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Relaxometric Study of Copper [15]Metallacrown-5 Gadolinium Complexes Derived from α-Aminohydroxamic Acids

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Abstract: Proton nuclear magnetic relaxation dispersion (NMRD) profiles were recorded between 0.24 mT and 1.4 T for lanthanum(III)- and gadolinium(III)-containing [15]metallacrown-5 complexes derived from α-aminohydroxamic acids and with copper(II) as the ring metal. The influence of the different R-groups on the proton relaxivity was investigated, and a linear relationship between the relaxivity and the molecular mass of the metallacrown complex was found. The selectivity of the metallacrown complexes was tested by transmetalation experiments with zinc(II) ions. The crystal structure of the copper [15]metallacrown-5 gadolinium complex with glycine hydroximate ligands is reported.

Keywords: hydroxamic acid · lanthanides · metallacycles · N,O ligands · rare earths

Introduction

Metallacrowns are a novel class of macrocyclic compounds, in which the metal is an integral part of the macrocycle ring. They were discovered by Pecoraro in 1989.[1,2] The α-aminohydroximates as the ditopic ligand, and the copper(II) ions as the ring metals give rise to the formation of a metallamacrocycle with five copper(II) ions. These [15]metallacrown-5 compounds have a cavity capable of coordinating an additional ion, such as a trivalent lanthanide ion.[3–9] These lanthanide(III)-containing metallacrown compounds are stable in different solvents, one of which is water.[3,6] The close proximity of paramagnetic centers has a direct influence on the enhancement of the proton relaxation rate of the coordinated water molecules. Three to four coordination sites on the lanthanide(III) ion in the central cavity (which is already coordinated by five oxygen atoms that form the ring) are available for additional ligand molecules, such as water molecules. Water molecules can also coordinate to the copper(II) ions from the ring and experience an additional paramagnetic form of relaxation. Pecoraro and co-workers mentioned the potential of gadolinium(III)-containing metallacrown complexes as a contrast agent for magnetic resonance imaging (MRI) applications, and they measured the proton longitudinal relaxivity r_1 for several metallacrown complexes with α-amino- and picoline hydroximate ligands.[2,3] These [15]metallacrown-5 complexes have a planar ring geometry and relatively high molecular weights ($M_w > 1000\ g\,mol^{-1}$), which could favorably affect the rotational correlation time τ_R. For metal ions with long longitudinal electron-spin relaxation times, T_{1e} and T_{2e}, such as gadolinium(III), the increase in τ_R is one of the most important sources of relaxivity enhancement.[9]

Other parameters that affect the relaxivity efficiency of gadolinium(III) complexes are the number of water molecules in the first coordination sphere of the paramagnetic ion and the residence time of these molecules. The residence time of water, τ_M, can limit the relaxivity of the paramagnetic complex. Insight into how to tune this parameter is crucial in the design of new MRI contrast agents.[10]

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The aim of this work was to investigate the influence of ligand substituents on the relaxometric behavior of gadolinium(III)-containing metallacrown compounds derived from α-aminohydroxamic acids (Figure 1). We synthesized five metallacrown complexes with the α-aminohydroxamic acids derived from glycine, L-valine, L-leucine, L-phenylalanine, and L-tyrosine as chelating ligands, with copper(II) as the ring metal and gadolinium(III) as the central metal ion. The proton relaxation properties of these complexes were analyzed by measuring the nuclear magnetic relaxation dispersion (NMRD) profiles between 0.24 mT and 1.4 T, and by measuring the proton relaxation rate as a function of the temperature at 0.47 T. To identify the contribution of the copper(II) centers to the total relaxivity, we also measured the NMRD profiles of two lanthanum(III)-containing metallacrown complexes. The stability of the complexes versus transmetalation by the important endogenous zinc(II) ion was also studied. The crystal structure of the gadolinium(III)-containing metallacrown derived from glycine hydroximate is described.

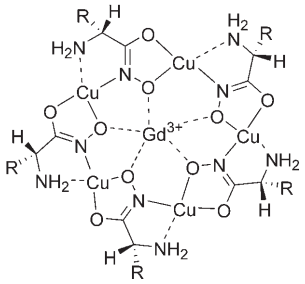

Figure 1. Structure of a gadolinium(III)-containing [15]metallacrown-5 complex with an α-aminohydroxamic acid ligand. R = H (glyha), $CH(CH_3)_2$ (L-valha), $CH_2CH(CH_3)_2$ (L-leuha), $CH_2C_6H_5$ (L-pheha), $CH_2C_6H_4OH$ (L-tyrha). The nitrate groups are omitted for the sake of clarity.

Table 1. Mass spectral data (ESI-MS) for gadolinium(III)-containing [15]metallacrown-5 complexes derived from α-aminohydroxamic acids and with copper(II) ions as the ring metal.

