand used in this work was only 92%.[12] However, the stability constant published by Kunbazarov et al. for Y(EDTMP) ($\log K_{ML}$ = 23.72) seems to be too high.[14] For Ho(EDTMP), Ernestová et al. reported the value $\log K_{ML}$ = 20.20 (0.1 M NaCl, 25 °C),[23] which is comparable with the $\log K_{ML}$ values determined by us for Sm(EDTMP) and Y(EDTMP). The large differences in the stability constant values of the Ln(EDTMP) complexes published in the literature generally resulted from the impurities of the ligand and by the low solubilities and the formation of precipitates of the protonated species formed at lower pH values.[19]

For interpreting the equilibrium data, Jarvis et al. assumed that the stability constants of the EDTMP complexes are lower than those of the EDTA complexes.[9] The spectrophotometric study of the Ce^{3+} complexes we made, unambiguously proved that at a 1:1:1 concentration ratio of the Ce^{3+}, EDTMP and EDTA at pH = 9, the Ce^{3+} was present predominantly in the form of $Ce(EDTMP)^{5-}$, which indicated the higher stability of the EDTMP complexes and indirectly showed the reliability of the stability constants, obtained by us for $Sm(EDTMP)^{5-}$ and $Y(EDTMP)^{5-}$.

It is interesting, however, that although the $\log K_{ML}$ values obtained by various authors differ very considerably, the protonation constants of complexes are similar (Table 3). The protonation of the Ln(EDTMP) or Cu(EDTMP) complexes probably occurs at the phosphonate oxygen atoms, so the first, second and third protonation constants can be compared with the third, fourth and fifth protonation constants of the EDTMP ligand, respectively. By comparing the data presented in Tables 1 and 3, it is seen that the protonation constants of complexes are similar to or only somewhat lower than those of the ligand. The similarities or even the small differences in the appropriate protonation constants of the ligand and complexes (e.g., $\log K_3^H$ and $\log K_{MHL}$, etc.) are quite surprising, because this finding means that contrary to the expectations, the proton affinities of the oxygen donor atoms of the free and coordinated ligands are similar. This unexpected result can be interpreted with the more open structure of the EDTMP complexes, assumed by Oaks for interpreting the water proton relaxation rates obtained in the presence of some complexes.[25] Besides, the protonation constants K_3^H, K_4^H, K_5^H and K_6^H of EDTMP are relatively lower, because of the strong H-bonds formed in $(H_2EDTMP)^{6-}$ between the protons attached to the two nitrogen atoms and the phosphonate oxygen atoms (for splitting of the H-bonds higher $[H^+]$ is needed). Similarly, H-bonds are not formed in the $Ln(EDTMP)^{5-}$ complexes, where protonation is hindered, because of the coordination of the oxygen donor atoms.

The study of the complexation of EDTMP with Ca^{2+} is also important because the concentration of Ca^{2+} in blood plasma is relatively high (2.5 mM[26]), so Ca^{2+} might compete with Sm^{3+} or Y^{3+} for EDTMP. The stability and protonation constants of the Ca^{2+} complexes were determined by pH–potentiometry and the results are listed in Table 3. The stability constant of Ca(EDTMP) is lower than that of Ca(EDTA) ($\log K$ = 10.7[28]), which indicates the higher affinity of Ca^{2+} for the polycarboxylates than polyphosphonates. The first protonation constant of Ca(EDTMP) is very high, which suggests that the first proton protonates a nitrogen atom of the ligand, which is followed by the protonation of the phosphonate oxygen atoms.

The protonation constants of the Sm(EDTMP) and Y(EDTMP) complexes were found to be lower in the presence of Ca^{2+}, which indicated the formation of dinuclear Ln(EDTMP)Ca complexes. The stability constants of dinuclear complexes were determined by pH–potentiometric titration on the basis of the competition between the Ca^{2+} and H^+ ions for the $Ln(EDTMP)^{5-}$ complexes. The stability constants are shown in Table 4.

Table 4. Stability and protonation constants (log K) of the dinuclear complexes formed between Sm(EDTMP), Y(EDTMP) and Ca^{2+} (0.15 M NaCl, 25 °C).

