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Equilibrium Studies on the Gd^{3+}, Cu^{2+} and Zn^{2+} Complexes of BOPTA, DTPA and DTPA-BMA Ligands: Kinetics of Metal-Exchange Reactions of $[Gd(BOPTA)]^{2-}$

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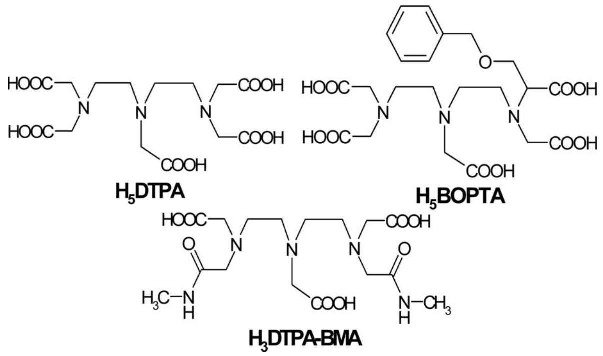
The stability and protonation constants of the complexes formed between the ligand BOPTA [H_5BOPTA: 4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid] and Gd^{3+}, Cu^{2+}, and Zn^{2+} have been determined by pH potentiometry (Gd^{3+}, Zn^{2+}) and spectrophotometry (Cu^{2+}) at 25 °C and at constant ionic strength maintained by 0.15 M NaCl. For comparison, the stability and protonation constants of the complexes of Gd^{3+}, Cu^{2+}, and Zn^{2+} formed with DTPA and DTPA-BMA {H_5DTPA: diethylenetriamine-*N*,*N*,*N*′,*N*′′,*N*′′-pentaacetic acid, H_3DTPA-BMA: 2,2′-[(carboxymethyl)imino]bis[ethylenebis(methylcarbamoylmethyl)imino]diacetic acid} have also been determined under similar conditions. The stability constants ($\log K_{ML}$) of the complexes of BOPTA and DTPA are very similar, but in 0.15 M NaCl the protonation constants of the ligands ($\log K_i^H$) and the $\log K_{ML}$ values are lower than those obtained in 0.1 M KCl or Me_4NCl by 0.3–0.9 $\log K$ units. The order of selectivity of the ligands for Gd^{3+} over Zn^{2+} is BOPTA > DTPA > DTPA-BMA. The complex $[Cu(DTPA\text{-}BMA)]^-$ deprotonates in the pH range 7–10 with the dissociation of an amide NH group and the coordination of the amide N atom. The kinetics of the exchange/transmetallation reactions between the complex $[Gd(BOPTA)]^{2-}$ and the metal ions Cu^{2+}, Zn^{2+}, and Eu^{3+} have been studied by spectrophotometry (Cu^{2+}, Eu^{3+}) and relaxometry (Zn^{2+}) in the pH range 3.3–6 at 25 °C in 0.15 M NaCl. The reactions with Cu^{2+} and Zn^{2+} occur predominantly with direct attack of the metal ions on the $[Gd(BOPTA)]^{2-}$ complex. The kinetic activity of Eu^{3+} is lower, and in the exchange reactions with Eu^{3+}, the proton-assisted dissociation of $[Gd(BOPTA)]^{2-}$ (which is followed by fast reaction between the free ligand and Eu^{3+}) could be also investigated. The rate constants, characterizing the proton-assisted dissociation of $[Gd(BOPTA)]^{2-}$ and the exchange reactions occurring with the direct attack of Cu^{2+}, Zn^{2+}, and Eu^{3+} on the complex, are lower by about 30–90 % than the rate constants obtained earlier for similar transmetallation reactions of $[Gd(DTPA)]^{2-}$. The half-time for the dissociation of $[Gd(BOPTA)]^{2-}$ at pH 7.4 and at 25 °C in the presence of 1×10^{-5} M Zn^{2+} and 1×10^{-6} M Cu^{2+} is 169 h.

Introduction

$[Gd(BOPTA)]^{2-}$ [H_5BOPTA: 4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid] is a clinically used contrast agent in magnetic resonance imaging (MRI), which increases the relaxation rates of protons (mainly water protons) in the body. The ligand BOPTA is a derivative of DTPA (H_5DTPA: diethylenetriamine-*N*,*N*,*N*′,*N*′′,*N*′′-pentaacetic acid), which contains a benzyloxymethyl substituent attached to the methylene carbon atom of a terminal acetate group (Scheme 1). Because of the presence of the lipophilic benzyloxymethyl group, the $[Gd(BOPTA)]^{2-}$ complex, administered intravenously, is eliminated from the body mainly through the kidneys and partially through the hepatobiliary system, so it is a suitable contrast agent for the investigation of the liver.[1,2]



Scheme 1. The ligands H_5DTPA, H_5BOPTA, and H_3DTPA-BMA.

The complexes of Gd^{3+} used as contrast enhancement agents in MRI must have high in vivo stability for safety reasons, which means that the complex must remain chelated while in the body and excreted intact.[3,4] For the real-

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ization of this requirement, the kinetic inertness of the Gd^{3+} complex is particularly important, because its excretion from the body is relatively slow (the half-time of excretion, $t_{1/2}$, is about 1.5 h).[5–7] The situation is even worse in the case of patients with advanced renal disease, when the half-time of excretion is much longer ($t_{1/2}$ is about 30–40 h)[7] and the extent of in vivo dissociation of the complexes can be greater, therefore the "system" is shifted in the direction of equilibrium. For characterizing such systems, the knowledge of the stability constants of complexes formed between the chelating agents and Gd^{3+} and the endogenous metals present in body fluids (such as Zn^{2+} and Cu^{2+}) is important. For a full characterization of these systems ("blood plasma model"), the stability constants of the complexes formed with the most important endogenous ligands (citrate, lactate, etc.) must also be taken into account.[7–9]

The complex $[Gd(BOPTA)]^{2-}$ was introduced into clinical practice several years ago, and its structure and chemical and relaxation properties have been studied in detail.[10,11] However, the complexes of BOPTA formed with endogenous Zn^{2+} and Cu^{2+}, which may participate in transmetallation reactions, and also the kinetics of the transmetallation processes have not been investigated. The stability constants for the aminopolycarboxylate complexes of Gd^{3+}, Cu^{2+}, and Zn^{2+} were generally determined at constant ionic strength, which was maintained with 0.1 M KCl, KNO_3, or Me_4NCl.[12] In order to be close to physiological conditions, we recently determined the stability constants of the BOPTA complexes of Gd^{3+}, Cu^{2+}, and Zn^{2+} in 0.15 M NaCl solution. To compare these results to the equilibrium behavior of some other MRI contrast agents, the stability constants of complexes formed between the ligands DTPA and DTPA-BMA {H_3DTPA-BMA: 2,2′-[(carboxymethyl)imino]-bis[ethylenebis(methylcarbamoylmethyl)imino]diacetic acid} and the metal ions Gd^{3+}, Cu^{2+}, and Zn^{2+} were also determined in 0.15 M NaCl at 25 °C. The kinetics of the transmetallation reactions taking place between the complexes $[Gd(DTPA)]^{2-}$, [Gd(DTPA-BMA)] and Cu^{2+}, Zn^{2+}, and Eu^{3+} were studied in 1.0 M KCl solution. To obtain information on the kinetic inertness of $[Gd(BOPTA)]^{2-}$, the rates of exchange reactions occurring between the complex $[Gd(BOPTA)]^{2-}$ and Cu^{2+}, Zn^{2+}, and Eu^{3+} ions was also studied.