Ligand	$Gd(NO_3)_3$ [15-MC-5] M_w	$\{Gd(NO_3)_2$[15-MC-5]$\}^+$ *m*/*z* exptl	*m*/*z* calcd	$\{Gd(NO_3)$[15-MC-5]$\}^{2+}$ *m*/*z* exptl	*m*/*z* calcd
glyha	1101.3	1039	1039.3	488.5	488.7
L-valha	1311.7	1249	1249.7	593.5	593.9
L-leuha	1381.9	1319	1319.9	627.5	627.5
L-pheha	1551.9	1489	1489.9	713.5	713.5
L-tyrha	1631.9	1569	1569.9	753.5	753.5

Results and Discussion

Synthesis and characterization of the metallacrown complexes: The metallacrown complexes were synthesized in aqueous solution by using a two-step method. In the first step, equimolar amounts of the copper(II) salt and the α-aminohydroxamic acid were mixed and the solution turned green. In the second step, the lanthanide(III) salt was added to the solution (0.2 equivalent) and the solution turned blue. The lanthanide(III)-containing [15]metallacrown-5 complexes were analyzed by using different techniques (electrospray mass spectrometry (ESI-MS), CHN elemental analysis, and UV-visible absorption spectroscopy). NMR methods were used to analyze the lanthanum(III)-containing complexes, but could not be used for the characterization of the gadolinium(III)-containing complexes because of the severe line-broadening due to the presence of the strongly paramagnetic gadolinium(III) centers.

The ESI-MS spectra recorded in positive-ion mode confirm the composition of the complexes. Signals corresponding to the ions $\{Gd(NO_3)_2[15\text{-}MC_{Cu^{II}N(aminoha)}\text{-}5]\}^+$ and $\{Gd(NO_3)[15\text{-}MC_{Cu^{II}N(aminoha)}\text{-}5]\}^{2+}$ were observed in the mass spectra for the five [15]metallacrown-5 complexes, and the data are summarized in Table 1. The isotopic profiles of the peaks are consistent with the proposed stoichiometry. Moreover, no evidence was found for monomeric or dimeric copper(II) species. These experimental data indicate that the [15]metallacrown-5 unit is stable in protic polar solvents. This is a necessary condition for their possible use as MRI contrast agents, because small amounts of ligand, free copper(II) ions, or free gadolinium(III) ions would be toxic.[11] The CHN elemental analysis results are given in the Experimental Section.

The metallacrown complexes of the ligands glyha, L-leuha, L-pheha and L-tyrha were also characterized in water by using UV-visible absorption spectroscopy. A titration of gadolinium(III) nitrate in aqueous solutions of equal amounts of α-aminohydroxamic acid and copper(II) acetate was monitored by recording the absorption spectra. Prior to addition of the gadolinium(III) ions (Figure 2), the solutions

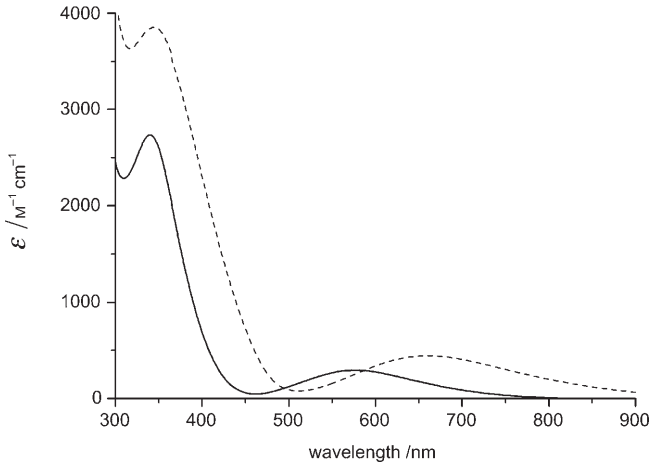

Figure 2. UV/Vis absorption spectrum of a solution of L-tyrosine hydroxamic acid and copper(II) acetate (1:1) in water (2 mM), before (-----) and after (——) addition of 0.2 equiv of gadolinium(III) nitrate. The molar absorptivity is expressed per [15]metallacrown-5 unit.

were green and showed two prominent absorption bands with maxima at 345 and 655 nm. The differences between the spectra of the different ligands are negligible. The absorption maximum at 655 nm is very close to the calculated λ_{max} value (648 nm) of the polynuclear $[Cu_5L_4]^{2+}$ species (L = L-alaha^{2-}).[12] During titration, the maximum at 655 nm is shifted to lower wavelength (blue-shift). After addition of 0.2 equivalent of gadolinium(III) (Figure 2), the solutions became a deep-blue color. Addition of more than 0.2 equivalent of gadolinium(III) caused no further changes in the spectra. This indicates that a polynuclear species is formed in solution with a Gd^{III}/Cu^{II} ratio of 1:5. The spectra for all four gadolinium(III)-containing [15]metallacrown-5 complexes with glyha, L-leuha, L-pheha, and L-tyrha as ligands are nearly identical (Figure 3), with the absorption maximum for the ligand-field band at around 575 nm.

