616 *Inorg. Chem.* **2010**, *49*, 616–625
DOI: 10.1021/ic901848p

Inorganic Chemistry
Article

Dramatic Increase of Selectivity for Heavy Lanthanide(III) Cations by Tuning the Flexibility of Polydentate Chelators

Lorenzo Tei,[†] Zsolt Baranyai,[‡] Ernő Brücher,[‡] Claudio Cassino,[†] Fabio Demicheli,[†] Norberto Masciocchi,[§] Giovanni B. Giovenzana,[∥] and Mauro Botta*[,†]

[†]*Dipartimento di Scienze dell'Ambiente e della Vita, Università del Piemonte Orientale "A. Avogadro", Viale T. Michel 11, I-15121, Alessandria, Italy,* [‡]*Department of Inorganic and Analytical Chemistry, University of Debrecen, H-4010 Debrecen, P.O. Box 21, Hungary,* [§]*Dipartimento di Scienze Chimiche e Ambientali, Università degli Studi dell'Insubria, Via Valleggio 11, I-22100, Como, Italy, and* [∥]*DISCAFF and DFB Center, Università del Piemonte Orientale "A. Avogadro", Via Bovio 6, 28100 Novara, Italy*

Received September 18, 2009

Two novel octadentate ligands have been synthesized by attaching two terminal iminodiacetic groups to either 1,4-diazepane (BCAED) or piperazine (BCAEP) as central scaffold. The introduction of the seven- or six-membered ring into the ligand backbone is expected to modify their overall flexibility and then to affect the stability of the corresponding lanthanide(III) complexes. In this work, thermodynamic stability data are determined for the formation of the complexes of BCAED and BCAEP with La^{3+}, Nd^{3+}, Eu^{3+}, Gd^{3+}, Ho^{3+}, and Lu^{3+}. The ligand BCAED shows a strong binding affinity for Lu^{3+} (log*K*=20.99), moderate for Gd^{3+} (log*K*=17.15) and rather weak for La^{3+} (log*K*=12.77). Thus, the variation of log*K* across the Ln series assumes the remarkable value of 8.22, the largest so far reported. This points to a predominant role of a suitable size match between the metal ion and the ligand cavity, determined by its structure and flexibility. The ligand BCAEP forms less stable complexes with lanthanide(III) cations although it retains a good selectivity ($\Delta\log K_{La-Lu}$=5.66). The Gd(III) complexes have been investigated in aqueous solution by measuring their relaxivity as a function of pH, at 20 MHz and 25 °C. The results can be interpreted very well in terms of the species distribution curves calculated from the thermodynamic data and indicate that in these complexes Gd^{3+} is octacoordinated, without any bound water molecule. This coordination geometry is maintained in the solid state as shown by the X-ray crystal structure of $[Na(H_2O)_2][Gd(BCAED)]$ where the metal ion is at the center of a bicapped-trigonal prism. Finally, the ^{13}C NMR spectra (9.4 T, 25 °C) of the diamagnetic La^{3+}, Y^{3+}, and Lu^{3+} complexes show that a pronounced stereochemical rigidity is associated with the thermodynamically more stable complexes.

Introduction

The separation of individual lanthanides from each other is made difficult by the small differences in their physical and chemical properties.[1] The general separation procedures are based on the exploitation of the small modification of chemical properties associated with the well-known phenomenon of lanthanide contraction, that is, the steady decrease in the size of the trivalent cations with increasing atomic number from lanthanum (1.061 Å) through lutetium (0.850 Å).[2] Owing to the important role played by lanthanides in a variety of applications ranging from biomedicine (i.e., Magnetic Resonance Imaging (MRI) contrast agents, radioisotope labeling, antisense technology) to high-tech devices (i.e., luminescent sensors, molecular light-converters), the design of ligands able to selectively coordinate a given trivalent cation of the lanthanide series represents a relevant objective of the current research in coordination chemistry.[3,4] Several macrocyclic platforms functionalized with various pendant arms have been used to discriminate lanthanide(III) ions: crown ethers,[5] diazapolyoxocycloalkanes,[5,6]

*To whom correspondence should be addressed. E-mail: mauro.botta@mfn.unipmn.it. Phone: +39 0131360253. Fax: +39 0131360250.

(1) Nash, K. L.; Jensen M. P. In *Handbook on the Physics and Chemistry of Rare Earths*; Gschneidner, J. K. A., Eyring L., Eds.; Elsevier: Amsterdam, 2000; Vol. *28*, pp 311−371.
(2) Seitz, M.; Oliver, A. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 11153–11160.
(3) Bunzli, J.-C. G.; Choppin, G. R. In *Lanthanide Probed in Life, Chemical and Earth Sciences*; Bunzli, J.-C. G., Choppin G. R., Eds.; Elsevier: Amsterdam, 1989.
(4) (a) Piguet, C.; Bunzli, J.-C. G. *Chem. Soc. Rev.* **1999**, *28*, 347–358. (b) Floquet, S.; Borkovec, M.; Bernardinelli, G.; Pinto, A.; Leuthold, L.-A.; Hopfgartner, G.; Imbert, D.; Bunzli, J.-C. G.; Piguet, V. *Chem.—Eur. J.* **2004**, *10*, 1091–1105.
(5) (a) Gokel, G. W.; Korzeniowski, S. H. *Macrocyclic Polyether Synthesis*; Springer: Berlin, 1982. (b) Gokel, G. W. *Crown Ethers and Cryptands*; Royal Society of Chemistry: Cambridge, 1990. (c) Liu, Y.; Han, B.-H.; Li, Y.-M.; Chen, R.-T.; Ouchi, M.; Inoue, Y. *J. Chem. Phys.* **1996**, *100*, 17361–17364.
(6) (a) Cathala, B.; Picard, L.; Cazauxa, C.; Tisnes, P.; Momtchev, M. *Tetrahedron* **1995**, *51*, 1245–1252. (b) Chang, C. A.; Chang, P. H. L.; Manchanda, V. K.; Kasprzyk, S. P. *Inorg. Chem.* **1988**, *27*, 3786–3789.

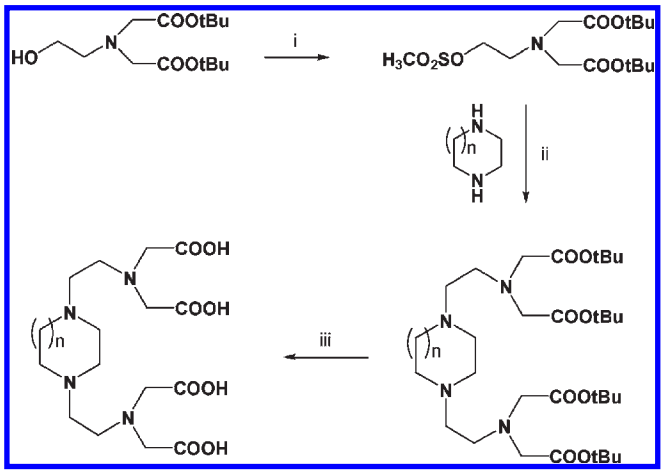
 Published on Web 12/09/2009 © 2009 American Chemical Society

polyazacycloalkanes,[7] and calixarenes.[8] As a general result, it has been found that the stability can be slightly improved by adjusting the ring size, the number of donor atoms, and the number of pendant arms of the ligand. The best match between these structural properties of the chelator and the ionic radius of the Ln(III) ion determines the stability of the complex. Since the chemistry of Ln(III) cations in aqueous media is dominated by their oxophilicity, most ligands studied contain carboxylate or phosphonate groups as O-donors.[9,10] Although amines alone are poor donors for lanthanides in water, when incorporated into aminocarboxylates or aminophosphonates chelators they contribute to form quite stable Ln(III) complexes. In fact, the N-donor atom coordination takes place after that of the anionic oxygen atoms that initially disrupt the hydration sphere of the metal ion and allow the anchoring of the ligand.[9]

The trends in the stability constants of Ln(III) complexes with polydentate ligands can be divided qualitatively into three types. For the first type, the stability constants (log$K$) regularly increase with the increase of the atomic number of the Ln^{3+} ions, as expected on the basis of the simple electrostatic interaction between the Ln^{3+} ions and the donor atoms.[11] The ligands in the second group form complexes for which the log$K$ values increase from La^{3+} to the middle of the series whereas the heavier Ln^{3+} ions form complexes of similar stability.[12] The log$K$ values of complexes formed with the third type of ligands show a maximum with the increase of the atomic number.[13,14,30] For example, the ligands EDTA and DOTA belong to the first group, and the increase in the log$K$ values from La^{3+} to Lu^{3+} are 4.8 and 2.7 log$K$ units, respectively (H_4EDTA = ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid, H_4DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid).[15] However, in most cases the difference in stability constants is not enough to guarantee discrimination between neighboring lanthanide cations.

