0.110; H atoms treated by a riding model; max. and min. residual electron densities were +0.550 and −0.453, respectively. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-55327. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Susceptibilities from a Pd-standard-calibrated Quantum Design MPMS5S SQUID, at a field of 0.1 T. The diamagnetic correction applied for **1** was $-5.32 \times 10^{-4}\ cm^3\ mol^{-1}$.

Received: January 9, 2001
Revised: October 4, 2001 [Z16393]

[1] D. Gatteschi, *Adv. Mater.* **1994**, *6*, 635.
[2] R. J. Bushby, J.-L. Paillaud in *An Introduction to Molecular Electronics* (Eds.: M. C. Petty, M. R. Bryce, D. Bloor) Edward Arnold, London, **1995**.
[3] a) M. A. Halcrow, G. Christou, *Chem. Rev.* **1994**, *94*, 2421; b) E. Jabri, M. B. Carr, R. P. Hausinger, P. A. Karplus, *Science* **1995**, *268*, 998.
[4] C. J. Matthews, K. Avery, Z. Xu, L. K. Thompson, L. Zhiao, D. O. Miller, K. Biradha, M. J. Zaworotko, C. Wilson, A. E. Goeta, J. A. K. Howard, *Inorg. Chem.* **1999**, *38*, 5266.
[5] a) A. Escuer, R. Vicente, S. B. Kumar, F. A. Mautner *J. Chem. Soc. Dalton. Trans.* **1998**, 3473. b) During preparation of this manuscript, the first mixed-magnetism Ni_4 cubane was reported: J. M. Clemente-Juan, B. Chansou, B. Donnadieu, J.-P. Tuchagues, *Inorg. Chem.* **2000**, *39*, 5515.
[6] J. M. Clemente-Juan, H. Andres, J. J. Borrás-Almenar, E. Coronado, H. U. Güdel, M. Aebersold, G. Kearly, H. Büttner, M. Zolliker, *J. Am. Chem. Soc.* **1999**, *121*, 10021.
[7] C. J. Gómez-García, J. J. Borrás-Almenar, E. Coronado, L. Ouahab, *Inorg. Chem.* **1994**, *33*, 4016.
[8] M. S. El Fallah, E. Rentschler, A. Caneschi, D. Gatteschi, *Inorg. Chim. Acta* **1996**, *247*, 231.
[9] Z. E. Serna, L. Lezama, M. K. Urtiaga, M. I. Arriortua, M. G. Barandika, R. Cortés, T. Rojo, *Angew. Chem.* **2000**, *112*, 352; *Angew. Chem. Int. Ed.* **2000**, *39*, 344.
[10] A. Escuer, M. Font-Bardía, S. J. Kumar, X. Solans, R. Vicente, *Polyhedron* **1999**, *18*, 909.
[11] F. Birkelbach, M. Winter, U. Flörke, H.-J. Haupt, C. Butzlaff, M. Lengen, E. Bill, A. A. X. Trautwein, K. Wieghardt, P. Chaudhuri, *Inorg. Chem.* **1994**, *33*, 3990.
[12] V. V. Pavlishchuk, S. V. Kolotilov, A. W. Addison, M. J. Prushan, R. J. Butcher, L. K. Thompson, *Inorg. Chem.* **1999**, *38*, 1759.
[13] In a strict "butterfly" geometry, the two "wings" are "beating" in-phase, and there is no center of symmetry; this "chair" structure might thus be considered an "out-of-phase butterfly".
[14] V. V. Pavlishchuk, S. V. Kolotilov, A. W. Addison, R. J. Butcher, E. Sinn, *J. Chem. Soc. Dalton Trans.* **2000**, 335.
[15] K. Kambe, *J. Phys. Soc. Jpn.* **1950**, *5*, 48.
[16] E. Sinn, *Coord. Chem. Rev.* **1970**, *5*, 313. Care is required in comparing *J* values: some authors use a "2*J*" exchange integral as here, while others use "*J*".
[17] J. H. van Vleck, *The Theory of Electric and Magnetic Susceptibilities*, Oxford University Press, Oxford, **1932**. ρ is the fraction of the nickel atoms present as paramagnetic impurity, while the other symbols have their usual meanings. $R^2 = \frac{\Sigma(\chi_{obs} - \chi_{calcd})^2}{\Sigma\chi^2_{obs}}$.
[18] J. K. McCusker, J. B. Vincent, E. A. Schmitt, M. L. Mino, K. Shin, D. K. Coggin, P. M. Hagen, J. C. Huffman, G. Christou, D. N. Hendrickson, *J. Am. Chem. Soc.* **1991**, *113*, 3012: $J_a \equiv J_{BW}$, $J_b \equiv J_{BB}$.
[19] R. D. Cannon, U. A. Jayasooriya, R. Wu, S. K. Arapkoske, J. A. Stride, O. F. Nielsen, R. P. White, G. J. Kearley, D. Summerfield, *J. Am. Chem. Soc.* **1994**, *116*, 11869.
[20] O. Kahn, *Molecular Magnetism*, VCH, Weinheim, **1993**.
[21] O. Kahn, *Chem. Phys. Lett.* **1997**, *265*, 109.
[22] K. K. Nanda, L. K. Thompson, J. N. Bridson, K. Nag, *J. Chem. Soc. Chem. Commun.* **1994**, 1337.
[23] M. A. Halcrow, J.-S. Sun, J. C. Huffman, G. Christou, *Inorg. Chem.* **1995**, *34*, 4167.