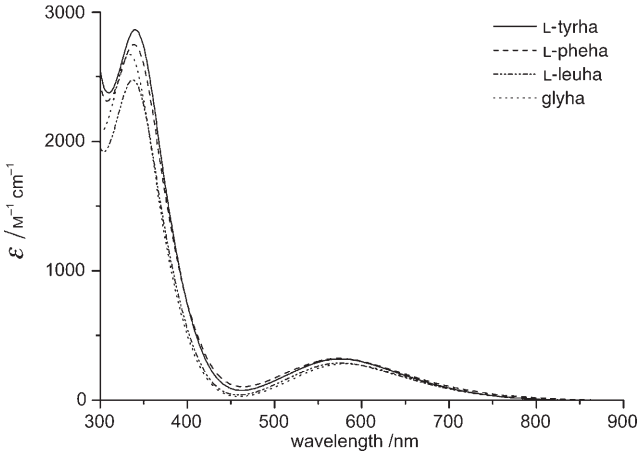

Figure 3. UV/Vis absorption spectrum of gadolinium(III)-containing [15]metallacrown-5 complexes with different α-aminohydroxamic acids as ligand. The molar absorptivity is expressed per 15-MC-5, and [15-MC-5] = 4×10^{-4} M.

each of the five glycine hydroximate ligands. The crystallographic data are summarized in Table 2. Charge balance is achieved by three nitrate anions. One of the nitrate groups is coordinated to the gadolinium(III) ion in a bidentate fashion. The position of the gadolinium(III) ion is displaced from

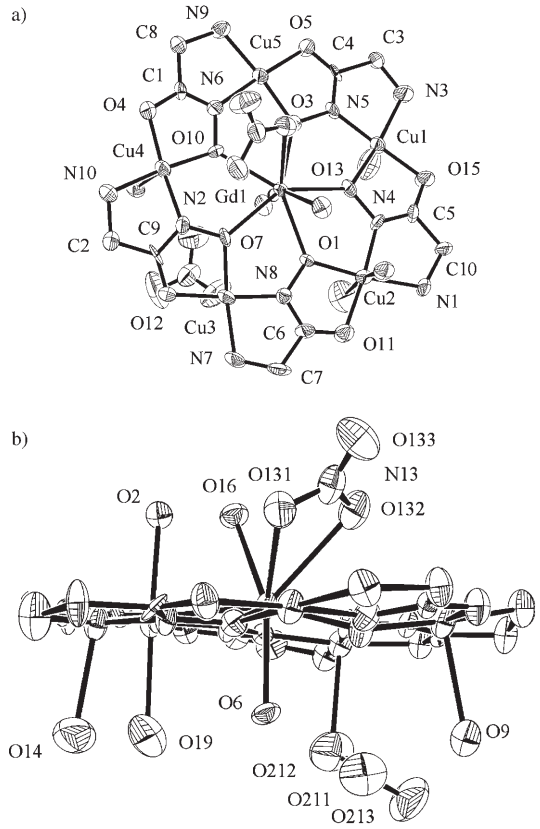

Figure 4. ORTEP diagram of the [15]metallacrown-5 moiety in {Gd-$(NO_3)(H_2O)_2$[15-$MC_{Cu^{II}N(glyha)}$-5]$(NO_3)(H_2O)_4$}·NO_3·5H_2O; (a) top view, (b) side view. Thermal ellipsoids are at the 50% probability level.

Crystal structure of {Gd(NO_3)-$(H_2O)_2$[15-$MC_{Cu^{II}N(glyha)}$-5]-$(NO_3)(H_2O)_4$}·NO_3·5H_2O: The crystal structure of the [15]metallacrown-5 derived from glycine hydroximate ligands and incorporating gadolinium(III) nitrate (compound **1**) was determined. The five glycine hydroximate ligands (glyha^{2-}) and five copper(II) ions form the almost planar [15]metallacrown-5 ring and encapsulate a gadolinium(III) ion in the center (Figures 4 and 5). The ring with Cu–N–O–Cu linkages is formed by the five copper(II) ions and the nitrogen and oxygen atoms of