Results and Discussion

Protonation and Complexation Equilibria of the Ligands BOPTA, DTPA, and DTPA-BMA

The chemical properties of the ligand BOPTA and its protonation constants and protonation sequence were found to be very similar to those of DTPA. The stability constants of $[Gd(BOPTA)]^{2-}$ and $[Gd(DTPA)]^{2-}$ were also found to be very similar, which indicates that the attachment of the benzyloxymethyl group to a terminal acetate arm of DTPA seems to have practically no effect on the complexation behavior of the ligand.[10] The change in the medium from 0.1 M KCl to 0.15 M NaCl solution will presumably not alter the behavior of BOPTA and DTPA in this respect, but the stability constants of the complexes are expected to be lower, because of the stronger interaction of the aminopolycarboxylate ligands with Na^+ than with the larger K^+.[12]

In order to calculate the stability constants of the complexes, the protonation constants of the ligands BOPTA, DTPA and DTPA-BMA were first determined at an ionic strength of 0.15 M NaCl by pH potentiometric titration. The protonation constants ($K_i^H = [H_iL]/[H_{i-1}L][H^+]$; i = 1,2, ..., 5) calculated from the titration data are presented in Table 1 with the standard deviations in parenthesis. For comparison, the $\log K_i^H$ values determined in 0.1 M KCl or 0.1 M Me_4NNO_3 solution are also presented. The protonation constants of DOTA (H_4DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) were also determined because DOTA was used as a competing ligand for determining the stability constants of $[Cu(BOPTA)]^{3-}$ and $[Cu(DTPA)]^{3-}$.

Table 1. Protonation constants of the ligands BOPTA, DTPA, DTPA-BMA and DOTA at 25 °C.

	BOPTA	DTPA	DTPA-BMA	DOTA
	0.15 M NaCl	0.15 M NaCl	0.15 M NaCl	0.15 M NaCl
$\log K_1^H$	9.85(1)	9.93(1)	8.98(1)	9.14(1)
$\log K_2^H$	7.91(1)	8.37(1)	4.36(1)	9.21(1)
$\log K_3^H$	4.29(1)	4.18(1)	3.21(1)	4.48(1)
$\log K_4^H$	2.83(1)	2.71(1)	1.50(1)	4.03(1)
$\log K_5^H$	1.96(1)	2.00(1)	–	1.99(1)
	0.1 M KCl[10]	0.1 M KCl[12]	0.1 M KCl	0.1 M $(CH_3)_4NNO_3$[13]
$\log K_1^H$	10.71	10.54	9.24(1)	12.09
$\log K_2^H$	8.27	8.56	4.44(1)	9.68
$\log K_3^H$	4.35	4.30	3.50(1)	4.55
$\log K_4^H$	2.83	2.77	1.86(1)	4.13
$\log K_5^H$	2.07	2.0	–	–

Comparison of the protonation constants presented in Table 1 shows that the $\log K_1^H$ and $\log K_2^H$ values obtained for the BOPTA, DTPA, and DOTA in 0.15 M NaCl are significantly lower than those determined in 0.1 M KCl or Me_4NNO_3, while for DTPA-BMA, the differences are significantly smaller. These findings indicate that BOPTA, DTPA, and DOTA form more stable complexes with Na^+ than with the larger K^+. The complex $[Na(DTPA\text{-}BMA)]^{2-}$ is very weak probably because of the lower negative charge of the ligand, so the $\log K_{ML}$ values of DTPA-BMA do not differ considerably in KCl and NaCl solutions.

The protonation constants of BOPTA obtained by Alderighi et al. in 0.15 M NaCl and 0.1 M Me_4NNO_3 solution are very similar, so the data reported for 0.15 M NaCl do not seem to be reliable, because the $\log K_1^H$ values of the aminopolycarboxylate ligands, possessing 4– or 5– charges, are always significantly lower in NaCl than in Me_4NNO_3 (or Me_4NCl) solution.[11,12]

The equilibrium constants used to characterize the complexation equilibria are defined by Equations (1)–(5). The stability constant of the complexes ML is given in Equation (1).

$$K_{\mathrm{ML}} = \frac{[\mathrm{ML}]}{[\mathrm{ML}][\mathrm{L}]} \qquad (1)$$

where [M], [L], and [ML] are the concentrations of the metal ions, ligands, and complexes, respectively. The complexes of aminopolycarboxylate ligands can form protonated MLH_i species at lower pH values, while in basic solution, deprotonated species MLH_{-i} are formed. The formation of protonated complexes are characterized by the protonation constants, defined by Equation (2).

$$K_{\mathrm{MLH}_i} = \frac{[\mathrm{MLH}_i]}{[\mathrm{MLH}_{i\text{-}1}][\mathrm{H}^+]} \quad i = 1, 2, 3 \qquad (2)$$

The deprotonation equilibria of complexes are described by Equation (3) for protonation of the deprotonated species MLH_{-i}.

$$K_{\mathrm{MLH}_{\text{-}i}} = \frac{[\mathrm{MLH}_{\text{-}i+1}]}{[\mathrm{MLH}_{\text{-}i}][\mathrm{H}^+]} \quad i = 1, 2 \qquad (3)$$

The multidentate aminopolycarboxylate ligands can form dinuclear complexes. The formation and protonation of dinuclear complexes are characterized with the equilibrium constants $K_{\mathrm{M_2L}}$ and $K_{\mathrm{M_2LH}}$ shown in Equations (4) and (5), respectively.

$$K_{\mathrm{M_2L}} = \frac{[\mathrm{M_2L}]}{[\mathrm{ML}][\mathrm{M}]} \qquad (4)$$

$$K_{\mathrm{M_2LH}} = \frac{[\mathrm{M_2LH}]}{[\mathrm{M_2L}][\mathrm{H}^+]} \qquad (5)$$

The stability constants and protonation constants of $[\mathrm{Gd(BOPTA)}]^{2-}$ and $[\mathrm{Gd(DTPA)}]^{2-}$ were determined by pH potentiometric titration. The calculations were made with the use of the volume NaOH/pH data pairs obtained in the pH range 1.7–3.0, by assuming the formation of the species ML and MLH. The formation of [Gd(DTPA-BMA)] was complete at pH of about 2, therefore a competition reaction was used for the determination of its stability constant. The systems Gd^{3+}/DTPA-BMA/BOPTA were titrated at 1:1:1 concentration ratios and the data obtained in the pH range 1.8–3.0 were used for the calculation of the $\log K_{\mathrm{GdL}}$ value (Table 2). The protonated [Gd(DTPA-BMA)] complex did not form, because the assumption of the formation of the MLH species led to a higher error and hence to an increase in the fitting parameter.

The equilibrium constants, characterizing the formation of the BOPTA, DTPA, and DTPA-BMA complexes of Zn^{2+} were determined by pH potentiometry at 1:1 and 2:1 metal-to-ligand concentration ratios. The equilibrium constants obtained are presented in Table 2, where some published data are also shown for comparison.