In the search for new and efficient contrast agents for MRI, we previously reported a systematic investigation of the solution structure and dynamics and relaxation properties on the Ln(III) complexes of the simple acyclic ligand EGTA (H_4EGTA = ethylene glycol-bis(2-aminoethylether)- *N*,*N*,*N*′,*N*′-tetraacetic acid) and of its derivatives containing an aromatic moiety into the ligand backbone.[16,17] In the case both of EGTA and of its more rigid derivatives the increase in the stability constants across the series was rather small (i.e., $\log K_{LuL} - \log K_{LaL} = \Delta\log K_{La-Lu} = 2.26$ for EGTA), likely because of the flexibility of the ligand which can easily adapt to Ln(III) ions of different size. Although the EGTA platform exhibits a poor selectivity toward Ln(III) ions, we designed two novel octadentate polyaminocarboxylate ligands that can be considered as derivatives of EGTA by substitution of the 1,2-ethylenedioxy bridge with 1,4-diazacycloalkanes. The novel ligands present four nitrogen- and four oxygen-donor atoms and combine structural features of both linear and cyclic moieties which could enhance their selectivity. In fact, we used the six and seven-membered heterocycles piperazine and 1,4-diazepane as central scaffolds, which can impart a rigid[18] and hindered structure to the Ln(III) complexes,[19] and two linear *N*,*N*-bis(carboxymethyl)aminoethyl acid moieties attached to the heterocyclic nitrogen atoms, which represent the flexible part of the chelator favoring the encapsulation of the Ln(III) ion.

Scheme 1. Synthesis of BCAEP (n = 1) and BCAED (n = 2): (i) CH_3SO_2Cl, Et_3N, AcOEt; (ii) AcOEt, NEt_3; (iii) TFA, CH_2Cl_2 (1:1, v/v)



In this work we report the synthesis of the two new ligands, shown in Scheme 1, BCAED (H_4BCAED = *N*,*N*′-{2-[bis(carboxymethyl)amino]-ethyl}-1,4-diazepane) and BCAEP (H_4BCAEP = *N*,*N*′-{2-[bis(carboxymethyl)amino]-ethyl}-piperazine), their protonation constants, and the thermodynamic stability constants of the corresponding Mg(II), Ca(II), La(III), Nd(III), Eu(III), Gd(III), Ho(III), and Lu(III) complexes as determined by pH potentiometry. The crystal structure of $[Na(H_2O)_2][Gd(BCAED)]$ and a proton NMR relaxometric study on the Gd(III) complexes of BCAED and BCAEP in aqueous solution are also reported. Finally, information on solution structure and dynamics of the La(III), Y(III), and Lu(III) complexes were obtained by variable temperature ^{1}H and ^{13}C NMR in D_2O solution.

Experimental Section

All chemicals were purchased from Sigma-Aldrich Srl (Milan, Italy) and were used without purification. Mass spectra were recorded with a Waters Micromass ZQ single-quadrupole instrument equipped with an electrospray ionization source. *N*,*N*-bis(*tert*-butoxycarbonylmethyl)ethanolamine was prepared following the reported procedures.[20]

(7) (a) Clarke, T. E.; Martell, A. E. *Inorg. Chim. Acta* **1991**, *190*, 37–46. (b) Song, B.; Storr, T.; Liu, S.; Orvig, C. *Inorg. Chem.* **2002**, *41*, 685–692.
(8) Ludwig, V.; Dzung, N. T. K. *Sensors* **2002**, *2*, 397–416.
(9) Choppin, G. R. *Pure Appl. Chem.* **1971**, *27*, 23–41.
(10) Moeller, T. In *The Lanthanides*; Moeller, T., Ed.; Pergamon: Oxford, 1973; Vol. *4*, p 1.
(11) (a) Caravan, P.; Hedlund, T.; Liu, S.; Sjoberg, S.; Orvig, C. *J. Am. Chem. Soc.* **1995**, *117*, 11230–11238. (b) Chapon, D.; Morel, J.-P.; Delangle, P.; Gateau, C.; Pecaut, J. *Dalton Trans.* **2003**, 2745–2749.
(12) Sarka, L.; Banyai, I.; Brucher, E.; Kiraly, R.; Platzek, J.; Raduchel, B.; Schmitt-Willich, H. *J. Chem. Soc., Dalton Trans.* **2000**, 3699–3703.
(13) Roca-Sabio, A.; Mato-Iglesias, M.; Esteban-Gomez, D.; Toth, E.; de Blas, A.; Platas-Iglesias, C.; Rodriguez-Blas, T. *J. Am. Chem. Soc.* **2009**, *131*, 3331–3341.
(14) (a) Chang, C. A.; Rowland, M. E. *Inorg. Chem.* **1983**, *22*, 3866–3869. (b) Brucher, E.; Gyori, B.; Emri, J.; Solymosi, P.; Sztanyik, L. B.; Varga, L. *J. Chem. Soc., Chem. Commun.* **1993**, 574–575.
(15) Moeller, T.; Martin, D. F.; Thompson, L. C.; Ferrus, R.; Feistel, G. R.; Randall, W. *J. Chem. Rev.* **1965**, *65*, 1–50.
(16) Aime, S.; Barge, A.; Borel, A.; Botta, M.; Chemerisov, S.; Merbach, A. E.; Müller, U.; Pubanz, D. *Inorg. Chem.* **1997**, *36*, 5104–5112.
(17) Tei, L.; Baranyai, Z.; Botta, M.; Piscopo, L.; Aime, S.; Giovenzana, G. B. *Org. Biomol. Chem.* **2008**, *6*, 2361–2368.
(18) (a) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1–8. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms,* 3rd ed.; Plenum Press: New York, 1990; pp 141−150.
(19) Lázár, I.; Egri, A.; Király, R.; Baranyai, Z.; Iványi, T.; Brücher, E. *Eur. J. Org. Chem.* **2002**, 351–360.
(20) Williams, M. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1151–1158.

***N,N′*-{2-[bis(*tert*-butoxycarbonylmethyl)amino]-ethyl}-1,4-diazepane (2).** Methanesulfonyl chloride (3 mL, 38 mmol) was added dropwise in 30 min to a cooled (−10 °C) solution of *N, N*-bis(*tert*-butoxycarbonylmethyl)ethanolamine (10 g, 35 mmol) and NEt_3 (5.8 mL, 42 mmol) in ethylacetate (40 mL). The mixture was stirred at 0 °C for 1 h and then filtered. The precipitate was washed with cold ethylacetate (20 mL), and the filtrate *N,N*-bis(*tert*-butoxycarbonylmethyl)-2-aminoethyl methanesulfonate (**1**) was used in the successive step without further purification. TLC, silica gel: ethylacetate/MeOH/NH_3 95:5:0.5, R_f = 0.6. 1,4-Diazepane (15 g, 15 mmol) was added portion wise to the solution of the intermediate **1** and Et_3N (5.8 mL, 42 mmol). The reaction was stirred at 50 °C for 20 h, and then the solvent was removed by evaporation in vacuo to obtain a reddish oil which was purified by silica gel column chromatography (ethyl acetate/MeOH/NH_3 9:1:0.1, R_f = 0.8). The final product was obtained as a colorless oil (11.4 g, 18 mmol, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.40 (s, CH_2-COO*t*Bu, 8H), 2.76 (t, J = 6.8 Hz, $N_{Ring}CH_2CH_2N_{Arm}$, 4H), 2.65 (m, CH_2N_{Ring}, 8H), 2.58 (t, J = 6.8 Hz, $N_{Ring}CH_2CH_2N_{Arm}$, 4H), 1.70 (q, J = 5.3 Hz, $CH_2CH_2CH_2$, 2H), 1.39 (s, $C(CH_3)_3$, 36H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 170.7 ($C_{carboxylate}$, 4C), 80.8 ($C(CH_3)_3$, 4C), 56.9, 56.3, 55.3, 54.5, 51.6 (CH_2N 12C), 28.1 ($C(CH_3)_3$, 12C), 27.2 ($CH_2CH_2CH_2$, 1C). MS (ESI$^+$): *m*/*z*: calcd for $C_{33}H_{66}N_4O_8$ $[M + H]^+$: 642.46; found: 642.87.

***N,N′*-{2-[bis(carboxymethyl)amino]-ethyl}-1,4-diazepane (BCAED).** Trifluoroacetic acid (10 mL) was added to a solution of **2** (11 g, 18 mmol) in $CHCl_3$ (10 mL). The solution was stirred at room temperature overnight and then evaporated in vacuo. The product was taken up with excess diethyl ether, isolated by centrifugation, washed thoroughly with diethyl ether (3 × 15 mL) obtaining a white solid (4.5 g, 11.3 mmol, 90% yield). ^{1}H NMR (D_2O, 400 MHz) δ = 3.81 (s, CH_2COOH, 8H), 3.48 (t, J = 5.8 Hz, $N_{Arm}CH_2$, 4H), 3.35 (s, $N_{Ring}CH_2CH_2N_{Ring}$, 4H), 3.29 (t, J = 6.0 Hz, $N_{Ring}CH_2$, 4H), 3.25 (t, J = 5.8 Hz, $N_{Arm}CH_2CH_2N_{Ring}$, 4H), 2.16 (q, J = 6.0 Hz, $CH_2CH_2CH_2$, 2H); ^{13}C NMR (D_2O, 100 MHz) δ = 173.2 ($C_{carboxylate}$, 4C), 56.9 (CH_2COO, 4H), 54.0, 50.9, 50.7, 49.0 (CH_2N, 8C), 22.0 ($CH_2CH_2CH_2$, 1C). MS (ESI$^+$): *m*/*z*: calcd for $C_{17}H_{30}N_4O_8$ $[M + H]^+$: 418.21; found: 418.44.