Ln^{3+}	Sm^{3+}	Y^{3+}
$LnL + Ca^{2+}$	3.47(0.05)	3.91(0.04)
$LnLCa + H^{+}$	6.22(0.08)	6.62(0.06)

The stability and protonation constants of the complexes and ligands presented in Tables 1–4 give the possibility to calculate the species distribution in a simplified plasma model, containing Sm^{3+} and EDTMP, Zn^{2+} and Ca^{2+} and the citrate, histidine and cysteine ligands. Of the endogenous metals, first of all Zn^{2+} can compete with Sm^{3+} for EDTMP, whereas Ca^{2+} can form a dinuclear complex with Sm(EDTMP). The citrate ligand has a high affinity for Sm^{3+}, whereas histidine and cysteine form strong complexes with Zn^{2+}. The concentration of Sm^{3+} and EDTMP, used in the simple plasma model, was calculated from the composition of a clinically used kit (^{153}Sm–Multibone). The concentration of the other metal ions and ligands were the same as those used in the plasma model of May et al.[26] These concentrations are listed in Table 5. Assuming an equilibrium in the model system, the species distribution was calculated (pH = 7.4) with the use of the PSEQUAD program.[27] The equilibrium concentrations of the different complexes were calculated with the use of the protonation and stability constants determined in this work and those obtained by others.[28] The species distribution data are presented in Table 5.

Table 5. Species distribution (M) in the model system containing Sm^{3+} (4×10^{-7} M), EDTMP (1×10^{-5} M), Ca^{2+} (1.1×10^{-3} M), Zn^{2+} (1×10^{-5} M), citrate (1.1×10^{-4} M), cysteine (2.5×10^{-5} M) and histidine (8.5×10^{-5} M) (pH = 7.4).

Sm(HEDTMP)Ca	3.97×10^{-7}
Sm(EDTMP)Ca	2.0×10^{-9}
Sm(EDTMP)	6.7×10^{-10}
Sm^{3+}(aq.)	4.8×10^{-16}
$Sm(cit)_2$	2.9×10^{-16}
Ca^{2+}(aq.)	1.0×10^{-3}
Ca(cit)	7.6×10^{-5}
Ca_2(HEDTMP)	3.1×10^{-7}
Ca_2(EDTMP)	2.1×10^{-7}
Ca(HEDTMP)	1.5×10^{-8}
Zn(HEDTMP)	7.4×10^{-6}
$Zn(H_2EDTMP)$	1.1×10^{-6}
$Zn(citH_{-1})$	8.6×10^{-7}
Zn(EDTMP)	5.0×10^{-7}
$Zn(cis)_2$	7.8×10^{-8}
$Zn(his)_2$	1.3×10^{-8}

The data show that almost the total amount of Sm^{3+} is in the form of the protonated $[Sm(HEDTMP)Ca]^{2-}$ dinuclear complex, because of the high concentration of Ca^{2+} in the plasma. Because of the large excess of EDTMP, 90% of Zn^{2+} is in the form of Zn(EDTMP) complexes, which are excreted from the body in the urine, as it was found in human experiments.[9] It can also be seen that the concentration of the complexes formed with citrate, histidine and cysteine is negligible.

Dissociation Rates of Sm(EDTMP) and Y(EDTMP)

Metal chelates used in medical diagnosis and therapy must fulfill strict requirements. Among these requirements, the high thermodynamic stability and kinetic inertness are of high importance. Radioactive or paramagnetic metal ions can be delivered to the disease sites of the body in the form of inert, target-specific complexes. The kinetic inertness is often characterized with the rate of dissociation of the complexes. For obtaining information on the rates of dissociation, the kinetics of metal exchange (transmetallation) reactions are studied, which occur between the complex and a suitable exchanging metal ion. For studying the dissociation of the Sm(EDTMP) and Y(EDTMP) complexes, we used Cu^{2+} as a displacing ion and the rates of the exchange reactions [Equation (2)] were investigated by spectrophotometry, because the absorption spectra of Cu(EDTMP) and Cu(cit) differ considerably (Figure 1).

$$Ln(edtmp) + Cu(cit) \rightleftharpoons Cu(edtmp) + Ln(cit) \quad (2)$$

The rates of the metal exchange reactions [Equation (2)] were studied by the stopped-flow method, with the use of a 10–35-fold excess of Cu(cit) in the pH range 7–9 in 0.15 M NaCl. For keeping the pH constant, 0.02 M HEPES or dimethylpiperazine buffer was used. In the presence of an excess amount of Cu(cit), Equation (2) can be regarded as a pseudo-first-order one and the rate of exchange can be expressed by Equation (3), where k_d is a pseudo-first-order rate constant and $[LnL]_t$ is the total concentration of the Sm(EDTMP) or Y(EDTMP) complex.