Table 2. Equilibrium constants characterizing the complex formation between BOPTA, DTPA, and DTPA-BMA and the metal ions Gd^{3+} and Zn^{2+} (0.15 м NaCl, 25 °C).

	BOPTA	DTPA	DTPA-BMA
$\log K_{\mathrm{GdL}}$	21.91(1)	22.03(1)	16.64(2)
	22.59[10]	22.46[14b]	16.85[15]
$\log K_{\mathrm{GdLH}}$	1.65(1)	1.96(1)	–
$\log K_{\mathrm{ZnL}}$	17.04(4)	17.58(2)	12.42(2)
	–	18.3[16a]	12.04[15]
$\log K_{\mathrm{ZnHL}}$	5.77(1)	5.37(1)	4.15(1)
	–	5.60[16a]	4.04[15]
$\log K_{\mathrm{ZnH_2L}}$	2.40(1)	2.38(2)	1.71(3)
$\log K_{\mathrm{ZnLH_{-1}}}$	–	–	10.52(2)
$\log K_{\mathrm{Zn_2L}}$	4.83(4)	4.33(3)	3.24(3)
	–	4.48[16a]	–

The stability constants of the $[\mathrm{Cu(BOPTA)}]^{3-}$ and $[\mathrm{Cu(DTPA)}]^{3-}$ complexes were determined by spectrophotometry; the competition reactions between BOPTA and DOTA and between DTPA and DOTA for $\mathrm{Cu}^{2+}$was also investigated. The study of the competition reactions was possible because the spectra of $[\mathrm{Cu(BOPTA)}]^{3-}$ and $[\mathrm{Cu(DTPA)}]^{3-}$ differ considerably from that of $[\mathrm{Cu(DOTA)}]^{2-}$, as seen in Figures S1 and S2. The spectrophotometric studies were carried out in the pH range 6.8–7.2, where the only species present were $[\mathrm{Cu(BOPTA)}]^{3-}$ and $[\mathrm{Cu(DOTA)}]^{2-}$ or $[\mathrm{Cu(DTPA)}]^{3-}$ and $[\mathrm{Cu(DOTA)}]^{2-}$, as indicated by the appearance of isosbestic points. For the calculation of the stability constants of $[\mathrm{Cu(BOPTA)}]^{3-}$ and $[\mathrm{Cu(DTPA)}]^{3-}$ from the spectrophotometric data, the $\log K_{\mathrm{CuL}}$ value of $[\mathrm{Cu(DOTA)}]^{2-}$ was determined in 0.15 м NaCl by spectrophotometry and through the protonation constants of $[\mathrm{Cu(DOTA)}]^{2-}$; the stability constants of the dinuclear and protonated dinuclear $[\mathrm{Cu_2(DOTA)}]$ complexes were obtained by pH potentiometry (Table 3).

Table 3. Equilibirum constants characterizing the formation of Cu^{2+} complexes with BOPTA, DTPA, DTPA-BMA, and DOTA (0.15 м NaCl, 25 °C).

	BOPTA	DTPA	DTPA-BMA	DOTA
$\log K_{\mathrm{CuL}}$	22.80(6)[a]	23.40(6)[a]	16.30(3)[b]	22.00(1)
	–	21.5[17]	13.03[15]	22.21[13]
$\log K_{\mathrm{CuHL}}$	5.06(2)	4.63(1)	3.48(3)	4.10(1)
	–	4.74[17]	3.36[15]	4.30[13]
$\log K_{\mathrm{CuH_2L}}$	2.78(2)	2.67(1)	1.46(1)	3.41(1)
	–	–	–	3.58[13]
$\log K_{\mathrm{CuH_3L}}$	1.91(2)	2.03(1)	–	–
$\log K_{\mathrm{CuLH_{-1}}}$	–	–	8.95(2)	–
$\log K\mathrm{CuLH}_{-2}$	–	–	11.41(2)	–
$\log K_{\mathrm{Cu_2L}}$	7.59(2)	6.56(1)	3.95(2)	2.42(5)
	–	–	–	2.23[13]
$\log K_{\mathrm{Cu_2LH}}$	2.37(2)	2.20(2)	–	3.83(6)

[a] Spectrophotometry (competition reaction with DOTA in the pH range 6.8–7.2). [b] Spectrophotometry (competition reaction with EGTA in the pH range 6.9–7.0).

The equilibrium constants characterizing the complex formation in the Cu^{2+}/DTPA-BMA system were determined by pH potentiometric titration at 1:1 and 2:1 metal-to-ligand concentration ratios. The equilibrium system could be described by the formation of the species CuL, CuLH, $CuLH_2$, $CuLH_{-1}$, $CuLH_{-2}$, and Cu_2L, and the stability constants were calculated for all but the complex CuL, which is highly stable, as its formation is practically complete at about pH = 2. To determine the $\log K_{CuL}$ value, we studied the competition reactions between DTPA-BMA and EGTA for Cu^{2+} by spectrophotometry in the wavelength range 270–330 nm [H_4EGTA = 3,12-bis(carboxymethyl)-6,9-dioxa-3,12-diazatetradecane-1,14-dioic acid]. The pH of the samples was 6.9–7.1, where only $[Cu(DTPA\text{-}BMA)]^-$ and $[Cu(EGTA)]^{2-}$ are present, which can be seen by the appearance of isosbestic points in the spectra (Figure S3).

For the calculation of the stability constant of $[Cu(DTPA\text{-}BMA)]^-$, the absorbance and molar absorptivity values were determined at 10 different wavelengths. The $\log K_{CuL}$ value obtained is shown in Table 3. For the calculation of $\log K_{CuL}$, the protonation constants of EGTA and the stability constants characterizing the formation of the complexes $[Cu(H_xEGTA)]^{x-2}$ were determined by pH potentiometry in 0.15 M NaCl at 25 °C. The protonation constants of EGTA are as follows: $\log K_1^H = 9.02(1)$, $\log K_2^H = 8.45(1)$, $\log K_3^H = 2.77(1)$, $\log K_4^H = 2.10(1)$ and $\log K_5^H = 1.50(2)$. The equilibrium constants ($\log K$) characterizing the formation of different [Cu(EGTA)] species are as follows, CuL: 16.50(3), CuLH: 4.10(2), $CuLH_2$: 2.51(2), Cu_2L: 6.48(2), Cu_2LH_{-1}: 6.73(4), Cu_2LH_{-2}: 7.88(4).