***N,N′*-{2-[bis(*tert*-butoxycarbonylmethyl)amino]-ethyl}-piperazine(3).** Piperazine (1.2 g, 14 mmol) was added portion wise to the solution of the intermediate **1** and Et_3N (6 mL, 42 mmol). The reaction was stirred at 50 °C for 20 h, and then the solvent was evaporated in vacuo to obtain a reddish oil which was suspended in H_2O and extracted in CH_2Cl_2 (3 × 20 mL). The collected organic phases were dried over Na_2SO_4, filtered, and evaporated in vacuo. The pale yellow oil obtained was purified by silica gel column chromatography (ethyl acetate/MeOH/NH_3 95:5:0.05, R_f = 0.5) to yield the final product as a colorless oil (11.7 g, 18 mmol, 69% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.47 (s, $CH_2COOtBu$, 8H), 2.84 (t, J = 6.9 Hz, $N_{Ring}CH_2$-CH_2N_{Arm}, 4H), 2.49 (t, J = 6.9 Hz, $N_{Ring}CH_2CH_2N_{Arm}$, 4H), 2.47 (s, CH_2N_{Ring}, 8H), 1.44 (s, $C(CH_3)_3$, 36H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 170.8 ($C_{carboxylate}$, 4C), 81.0 ($C(CH_3)_3$, 4C), 57.1, 56.5, 53.3, 50.8 (CH_2N 12C), 28.2 ($C(CH_3)_3$, 12C). MS (ESI$^+$): *m*/*z*: calcd for $C_{32}H_{64}N_4O_8$ $[M + H]^+$: 630.46; found: 630.86.

***N,N′*-{2-[bis(carboxymethyl)amino]-ethyl}-piperazine (BCAEP).** Trifluoroacetic acid (10 mL) was added to a solution of **3** (11 g, 17 mmol) in $CHCl_3$ (6 mL). The solution was stirred at room temperature overnight and then evaporated in vacuo. The product was dissolved in CH_3CN (2 mL) and precipitated with excess diethyl ether, isolated by centrifugation, and washed thoroughly with diethyl ether (3 × 15 mL). A white amorphous solid was obtained after drying in vacuo (4.3 g, 10.6 mmol, 92% yield). ^{1}H NMR (D_2O, 400 MHz) δ = 3.62 (s, CH_2COOH, 8H), 3.26 (t, J = 5.7 Hz, $N_{Ring}CH_2CH_2N_{Arm}$, 4H), 3.13 (s, CH_2N_{Ring}, 8H), 3.06 (t, J = 5.7 Hz, $N_{Ring}CH_2CH_2N_{Arm}$, 4H); ^{13}C NMR (D_2O, 100 MHz) δ = 174.5 ($C_{carboxylate}$, 4C), 58.0 (CH_2COO, 4H), 52.4, 50.8 (CH_2 arm, 4C), 51.0 (NCH_2 ring, 4C). MS (ESI$^+$): *m*/*z*: calcd for $C_{16}H_{28}N_4O_8$ $[M + H]^+$: 404.19; found: 404.42.

Synthesis of Ln(III)BCAED Complexes. $Ln(NO_3)_3 \cdot 6H_2O$ (0.05 mmol) was added in small portions to an aqueous solution (0.5 mL, pH = 6) of BCAED (21 mg, 0.05 mmol) under magnetic stirring. After 2 h reaction, the solution was filtered and lyophilized to obtain a white powder.

[La(BCAED)]$^-$. ^{1}H NMR (D_2O, 400 MHz) δ = 3.66 (m, H5, H6, H7, H8, H9 H12, 6H), 3.53 (m, H15, H17, 2H), 3.29 (m, H10, H11, 2H), 3.05 (m, H13, H14, 2H), 2.90 (m, H13′, H14′, 2H), 2.82 (m, H9′, H10′, H11′, H12′, H15′, H17′, 6H), 2.35 (m, H16, 1H), 2.28 (m, H16′, 1H). ^{13}C NMR (D_2O, 100 MHz) δ = 180.4, 179.6 (C1, C2, C3,C4), 61.7, 60.8 (C5, C6, C7, C8), 56.7 (C13, C14), 56.2 (C15, C17), 54.3 (C10, C11), 49.8 (C9, C12), 23.2 C16). MS (ESI$^-$): *m*/*z*: calcd for $C_{17}H_{26}LaN_4O_8$ $[M]^-$: 553.33; found: 553.43.

[Y(BCAED)]$^-$. ^{1}H NMR (D_2O, 400 MHz) δ = 3.77−3.32 (m, H5, H6, H7, H8, H10 H12, 6H), 3.15 (m, H9, H11, H17, H17′, 4H), 2.99 (m, H13, 1H), 2.68 (m, H9′, H10′, H12′, H13′, H14, 5H), 2.57 (m, H11′, H14′, H15, H15′, 4H), 2.19 (m, H16, 1H), 1.84 (m, H16′, 1H). ^{13}C NMR (D_2O, 100 MHz) δ = 181.9, 180.8, 180.7, 180.4 (C1, C2, C3,C4), 64.0, 63.8, 63.0, 62.8 (C5, C6, C7, C8), 58.0 (C11), 57.0 (C13), 56.8 (C14), 55.8 (C17), 55.6 (C15), 55.3 (C10), 49.8 (C12), 47.4 (C9), 23.2 (C16). MS (ESI$^-$): *m*/*z*: calcd for $C_{17}H_{26}N_4O_8Y$ $[M]^-$: 503.08 ; found: 503.15.

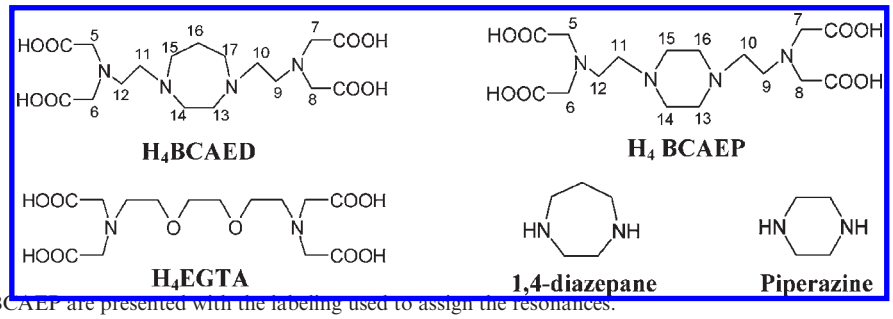
[Lu(BCAED)]$^-$. ^{1}H NMR (D_2O, 400 MHz) δ = 3.84−3.40 (m, H5, H6, H7, H8, H10 H12, 6H), 3.23 (m, H9, H11, H17, H17′, 4H), 3.05 (m, H13, 1H), 2.75 (m, H9′, H10′, H12′, H13′, H14, 5H), 2.60 (m, H11′, H14′, H15, H15′, 4H), 2.28 (m, H16, 1H), 1.89 (m, H16′, 1H), ^{13}C NMR (D_2O, 100 MHz) δ = 182.6, 181.6, 181.4, 181.1 (C1, C2, C3,C4), 64.0, 63.7, 62.8, 62.6 (C5, C6, C7, C8), 58.4 (C11), 57.2 (C13), 56.8 (C14), 55.9 (C17), 55.6 (C15), 55.4 (C10), 49.9 (C12), 47.1 (C9), 23.3 (C16). MS (ESI$^-$): *m*/*z*: calcd for $C_{17}H_{26}LuN_4O_8$ $[M]^-$: 589.39; found: 589.46.

Synthesis of Ln(III)BCAEP Complexes. $Ln(NO_3)_3 \cdot 6H_2O$ (0.04 mmol) was added in small portions to an aqueous solution (2.0 mL, pH = 5) of BCAEP (16 mg, 0.04 mmol) under magnetic stirring. The solution was heated to 50 °C, stirred for 24 h and then filtered and lyophilized to obtain a white powder. [La-(BCAEP)]$^-$ MS: (ESI$^-$): *m*/*z*: calcd for $C_{16}H_{24}LaN_4O_8$ $[M]^-$: 539.30; found: 539.38. [Y(BCAEP)]$^-$: MS (ESI$^-$): *m*/*z*: calcd for $C_{16}H_{24}N_4O_8Y$ $[M]^-$: 489.06 ; found: 489.15.[Lu(BCAEP)]$^-$: MS (ESI$^-$): *m*/*z*: calcd for $C_{16}H_{24}LuN_4O_8$ $[M]^-$: 575.36; found: 575.41.