$$-\frac{d[LnL]_t}{dt} = k_d[LnL]_t \quad (3)$$

The k_d values, characterizing the rates of the exchange reactions, increase with an increase in the H^+ concentration, as it is seen in Figures 2 and 3. However, the k_d values obtained at different Cu(cit) concentrations do not differ, which indicates that the rate of the exchange is independent of the concentration of Cu(cit). In Figure 2, the k_d values show a second-order dependence on $[H^+]$, so the k_d values characterizing the rates of exchange of Sm(EDTMP) can be expressed by Equation (4).

For the exchange reactions of Y(EDTMP), the k_d values are directly proportional to $[H^+]$ (Figure 3), and for this reaction, the third term of Equation (4) is negligible. A few exchange reactions were studied in the presence of Ca^{2+} and it was found that the rates of the reactions were nearly the same in the presence and absence of Ca^{2+}. The rate law, obtained by substituting Equation (4) into Equation (3), indicates that the exchange reactions in Equation (2) take place through the spontaneous and proton-assisted dissociation of the Ln(EDTMP) complexes. In the rate law, k_0

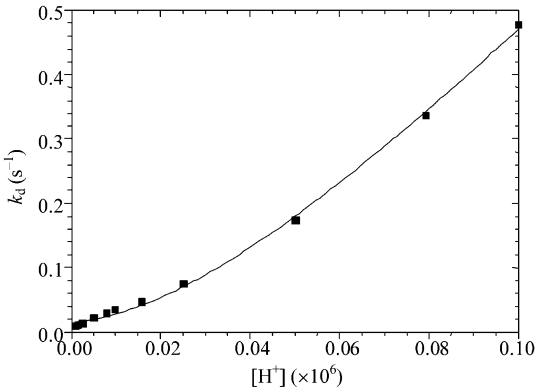

Figure 2. Dependence of the dissociation rates (k_d) of Sm(EDTMP) on the H^+ concentration.

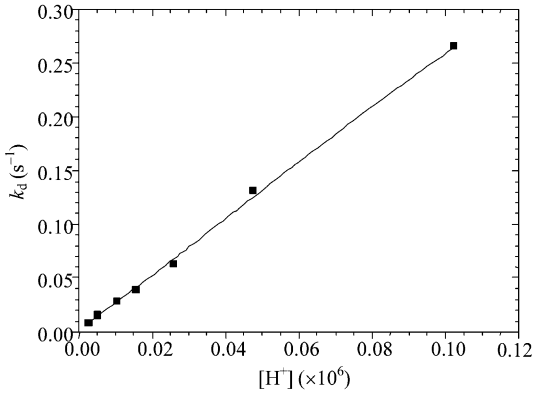

Figure 3. Dependence of the dissociation rates (k_d) of Y(EDTMP) on the H^+ concentration.

$$k_d = k_0 + k_1[H^+] + k_2[H^+]^2 \quad (4)$$

characterizes the rate of spontaneous dissociation, whereas k_1 and k_2 are the rates of proton-assisted dissociation of the complexes. The relatively slow dissociation of the complexes is followed by the fast reaction between the H_xEDTMP free ligand and Cu(cit).

The rate constants k_0, k_1 and k_2, obtained by fitting the k_d values into Equation (4), are presented in Table 6, where some data are also shown for the similar exchange reactions of Sm(EDTA) and Y(EDTA).[29,30] A comparison of the rate data presented in Table 6 shows that the proton-assisted dissociation of the Sm(EDTMP) and Y(EDTMP) complexes is much faster than the similar reactions of the Sm(EDTA) and Y(EDTA) complexes [the spontaneous dissociation of the Ln(EDTA) complexes is very slow, so the k_0 values were not determined].

The large differences in the rates of proton-assisted dissociation of the Ln(EDTMP) and Ln(EDTA) complexes can be explained with the very different propensity of the complexes to undergo protonation. The protonation constants of the Ln(EDTMP) complexes are large as it seen in Table 3, and in the pH range 7–9 the concentration of the monoprotonated Ln(HEDTMP)$^{4-}$ complexes is significant and the presence of the diprotonated Ln(H_2EDTMP)$^{3-}$ species cannot be neglected. However, the protonation constants ($\log K_{MHL}$) of Sm(EDTA) and Y(EDTA) are 1.69 and 1.0, respectively,[31] that is, the concentration of the protonated species at pH ≈ 7 is extremely low, which results in the very slow proton-assisted dissociation of these complexes.