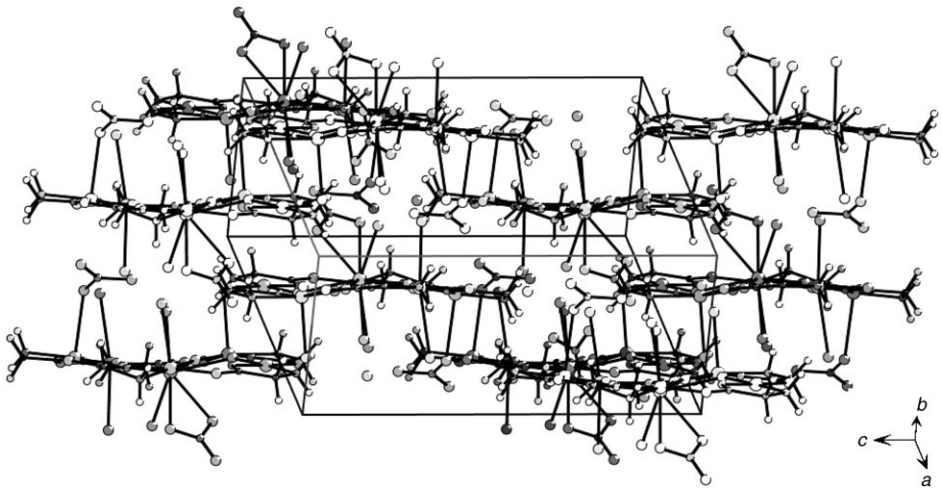

Figure 5. Packing of the [15]metallacrown-5 rings in the crystal structure of {Gd$(NO_3)(H_2O)_2$[15-$MC_{Cu^{II}N(glyha)}$-5]$(NO_3)(H_2O)_4$}·NO_3·5H_2O.

Table 2. Summary of crystal data, intensity measurements, and structure refinement for gadolinium(III) compound **1**.

	1
formula	$GdCu_5O_{30}C_{10}N_{13}H_{47}$
M_w	1304.53
crystal size [mm^3]	$0.2\times0.2\times0.1$
crystal system	triclinic
space group	$P\bar{1}$
a [Å]	10.705(2)
b [Å]	11.514(2)
c [Å]	16.857(3)
α [°]	72.923(14)
β [°]	87.419(16)
γ [°]	74.062(16)
V [Å^3]	1908.4(6)
Z	2
ρ_{calcd} [g cm^{-3}]	2.397
θ range for data collection [°]	1.92–24.42
limiting indices	$-12\le h\le12$ $-12\le k\le12$ $-19\le l\le19$
μ [mm^{-1}]	4.566
absorption correction	numerical
$F(000)$	1290
measured reflns	15354
unique reflns	5706
observed reflns [$I_o>4\sigma(I_o)$]	2534
parameters refined	534
goodness-of-fit (F^2)	0.815
R_1	0.0519
wR_2	0.1080
R_1 (all data)	0.1146
wR_2 (all data)	0.1173

the center of the plane through the five coordination oxygen donor atoms by approximately 0.3 Å. Two coordinating water molecules ($r_{Gd-O}=2.358(11)$ and 2.401(10) Å) complete a nine-coordination of the inner sphere of the gadolinium(III) ion. A second nitrate anion coordinates in a monodentate fashion to the copper(II) ion Cu3. This is a weak axial bond with a length of 2.548(14) Å. The copper(II) ions Cu1 and Cu4 have square-pyramidal environments by forming weak axial bonds on the same face of the metallacrown ring to water molecules, with bond lengths of 2.399(15) and 2.577(12) Å, respectively. Cu2 exhibits a slightly distorted octahedral coordination sphere with two axial water molecules, with bond lengths of 2.572(12) and 2.749(19) Å, respectively. Cu5 has a square-planar environment. The third nitrate anion and five other water molecules do not coordinate to the metallacrown ring, but form a net of hydrogen bonding. The average bite angle of the metallacrown ring is approximately 71°. The relatively high residual ($R_{all}=0.1146$) is probably caused by the remarkable mobility of the five non-coordinated water molecules, and a slight disorder of one nitrate, as is indicated by the relatively high displacement parameters of the respective atoms. The crystal structure of a [15]metallacrown-5 with the glycine hydroximate ligand and incorporating a europium(III) ion was described previously by Pecoraro and co-workers.[3] Although their europium(III) compound was synthesized under comparable conditions, and despite the rather small difference between the ionic radii of europium(III) and gadolinium(III) (1.07 and 1.05 Å, respectively), the structures exhibit some significant differences. Charge balance in the europium(III)-containing [15]metallacrown-5 compound is achieved by two nitrate groups and one hydroxide group, which coordinate to the europium(III) ion. In this structure, the europium(III) ion is only eight-coordinate, whereas in the structure of our gadolinium(III) compound, the gadolinium(III) ion is nine-coordinate.