Equilibrium Measurements. The chemicals used for the experiments were of the highest analytical grade. The $LnCl_3$ solutions were prepared from $LnCl_3 \cdot xH_2O$ (x = 5−7). The concentration of the $MgCl_2$, $CaCl_2$, and $LnCl_3$ solutions were determined by complexometric titration with standardized Na_2-H_2EDTA and Xylenol Orange ($LnCl_3$), Patton & Reeder ($CaCl_2$) and Eriochrome Black T ($MgCl_2$) as indicator. The concentration of the BCAED and BCAEP were determined by pH-potentiometric titration in the presence and absence of a large (40-fold) excess of $CaCl_2$. For the pH measurements and titration, a Radiometer PHM93 pH-meter, an ABU 80 autoburet, and a Metrohm-6.0234.100 combined electrode were used. Equilibrium measurements have been carried out at a constant ionic strength (0.1 M, KCl) in 10 mL samples at 25 °C. The solutions were stirred, and N_2 was bubbled through them. The titrations were made in the pH range 1.7−11.7. For the calibration of the pH meter, KH-phthalate (pH = 4.005) and borax (pH = 9.177) buffers were used. For the calculation of $[H^+]$ from the measured pH values, the method proposed by Irving et al. was used.[21] A 0.01 M HCl solution was titrated with the standardized KOH solution. The differences between the

(21) Irving, H. M.; Miles, M. G.; Pettit, L. *Anal. Chim. Acta* **1967**, *28*, 475–488.

Scheme 2. Structures of the Ligands of Interest[a]



[a] H_4BCAED and H_4BCAEP are presented with the labeling used to assign the resonances.

measured and calculated pH values were used to obtain the H^+ concentration from the pH values, measured in the titration experiments. The protonation and stability constants were calculated with the program PSEQUAD.[22]

NMR Experiments. ^{1}H and ^{13}C NMR spectra were run at 9.4 T (399.8 MHz, ^{1}H; 100.5 MHz, ^{13}C) on a JEOL ECP400 spectrometer. Chemical shifts are reported in δ values. The temperature was controlled with JEOL thermostating unit and measured by the chemical shift difference of the methanol resonances. For measurement in D_2O, *tert*-butyl alcohol was used as an internal standard with the methyl signal calibrated at $\delta = 1.2$ (^{1}H) and 30.3 ppm (^{13}C). Spectra assignments were based on COSY and HMQC experiments. The protonation process of BCAED and BCAEP ligands was followed by ^{1}H NMR spectroscopy. For these experiments, 0.01 M solution of the ligand in D_2O was prepared. The pH was adjusted by stepwise addition of a solution of KOH and HCl (both prepared in D_2O). The pH values reported for the ligand were corrected for the deuterium effect by using the relationship pD = pH + 0.4.[23] The calculations were performed by using the computer program Micromath Scientist, version 2.0 (Salt Lake City, UT, U.S.A.).

Relaxometric Measurements. The relaxivity values were calculated from the longitudinal relaxation times of the water protons (T_1) measured with a Bruker MQ20 NMR spectrometer operating at 20 MHz. The temperature of the sample holder was controlled with a thermostatted air stream. The longitudinal relaxation times were measured by the "inversion recovery" method (180° - τ - 90°) by using 10 different τ values. The measurements were carried out on 0.001 M solutions of the Gd(III)-complexes.

Single Crystal Diffraction Analysis. The X-ray diffraction data from a prismatic crystal of $[Na(H_2O)_2][Gd(BCAED)]$, mounted on the tip of a glass fiber of a goniometer head, were measured at room temperature by means of a Nonius CAD4 diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å). Local programs were used for cell refinement and data reduction. An empirical absorption correction was applied to all of the data (ψ-scan). The structure was solved by direct methods using SHELXS-97,[24] with the WinGX graphical user interface.[25] Structural refinement was carried out using SHELXL-97. All non-H atoms were refined anisotropically, while hydrogen atoms, set into idealized positions, were constrained to ride on their parent atom with $U_{iso} = 1.2\ U_{eq}$(parent atom).

Crystal data for $[Na(H_2O)_2][Gd(BCAED)]$: $C_{17}H_{30}GdN_4NaO_{10}$, fw = 630.69 g mol^{-1}; orthorhombic, $Pbn2_1$, a = 9.668(4), b = 15.027(4), c = 15.928(3) Å, V = 2314(1) Å^3, Z = 4; ρ_{calc} = 1.810 g cm^{-3}; $F(000)$ = 1260; μ(Mo Kα) = 29.4 cm^{-1}. R and $wR2$, = 0.024 and 0.060, for 2168 collected data and 298 refined parameters. CCDC No. 741303 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.

Results and Discussion

Synthesis of Ligands. The synthesis of the two ligands BCAED and BCAEP was carried out starting from 1, 4-diazepane and piperazine, respectively. *N*,*N*-bis(*tert*-butoxycarbonylmethyl)-2-aminoethyl methanesulfonate was used for the efficient alkylation of the secondary amines of the six and seven membered heterocycles slightly modifying the procedure reported by Williams and Rapoport for the *N*,*N*-dialkylation of aminoacids as a direct method for the construction of protected DTPA analogues.[20] Deprotection of the *tert*-butyl esters with trifluoroacetic acid yielded the final ligands as analytically pure white solids after precipitation with diethyl ether.

Solution Equilibrium Studies. The chemical structure of BCAED and BCAEP can be regarded as a combination of the known ligands EGTA and 1,4-diazepane and piperazine, respectively. The 1,2-ethylenedioxy bridge of the former has been replaced by the 1,4-diazepane or piperazine moieties of BCAED and BCAEP (Scheme 2). The presence of the seven- or six-membered ring provides the ligands with a different degree of flexibility that could affect their ability to wrap around the metal ion using the four nitrogen and four oxygen atoms and thus the stability of the resulting complexes. For all these reasons, the novel polyaminopolycarboxylic ligands BCAED and BCAEP, combining flexible and rigid structural motifs, are expected to show distinct complexation behavior.

Protonation Equilibria. The protonation constants ($\log K_i^H$) of H_4BCAED and H_4BCAEP were determined by pH-potentiometry and are reported in Table 1 together with those of EGTA, 1,4-diazepane, and piperazine for comparison (standard deviations are shown in parentheses). The protonation constants are defined as follows:

$$K_i^H = \left[\frac{H_iL}{[H_{i-1}L][H^+]}\right] \qquad i = 1-5 \qquad (1)$$

The protonation constants were also determined by analysis of the pH-dependent variation of ^{1}H NMR chemical shifts of the non-labile protons of H_4BCAED and H_4BCAEP. The ^{1}H NMR titration curves (Figure 1) display sharp changes at different pH values, which are related to the protonation sequence of the ligands. Since

(22) Zékány, L.; Nagypál, I. In *Computational Method for Determination of Formation Constants*; Legett, D. J., Ed.; Plenum: New York, 1985; pp 291−353.
(23) Glasoe, P. K.; Long, F A. *J. Phys. Chem.* **1960**, *64*, 188–190.
(24) Sheldrick, G. M. *Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
(25) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.

Table 1. Protonation Constants of the Ligands H_4BCAED, H_4BCAEP, EGTA, 1,4-Diazepane and Piperazine (298 K)

	H_4BCAED[a]	H_4BCAEP[a]	H_4BCAED[a,b]	H_4BCAEP[a,b]	EGTA[a]	1,4-diazepane[c]	piperazine[a,d]
$\log K_1^H$	10.68 (0.01)	9.83 (0.01)	10.76 (0.02)	9.80 (0.03)	9.47 (0.01)	10.26	9.82
$\log K_2^H$	9.28 (0.01)	9.11 (0.01)	9.32 (0.03)	9.05 (0.04)	8.83 (0.01)	6.6	5.64
$\log K_3^H$	5.07 (0.01)	4.75 (0.02)	4.92 (0.08)	4.55 (0.02)	2.81 (0.02)		
$\log K_4^H$	2.96 (0.02)	2.69 (0.02)			1.93 (0.02)		
$\log K_5^H$	2.31 (0.02)	1.86 (0.03)			1.89 (0.02)		
$\sum \log K_i^H$	30.3	28.24			24.93		

[a] 0.1 M KCl. [b] Obtained by ^{1}H NMR titration. [c] Ref 26. [d] Ref 27.