A comparison of the stability constants presented in Tables 2 and 3 shows that the $\log K_{ML}$ values are generally lower in 0.15 M NaCl than in 0.1 M KCl or KNO_3, because the complexes formed between the ligands and Na^+ are stronger than those formed with K^+. The $\log K_{ML}$ values for the complexes $[Zn(DTPA\text{-}BMA)]^-$ and $[Cu(DTPA\text{-}BMA)]^-$ determined by us in 0.15 M NaCl are higher than those obtained by Cacheris et al. in 0.1 M NaCl.[15] The higher $\log K_{ML}$ values result in an alteration of the selectivity order of the ligands reported by Cacheris et al.[15] The selectivity of ligands for Gd^{3+} over Zn^{2+} (Gd^{3+} can be displaced in vivo by Zn^{2+}) can be expressed as the difference between the two stability constants: $\log K_{GdL} - \log K_{ZnL}$. The selectivity values reported by Cacheris et al. for DTPA and DTPA-BMA are 3.76 and 4.81, respectively, which indicates the superiority of DTPA-BMA with respect to DTPA.[15] With the use of the $\log K_{GdL}$ and $\log K_{ZnL}$ values obtained in 0.15 M NaCl (Table 2), the selectivity of BOPTA, DTPA, and DTPA-BMA can be expressed as 4.87, 4.45, and 4.22, respectively, i.e. the selectivity for DTPA-BMA is the lowest. For the calculation of these selectivities, we used the stability constants, which were determined under similar conditions (0.15 M NaCl, 25 °C). In contrast, the stability constants of [Gd(DTPA-BMA)] and $[Zn(DTPA\text{-}BMA)]^-$ were determined by Cacheris et al. at 25 °C in 0.1 M NaCl solution, but the $\log K_{ML}$ values for $[Gd(DTPA)]^{2-}$ and $[Zn(DTPA)]^{3-}$ were from the literature and were determined at 25 °C and at an ionic strength maintained by 0.1 M KNO_3. Furthermore, the stability constants used for the calculation of the selectivities were chosen arbitrarily.[15] The stability constants of $[Gd(DTPA)]^{2-}$ were determined by Harder et al. ($\log K_{GdL} = 23.01$)[14a] and by Moeller et al. ($\log K_{GdL} = 22.46$)[14b] in 0.1 M KNO_3 at 25 °C. For $[Zn(DTPA)]^{3-}$, the published $\log K_{ZnL}$ values determined at 25 °C in 0.1 M KNO_3 are 18.3 (18.13)[16a] and 18.8.[16b] With the use of these stability constants, very different (lower and higher) selectivities can be calculated (Cacheris et al. used the lowest possible value for DTPA).[15] These considerations indicate that reliable selectivities can be obtained only if the stability constants used for the calculations are determined under similar conditions. However, the selectivity itself, defined in this way, is of lower importance because for a correct description of the behavior of the complexes in the plasma, a species distribution calculation should be made with the use of the concentration of all the metal ions and ligand species present in body fluids.[8]

The stability constants and protonation constants of the complexes formed with BOPTA and DTPA are very similar, which shows that the presence of the benzyloxymethyl group in BOPTA has practically no effect on the equilibrium properties of the ligand.

There are several complexes, such as the dinuclear M_2L species in the Zn^{2+}/DTPA-BMA and Cu^{2+}/DTPA-BMA systems, which were not detected in the earlier equilibrium studies.[15] Similarly, the formation of deprotonated species MLH_{-1} was also not observed. The formation of the species $CuLH_{-1}$ and $CuLH_{-2}$ in the Cu^{2+}/DTPA-BMA system is particularly interesting, because in this case the dissociation of an amide hydrogen is also possible, but it was not detected earlier. The titration curve of the $[Cu(DTPA\text{-}BMA)]^-$ complex (at a 1:1 metal-to-ligand concentration ratio) indicates the presence of two deprotonation steps in the pH range 7–12, which is interpreted as being the result of the formation of the species $CuLH_{-1}$ and $CuLH_{-2}$ (Table 3). The formation of the deprotonated species was studied by spectrophotometry. The maxima of the absorption bands of the Cu^{2+}/DTPA-BMA solutions are shifted from about 740 to 690 nm in the pH range 2–7. At pH values of about 5–7, the species $[Cu(DTPA\text{-}BMA)]^-$ predominates. A further increase in the pH results in a "blue"shift of the band maximum, and at pH about 10, the band maximum is at about 670 nm. This "blue"shift of the band can be ex-

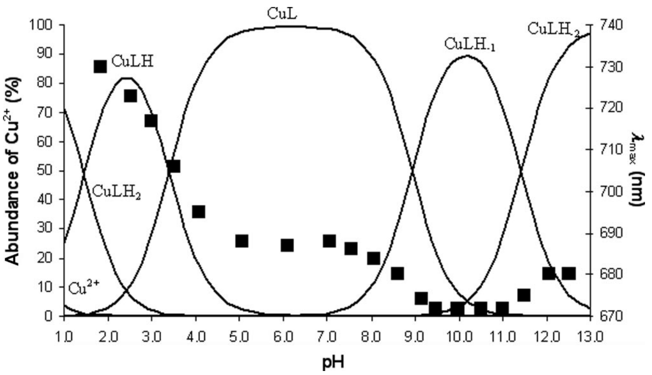

Figure 1. The position of the absorption band maxima for the Cu^{2+}/DTPA-BMA system (■) and the species distribution curves as a function of pH ($[Cu^{2+}]$ = [DTPA-BMA] = 5.0 mM, 0.15 M NaCl, 25 °C).

plained by the deprotonation of an amide NH group of DTPA-BMA and the coordination of an amide N^- atom to Cu^{2+}, to form the species $CuLH_{-1}$.[18] A further increase in the pH to about 12 results in a "red"shift of the absorption maximum to about 680 nm, which can be explained by the coordination of an OH^- group to Cu^{2+} instead of a carboxylate or amide oxygen atom to form the species $CuLH_{-2}$.[18] In Figure 1, the absorption band maxima and the species distribution is presented as a function of pH.

The data presented in Figure 1 indicate the relationship between the maxima of the absorption bands and the composition of the complexes.

Kinetics of the Exchange Reactions of $[Gd(BOPTA)]^{2-}$ with Cu^{2+}, Zn^{2+}, and Eu^{3+}

The aminopolycarboxylate complexes of Gd^{3+} used as contrast agents in MRI are kinetically inert compounds, but a number of animal studies and human experiments indicate that the excretion of Gd^{3+} from the body is not complete, which was explained by assuming the in vivo dissociation of a small amount of the Gd^{3+} complexes.[19–25] To understand the in vivo fate of Gd^{3+}-containing contrast agents, we have to know the rates of dissociation of complexes, which presumably take place in the exchange (or transmetallation) reactions with endogenous Zn^{2+} and Cu^{2+}. Calcium(II) ions can not participate in the exchange reactions because the stability constants of the Ca^{2+} complexes are very low relative to those of the Gd^{3+} complexes.[12] The rates of dissociation of the Gd^{3+} complexes formed with the macrocyclic ligands such as DOTA are often studied in 0.1 M HCl.[7,19] A similar study of the dissociation rates of the DTPA derivative complexes is not possible, because the reactions are too fast in 0.1 M HCl, and the role of Zn^{2+} and Cu^{2+} cannot be investigated. In order to obtain information on the rates of dissociation of the complex $[Gd(BOPTA)]^{2-}$, the kinetics of the exchange reaction (6) were studied in 0.15 M NaCl solution at 25 °C.

$$[Gd(BOPTA)]^{2-} + M^{n+} \rightleftharpoons [M(BOPTA)]^{n-5} + Gd^{3+} \qquad (6)$$

where $M^{n+} = Cu^{2+}, Zn^{2+}$, and Eu^{3+}. The rates of the exchange reaction (6) were studied in the pH range 3.3–6.0, because the exchanging metal ions hydrolyze at higher pH values.