Relaxation rate measurements: The presence of paramagnetic centers induces an increase in the proton relaxation rate of water because of short magnetic dipolar interactions between the paramagnetic center and the water protons (the *inner-sphere contribution*)[13] and longer dipolar interactions between closely diffusing water molecules and the paramagnetic complex (the *outer-sphere contribution*).[14] The *outer-sphere contribution* is related to the relative diffusion of water molecules and the paramagnetic chelate complex, and is thus more efficient at lower temperatures. The longitudinal relaxation enhancement induced by the *inner-sphere mechanism* results from the exchange of water molecules between the primary coordination sphere of the gadolinium(III) ion and the bulk solvent. One of the limiting parameters of this relaxation mechanism is the residence time of water, τ_M. The inner-sphere relaxation can, therefore, be quenched at low temperatures if the water exchange is not fast enough.[15] If, on the other hand, the water exchange is fast enough ($\tau_M \ll T_{1M}$, in which T_{1M} is the relaxation time of the bound water molecules), the proton relaxation rate enhancement experienced by the bulk solvent will depend on $1/T_{1M}$. In this latter case, and at medium and high magnetic fields, the relaxation rate increases as the temperature decreases. The proton longitudinal relaxivity r_1 (defined as the paramagnetic contribution to the observed proton relaxation rate induced by one millimole per liter of the gadolinium(III) chelate) of the [15]metallacrown-5 complexes was measured between 5 and 45 °C at 0.47 T to evaluate the influence of the residence time of water, τ_M (Figure 6). For all five [15]metallacrown-5 complexes, the relaxivity increases by a factor of 1.65–2 as the temperature decreases from 45 to 5 °C, as was observed for Gd–DTPA and Gd–DOTA.[16,17] This indicates that τ_M does not limit the relaxation rate and that the value at 310 K must be lower than 400 ns, a value for which a limitation of r_1 below room temperature has already been observed.[18] The water molecules can thus exchange easily with the metal ions; they approach the ions from both sides of the metallacrown ring in the case of the complex with glycine hydroximate as ligand, and from the hydrophilic site of the ring in the case of the chiral metallacrowns with L-α-aminohydroximate ligands.

Figure 7 shows the proton NMRD profiles at 310 K of two of the gadolinium(III)- and lanthanum(III)-containing [15]metallacrown-5 complexes. The paramagnetic contribution due to the copper(II) ions is lower than that due to the gadolinium(III) ion. This is in good agreement with the results reported previously at 30 MHz and 293 K.[3] For the L-

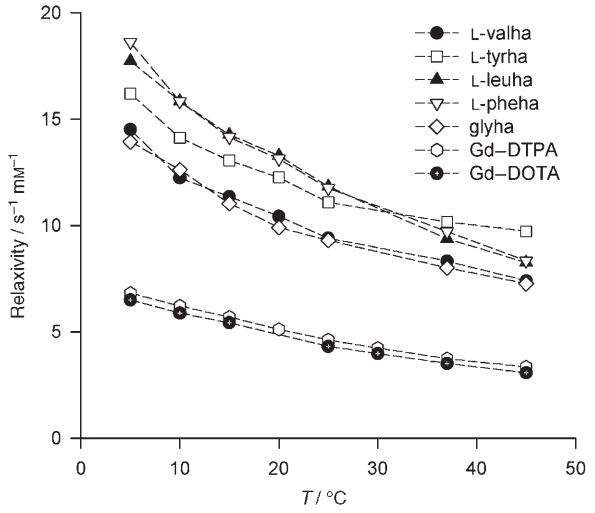

Figure 6. Temperature dependence of the proton relaxivities of the gadolinium(III)-containing [15]metallacrown-5 complexes with the different α-aminohydroxamic acids as ligand (B_o = 0.47 T). The data for Gd–DTPA and Gd–DOTA are shown for comparison.

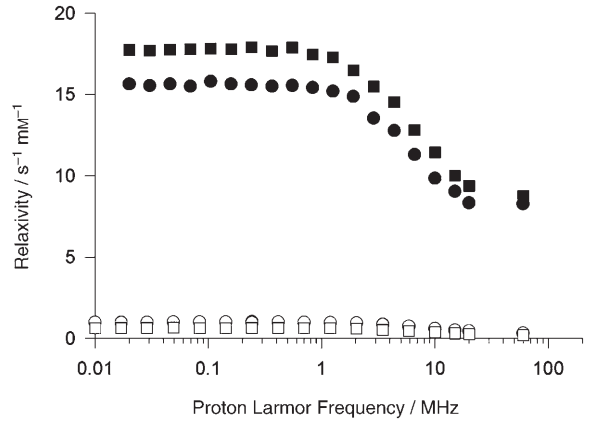

Figure 7. ^{1}H NMRD relaxivity profiles of the gadolinium(III)-containing [15]metallacrown-5 complexes with L-valha (■) and L-leuha (●), and of the lanthanum(III)-containing [15]metallacrown-5 complexes with L-valha (□) and L-leuha (○) (T = 37 °C).

valha complex, the contribution due to the copper(II) centers ranges from 3.9% at low field (0.47 mT) to 2.4% at 1.4 T. For the L-leuha complex, the contribution of the copper(II) ions is slightly higher: 5.6% at 0.47 mT and 3.7% at 1.4 T.

At magnetic field strengths greater than 1 Tesla, the relaxivities show a linear dependence on the molecular weight (Figure 9).