A Calix[4]arene Gd^{III} Complex Endowed with High Stability, Relaxivity, and Binding Affinity to Serum Albumin**

Silvio Aime, Alessandro Barge, Mauro Botta,* Alessandro Casnati,* Marco Fragai, Claudio Luchinat, and Rocco Ungaro

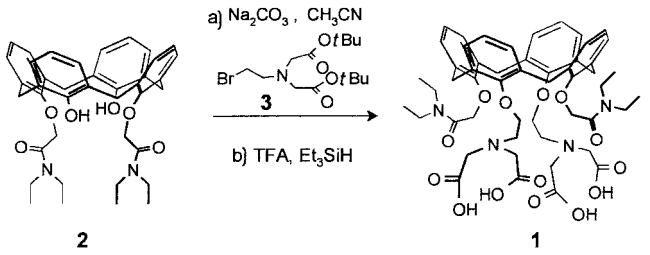
An interesting class of macrocyclic ligands uses calixarenes as a molecular platform. These ionophores[1] are characterized by high lipophilicity and have been mainly used as selective extractants or carriers of alkali,[2] alkaline earth,[3] lanthanide, and actinide metal ions.[4] The complexation of lanthanide ions by calix[4]arene ligands has also been studied with the purpose of developing new luminescent probes.[5] Very little is known on the use of calixarene lanthanide complexes as contrast agents for magnetic resonance imaging (MRI),[6] although this possibility has been envisaged[7] and a recent example has been reported.[8] To develop efficient systems for MRI the problem of water solubility and stability of the complexes has to be solved. Several years ago we reported the luminescent properties of lanthanide complexes of a calix[4]-arene tetraamide derivative in water.[9] However, the complexes were not very stable and after a short time the free ligand precipitated out of the solution. One efficient way to complex hard divalent and trivalent metal ions in water is to use aminopolycarboxylic acid derivatives.[10] Herein we report the synthesis of a new calix[4]arene-based ligand which presents two acetamide and two ethylenaminodicarboxy groups at the lower rim of the macrocycle, able to form complexes with Gd^{III} in water, these complexes are characterized by high values of relaxivity.[6]

The diamide tetraacid derivative **1** was synthesized in 45% overall yield, by alkylation of the diamide of calix[4]arene **2**[11] with Na_2CO_3 and 2-[*N*,*N*-bis(*tert*-butyloxycarbonylmethyl)-amino]-1-bromo-ethane (**3**)[12] in acetonitrile, followed by hydrolysis of *tert*-butyl esters using trifluoroacetic acid (TFA) and triethyl silane (Scheme 1). The ^1H NMR spectrum of **1** in CD_3OD, clearly show that the calixarene ligand is in the cone