The results of earlier kinetic studies on the transmetallation reactions of $[Gd(DTPA)]^{2-}$ with Cu^{2+}, Zn^{2+}, and Eu^{3+} have shown that the reactions take place with direct attack of the exchanging metal ions on the complex and also with proton-assisted dissociation of the complex (followed by fast reaction between the metal ions and the free ligands).[26] The preliminary studies indicate that the reactions between $[Gd(BOPTA)]^{2-}$ and Cu^{2+} or Zn^{2+} occur predominantly with direct attack of Cu^{2+} or Zn^{2+} on the complex. Therefore, in order to obtain information on the rate of the proton-assisted dissociation of Gd(BOPTA), we studied the rates of the exchange reactions with Eu^{3+}, which has a lower kinetic activity than Zn^{2+} or Cu^{2+}.[26]

The rates of the reaction (6) were investigated in the presence of excess exchanging metal ions. The $\log K_{ML}$ values of the BOPTA complexes of Gd^{3+} and Cu^{2+} are similar, but the reaction proceeds to completion even at a five-fold excess of Cu^{2+} because of the formation of highly stable dinuclear Cu_2L complexes. The stability of $[Eu(BOPTA)]^{2-}$ is presumably similar to that of $[Gd(BOPTA)]^{2-}$. In this case, the conversion of the reaction is 80 to 95% with a five- to twenty-fold excess of Eu^{3+}, and pseudo-first-order rate constants could be obtained for conversions up to 50–60%. The $\log K_{ML}$ value of $[Zn(BOPTA)]^{3-}$ is lower than that of $[Gd(BOPTA)]^{2-}$, therefore despite the high stability of the dinuclear Zn_2L complex, a large (100–150 fold) excess of Zn^{2+} is needed to reach a conversion of 70–80%. For these reactions (where the ionic strength is not constant because of the high excess of Zn^{2+}), pseudo-first-order rate constants could be obtained for conversions of up to 40–50% .

In the presence of excess exchanging metal ion, the rate of reaction (6) can be expressed as follows in Equation (7).

$$-\frac{d[GdL]_t}{dt} = k_d[GdL]_t \qquad (7)$$

where k_d is a pseudo-first-order rate constant and $[GdL]_t$ is the total concentration of $[Gd(BOPTA)]^{2-}$. The rates of the exchange reactions were studied at different concentrations of Eu^{3+}, Cu^{2+}, and Zn^{2+} at various pH values.

The rates (k_d values) of the exchange reactions between Gd(BOPTA) and Eu^{3+} show a quadratic dependence on the H^+ concentration, but the effect of the increase in the Eu^{3+} concentration is not considerable. For presenting the k_{obs} data, it seemed more clear to show the k_d vs. $[Eu^{3+}]$ plots (Figure 2). The increase in the H^+ concentration (between pH = 3.3 and 6) results in a more than three orders of magnitude increase in the k_d values. On the other hand, the dependence of k_d on the Eu^{3+} concentration is quite peculiar: at the lowest $[H^+]$ values, the rates of exchange increase, while at higher $[H^+]$ values, the rates of exchange decrease with an increase in $[Eu^{3+}]$ (Figure 3). A similar phenomenon was observed in the study of the exchange reaction between $[Gd(DTPA)]^{2-}$ and Eu^{3+}.[26] The explanation for the phenomenon is also similar. The exchange between $[Gd(BOPTA)]^{2-}$ and Eu^{3+} occurs mainly with proton-assisted dissociation of the complex, which follows from the strong pH dependence of the k_d values (Figure 2). However, the exchange reaction can take place with direct attack of Eu^{3+} on $[Gd(BOPTA)]^{2-}$, presumably via the formation of a dinuclear $[Gd(BOPTA)Eu]^+$ complex. The formation of dinuclear complexes $[Ln_2(DTPA)]^+$ has been detected earlier.[26,27] The Eu^{3+} and H^+ ions compete for the complex, and at lower $[H^+]$, the reaction can take place through the formation of the dinuclear complex when the k_d values increase with an increase in $[Eu^{3+}]$. However, at higher H^+ concentrations, where the exchange reactions predominantly occur with proton-assisted dissociation of $[Gd(BOPTA)]^{2-}$, the increase in $[Eu^{3+}]$ reduces the concentration of the protonated complexes, and thus the k_d values decrease too.

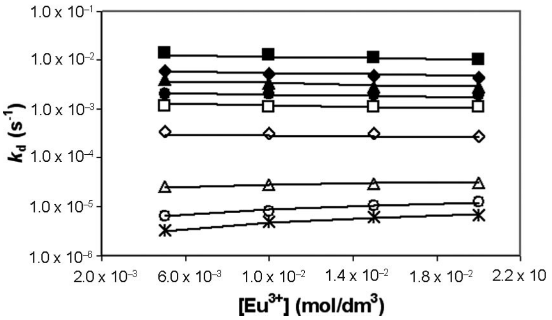

Figure 2. The k_d values characterizing the rates of the exchange reaction between $[Gd(BOPTA)]^{2-}$ and Eu^{3+} ($[Gd(BOPTA)]^{2-}$ = 0.001 м, pH = 3.3 (■), 3.45 (♦), 3.6 (▲), 3.75 (●), 3.9 (□), 4.2 (◇), 4.8 (Δ), 5.4 (○) and 6.04 (∗), 0.15 м NaCl, 25 °C).

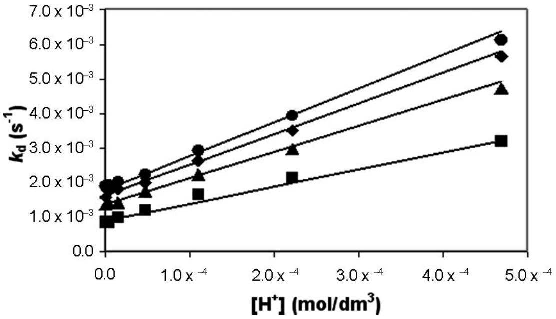

Figure 3. The k_d values characterizing the rates of the exchange reaction between $[Gd(BOPTA)]^{2-}$ and Zn^{2+} ($[Gd(BOPTA)]^{2-}$ = 5×10^{-4} м, $[Zn^{2+}]$ = 0.05 м (■), 0.115 м (▲), 0.18 м (♦) and 0.25 м (●), 0.15 м NaCl, 25 °C).

The k_d values obtained for the reactions between $[Gd(BOPTA)]^{2-}$ and Zn^{2+} and Cu^{2+} are shown in Figures 3 and 4 as a function of the H^+ concentration. The rate data presented in Figures 3 and 4 show that the k_d values are directly proportional to the H^+ concentration and increase with an increase in the Zn^{2+} and Cu^{2+} concentration. However, the straight lines intercept the abscissa, which indicates that there is a reaction pathway in which the Zn^{2+} and Cu^{2+} ions directly attack the complex $[Gd(BOPTA)]^{2-}$.