The relaxivity of the complexes is nearly twice as high as the relaxivity of Gd–DTPA and Gd–DOTA over the whole frequency range. This can be explained by the presence of two coordinated water molecules in the first coordination sphere of the metallacrown complexes (compared to one for Gd–DTPA or Gd–DOTA) and by the slower tumbling rate attributed to the larger molecular size of the complexes. However, the relaxation profiles do not exhibit the dispersion peak at high frequency, which is characteristic for slow-rotating paramagnetic molecules.[15,19,20] Thus, the decrease in mobility of the metallacrown complexes caused by increasing their molecular weight through attaching larger R-groups to the α-aminohydroxamic acid is insufficient to maximize the relaxation at frequencies used in clinical applications (Figure 8).

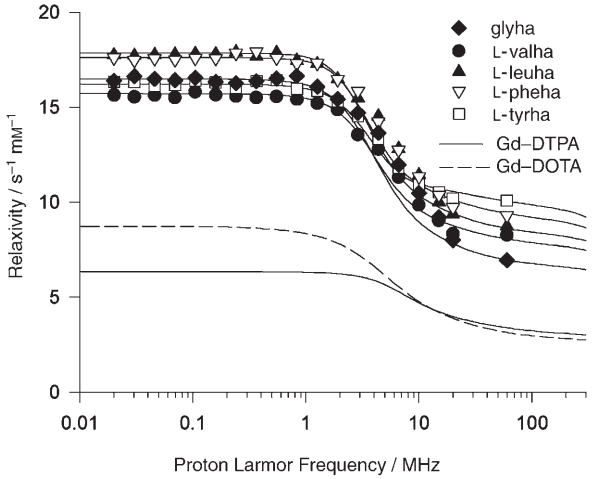

Figure 8. ^{1}H NMRD relaxivity profiles of the gadolinium(III)-containing [15]metallacrown-5 complexes with the different α-aminohydroxamic acids as ligands. The lines drawn through the data are merely guidelines. The NMRD profiles of Gd–DTPA and Gd–DOTA are shown for comparison (T = 37 °C).

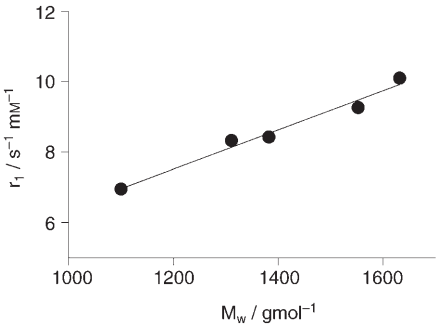

Figure 9. Relaxivity of the gadolinium(III)-containing [15]metallacrown-15 complexes at 37 °C and 0.47 T versus the molecular weight of the complexes.

Transmetalation experiments: The transmetalation of gadolinium(III) by zinc(II) in the metallacrown complexes was assessed by measuring proton relaxometry at 0.47 T. In a phosphate buffer (pH 7), a precipitation of gadolinium(III) phosphate is observed if the gadolinium(III) ions are expelled from the metallacrown complex by the zinc(II) ions. This results in a decrease in the proton relaxation rate of the solution. It is known that open-chain complexes (Gd–DTPA, Gd–DTPABMA) are less stable than macrocyclic complexes (Gd–DOTA, Gd–HPDO3A) towards transmetalation.[21] The time profile of the water proton relaxation rate of the metallacrown complexes with L-tyrosine, L-phenylalanine,

and L-leucine hydroximate ligands reveals a faster and more extensive transmetalation than the Gd–DTPA complex. However, the metallacrown complexes with L-valine and glycine hydroximate ligands are characterized by a transmetalation behavior intermediate between those of the open-chain Gd–DTPA complex and the macrocyclic Gd–DOTA complex (Figure 10, R_1^p = proton longitudinal paramagnetic relaxation rate).[21] These two [15]metallacrown-5 complexes are thus remarkably stable in the presence of zinc(II) ions.

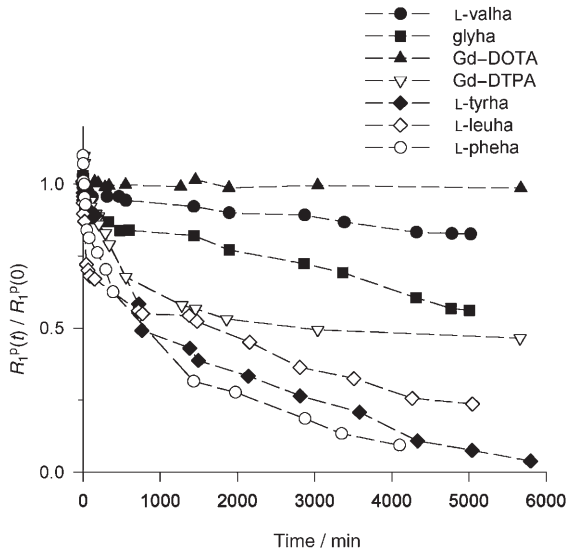

Figure 10. Evolution of the transmetalation process as measured by the decrease in the $R_1^p(t)/R_1^p(t=0)$ ratio as a function of time for the gadolinium(III)-containing [15]metallacrown-5 complexes and for Gd–DTPA and Gd–DOTA.