[*] Prof. M. Botta
Dipartimento di Scienze e Tecnologie Avanzate
Università del Piemonte Orientale "Amedeo Avogadro"
Corso Borsalino 54, 15100 Alessandria (Italy)
Fax: (+39) 011-6707855
E-mail: botta@ch.unito.it
Prof. A. Casnati, Prof. R. Ungaro
Dipartimento di Chimica Organica e Industriale
Università di Parma
Parco Area delle Scienze 17/A, 43100 Parma (Italy)
Fax: (+39) 0521-905472
E-mail: casnati@ipruniv.cce.unipr.it
Prof. S. Aime, Dr. A. Barge
Dipartimento di Chimica I.F.M.
Università di Torino
Via P. Giuria 7, 10125 Torino (Italy)
Dr. M. Fragai, Prof. C. Luchinat
CERM, University of Florence
Via L. Sacconi 6, 50019 Sesto Fiorentino (Italy)

[**] This work was supported by CNR (Programma M.U.R.S.T. - Chimica Legge 95/95) "Agenti di contrasto, di shift e sonde luminescenti". We thank C.I.M. (Centro Interdipartimentale Misure) dell'Università di Parma for the NMR and mass spectroscopy facilities.

  1433-7851/01/4024-4737 $ 17.50+.50/0



Scheme 1.

conformation: two doublets ($\delta = 4.36$ and 3.25, $J = 13.1$ Hz) for the methylene protons bridging the aromatic nuclei.[13] This conformation also ensures that all potential binding groups are located on the same side of the macrocycle.

The [Gd^{III}(**1**)] complex has a relaxivity of 9.6 $mM^{-1}s^{-1}$ in water, at 20 MHz and 25 °C, which is constant in the pH range 4–9, which indicates that the structure of the complex is stable over a change in proton concentration of five orders of magnitude. This value is about two times higher than that of the monoaquo complexes $[Gd(dota)(H_2O)]^-$ and $[Gd(dtpa)(H_2O)]^{2-}$ (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, DTPA = diethylenetriaminepentaacetic acid) which suggest a higher hydration of the metal ion in our case.[14] The nuclear magnetic relaxation dispersion (NMRD) profile of [Gd^{III}(**1**)][15] (Figure 1),

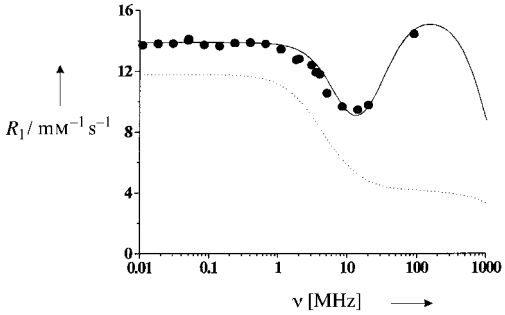


Figure 1. NMRD profile of [Gd^{III}(**1**)] in water at 25 °C and pH 6.8. The solid curve through the experimental data is the best-fit of the equations for inner- and outer-sphere paramagnetic relaxation. The lower dotted curve represents the calculated profile of the commercial MRI contrast agent $[Gd(dota)]^-$.[6a] ν = proton Larmor frequency, R_1 = longitudinal water-proton relaxivity.