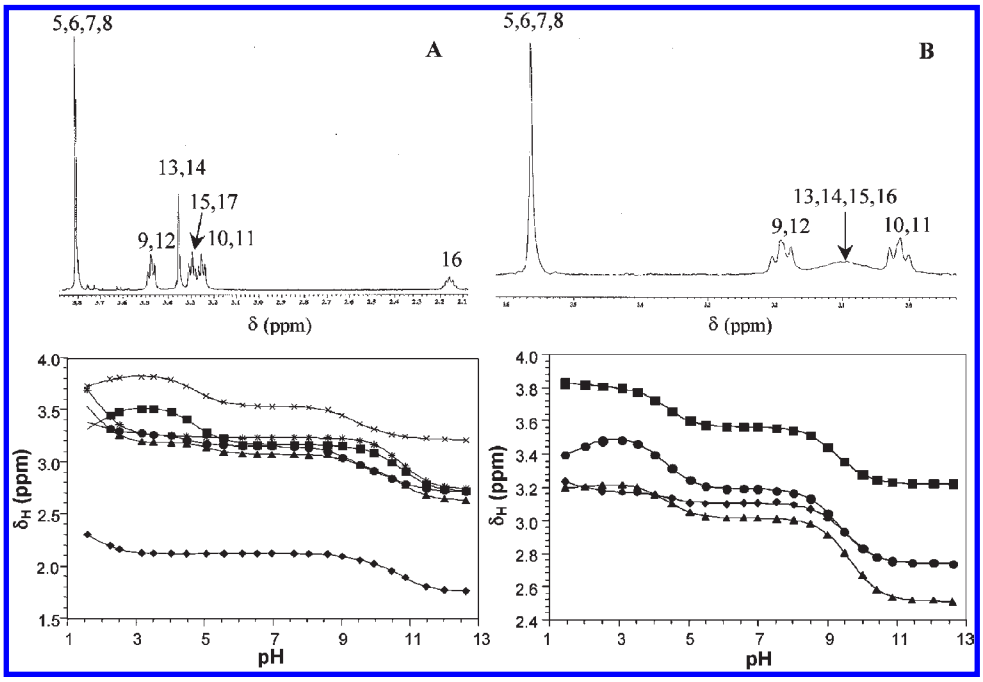


Figure 1. ^{1}H NMR spectra and titration curves of the ligands H_4BCAED (A) and H_4BCAEP (B) (Spectrum A: pH = 2.51; Spectrum B: pH = 6.58; **A**: 16 (♦); 15,17 (●); 13,14 (*); 10,11 (▲); 9,12 (■); 5,6,7,8 (×); **B**: 13,14,15,16 (♦); 10,11 (▲); 9,12 (●); 5,6,7,8 (■); 0.1 M KCl, 25 °C).

protonation/deprotonation of the ligands is fast on the NMR time scale, the chemical shifts of the observed signals represent a weighted average of the shifts of the different H_iL species involved in a specific protonation step (eq 2):[28]

$$\delta_{H(obs)} = \sum x_i \delta_H^{H_iL} \quad (2)$$

In eq 2, $\delta_{H(obs)}$ is the observed chemical shift of a given peak, x_i and are the molar fraction and the chemical shift of the involved species, respectively. The observed chemical shifts, $\delta_{H(obs)}$, were fitted to eq 2 by expressing the molar fractions x_i of the different protonated species in terms of the protonation constants K_i^H. The results of the best fits to the experimental data points are shown in Figure 1 and the obtained $\log K_i^H$ values are listed in Table 1. The $\log K_i^H$ values calculated from the ^{1}H NMR data are in good agreement with those obtained by pH-potentiometry (Table 1).

The first three protonation constants of the BCAED and BCAEP ligands describe the protonation of the nitrogen atoms (Table 1). Whereas the two iminodiacetate nitrogens can be protonated quite independently, as for EGTA, one of the two ring nitrogen atoms shows a high basicity. By considering the size of the 1,4-diazepane and piperazine rings, the protonation of the remaining nitrogen atom is expected to occur at low pH values because of the electrostatic repulsion between the protonated atoms. The protonation of the carboxylate groups takes place in the acidic pH range.The protonation sequence of H_4BCAED and H_4BCAEP has been assessed on the basis of the pH dependence of the ^{1}H NMR chemical shifts over the range 1.5 to 12.5 at 25 °C. In the proton NMR spectrum of H_4BCAED at pH < 3 (Figure 1A) the methylenic protons of the ring (labeled 13−17 according to Scheme 2) give rise to a quintet (16), a triplet (15,17), and a singlet (13,14), whereas the methylenic protons of the aminoethyl (10, 11 and 9, 12) and acetate (5−8) groups generate two triplets and a singlet, respectively. The ^{1}H NMR spectrum of H_4BCAEP at pH 6.5 shows a broad singlet resulting from the interconversion process between the axial and equatorial protons of the ring protons 13−16 (Figure 1B). As for H_4BCAED, the methylenic protons of the aminoethyl (10, 11 and 9, 12) and acetate (5−8) groups give rise to two triplets and a singlet, respectively.

(26) Schwarzenbach, G.; Maissen, B.; Ackermann, H. *Helv. Chim. Acta* **1952**, *35*, 2333–2336.
(27) Dega-Szafran, Z.; Jaskólski, M.; Kurzyca, I.; Barczyński, P.; Szafran, M. *J. Mol. Struct.* **2002**, *614*, 23–32.
(28) Sudmeier, J. L.; Reilley, C. N. *Anal. Chem.* **1964**, *9*, 1698–1706.

Table 2. Protonation and Stability Constants of the Metal Complexes of the Ligands BCAED, BCAEP, and EGTA (25°C)

	BCAED[a]			BCAEP[a]		EGTA[b,c]	
	$\log K_{ML}$	$\log K_{MHL}$	$\log K_{MH2L}$	$\log K_{ML}$	$\log K_{MHL}$	$\log K_{ML}$	$\log K_{MHL}$
Mg^{2+}	4.69 (0.03)	9.45 (0.05)		3.76 (0.04)	9.14 (0.06)	5.28	7.62
Ca^{2+}	9.05 (0.01)	5.18 (0.09)		4.78 (0.01)	7.98 (0.06)	10.86	3.79
La^{3+}	12.77 (0.01)	4.67 (0.04)		10.37 (0.04)	5.52 (0.08)	15.55	
Nd^{3+}	14.85 (0.02)	4.51 (0.07)		11.44 (0.04)	5.27 (0.08)	16.28	
Eu^{3+}	17.23 (0.02)	3.91 (0.06)		12.26 (0.05)	5.08 (0.08)	17.10	
Gd^{3+}	17.15 (0.02)	3.92 (0.06)		12.42 (0.03)	4.85 (0.06)	16.97	
Ho^{3+}	19.00 (0.04)	3.86 (0.04)	3.39 (0.02)	14.14 (0.03)	4.20 (0.07)	17.38	
Lu^{3+}	20.99 (0.02)	3.11 (0.02)	2.85 (0.03)	16.03 (0.03)	3.07 (0.08)	17.81	

[a] 0.1 M KCl. [b] 0.1 M KNO_3. [c] Ref 29.

The chemical shifts of the different methylene protons of H_4BCAED and H_4BCAEP present a rather similar pH dependency, indicating that the protonation sequence of the donor atoms of the two ligands is quite comparable. From pH 12 to 7 two amino groups are protonated, and nearly all the methylene resonances are significantly shifted. These protonation steps ($\log K_1^H$ and $\log K_2^H$) take place at the ring nitrogen and at one of the pendant arm nitrogen, although the protonation order cannot be firmly assessed. In the pH range 4−6 the signals of the methylene groups next to the pendant arm nitrogens are significantly shifted to higher frequencies, whereas the peaks corresponding to the ring protons are not perturbed. These data indicate that the third protonation occurs on an iminodiacetate nitrogen. At pH < 3 the signals of both the ring and acetate methylene protons experience a significant shift to show that the $\log K_4^H$ and $\log K_5^H$ values are associated with the protonation of the second ring nitrogen and an acetate group.

Both pH potentiometric and ^{1}H NMR spectroscopic data on the protonation equilibria of BCAED and BCAEP support the view that these ligands can be regarded as derivatives of EGTA containing the 1,4-diazepane and piperazine rings. The $\sum \log K_i^H$ values presented in Table 1 also show that the replacement of the ether oxygen atoms of EGTA by nitrogen atoms results in an higher basicity for BCAED and BCAEP.

Complexation Properties of BCAED and BCAEP. It is generally accepted that the coordinating ability of polydentate ligands is affected by the basicity and the charge of the different donor groups. By taking into account the higher basicity of BCAED and BCAEP and the presence of four nitrogen atoms and four carboxylate groups, the stability constants of the complexes of BCAED and BCAEP with the lanthanide(III) ions are expected to be higher than those of EGTA. The presence of the six- and seven-membered rings influences the nature and the stability of the coordination polyhedra. In addition, the size match between the trivalent lanthanide ion and the coordination polyhedron, dictated by the ligand structure and flexibility, may also play an important role in determining the stability of the metal complexes. Therefore, the equilibrium study of the metal complexes formed with BCAED and BCAEP may provide some new information about the effects of the relative rigidity of the ligands on the stability constants of complexes.

(29) Mackey, J. L.; Hiller, M. A.; Powell, J. E. *J. Phys. Chem.* **1962**, *66*, 311–314.