Notably, the transmetalation of the copper ions by zinc ions and the degradation of the hydroxamic acid could also contribute to the decrease in the relaxation rate and to the in vivo toxicity of the complexes.

Conclusion

For all five gadolinium(III)-containing [15]metallacrown-5 complexes, the exchange time τ_M of the coordinated water molecules does not limit the proton relaxivity at 0.47 T. The coordination of two water molecules in the first coordination sphere of the gadolinium(III) ion and the relatively slow tumbling rate of the complexes result in an increased proton relaxivity of nearly double that of Gd–DTPA and Gd–DOTA over the whole frequency range. In solutions containing zinc(II) ions, the gadolinium(III)-containing [15]metallacrown-5 complexes with L-valine and glycine hydroximate ligands show a weaker transmetalation behavior than the gadolinium(III)-containing metallacrown complexes with L-phenylalanine, L-tyrosine, and L-leucine hydroximate ligands. However, additional experiments devoted to analysis of the possible degradation of the hydroxamic acids and of the transmetalation of the copper ions are necessary to establish the overall stability of the complex in vivo.

Experimental Section

General: Elemental analysis was performed by using a CE Instruments EA-1110 elemental analyser. Electrospray ionization mass spectra were recorded by using a Q-tof 2 mass spectrometer (Micromass, Manchester, UK). The sample (0.1 mg) was dissolved in a water/methanol (50:50) mixture and the solution was injected into the apparatus at a flow rate of 5 $\mu L\,min^{-1}$. NMR spectra were recorded by using a Bruker Avance 300, operating at 300 MHz. Proton nuclear magnetic relaxation dispersion (NMRD) profiles were recorded between 0.24 mT and 0.35 T by using a Fast Field Cycling Relaxometer (Stelar, Mede, Italy). Additional measurements at 0.47 and 1.41 T were obtained by using Minispec PC-120 and Mq Series systems, respectively (Bruker, Karlsruhe, Germany). The kinetics of the transmetalation was monitored by using a Bruker Minispec PC-120 (20 MHz) spin analyzer at 310 K. This technique is based on the time evolution of the proton longitudinal paramagnetic relaxation rate (R_1^p) of a phosphate buffer solution (pH 7, $[H_2PO_4^-]+[HPO^{2-}]+[PO_4^{3-}]=67$ mM) containing 2.5 mM of gadolinium(III) complex and 2.5 mM of $ZnCl_2$.[21]

Synthesis of the hydroxamic acids: All chemicals were obtained from Acros Organics. The ligands glycine hydroxamic acid, L-leucine hydroxamic acid, L-valine hydroxamic acid, L-phenylalanine hydroxamic acid, and L-tyrosine hydroxamic acid were prepared via their respective methyl ester by following a literature method.[22]

Characterization by ^{1}H NMR (300 MHz, DMSO): L-valha: $\delta_H=0.83$ (q, 6H; $(CH_3)_2$), 1.69 (m, 1H; CH), 2.70 ppm (d, 1H; $_\alpha$CH); L-leuha: $\delta_H=0.85$ (q, 6H; $(CH_3)_2$), 1.29 (m, 2H; CH_2), 1.62 (m, 1H; CH), 3.05 ppm (t, 1H; $_\alpha$CH); L-pheha: $\delta_H=2.61$ (q, 1H; CH_2), 2.84 (q, 1H; CH_2), 3.25 (t, 1H; $_\alpha$CH), 7.25 ppm (m, 5H; H-aryl); L-tyrha: $\delta_H=2.50$ (q, 1H; CH_2), 2.71 (q, 1H; CH_2), 3.17 (t, 1H; $_\alpha$CH), 6.65 (d, 2H; H-aryl), 6.97 ppm (d, 2H; H-aryl); ^{1}H NMR (300 MHz, D_2O): glyha: $\delta_H=3.27$ ppm (s, 2H; $_\alpha$CH).

Synthesis of the gadolinium(III) complexes: The [15]metallacrown-5 complexes with different hydroximate ligands were synthesized by mixing equimolar amounts (1 mmol) of $Cu(OAc)_2\cdot H_2O$ and the α-aminohydroxamic acid in 50 mL of water. The solutions were stirred until the hydroximate ligands were completely dissolved. $Ln(NO_3)_3\cdot 6H_2O$ (0.2 mmol, $Ln^{III}=Gd^{III}$ or La^{III}) was added and the dark green solutions were stirred for several hours until they turned blue. Crystals formed in the solutions during slow evaporation of the solvent. Calculated and experimental values for the elemental analysis show some differences for the crystals that were not analyzed by X-ray diffraction, because the exact number and type of coordinating anions or lattice solvent molecules are unknown. Crystals suitable for X-ray diffraction studies were obtained for the gadolinium(III)-containing [15]metallacrown-5 complexes with glycine.