confirms this hypothesis as the best fit of the data to the equations for the inner- and outer sphere relaxation yields a hydration number q of 3, a Gd–water protons separation r of 3.1 Å and a reorientational correlation time τ_R of about 150 ps.[16] Thus, the higher relaxivity of the complex compared to that of the commercial MRI contrast agents is because of a higher number of coordinated water molecules and a longer reorientational correlation time, a consequence of its higher molecular weight. This result implies that only two coordinating arms of the ligand are involved in the complexation of the metal ion. Enhanced relaxivities are observed when the reorientational motion of the paramagnetic complex is slowed down upon formation of noncovalent adducts with macromolecular substrates.[14, 17] MRI contrast agents with such a binding capability, in particular towards serum albumin, have been devised as blood-pool agents for angiographic applications.[18] An important requisite is a high thermodynamic (and/or kinetic) stability to ensure integrity of the complex upon binding to the protein and increased retention time in vivo. Our results represents an advance in the design of calixarene–Gd^{III}-based contrast agents with respect to a recently reported example in which the Gd^{III} complex has a stability constant of only $2 \times 10^5\ M^{-1}$.[8] From relaxometric competition experiments we measured a lower limit of the stability constant of $1 \times 10^{13}\ M^{-1}$ for [Gd^{III}(**1**)] in water at pH 6.8, a value sufficiently high to ensure the integrity of the complex in the presence of the protein, although not yet adequate for in vivo use. The binding interaction with human serum albumin (HSA) was investigated by titrating a solution (0.037 mmol L^{-1}) of [Gd^{III}(**1**)] with the protein at 25 °C and monitoring the increase of the proton solvent relaxation rate R_1 at 20 MHz (Figure 2). From the analysis of the data

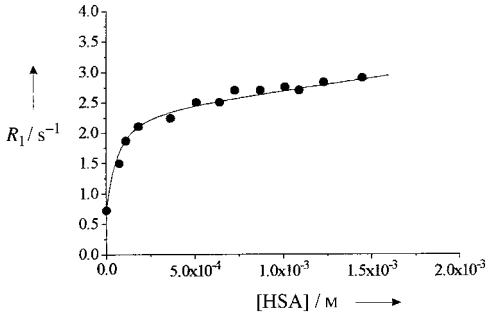


Figure 2. Relaxometric titration of a 0.037 mM solution of [Gd^{III}(**1**)] with HSA at 25 °C, pH 6.8, and 20 MHz. From the analysis of the data a relaxivity as high as 60 $mM^{-1}s^{-1}$ is calculated for the HSA bound adduct of the complex. Details of the general methods and instrumentation used are given in refs. [17b, c]; R_1 = longitudinal water-proton relaxation rate.

according to the equation of the proton relaxation enhancement (PRE),[17c] by assuming the presence of a single class of equivalent binding sites, we calculated an affinity constant K_A of $2.4 \times 10^4\ M^{-1}$ and an enhancement of six of the relaxivity of the macromolecular adduct over that of the free complex. The binding constant is in the upper range found for the noncovalent interaction of suitably functionalized DOTA and DTPA complexes to HSA.[17b, c] However, the NMRD profile of the complex in the presence of an excess of HSA (Figure 3) supports the view of the formation of a ternary complex involving the displacement of one or more coordinated water molecules by the protein, since a reasonable fitting of the data could only be obtained by considering a single coordinated water molecule.[19] In spite of the displacement of two water molecules by HSA, the relaxivity of the adduct reaches a peak of about 50 $mM^{-1}s^{-1}$ at 30 MHz. Interestingly, the calculated value of the residence lifetime τ_M for the coordinated water, approximately 40 ns, is considerably shorter (300 ns) than those for the clinically used MRI contrast agents $[Gd(dtpa)]^{2-}$ and $[Gd(dota)]^-$. This value is near optimal for attaining maximum relaxivities for macromolecular Gd^{III} complexes.[17c] An involvement of the donor groups on the surface of the protein in the coordination of the Gd^{III} ion has been recently reported for a Gd^{III} complex with a functionalized DO3A ligand (DO3A = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid.[20]

  1433-7851/01/4024-4738 $ 17.50+.50/0

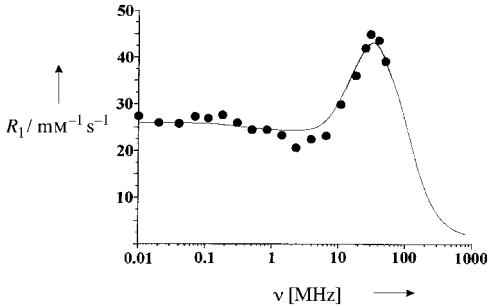


Figure 3. NMRD profile of the [Gd^{III}(**1**)] – HSA adduct 25 °C. The best-fit curve was calculated with the parameters: $\Delta = 0.023$ cm^{-1}, $\tau_R = 1.75$ ns, $\tau_V =$ 12 ps, D(ZFS) = 0.24 cm^{-1}, $\tau_M = 38$ ns, $q = 1$, $r = 3.1$ Å;[19] ν = proton Larmor frequency, R_1 = longitudinal water-proton relaxivity, τ_V = correlation time for electron relaxation, D(ZFS) = static zero-field splitting.