The dissociation of the protonated complexes can take place much faster, because the protonation occurs at a phosphonate or carboxylate oxygen atom, which results in the weakening of the metal–ligand interaction in the protonated complexes. The proton can be transferred from the oxygen to a nitrogen atom when half of the EDTMP or EDTA ligand is not coordinated and the dissociation of this intermediate is fast.

The proton-assisted dissociation of Y(EDTMP) is somewhat slower than that of Sm(EDTMP), probably because the interaction between Y^{3+} and the donor atoms of EDTMP is stronger due to the smaller size of Y^{3+}. The second-order dependence of the k_d values characterizing the rate of dissociation of Y(EDTMP) presumably appears at higher [H^+].

For the direct comparison of the kinetic behaviour of the Ln(EDTMP) and Ln(EDTA) complexes it seems more practical to calculate the rate constants k_{d1} and k_{d2}, which characterize the rates of dissociation of the monoprotonated [Ln(HEDTMP)$^{4-}$ and Ln(HEDTA)^0] and diprotonated [Ln(H_2EDTMP)$^{3-}$ and Ln(H_2EDTA)$^+$] complexes. In this case, the rate of dissociation of the complexes can be expressed as given in Equation (5).

$$-\frac{d[LnL]_t}{dt} = k_0[LnL] + k_{d1}[LnHL] + k_{d2}[LnH_2L] \quad (5)$$

Table 6. Rate constants characterizing the dissociation reactions of Sm(EDTMP), Y(EDTMP), Sm(EDTA) and Y(EDTA) (25 °C).

	Sm(EDTMP)	Y(EDTMP)	Sm(EDTA)[a]	Y(EDTA)[b]
k_0 (s^{-1})[c]	$(7.3 \pm 0.9) \times 10^{-3}$	$(2.2 \pm 0.6) \times 10^{-3}$	–	–
k_1 (M^{-1} s^{-1})[c]	$(2.3 \pm 0.2) \times 10^{6}$	$(2.5 \pm 0.13) \times 10^{6}$	1.18×10^{2}	30
k_2 (M^{-2} s^{-1})[c]	$(2.1 \pm 0.4) \times 10^{13}$	–	1.8×10^{6}	5.2×10^{5}
k_0 (s^{-1})[d]	$(7.4 \pm 0.8) \times 10^{-3}$	$(2.9 \pm 0.8) \times 10^{-3}$	–	–
k_{d1} (s^{-1})[d]	0.23 ± 0.03	0.14 ± 0.012	2.4	3.0
k_{d2} (s^{-1})[d]	8.2 ± 0.9	2.0 ± 0.21	–	–

[a] Ref.[29] [b] Ref.[30] [c] Calculated with Equation (4). [d] Calculated with Equation (6).

The total concentration of Ln(EDTMP) is $[LnL]_t = [LnL] + [LnHL] + [LnH_2L]$. By expressing the concentration of the protonated complexes with the protonation constants K_{LnHL} and K_{LnH2L}, the combination of Equations (3) and (5) leads to Equation (6).

$$k_d = \frac{k_0 + k_{d1}K_{LnHL}[H^+] + k_{d2}K_{LnHL}K_{LnH_2L}[H^+]^2}{1 + K_{LnHL}[H^+] + K_{LnHL}K_{LnH_2L}[H^+]^2} \quad (6)$$

By fitting the k_d values into Equation (6) with the fixed values of K_{LnHL} and K_{LnH_2L} obtained by pH–potentiometry (Table 3), the rate constants k_0, k_{d1} and k_{d2} were calculated, and they are presented in Table 6.