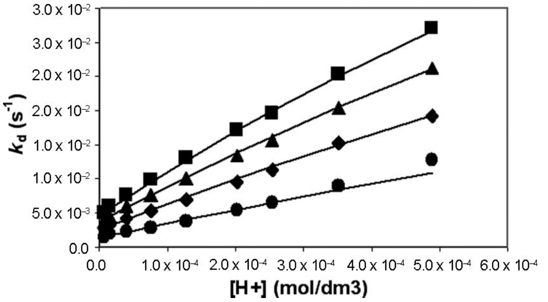

Figure 4. The k_d values characterizing the rates of the exchange reaction between $[Gd(BOPTA)]^{2-}$ and Cu^{2+} ($[Gd(BOPTA)]^{2-}$ = 5×10^{-4} м, $[Cu^{2+}]$ = 0.002 м (●), 0.004 м (♦), 0.006 м (▲) and 0.008 м (■), 0.15 м NaCl, 25 °C).

The rates of the exchange reactions, in general, increase with an increase in the $[H^+]$, which can be explained by the formation and faster dissociation of the protonated $[Gd(HBOPTA)]^-$ complexes. Protonation occurs at a carboxylate group when the carboxyl group formed is not coordinated. The proton can be transferred to a nitrogen atom when a free glycinate or iminodiacetate group is formed. The glycinate or iminodiacetate group can be recoordinated, or the stepwise de-coordination of the donor atoms of BOPTA proceeds and the complex dissociates. The attachment of a second proton to $[Gd(HBOPTA)]^-$ can accelerate the dissociation, which explains the second-order dependence of the k_d values. Free $[H_xBOPTA]^{x-5}$, formed by dissociation of the protonated complexes, reacts very fast with the exchanging Eu^{3+}, Zn^{2+} or Cu^{2+} ions. In principle, the deprotonated complex can also dissociate very slowly; the dissociation reactions of $[Gd(BOPTA)]^{2-}$ can be summarized in the reaction scheme shown in (8).

$$\begin{tikzcd}
\mathrm{GdL} \arrow[r, "k_0"] \arrow[d, shift left, "H^+"] & Gd^{3+} + \mathrm{L} \\
\mathrm{GdLH} \arrow[u, shift left, "K_{GdLH}"] \arrow[r, "k_{GdLH}"] \arrow[d, shift left, "H^+"] & Gd^{3+} + \mathrm{HL} \\
\mathrm{GdLH_2} \arrow[u, shift left, "K_{GdLH_2}"] \arrow[r, "k_{GdLH_2}"] & Gd^{3+} + \mathrm{LH_2}
\end{tikzcd} \tag{8}$$

The rate constants k_0, k_{GdLH} and k_{GdLH_2} characterize the dissociation rates of the non-protonated, monoprotonated, and diprotonated complexes, respectively.

The increase in the k_d values with an increase in the concentration of Eu^{3+}, Zn^{2+}, or Cu^{2+} (Figures 2, 3, and 4) can be explained by the direct reactions between $[Gd(BOPTA)]^{2-}$ and the exchanging metal ions, which occur via the formation of the dinuclear intermediate GdLM. In the first step of the formation of the dinuclear intermediate, a carboxylate group is probably coordinated to the attacking M^{n+} metal ion, and in the course of the reaction, the functional groups of BOPTA are slowly transferred to the metal M^{n+} step by step and the complex ML is formed [reaction (9)].

$$\mathrm{GdL} + M^{n+} \xrightleftharpoons{K_{GdLM}} \mathrm{GdLM} \xrightarrow{k_{GdLM}} Gd^{3+} + \mathrm{ML} \tag{9}$$

where K_{GdLM} is the stability constant of the dinuclear intermediate and k_{GdLM} is the rate constant characterizing the formation rate of ML.

For interpreting the dependence of the k_d values on the concentration of H^+ and M^{n+} ions, we had to assume a reaction pathway that occurs with the direct attack of the exchanging metal ion on the protonated complex [reaction (10).

$$\mathrm{GdLH} + M^{n+} \xrightarrow{k^{M}_{GdLH}} \mathrm{ML} + Gd^{3+} + H^+ \tag{10}$$

where k^{M}_{GdLH} is the rate constant characterizing the reaction.

$$-\frac{\mathrm{d}[\mathrm{GdL}]_\mathrm{t}}{\mathrm{d}t} = k_0[\mathrm{GdL}] + k_{\mathrm{GdLH}}[\mathrm{GdLH}] + k_{\mathrm{GdLH_2}}[\mathrm{GdLH_2}] + k_{\mathrm{GdLM}}[\mathrm{GdLM}] + k^{\mathrm{M}}_{\mathrm{GdLH}}[\mathrm{GdLH}][\mathrm{M}^{n+}] \tag{11}$$

By considering all the possible reaction pathways shown in the reactions in (8)–(10), the rate of the exchange reactions of $[\mathrm{Gd(BOPTA)}]^{2-}$ can be expressed as shown in Equation (11).

By taking into account the total concentration of the complex ($[\mathrm{GdL}]_\mathrm{t}$ = [GdL] + [GdLH] + [GdLM], where the concentration of the diprotonated complex, $\mathrm{GdLH_2}$, is neglected), the equations that define the protonation constants and the stability constant (K_{GdLM} = [GdLM]/[GdL][M^{n+}]), and Equations (7) and (11), the k_d value can be expressed as shown in Equation (12).

$$k_\mathrm{d} = \frac{k_0 + k_1[\mathrm{H}^+] + k_2[\mathrm{H}^+]^2 + k_3^{\mathrm{M}}[\mathrm{M}^{n+}] + k_4^{\mathrm{M}}[\mathrm{M}^{n+}][\mathrm{H}^+]}{1 + K_{\mathrm{GdLH}}[\mathrm{H}^+] + K_{\mathrm{GdLM}}[\mathrm{M}^{n+}]} \tag{12}$$

The rate constants k_1 ($k_1 = k_{\mathrm{GdLH}}K_{\mathrm{GdLH}}$) and k_2 ($k_2 = k_{\mathrm{GdLH_2}}K_{\mathrm{GdLH}}K_{\mathrm{GdLH_2}}$) characterize the proton-assisted dissociation of Gd(BOPTA). The reactions occurring with direct attack of the M^{n+} metal ion on the complex and the protonated complex are characterized by the rate constants k_3^{M} ($k_3^{\mathrm{M}} = k_{\mathrm{GdLM}}K_{\mathrm{GdLM}}$) and k_4^{M} ($k_4^{\mathrm{M}} = k^{\mathrm{M}}_{\mathrm{GdLH}}K_{\mathrm{GdLH}}$), respectively.

The rate constants characterizing the exchange reactions between $[\mathrm{Gd(BOPTA)}]^{2-}$ and Eu^{3+} were calculated by fitting the k_d values (Figure 2) to Equation (12). In the fitting procedure, a fixed value of K_{GdLH} (45, Table 2) was used, which was determined by pH potentiometry. The rate constants and the K_{GdLM} values obtained are presented in Table 4, where similar rate constants, characterizing the reaction of $[\mathrm{Gd(DTPA)}]^{2-}$, are also shown. The k_0 value is very low, and the error obtained for it is relatively high, therefore the dissociation of the non-protonated complex is negligible.