To surmise, the high binding affinity of [Gd^{III}(**1**)] to HSA is the result of a cooperative effect of the hydrophobic interaction brought about by the aromatic macrocyclic moiety and of the coordination of donor groups of the protein (probably Asp or Glu). These preliminary results augurs well for the development of a new class of stable, water soluble MRI contrast agents of enhanced efficacy (Gd^{III} complexes) and luminescent probes (Eu^{III}/Tb^{III} complexes) for biomedical studies.

Experimental Section

Melting points were determined with an electrothermal melting point apparatus in a capillary sealed under nitrogen. ^{1}H NMR spectra were recorded with a Bruker AC 300 spectrometer. Mass spectra were obtained either with a Finnigan MAT SSQ710 spectrometer (desorption chemical ionization (DCI) using methane as ionizing gas) or with a ZMD MICROMASS spectrometer (electrospray ionization (ESI) methanol/dichloromethane = 9/1). All solvents were purified with standard procedures; dry solvents were obtained by literature methods and stored over molecular sieves.

Synthesis of the *tert*-butyl ester of **1**: Na_2CO_3 (15 mL; 0.65 g, 6.15 mmol) and compound **3** (0.32 g, 0.92 mmol) were added under nitrogen atmosphere to a stirred solution of diamide **2** (0.20 g, 0.31 mmol) in dry acetonitrile. After 14 h reflux, the solvent was removed under vacuum and 1N HCl (20 mL) added. The water layer was then extracted with AcOEt (Ac = acetyl), and the organic phase washed twice with water. The tetra-*tert*-butyl ester of **1** was obtained by removing the solvent under vacuum. Yield = 51 %; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 6.60 - 6.54$ (m, 12H; ArH), 4.69 (s, 4H; OCH_2CO), 4.65 (d, $J = 13.6$ Hz, 4H; ArCH_2Ar ax), 4.12 (t, $J = 7.1$ Hz, 4H; OCH_2CH_2N), 3.45 (s, 8H; NCH_2CO), 3.40 – 3.27 (m, 8H; NCH_2CH_3), 3.25 (t, $J = 7.1$ Hz, 4H; OCH_2CH_2N), 3.17 (d, $J =$ 13.6 Hz, 4H; ArCH_2Ar eq), 1.42 (s, 36H; CCH_3), 1.16 – 1.08 (m, 12H; NCH_2CH_3); CI-MS m/z: 1193.8 [$(M+H)^+$].

1: Trifluoroacetic acid (5.9 mL, 62.90 mmol) was added to a solution of the tetra-*tert*-butyl ester of **1** (0.50 g, 0.42 mmol) and triethyl silane (3.3 mL, 20.96 mmol) dissolved in of dry CH_2Cl_2 (10 mL). After stirring at room temperature for 14 h, the solvent was removed under vacuum. Product **1** was obtained by precipitation with Et_2O from the CH_2Cl_2 solution. Yield = 90 %; m.p. 140 – 142 °C; ^{1}H NMR (300 MHz, CD_3OD, 25 °C, TMS) $\delta = 7.17$ (d, $J = 7.4$ Hz, 4H; ArH), 6.97 (t, $J = 7.4$ Hz, 2H; ArH), 6.28 (s, 6H; ArH), 4.54 – 4.51 (m, 8H; OCH_2CO, OCH_2CH_2N), 4.36 (d, $J = 13.1$ Hz, 4H; ArCH_2Ar ax), 4.22 – 4.12 (m, 12H; NCH_2COOH, OCH_2CH_2N), 3.51 – 3.44 (m, 4H; NCH_2CH_3), 3.25 (d, $J = 13.1$ Hz, 4H; ArCH_2Ar eq), 3.30 – 3.21 (m, 4H; NCH_2CH_3), 1.21 – 1.13 (m, 12H; NCH_2CH_3); ESI-MS m/z: 969.8 [$(M+H)]^+$.