For the exchange reactions of Sm(EDTA) and Y(EDTA), Equation (6) can be simplified, because the protonation constants K_{LnHL} and K_{LnH_2L} are very low, so the second and third terms in the denominator can be neglected at about pH > 4. Thus, by comparing Equations (4) and (6), it can be seen that $k_1 \approx k_{d1}K_{LnHL}$ and $k_2 \approx k_{d2}K_{LnHL}K_{LnH_2L}$. For the Sm(EDTA) and Y(EDTA) complexes only the first protonation constants K_{LnHL} are known, so the approximate values of k_{d1} could be calculated (Table 6). Comparison of the k_{d1} values obtained for the Ln(EDTMP) and Ln(EDTA) complexes shows that the rates of dissociation of the monoprotonated Ln(HEDTMP) complexes are about ten times lower than those of the Ln(EDTA) complexes. The dissociation rates of the monoprotonated Ln(HEDTMP) complexes are lower probably because the negative charge of the monoprotonated ligand $HEDTMP^{7-}$ is much larger than that of $HEDTA^{3-}$, which leads to a stronger electrostatic interaction between the Ln^{3+} ion and $HEDTMP^{7-}$.

For characterizing the kinetic inertia of the complexes the half-time of dissociation ($t_{1/2}$) is also a usual parameter. The $t_{1/2}$ values can be calculated from the pseudo-first-order rate constants, expressed by Equation (4), as $t_{1/2} = \ln 2/k_d$. The half-times of dissociation of the Sm(EDTMP) and Y(EDTMP) complexes at pH = 7.4 are 4.9 and 7.5 s, respectively. These dissociation half-time values are relatively short (at 37 °C they are even shorter), which do not predict the deposition of the ^{153}Sm or ^{90}Y isotopes in the bones in the form of intact Ln(EDTMP) [or Ln(HEDTMP)-Ca] complexes. It seems more probable that the sorption of the Sm^{3+} or Y^{3+} ions and the EDTMP ligands in the bones occurs after the dissociation of the complexes.

Conclusions

For determining the stability constants of the lanthanide(III)–EDTMP complexes the spectrophotometric study of the equilibria of the competition reactions between the lanthanide(III) and Cu^{II} ions for EDTMP is a usable method. The studies were made at pH ≈ 10 in the presence of an excess amount of citrate, where poorly soluble protonated EDTMP complexes were not formed.

The stability constants of the $Sm(EDTMP)^{5-}$ and $Y(EDTMP)^{5-}$ complexes in contrast to the results of some earlier studies were found to be higher by 2–3 $\log K$ units than those of $Sm(EDTA)^-$ and $Y(EDTA)^-$, probably because of the higher electrostatic interaction between $EDTMP^{8-}$ and the Ln^{3+} ions. $Ca(EDTMP)^{6-}$ is less stable than $Ca(EDTA)^{2-}$, whereas the $\log K_{ML}$ values of $Cu(EDTMP)^{6-}$ and $Cu(EDTA)^-$ are comparable.

The $Ln(EDTMP)^{5-}$ complexes, probably due to their high negative charges, form mono-, di- and triprotonated complexes and also a dinuclear complex with Ca^{2+}.

The species distribution calculations indicate that near to physiological conditions, where $^{153}Sm(EDTMP)$ is used as a palliative agent, Sm^{3+} is predominantly present in the form of the $[Sm(HEDTMP)Ca]^{2-}$ species. As a result of the presence of an excess amount of EDTMP in the clinically used kits, the endogenous metal ions, like Zn^{2+}, cannot replace the Sm^{3+} from the complex.

The rates of dissociation of the $Sm(EDTMP)^{5-}$ and $Y(EDTMP)^{5-}$ complexes in the pH range 7–9 are much higher than those of the analogous $Sm(EDTA)^-$ and $Y(EDTA)^-$ complexes. The dissociation of the $Ln(EDTMP)^{5-}$ complexes predominantly occurs through proton-assisted pathways. The half-times of dissociation of $Sm(EDTMP)^{5-}$ (4.9 s) and $Y(EDTMP)^{5-}$ (7.5 s) at pH = 7.4 and 25 °C are short, which suggest that the adsorption of the Ln^{3+} ions and the ligand on the surface of the bones occurs separately, after the dissociation of the complexes.

Experimental Section

Equilibrium Measurements: The chemicals used in the experiments were of the highest analytical grade. For the preparation of the $LnCl_3$ solutions, Ln_2O_3-s (Fluka, 99.9%) were dissolved in 6.0 M HCl, and the excess amount of acid was evaporated off. Concentration of the $LnCl_3$, $CaCl_2$ and $CuCl_2$ solutions were determined by complexometric titration with the use of standardized Na_2H_2EDTA and xylenol orange ($LnCl_3$), murexid ($CuCl_2$) and Patton & Reeder ($CaCl_2$) as indicator.