The stability and protonation constants of the metal complexes formed are defined as follows:

$$K_{ML} = \frac{[ML]}{[M][L]} \tag{3}$$

$$K_{MH_iL} = \frac{[MH_iL]}{[MH_{i-1}L][H^+]} \qquad i = 1-3 \tag{4}$$

The stability and protonation constants obtained from the pH potentiometric titration data for Mg^{2+}, Ca^{2+}, La^{3+}, Nd^{3+}, Eu^{3+}, Gd^{3+}, Ho^{3+}, and Lu^{3+} are reported in Table 2. The stability and protonation constants of the BCAED and BCAEP complexes have been calculated from the titration curves obtained at 1:1 metal to ligand concentration ratios. The best fitting was obtained by using the model which includes the formation of ML, MHL, and MH_2L species in equilibrium. The inspection and comparison of the data presented in Table 2 reveal that the complexation properties of BCAED, featuring a less rigid structure than BCAEP, are rather similar to those of EGTA. The stability constants of $[Mg(BCAED)]^{2-}$ and $[Ca(BCAED)]^{2-}$ do not differ significantly from those of $[Mg(EGTA)]^{2-}$ and $[Ca(EGTA)]^{2-}$, then suggesting a modest influence of the 1,4-diazepane ring on the selectivity of BCAED for Ca^{2+} over Mg^{2+}. On the other hand, the $\log K_{ML}$ values of $[Mg(BCAEP)]^{2-}$ and $[Ca(BCAEP)]^{2-}$ are remarkably lower than the corresponding values of $[Mg(EGTA)]^{2-}$ and $[Ca(EGTA)]^{2-}$. This implies that the rigidification introduced by the six-membered piperazine ring impacts on the ability of the donor atoms of the ligand to efficiently wrap around the divalent metal ions.

The stability constants of the Ln(III) complexes (Ln = La, Nd, Eu, Gd, Ho, and Lu) of BCAED and BCAEP show larger variations. The $\log K_{ML}$ values of the complexes with BCAEP are lower than the values of the corresponding $[Ln(EGTA)]^-$ complexes. On the other hand, in spite of the fact that $[La(BCAED)]^-$ and $[Nd(BCAED)]^-$ are less stable than $[La(EGTA)]^-$ and $[Nd(EGTA)]^-$, while the $\log K_{ML}$ values of $[Eu(BCAED)]^-$ and $[Gd(BCAED)]^-$ are quite similar to those of $[Eu(EGTA)]^-$ and $[Gd(EGTA)]^-$, $[Ho(BCAED)]^-$ and $[Lu(BCAED)]^-$ are characterized by stability constants higher than those of $[Ho(EGTA)]^-$ and $[Lu(EGTA)]^-$ by nearly 2 and 3 orders of magnitude, respectively (Table 2). Most surprisingly, the $\log K_{ML}$ values for BCAED and BCAEP show an increase of 8.22 and 5.66 $\log K$ units on passing from the La^{3+} to the Lu^{3+} complexes,

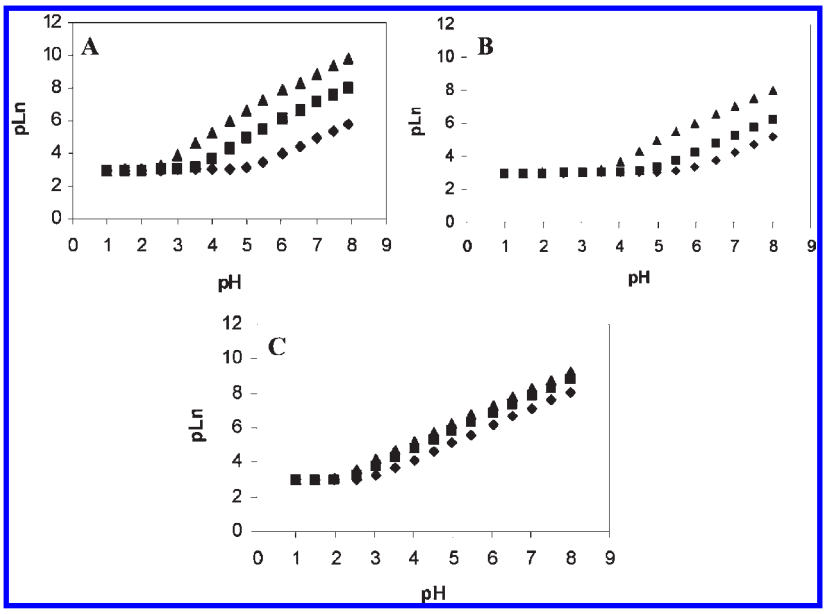


Figure 2. Calculated pLn = $-\log[Ln^{3+}]$ values of the Ln^{3+}-BCAED (**A**), Ln^{3+}- BCAEP (**B**) and Ln^{3+}-EGTA (**C**) systems as a function of pH. (La^{3+} (♦), Gd^{3+} (■), Lu^{3+} (▲), $[Ln^{3+}]$ = [BCAED] = [BCAEP] = [EGTA] = 0.001 M, 0.1 M KCl, 25 °C).

respectively. These $\log K_{LuL} - \log K_{LaL}$ values are remarkably high when compared with those observed for EGTA (2.26) or even for CDTA (5.22; H_4CDTA = *trans*-1,2-cyclohexanediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid).[30] The value of $\Delta\log K_{La-Lu}$ of 5.22 for CDTA represented the largest increase in stability constant over the lanthanide series observed so far. The corresponding value of 8.22 found for of BCAED is even higher than that of 6.9 recently reported for a derivative of 4,13-diaza-18-crown-6 in which a reversed selectivity is observed, the Ce(III) complex being more stable than the Lu(III) one.[13] The large differences observed in the log*K* values of the La(III), Nd(III), Eu(III), Gd(III), Ho(III), and Lu(III) complexes indicate that BCAED can represent a very efficient eluant for the ion-exchange separation of rare earths. In fact, the separation factors ($\Delta\log K_{ML}$ for two Ln(III) ions being separated) would be nearly twice as large as those with EDTA, which was commonly used for the chromatographic separation of rare earths.[31]

The unique properties of Ln(III)-BCAED complexes may be explained both by the ligand structure and by the basicity of the donor atoms. The presence of the seven-membered 1,4-diazepane ring into the ligand backbone introduces a structurally rigid motif that appears to facilitate the complexation of lanthanide ions of matching size, most likely by reducing the entropy of the reaction. It is known that a semi-rigid or rigid structure is associated with a significant increase of the complex stability. In fact, a rigidification of the molecular skeleton favors the spatial pre-organization of the donor atoms which may result into a more efficient complexation. The donor atoms of BCAED can efficiently accommodate the small Lu^{3+} ion in the cavity and form a highly stable complex. However, when the size match is not favorable (e.g., the large La^{3+} ion), the lack of flexibility results in lower stability constants, in spite of the presence of strongly basic donor atoms. The variation with pH of the pLn = $-\log[Ln^{3+}]$ values for the La(III), Gd(III), and Lu(III) complexes of BCAED, BCAEP, and EGTA is shown in Figure 2. The selectivity of BCAED toward lanthanides(III) cations is clearly evidenced by the different pH for the complex formation (La: ∼5, Lu: ∼2.5). The difference in pLn (pLu−pLa) in the pH interval 3−8 follows the order: BCAED > BCAEP ≫ EGTA.

Relaxometric Characterization of the Gd(III) Complexes. The pH dependency of the proton relaxivity (r_{1p}, $mM^{-1}\ s^{-1}$) of the Gd^{3+} complexes has been investigated, at 20 MHz and 25 °C, to ascertain the complex formation and the species distribution (Figure 3). The experimentally determined relaxivity represents the sum of the inner (r_{1p}^{is}) and outer (r_{1p}^{os}) sphere terms: $r_{1p} = r_{1p}^{is} + r_{1p}^{os}$. r_{1p}^{is} is related to the increase of the water proton relaxation rate arising from the exchange of the coordinated water molecule(s) whereas r_{1p}^{os} represents the contribution of the solvent molecules diffusing in the proximity of the paramagnetic complex.[32] The observed r_{1p} values at neutral pH and room temperature of $[Gd(BCAED)]^-$ (2.1 $mM^{-1}\ s^{-1}$) and $[Gd(BCAEP)]^-$ (2.0 $mM^{-1}\ s^{-1}$) are rather low and indicative of the absence of a water molecule in the inner coordination sphere of the metal ion.

In fact, the relaxivity values of $[Gd(BCAED)]^-$ and $[Gd(BCAEP)]^-$ are quite similar to that of the complex $[Gd(TTHA)]^{3-}$ (H_6TTHA = triethylenetetraminehexaacetic acid) which does not contain inner sphere water molecules.[33] Thus, in both complexes, the Gd^{3+} ion is in an octacoordinated ground state in aqueous solution at neutral pH. In the pH range 2−3.5, the relaxivity of the Gd^{3+}- BCAED system is 13 $mM^{-1}\ s^{-1}$ which represents

(30) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum Press: New York, 1974; Vol. *4*.

(31) (a) Spedding, F. H.; Powell, J. E.; Wheelwright, E. J. *J. Am. Chem. Soc.* **1954**, *76*, 612. (b) Spedding, F. H.; Powell, J. E.; Wheelwright, E. J. *J. Am. Chem. Soc.* **1954**, *76*, 2557.