Received: August 28, 2001 [Z17811]

[1] a) R. Ungaro, A. Pochini in *Calixarenes, a Versatile Class of Macrocyclic Compounds* (Eds.: J. Vicens, V. Böhmer), Kluwer, Dordrecht, **1991**, p. 127; b) M. A. McKervey, M.-J. Schwing in *Calixarenes, a Versatile Class of Macrocyclic Compounds* (Eds.: J. Vicens, V. Böhmer), Kluwer, Dordrecht, **1991**, p. 149; c) M. A. McKervey, M.-J. Schwing-Weill, F. Arnaud-Neu in *Comprehensive Supramolecular Chemistry*, *Vol. 1* (Ed.: F. Vögtle), Pergamon, Oxford, **1996**, p. 537; d) A. Casnati, R. Ungaro in *Calixarenes in Action* (Eds.: L. Mandolini, R. Ungaro), Imperial College Press, London, **2000**, p. 62.

[2] a) R. Ungaro, A. Casnati, F. Ugozzoli, A. Pochini, J.-F. Dozol, C. Hill, H. Rouquette, *Angew. Chem.* **1994**, *106*, 1551; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1506; b) C. Hill, J.-F. Dozol, V. Lamare, H. Rouquette, B. Tournois, J. Vicens, Z. Asfari, R. Ungaro, A. Casnati, *J. Inclusion Phenom.* **1994**, *19*, 399; c) A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M.-J. Schwing, R. J. M. Egberink, F. de Jong, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, *117*, 2767.

[3] a) J.-F. Dozol, H. Rouquette, R. Ungaro, A. Casnati, Patent FR 93-4566, 930419, **1993**; WO 94-FR432 940418, **1994** [*Chem. Abstr.* **1995**, *122*, 239730]; b) A. Casnati, L. Baldini, N. Pelizzi, K. Rissanen, F. Ugozzoli, R. Ungaro, *J. Chem. Soc. Dalton Trans.* **2000**, 3411; c) G. Arena, A. Contino, A. Magrì, D. Sciotto, J. D. Lamb, *Supramol. Chem.* **1999**, *10*, 5.

[4] a) L. H. Delmau, N. Simon, M. J. Schwing-Weill, F. Arnaud-Neu, J. F. Dozol, S. Eymard, B. Tournois, V. Böhmer, C. Gruttner, C. Musigmann, A. Tunayar, *Chem. Commun.* **1998**, 1627; b) S. Barboso, A. G. Carrera, S. E. Matthews, F. Arnaud-Neu, V. Böhmer, J. F. Dozol, H. Rouquette, M. J. Schwing-Weill, *J. Chem. Soc. Perkin Trans. 2* **1999**, 719; c) A. Arduini, V. Bohmer, L. Delmau, J. F. Desreux, J. F. Dozol, M. A. G. Carrera, B. Lambert, C. Musigmann, A. Pochini, A. Shivanyuk, F. Ugozzoli, *Chem. Eur. J.* **2000**, *6*, 2135.

[5] a) F. J. Steemers, H. G. Meuris, W. Verboom, D. N. Reinhoudt, E. B. van der Tol, J. W. Verhoeven, *J. Org. Chem.* **1997**, *62*, 4229; b) G. Ulrich, R. Ziessel, I. Manet, M. Guardigli, N. Sabbatini, F. Fraternali, G. Wipff, *Chem. Eur. J.* **1997**, *3*, 1815; c) L. Prodi, S. Pivari, F. Bolletta, M. Hissler, R. Ziessel, *Eur. J. Inorg. Chem.* **1998**, 1959; C. Fischer, G. Sarti, A. Casnati, B. Carrettoni, I. Manet, R. Schuurman, M. Guardigli, N. Sabbatini, R. Ungaro, *Chem. Eur. J.* **2000**, *6*, 1026.