The H_8EDTMP ligand was prepared with the method published in the literature.[32] The purity of the compound was determined by ^1H NMR spectroscopy and it was found to be at least 99%. The concentration of the EDTMP solution was determined by pH–potentiometric titration in the presence and absence of a large (40-fold) excess of $CaCl_2$.

The protonation constants of the EDTMP ligand and the stability constants of the complexes formed with Ca^{2+} and Cu^{2+} were determined by pH–potentiometric titration. The metal-to-ligand concentration ratios were 1:1 and 2:1 (the concentration of the ligand was generally 2.0 mM). For determining the protonation constants of the Ln(EDTMP) complexes and the stability constants of the dinuclear Ln(EDTMP)Ca complexes, the solutions of complexes, prepared at pH ≈ 10, were titrated with HCl in the absence and presence of $CaCl_2$.

For the determination of the stability constants of the Ln(EDTMP) complexes we used the competition reaction between Sm^{3+} or Y^{3+} and Cu^{2+} for the EDTMP at pH values 9.8–10.2. For keeping the Ln^{3+} and Cu^{2+} in solution, citrate ligand was used in excess, and the equilibrium [Equation (1)] was studied by spectrophotometry

in the UV range, where the absorption bands of the Cu(EDTMP) and Cu^{2+}–citrate complexes differ considerably (Figure 1). The concentrations of the reactants were as follows: 1.0×10^{-4} M EDTMP, 0.01 M citrate, 1.0×10^{-4} M Cu^{2+}, 1.0×10^{-4} to 50×10^{-4} M Sm^{3+} or Y^{3+}, pH: 9.8–10.2, I = 0.15 M NaCl, 25 °C. The absorbance values were determined at nine different wavelengths between 250 and 340 nm. The molar absorptivities of Cu(EDTMP) and Cu(citrate) were determined in separate experiments.

The protonation constants of the citrate ligand and the stability constants of the citrate complexes formed with Sm^{3+}, Y^{3+} and Cu^{2+} were also determined by pH–potentiometric titration at 25 °C and in the presence of 0.15 M NaCl at 1:1 and 1:2 metal-to-ligand concentration ratios.

For the calculation of $[H^+]$ from the measured pH values, the method proposed by Irving et al. was used. A 0.01 M HCl solution (0.15 M NaCl) was titrated with standardized NaOH solution. The differences between the measured and calculated pH values were used to obtain the H^+ concentrations from the pH values, measured in the titration experiments.[33] The ion product of water was determined from the same HCl/NaOH titration in the pH range 11.0–12.3 (pK_w = 13.68).

For the pH measurements and titrations a Radiometer PHM93 pH meter, an ABU 80 autoburette and a Metrohm 6.0234.100 combined electrode were used. The titrated samples (15 mL) were thermostatted at 25 °C. The solutions were stirred and Ar gas was bubbled through them. The titrations were made in the pH range 1.7–12.0. For the calibration of the pH meter, KH–phthalate (pH = 4.005) and borax (pH = 9.180) buffers were used.

The protonation and stability constants were calculated from the titration data with the PSEQUAD program.[27] For the calculation of the stability constants of the Ln(EDTMP) complexes, besides the concentrations and pH values, the measured absorbances and the molar absorptivity values of the Cu complexes were also taken into account.

Kinetic Studies: The rates of the exchange reactions between the Ln(EDTMP) and Cu(cit) complexes were studied by spectrophotometry with the use of a stopped-flow instrument (Applied Photophisics DX-17MV) at 310 nm in the pH range 7.0–9.0 (25 °C, 0.15 M NaCl). For keeping the pH values constant, HEPES buffer (0.02 M) was used in the pH range 7.0–8.0 and dimethylpiperazine (0.02 M) in the range 8.0–9.0. The concentration of the Ln(EDTMP) complexes was 1.0×10^{-4} M. In order to avoid the formation of hydroxide precipitate of the metals, citrate ligand was used. The concentration of Cu^{2+}–citrate was varied between 1.0×10^{-3} M and 3.5×10^{-3} M, that is, the exchange reactions were studied under pseudo-first-order conditions. For the calculation of the first-order rate constants (k_d), the absorbance values measured at different t times were fitted into Equation (7).

$$k_d = \frac{1}{t} \ln \frac{A_0 - A_e}{A_t - A_e} \quad (7)$$

where A_0, A_t and A_e are the absorbance values measured at the start of the reaction at time t and at equilibrium, respectively.

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