By fitting the k_d values obtained for the reactions of $[\mathrm{Gd(BOPTA)}]^{2-}$ with Zn^{2+} and Cu^{2+} (Figures 3 and 4) to Equation (12), the k_0, k_1, and k_2 rate constants were calculated with very high error because the contribution of the terms ($k_0 + k_1[\mathrm{H}^+] + k_2[\mathrm{H}^+]^2$) to the value of the numerator in Equation (12) is very low. The exchange reactions with Zn^{2+} and Cu^{2+} predominantly occur with direct attack of Zn^{2+} or Cu^{2+} on the complex. However, by neglecting the terms k_0, $k_1[\mathrm{H}^+]$, and $k_2[\mathrm{H}^+]^2$ in Equation (12), the fitting procedure gives reliable values (with acceptable errors) for the rate constants k_3^{M} and k_4^{M} and for the K_{GdLM} values (Table 4).

Comparison of the rate constants presented in Table 4, which characterize the transmetallation reactions of $[\mathrm{Gd(BOPTA)}]^{2-}$ and $[\mathrm{Gd(DTPA)}]^{2-}$, show that both the proton-assisted dissociation and the Zn^{2+}- and Cu^{2+}-assisted exchange reactions of $[\mathrm{Gd(BOPTA)}]^{2-}$ are slower by about 30–90% than the corresponding reactions of Gd(DTPA). These findings indicate that substitution of the benzyloxymethyl group in ligand DTPA results in a mild increase in the kinetic inertness of the complex $[\mathrm{Gd(BOPTA)}]^{2-}$.

Table 4. Rate contsants characterizing the metal-exchange reactions of $[\mathrm{Gd(BOPTA)}]^{2-}$ and $[\mathrm{Gd(DTPA)}]^{2-}$ with Eu^{3+},Cu^{2+}, and Zn^{2+} (25 °C).

	$[\mathrm{Gd(BOPTA)}]^{2-}$ (0.15 M NaCl)		
	Eu^{3+}	Cu^{2+}	Zn^{2+}
k_0 (s^{-1})	$(6.7 \pm 4.5) \times 10^{-7}$	–	–
k_1 ($\mathrm{M}^{-1}\mathrm{s}^{-1}$)	0.41 ± 0.1	–	–
k_2 ($\mathrm{M}^{-2}\mathrm{s}^{-1}$)	$(5.1 \pm 0.2) \times 10^{4}$	–	–
k_3^{M} ($\mathrm{M}^{-1}\mathrm{s}^{-1}$)	$(3.1 \pm 0.8) \times 10^{-4}$	0.68 ± 0.06	$(2.90 \pm 0.15) \times 10^{-2}$
k_4^{M} ($\mathrm{M}^{-2}\mathrm{s}^{-1}$)	110 ± 18	$(1.06 \pm 0.03) \times 10^{4}$	158.7 ± 9.6
K_{GdLM}	31 ± 6	50 ± 6	12 ± 1
	$[\mathrm{Gd(DTPA)}]^{2-}$ (1.0 M KCl)[26]		
	Eu^{3+}	Cu^{2+}	Zn^{2+}
k_1 ($\mathrm{M}^{-1}\mathrm{s}^{-1}$)	0.58	–	–
k_2 ($\mathrm{M}^{-2}\mathrm{s}^{-1}$)	9.7×10^{4}	–	–
k_3^{M} ($\mathrm{M}^{-1}\mathrm{s}^{-1}$)	4.9×10^{-4}	0.93	5.6×10^{-2}
k_4^{M} ($\mathrm{M}^{-2}\mathrm{s}^{-1}$)	40	–	–
K_{GdLM}	19	13	7

Conclusions

The DTPA derivative ligands BOPTA and DTPA-BMA behave differently in 0.15 M NaCl and 0.1 M KCl solutions used to maintain a constant ionic strength. The first protonation constant of $[\mathrm{BOPTA}]^{5-}$ and therefore the stability constants of its complexes formed with Gd^{3+} and Zn^{2+} – similarly to those of $[\mathrm{DTPA}]^{5-}$ – are lower in 0.15 M NaCl than in 0.1 M KCl solution. The difference in $\log K_1^{\mathrm{H}}$ values is lower for $[\mathrm{DTPA\text{-}BMA}]^{3-}$ probably because it forms a much weaker complex with Na^+ than $[\mathrm{BOPTA}]^{5-}$ does. The stability constants of $[\mathrm{Cu(DTPA\text{-}BMA)}]^-$ and $[\mathrm{Zn(DTPA\text{-}BMA)}]^-$ were found to be significantly higher in 0.15 M NaCl than those published earlier in 0.1 M NaCl. On the basis of the stability constants, the selectivity order of the ligands is BOPTA > DTPA > DTPA-BMA, which is the reverse of that found by Cacheris et al.[15]

The amide groups of the ligand DTPA-BMA behave similarly to those of the oligopeptides. The dissociation of the amide proton and the coordination of the amide N^- atom in the complex $[\mathrm{Cu(DTPA\text{-}BMA)}]^-$ at pH>7 was detected by spectrophotometry.

The metal-exchange reactions of $[\mathrm{Gd(BOPTA)}]^{2-}$ with excess $\mathrm{Cu^{II}}$ and $\mathrm{Zn^{II}}$ predominantly occur with the direct attack of the metal ions on the complex and the protonated complex via the formation of a dinuclear intermediate. In the exchange reaction between $[\mathrm{Gd(BOPTA)}]^{2-}$ and $\mathrm{Eu^{III}}$, the predominant pathway is the proton-assisted dissociation, which takes place with the formation and the dissociation of the mono- and diprotonated complexes. The rate constants characterizing the proton-assisted dissociation of $[Gd(BOPTA)]^{2-}$ and the direct attack of the exchanging metals (Cu^{II}, Zn^{II}, and Eu^{III}) on the complex are lower by 30–90% than the corresponding rate constants reported for the exchange reactions of $[Gd(DTPA)]^{2-}$. The results of the equilibrium and kinetic studies obtained for the BOPTA complexes show that the attachment of the benzyloxymethyl group to a terminal acetate group of DTPA has practically no effect on the stability constants of the complexes, but the kinetic intertness of $[Gd(BOPTA)]^{2-}$ is definitely higher than that of $[Gd(DTPA)]^{2-}$.

Experimental Section

Materials: The chemicals used for the experiments were of the highest analytical grade. $GdCl_3$ and $EuCl_3$ were prepared by dissolving Gd_2O_3 and Eu_2O_3 (99.9% Fluka) in 6 M HCl and by evaporating off the excess acid. The concentration of $GdCl_3$, $EuCl_3$, $CuCl_2$, and $ZnCl_2$ stock solutions was determined by complexometric titration with standardized Na_2H_2EDTA solution, with the use of xylenol orange ($GdCl_3$, $EuCl_3$, $ZnCl_2$) and murexide ($CuCl_2$) indicators. The concentration of the DTPA (Fluka), BOPTA (Bracco Imaging S.p.A.), DTPA-BMA (prepared as described in ref.[15]), EGTA (Serva), and DOTA (Bracco Imaging S.p.A.) solutions was determined by pH potentiometric titrations in the presence and absence of a 40-fold excess of Ca^{2+}. The pH potentiometric titrations were made with standardized 0.2 M NaOH.