[6] a) S. Aime, M. Botta, M. Fasano, E. Terreno, *Chem. Soc. Rev.* **1998**, *27*, 19; b) D. Parker, J. A. G. Williams, *J. Chem. Soc. Dalton Trans.* **1996**, 3613.

[7] a) E. M. Georgiev, D. M. Roundhill, *Inorg. Chim. Acta* **1997**, *258*, 93; b) A. M. Krishnan, R. Lohrmann, WO 95-US14801 [WO 96/14878 A2], **1996** [*Chem. Abstr.* **1995**, *125*, 109099].

[8] L. H. Bryant, Jr., A. T. Yordanov, J. J. Linnoila, M. W. Brechbiel, J. A. Frank, *Angew. Chem.* **2000**, *112*, 1686; *Angew. Chem. Int. Ed.* **2000**, *39*, 1641.

[9] N. Sabbatini, M. Guardigli, A. Mecati, V. Balzani, R. Ungaro, E. Ghidini, A. Casnati, A. Pochini, *J. Chem. Soc. Chem. Commun.* **1990**, 878.

[10] A. Bianchi, L. Calabi, F. Corana, S. Fontana, P. Losi, A. Maiocchi, L. Paleari, B. Valtancoli, *Coord. Chem. Rev.* **2000**, *204*, 309.

[11] A. Casnati, C. Fischer, M. Guardigli, A. Isernia, I. Manet, N. Sabbatini, R. Ungaro, *J. Chem. Soc. Perkin Trans. 2* **1996**, 395.

[12] M. A. Wiliams, H. Rapoport, *J. Org. Chem.* **1993**, *58*, 1151.

[13] C. D. Gutsche, L. J. Bauer, *J. Am. Chem. Soc.* **1985**, *107*, 6052.

[14] a) P. Caravan, J. J. Ellison, T. J. McMurry, R. B. Lauffer, *Chem. Rev.* **1999**, *99*, 2293; b) R. B. Lauffer, *Chem. Rev.* **1987**, *87*, 901; c) S. Aime, M. Botta, M. Fasano, E. Terreno, *Acc. Chem. Res.* **1999**, *32*, 941.

[15] a) S. H. Koenig, R. D. Brown III, *Prog. NMR Spectrosc.* **1990**, *22*, 487; b) C. Luchinat, *Magn. Reson. Chem.* **1993**, *31*, S145.

[16] a) L. Banci, I. Bertini, C. Luchinat in *Nuclear and Electron Relaxation*, VCH, Weinheim, **1991**; b) É. Tóth, L. Helm, A. E. Merbach in *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging* (Eds.: É. Tóth, A. E. Merbach), Wiley, Chichester, **2001**, p. 45.

[17] a) S. Aime, M. Botta, M. Fasano, S. Geninatti Crich, E. Terreno, *Coord. Chem. Rev.* **1999**, *185 – 186*, 321; b) S. Aime, M. Botta, M. Fasano, S. Geninatti Crich, E. Terreno, *J. Biol. Inorg. Chem.* **1996**, *1*, 312; c) S. Aime, M. Botta, M. Fasano, E. Terreno in *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging* (Eds.: É. Tóth, A. E. Merbach), Wiley, Chichester, **2001**, p. 193.

[18] P. A. Rink, *Magnetic Resonance in Medicine*, Blackwell, Oxford, **1993**.

[19] I. Bertini, O. Galas, C. Luchinat, G. Parigi, *J. Magn. Reson. A* **1995**, *113*, 151.

[20] S. Aime, E. Gianolio, E.Terreno, G. B. Giovenzana, R. Pagliarin, M. Sisti, G. Palmisano, M. Botta, M. P. Lowe, D. Parker, *J. Biol. Inorg. Chem.* **2000**, *5*, 488.

  1433-7851/01/4024-4739 $ 17.50+.50/0