(32) Aime, S.; Botta, M.; Terreno, E. In *Adv. Inorg. Chem.*; van Eldik, R., Bertini, I., Eds.; Elsevier: San Diego, 2005; Vol. *57*, pp 173−237.

(33) Geraldes, C. F. G. C.; Urbano, A. M.; Alpoim, M. C.; Sherry, A. D.; Kuan, K.-T.; Rajagopalan, R.; Maton, F.; Muller, R. N. *Magn. Reson. Imaging* **1995**, *13*, 401–420.

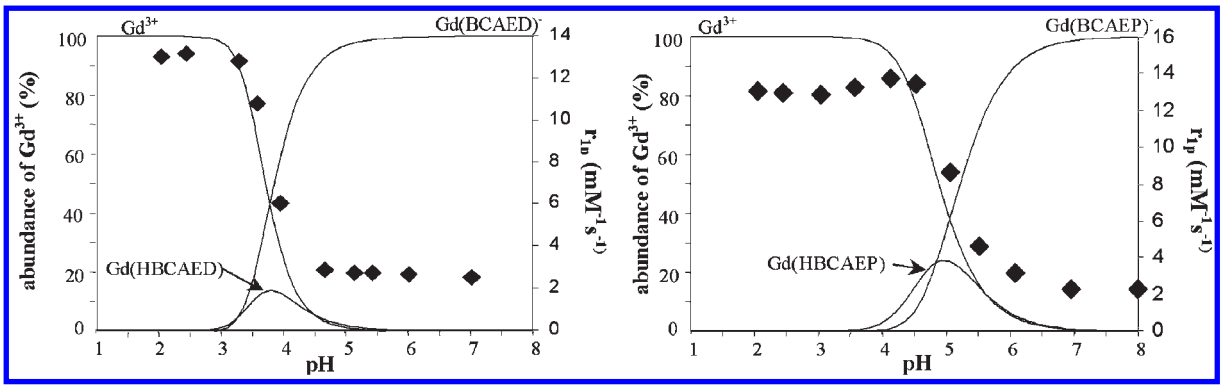


Figure 3. Relaxivity and species distribution of the Gd^{3+}- BCAED and Gd^{3+}- BCAEP systems as a function of pH ([Gd^{3+}] = [BCAED] = [BCAEP] = 0.001 M, 20 MHz, 0.1 M KCl, 25 °C).

the relaxivity of the Gd^{3+} aquaion. The decrease of the relaxivity at pH > 3.5 is the result of the formation of the Gd(HBCAED) and $[Gd(BCAED)]^-$ complexes. At pH > 4.5, only the $[Gd(BCAED)]^-$ and Gd(HBCAED) species are present in the aqueous solution. A further increase of pH results in a small decrease in relaxivity because of the deprotonation of Gd(HBCAED) and of the formation of $[Gd(BCAED)]^-$. At pH > 5, the relaxivity remains constant to indicate the only presence of the fully deprotonated complex $[Gd(BCAED)]^-$.

In the case of $[Gd(BCAEP)]^-$ the behavior does not differ significantly, with the only difference that a small relaxivity increase is observed at pH > 3.5, probably because of the formation of the protonated Gd(HBCAEP) complex for which a fast proton exchange with the bulk water could contribute to the observed relaxivity. The decrease in relaxivity in the pH range 4.5−6 and its constant value at pH > 6 are explained as for the complex with BCAED.

In conclusion, the pH dependence of the relaxivity for the two complexes is in very good agreement with the species distribution curves calculated from the equilibrium data determined by pH potentiometry.

Solid State Structure. The crystal structure of $[Na(H_2O)_2][Gd(BCAED)]$, shown in Figures 4a and 4b, is built upon a one-dimensional (1-D) sequence of complex anions, containing the lanthanide ion, and bis-hydrated Na^+ ions, linked by oxygen atoms belonging to the BCAED ligand. Na−O distances fall in the 2.310(4)−2.732(3) Å range, the lowest values being attributed to the water-bound molecules.

The overall coordination at the alkali-metal ion is nearly octahedral, with a significant distortion toward C_{2v} symmetry, as imposed by two chelating carboxylates, *cis* to each other. Further links between parallel $[Na(H_2O)_2][Gd(BCAED)]$ chains are present, thanks to evident hydrogen-bonds between water molecules and swinging carboxylates of neighboring chains (O2 and O4, with O−H···O distances in the 2.78−2.80 Å range).

The lanthanide portion of the crystal contains an octacoordinated Gd(III) atom with four nitrogen and four oxygen atoms belonging to the same polydentate BCAED tetraanion. Gd−N and Gd−O fall in the 2.557(3)−2.589(3), and 2.321(3)−2.365(3) Å ranges, respectively, demonstrating a higher affinity of Gd(III) toward (charged) oxygen atoms than to neutral nitrogen atoms. The overall coordination geometry is close to an idealized

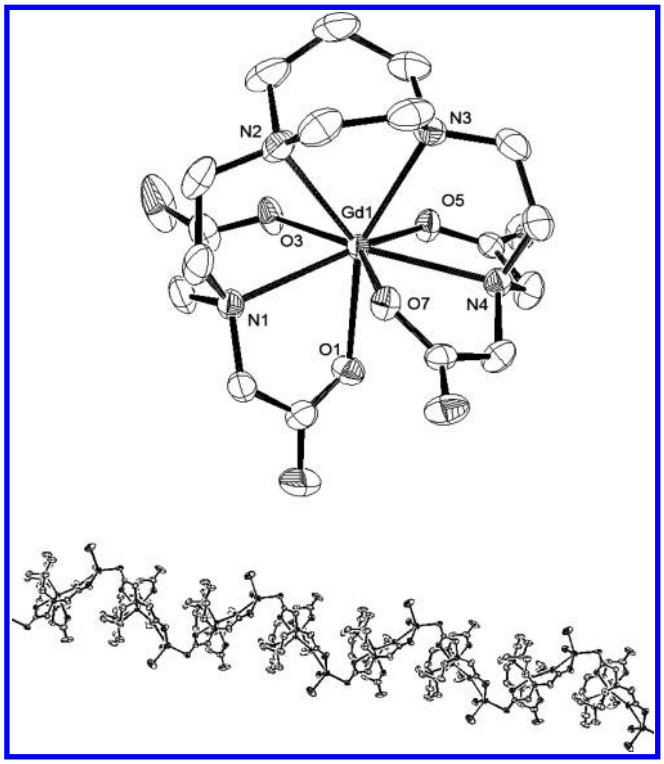


Figure 4. ORTEP drawing of (i) the $[Gd(BCAED)]^-$ anion, with partial labeling scheme, as derived from the crystal structure of its bis-aquo sodium salt (top); (ii) the one-dimensional chain build by the sequence of $[Na(H_2O)_2]^+$ and $[Gd(BCAED)]^-$ moieties (bottom), the sodium atoms being pseudooctahedrally hexacoordinated by oxygen atoms, four of which by two chelating carboxylates (*cis* to each other) from the BCAED ligand. Chains run along [010] and are generated by the glide plane normal to **a**. Thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms omitted for clarity.

C_{2v} bicapped-trigonal prismatic one (with N1 and N4 caps), with *transoid* X−Gd−X (X = N or O) angles widely scattered about 140°, although a D_{4d} square-antiprism description can also be adopted. The other known GdN_4O_4 stereochemistry found in the CSD (codes: LEDJET and PALHAL) show a significant distortion to D_4, as witnessed by nearly *trans* X−Gd−X bond angles well above 160°.

In the solid state structure of $[Er(EGTA)]^-$, isostructural with the corresponding Gd(III) complex,[16] the bound water molecule occupies a third capping position, above a plane defined by the two ether oxygen atoms and two oxygen atoms of two carboxylate groups. The