Elemental analysis calcd (%) for $Gd^{III}[15\text{-}MC_{Cu^{II}N(glyha)}\text{-}5](NO_3)_3(H_2O)_5$ ($C_{10}H_{30}Cu_5GdN_{12}O_{21}$) (1129.4): C 10.63, H 2.68, N 14.88; found: C 11.01, H 2.38, N 14.45; calcd (%) for $Gd^{III}[15\text{-}MC_{Cu^{II}N(L\text{-}valha)}\text{-}5](NO_3)_2(OH)(H_2O)_4$ ($C_{25}H_{59}Cu_5GdN_{12}O_{21}$) (1338.8): C 22.43, H 4.44, N 12.55; found: C 22.56, H 3.98, N 12.52; calcd (%) for $Gd^{III}[15\text{-}MC_{Cu^{II}N(L\text{-}leuha)}\text{-}5](NO_3)_2(OH)(H_2O)_4$ ($C_{30}H_{69}Cu_5GdN_{12}O_{21}$) (1408.9): C 25.57, H 4.94, N 11.93; found: C 25.07, H 4.12, N 11.21; calcd (%) for $Gd^{III}[15\text{-}MC_{Cu^{II}N(L\text{-}pheha)}\text{-}5](NO_3)_3(H_2O)_3$ ($C_{45}H_{56}Cu_5GdN_{13}O_{22}$) (1606.0): C 33.65, H 3.51, N 11.34; found: C 34.19, H 4.27, N 11.32; calcd (%) for $Gd^{III}[15\text{-}MC_{Cu^{II}N(L\text{-}tyrha)}\text{-}5](NO_3)_2(OH)(H_2O)_3$ ($C_{45}H_{59}Cu_5GdN_{12}O_{26}$) (1659.0): C 32.58, H 3.58, N 10.13; found: C 32.35, H 3.30, N 10.50; calcd (%) for $La^{III}[15\text{-}MC_{Cu^{II}N(L\text{-}leuha)}\text{-}5](NO_3)_3(H_2O)_9$ ($C_{30}H_{78}Cu_5LaN_{13}O_{28}$) (1525.6): C 23.62, H 5.15, N 11.94; found: C 23.32, H 4.76, N 11.54; calcd (%) for $La^{III}[15\text{-}MC_{Cu^{II}N(L\text{-}valha)}\text{-}5](NO_3)_2(OH)(H_2O)_4$ ($C_{25}H_{59}Cu_5LaN_{12}O_{21}$) (1525.6): C 22.74, H 4.50, N 12.73; found: C 22.40, H 4.48, N 12.68.

Characterization by ^{1}H NMR (300 MHz, D_2O): $La^{III}[15\text{-}MC_{Cu^{II}N(L\text{-}leuha)}\text{-}5]$: $\delta_H=1.22$ (s, 3H; CH_3), 0.17 (s, 3H; CH_3), 3.13 (s, 1H; $_\beta CH_2$), 1.81 (s, 1H;

$_{\beta}CH_2$), 15.92 (s, 1H; $_{\gamma}CH$), 33.38 ppm (s, 1H; $_{\alpha}CH$); La^{III}[15-$MC_{Cu^{II}N(L\text{-}valha)}$-5]: $\delta_H = 0.85$ (s, 3H; CH_3), 0.29 (s, 3H; CH_3), 15.44 (s, 1H; $_{\beta}CH$), 27.03 ppm (s, 1H; $_{\alpha}CH$).

Crystal structure determination: Purple, needlelike crystals of the [15]metallacrown-5 $\{Gd(NO_3)(H_2O)_2$[15-$MC_{Cu^{II}N(glyha)}$-5]$(NO_3)(H_2O)_4\}\cdot NO_3\cdot 5H_2O$ compound (**1**) were obtained by slow evaporation of an aqueous solution after synthesis. A single crystal was selected under the microscope and sealed in a thin-walled glass capillary. The quality of the crystal was checked by using film techniques and on a single-crystal X-ray diffractometer (Image Plate Diffraction System, IPDS II, STOE, Darmstadt). The same diffractometer was used to collect diffraction intensities ($Mo_{K\alpha}$ radiation). A numerical absorption correction was applied (program X-SHAPE[23]). Initial structure solutions were obtained by direct methods (program SHELXS-97[24]) and these were refined by using full-matrix least-squares procedures (program SHELXL-97[24]). Details of the structure solution process and crystal data are summarized in Table 2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined by using a riding model. No hydrogen atoms were refined for water molecules. CCDC 261084 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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