Equilibirum Measurements: All the equilibrium measurements were made at constant ionic strength maintained by 0.15 M NaCl at 25 °C. To determine the protonation constants of DTPA, BOPTA, DTPA-BMA, EGTA, and DOTA, two or three parallel pH potentiometric titrations were carried out with 0.2 M NaOH in 0.005 M ligand solutions. The $\log K_i^{H}$ values were calculated with the use of about 200 volume base/pH data points. The stability constants and protonation constants of the complexes $[Gd(DTPA)]^{2-}$ and $[Gd(BOPTA)]^{2-}$ were determined by direct pH potentiometric titration (0.002 M Gd^{3+} and 0.002 M ligand solutions), while those of [Gd(DTPA-BMA)] were obtained by pH potentiometric study of the competition reactions between the ligands DTPA-BMA and BOPTA for Gd^{3+}. The concentration of Gd^{3+}, DTPA-BMA, and BOPTA was 0.002 M each. For the calculation of the $\log K_{ML}$ and $\log K_{MLH_i}$ values, the volume base/pH data (70–80 data points) used were obtained in the pH range 1.7–3.0.

The equilibrium constants characterizing the formation of the Zn^{2+} complexes with DTPA, BOPTA, and DTPA-BMA were calculated from the data of the pH potentiometric titrations carried out at 1:1 and 2:1 metal-to-ligand concentration ratios (the number of data points was approximately 200).

The stability constants for $[Cu(BOPTA)]^{3-}$ and $[Cu(DTPA)]^{3-}$ were determined by spectrophotometry, with the use of competition reactions taking place between DOTA and BOPTA or DTPA for Cu^{2+} in the pH range 6.8–7.2. The concentration of Cu^{2+} in the samples (5samples for BOPTA and DTPA each) was 2 mM and that of DOTA was 2 mM or 5 mM, while the concentration of BOPTA and DTPA was varied between 2 mM and 10 mM. In order to reach equilibrium, the samples were kept at 50 °C for two weeks and then at 25 °C for another two weeks. The molar absorptivity of $CuCl_2$ and the complexes $[Cu(DOTA)]^{2-}$, $[Cu(BOPTA)]^{3-}$, and $[Cu(DTPA)]^{3-}$ were determined in 1.5, 2.0, 3.0, 5.0, and 7 mM solutions. Spectrophotometric measurements were made between 575 and 775 nm at 11 wavelengths. The protonation constants for the complexes CuL and the stability constants of the dinuclear complexes Cu_2L were determined by pH potentiometric titrations carried out at 1:1 and 2:1 metal-to-ligand concentration ratios with the knowledge of the $\log K_{CuL}$ values (the number of data points was approximately 200).

The stability constant of the complex $[Cu(DTPA-BMA)]^{-}$ was determined by spectrophotometry with the use of competition reactions between DTPA-BMA and EGTA for Cu^{2+} at pH values 6.9–7.1. The concentration of Cu^{2+} and DTPA-BMA was 0.1 mM, while that of EGTA was varied between 0.5 and 7.5 mM (5 samples). The samples were kept at 50 °C for two weeks and then at 25 °C for another two weeks. The absorbance values and the molar absorptivities of $CuCl_2$, $[Cu(DTPA-BMA)]^{-}$, and $[Cu(EGTA)]^{2-}$ were determined at 10 wavelengths between 275 and 330 nm. The molar absorptivities of $CuCl_2$, $[Cu(DTPA-BMA)]^{-}$, and $[Cu(EGTA)]^{2-}$ were determined in 0.05, 0.1, 0.2, 0.3, and 0.4 mM solutions. The absorbance and pH values were determined in the samples after equilibrium was reached (the time needed to reach equilibrium was determined by spectrophotometry). The spectrophotometric measurements were carried out in 1.0-cm cells with a Cary 1E spectrophotometer at 25 °C.

The pH potentiometric titrations were carried out with a 702SM Titrino titration workstation with the use of a Metrohm-6.0233.100 combined electrode. The titrated solutions (10 mL) were thermostatted at 25 °C. The samples were stirred with a magnetic stirrer and to avoid the effect of CO_2, N_2 gas was bubbled through the solutions. The titrations were carried out in the pH range 1.7–11.7. For the calibration of the pH meter, potassium hydrogen phthalate (pH = 4.005) and borax (pH = 9.177) buffers were used. For the calculation of the H^+ concentration from the measured pH values, the method proposed by Irving et al. was used.[28] A 0.01 M HCl (0.15 M NaCl) solution was titrated with the 0.2 M NaOH, and the difference between the measured and calculated pH values was used to calculate the $[H^+]$ from the pH values determined in the titration experiments. For the calculation of the equilibrium constants, the program PSEQUAD was used.[29]

Kinetic Measurements: The rates of the metal-exchange reactions of $[Gd(BOPTA)]^{2-}$ with Cu^{2+} and Eu^{3+} were studied by spectrophotometry, following the formation of the Eu^{3+} or Cu^{2+} complexes at 280 and 320 nm, respectively, with a Cary 1E spectrophotometer. The concentration of the complex $[Gd(BOPTA)]^{2-}$ was 1×10^{-3} and 5×10^{-4} M in the experiments with Eu^{3+} and Cu^{2+}, respectively, while the concentration of Eu^{3+} and Cu^{2+} was 5–15 and 4–16 times higher, respectively, in order to guarantee pseudo-first-order conditions. The progress of transmetallation with Zn^{2+} was followed by measuring the water proton relaxation rates ($1/T_1$) of the samples with an MS-4 NMR spectrometer (Institute Jozef Stefan, Ljubljana) at 9 MHz. The longitudinal relaxation times were measured by the "inversion recovery" method (180°–τ–90°) by using 6–8 different τ values. The measurements were carried out with a 5×10^{-4} M $[Gd(BOPTA)]^{2-}$ solution with a high excess of Zn^{2+}. The relaxivity of $[Gd(BOPTA)]^{2-}$ (r_1 = 6.9 mM^{-1} s^{-1}) differs considerably from that of Gd^{3+} (r_1 = 17.0 mM^{-1} s^{-1}) at 25 °C. The temperature was maintained at 25 °C and the ionic strength of the solutions was kept constant (0.15 M NaCl). For maintaining a constant pH value, 1,4-dimethylpiperazine (pH range 3.3–4.1), *N*-methylpiperazine (pH range 4.1–5.2), and piperazine ($5.2 < pH < 6$) buffers (0.02 M) were used. The pseudo-first-order rate constants (k_d) were calculated by Equation (13).

$$A_t = (A_0 - A_p)e^{-k_d t} + A_p \qquad (13)$$

where A_t, A_0, and A_p are the absorbance or water proton relaxation rate values at time t, at the start and at equilibrium of the reactions, respectively.

Supporting Information (see footnote on the first page of this article): Absorption spectra of the $[Cu(BOPTA)]^{3-}$, $[Cu(DOTA)]^{2-}$, and Cu^{2+}/BOPTA-DOTA systems, of the $[Cu(DTPA)]^{3-}$, $[Cu(DOTA)]^{2-}$, and Cu^{2+}/DTPA-DOTA systems, and of the $[Cu(DTPA-BMA)]^{-}$, $[Cu(EGTA)]^{2-}$, and Cu^{2+}/EGTA/DTPA-BMA systems.

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