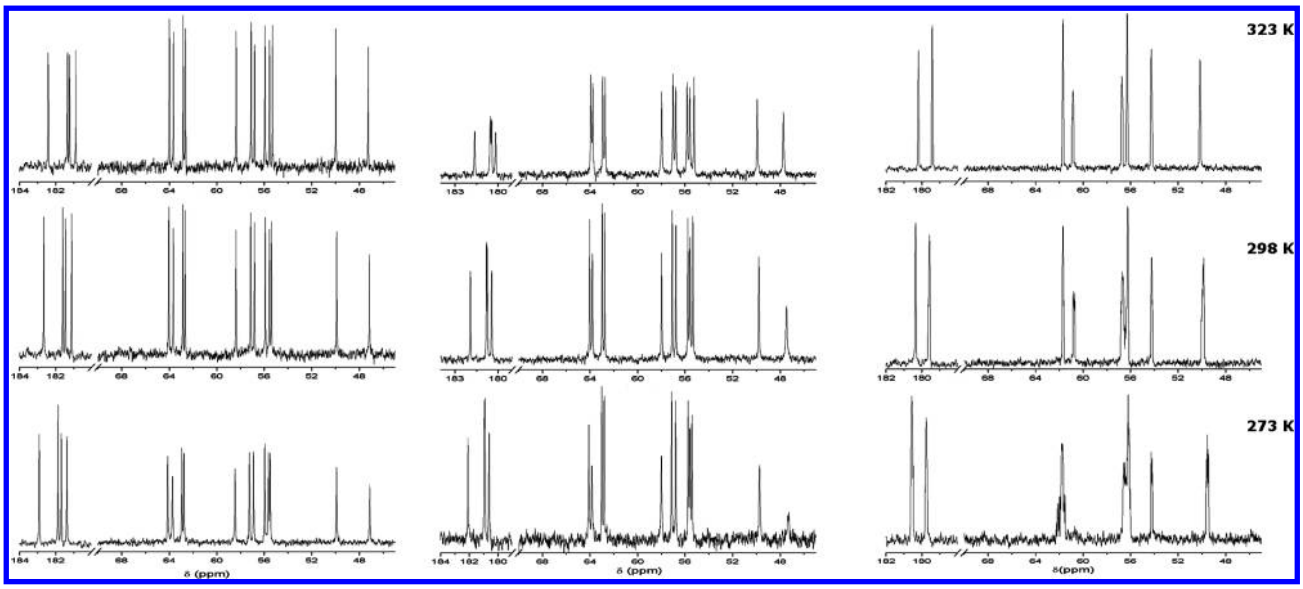


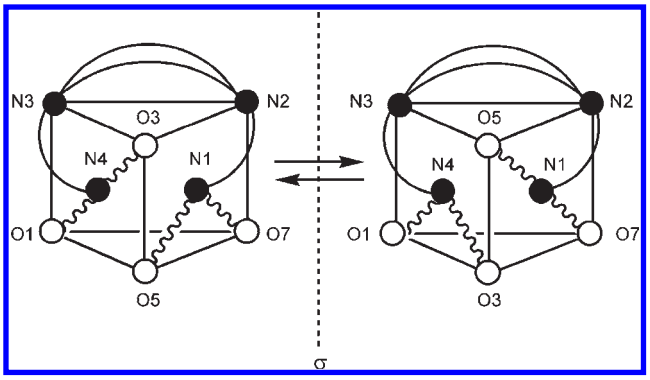
Figure 5. Variable temperature ^{13}C NMR spectra of the Lu^{3+} (left), Y^{3+} (middle), and La^{3+} (right) complexes of $BCAED^{4-}$. Signal of carbon 16 was omitted for clarity.

corresponding spatial position in the complex [Gd(BCAED)]$^-$ is now occupied by the propyl group of 1,4-diazepane which sterically hinders the access of a solvent molecule. Then, both in solution and in the solid state the Gd^{3+} ion is octacoordinated.

NMR Spectra of [Ln(BCAED)]$^-$ (Ln = La, Y, Lu) Complexes. The ^{13}C NMR spectrum of [Lu(BCAED)]$^-$ shows 17 resonances at room temperature to indicate the occurrence in aqueous media of an unsymmetrical structure in which all the 17 carbon atoms of the ligand are magnetically non equivalent thus originating separate resonances (Figure 5 left). This is in agreement with a solution state structure corresponding to that found in the solid state for [Gd(BCAED)]$^-$: the metal ion is encapsulated into a coordination polyhedron that is best described as a bicapped trigonal prism. The capping positions are occupied by the two nitrogen atoms of the aminoethyl arms, and the trigonal faces are formed by the nitrogen atoms of the diazepane ring and by the oxygen atoms of the carboxylate groups. This structure is reminiscent of that one used for describing the solution behavior of the complexes [Ln(EGTA)(H_2O)]$^-$ (Ln = Tb−Lu).[16] The structure is very rigid, and this leads to the magnetic inequivalence of all the ligand atoms. The same features are present in the carbon spectrum of [Lu(BCAED)]$^-$ at 323 K. Increasing the temperature up to 323 K does not promote any dynamic process fast enough (on the NMR time scale) to increase the symmetry of the structure.

The ^{13}C NMR spectra of [Y(BCAED)]$^-$ are quite similar to that of [Lu(BCAED)]$^-$ (Figure 5 middle). The structure is rigid, and all the ligand atoms are magnetically inequivalent. Increasing the ionic radius from 85 pm (Lu^{3+}) to 89.3 pm (Y^{3+}) does not change the structure of the complex and has a little effect on its stereochemical rigidity. The carbon resonances are slightly broadened as compared to those of [Lu(BCAED)]$^-$. This effect becomes evident in the spectrum recorded at 323 K and could be explained with a slow motion of the complex. In fact, at 353 K the two central carboxylate peaks coalesce

Scheme 3. Interconversion Process Occurring in Solution for the [Ln(BCAED)]$^-$ Complexes Involving Two Carboxylate Groups Located on Adjacent Vertices of the Two Trigonal Planes



and the remaining two are extremely broad and barely detectable to indicate the occurrence of a fluxional behavior that averages pairs of resonances (see Supporting Information). The increase of the non stereochemical rigidity across the lanthanide series from heavy to light members is confirmed by the NMR data for [La(BCAED)]$^-$. In this case the ^{13}C NMR spectrum shows 9 resonances at 298 K. If we assume the presence of a coordination polyhedron similar to that observed for [Gd(BCAED)]$^-$, [Lu(BCAED)]$^-$, and [Y(BCAED)]$^-$, then we are in the presence of a dynamic process fast enough, at room temperature, to average out the number of carbon resonances to 9. The interconversion motion can be described by the rapid exchange of two carboxylate groups located on adjacent vertices of the two trigonal planes containing the capping positions (Scheme 3). Looking at the carbon spectrum recorded at low temperature (273 K), it is possible to observe the broadening of all the peaks as a consequence of the slowing down of the dynamic process.

The NMR spectra for the corresponding [Ln(BCAEP)]$^-$ complexes do not add further information. Even in the case of the Lu(III) derivative the peaks are

much broader and not easily assignable. Clearly, the complexes are significantly more fluxional, and this can be tentatively related to the lower coordinating ability of the BCAEP ligand imparted by the piperazine ring.

Conclusions

In summary, we have shown that the incorporation of diazacycloalkanes into aminocarboxylates chelators provides the ligands with improved selectivity toward complexation of lanthanide(III) cations. Two main factors are responsible of this result: the basicity of the donor atoms and the ability of the ligand to wrap around metal ions of decreasing size across the lanthanide series. This latter property is affected by the degree of flexibility of the ligand backbone. The flexible EGTA is able to form complexes of high stability with the various Ln(III) cations and then it has a poor selectivity ($\Delta\log K_{La-Lu} = 2.05$). The introduction of a "rigid" moiety into the ligand backbone enhances the selectivity of the new chelators by imposing the requisite of the proper size match between the metal ion and the cavity formed by the donor atoms of the ligand. The resulting effect is particularly relevant for BCAED and large both at the beginning ($\Delta\log K_{Gd-La} = 4.38$) and at the end of the Ln series ($\Delta\log K_{Lu-Gd} = 3.84$). Then, the variation of the stability constants across the series from La(III) to Lu(III), $\Delta\log K_{La-Lu} = 8.22$, is the largest so far observed, and it could find various and useful applications in f element coordination chemistry.

Passing from a seven- to a six-membered ring significant differences are observed. The log$K$ values of the $[Ln(BCAEP)]^-$ complexes are lower than those for the corresponding complexes with either BCAED and EGTA, even though a good selectivity is maintained. In principle, another contribution could affect the relative stability and selectivity of the two ligands toward lanthanide ions: the size of the metallacycles formed upon metal binding. In the $[Ln(BCAEP)]^-$ complexes the piperazine unit forms two five-membered cycles whereas in the corresponding $[Ln(BCAED)]^-$ complexes a five- and a six-membered rings are involved. In spite of the large preference of lathanides for five member rings the stability of the complexes formed with BCAED is higher across the entire Ln series to indicate that this contribution is not predominant in the present case.[34]

All these results show that a proper mixing of rigid and flexible motifs can profoundly impact the coordination properties of the resulting polyamino-polycarboxylate ligand and thus stimulate the exploration of new chelators and further investigation in this direction.

Acknowledgment. The authors thank MIUR (PRIN projects) and Regione Piemonte (Ricerca Sanitaria Finalizzata 2007, Converging Technologies 2007 − NanoIGT project), OTKA K 69098 (E.B.) and EMIL Project funded by the EC FP6 Framework program (E.B.) for financial assistance. The work was carried out under the collaborative scheme of EU-COST D38 action.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the Lu^{3+}, Y^{3+}, and La^{3+} complexes of **BCAED** $^{4-}$. VT ^{13}C NMR spectra (carboxylate region) of the Y^{3+} complex of **BCAED** $^{4-}$. This material is available free of charge via the Internet at http://pubs.acs.org.

(34) Martell, A. E.; Hancock, R. D. *Metal Complexes in Aqueous Solutions*; Plenum Press: New York, 1996; Chapter 3.