Synthesis and Structure of a New Macrocyclic Polyhydroxylated Gadolinium Chelate Used as a Contrast Agent for Magnetic Resonance Imaging

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Three approaches to the synthesis of a new ligand 1,4,7-tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane (**6**) are described. This ligand forms the both thermodynamically and kinetically very stable gadolinium chelate Gadobutrol (**1),** which is a neutral and highly hydrophilic compound that is used for magnetic resonance imaging in the clinic. According to the crystal structure the Gd(III) ion in **1** is nine coordinated. The ligand provides eight coordination sites whereas the ninth coordination partner surprisingly is a carboxylate oxygen of a neighboring centrosymmetrically-related complex molecule. Ligand **6** was also utilized to prepare the calcium complex **12** which is used as an additive in the pharmaceutical formulation of **1**. For the calcium complex **12**, two complex molecules adopting almost identical conformations are present in the crystal.

Introduction

The administration of contrast agents in magnetic resonance imaging (MRI) has greatly improved the potential of this modality.[1] MRI contrast agents have an indirect mode of action. Since they contain paramagnetic metal ions they influence the signal intensity primarily by altering proton relaxation rates in tissue.[2] Pure metal salts are poorly tolerated, thus the metals are administered as complexes. Gadolinium(III) is the most effective relaxation enhancer and almost all of the commercially available MRI contrast agents contain Gd(III) complexes. The diagnostic potential of Gd(III) complexes was first demonstrated by using Gd(III) diethylenetriamine pentaacetate (Magnevist).[3,4] Important issues in the development of Gd(III)-containing MRI contrast agents are high solubility, high relaxivity, low toxicity, low osmolality, high thermodynamic and/or kinetic stability, and the presence of at least one water molecule in the inner coordination sphere of the metal ion. Other agents introduced into clinical practice include the macrocyclic ionic complex Gd−DOTA (Dotarem),[3,4] as well as two the following low osmolar agents: the macrocylic complex Gd−HP-DO3A (Prohance)[5−8] and the open chain DTPA derivative Gd−DTPA-BMA (Omniscan).[9−11]

Hydrophilicity is an important issue for diagnostically used pharmaceuticals. High overall hydrophilicity is generally associated with very low protein binding and good biological tolerance. By masking hydrophobic regions with hydrophilic groups, one can create a pattern of protection around parts of a molecule that might otherwise exert toxic effects. In practical terms this means that contrast agents should exhibit an extremely low systemic toxicity and, thus, a favorable safety profile. Here we demonstrate the use of a trihydroxybutyl group attached to the macrocycle Gd−DO3A to ensure high hydrophilicity. This results in the synthesis of Gadobutrol (**1**),[12] a new stable low-osmolar extracellular contrast agent for MRI. The preclinical evaluation and first results after intravenous injection in healthy volunteers are reported elsewhere.[13,14]

In this paper we describe for the first time in detail three synthetic approaches to DO3A-butrol (**6**) as well as the preparation of the corresponding Gd(III) complex **1** and the Ca-(II) complex **12**. The route outlined in Scheme 2 is preferred since it allows the upscaling necessary to produce enough material for the clinical investigation of **1**.

The ligand contains two chiral carbons at C13 and C14 (numbering adopted from **1**; see Figure 1) and thus represents a racemic mixture of (13*R*,14*S*)- and (13*S*,14*R*)-**6**. For the sake of clarity only one enantiomer is shown in the formulas of Schemes 1−3.

Experimental Section

General Considerations. NMR spectra were obtained on a QE300 (300 MHz, General Electric), AC400 (400 MHz, Bruker), or an

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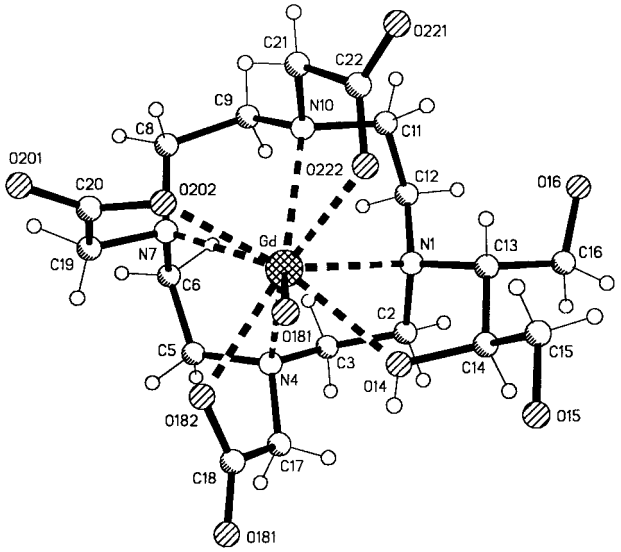


Figure 1. Structure of Gadobutrol (**1**) in the crystal showing the atomic numbering scheme. The "cap atom" O181 is provided by a centrosymmetrically related complex molecule.

AMX500 (500 MHz, Bruker). ^{1}H and ^{13}C spectra were referenced to internal TMS ($CDCl_3$, DMSO) or TSP (D_2O). FT-IR spectra were recorded on a Nicolet 20SXB or on a Nicolet 710. Mass spectra were recorded on a VG ZAB-E or on a Fisons Autospec using FAB techniques with various matrices.

HPLC: Hypersil phenyl 5 μm, column length 25 cm, diameter 4.6 mm; mobile phase, 1 g triethyl amine/L of water acidified with concentrated ortho-phosphorous acid to a pH of 7.4, flow rate 2 mL/min, UV detection at 196 nm.

Synthesis. 1,4,7,10-Tetraazatricyclo[5.5.1.0]tridecane (3) (Scheme 1).[27] A 106.94 g (620 mmol) amount of 1,4,7,10-tetraazacyclododecane (**2**), 102.8 g (713.8 mmol) of *N*,*N*-dimethylformamide dimethyl acetal, and 900 mL of toluene were combined and heated to 120 °C under nitrogen while the methanol/toluene azeotrope distilled off during 100 min. Distillation of toluene was continued for additional 60 min. The reaction mixture was concentrated in vacuo at 70 °C. The residue was a yellow oil and used in the next step without purification.

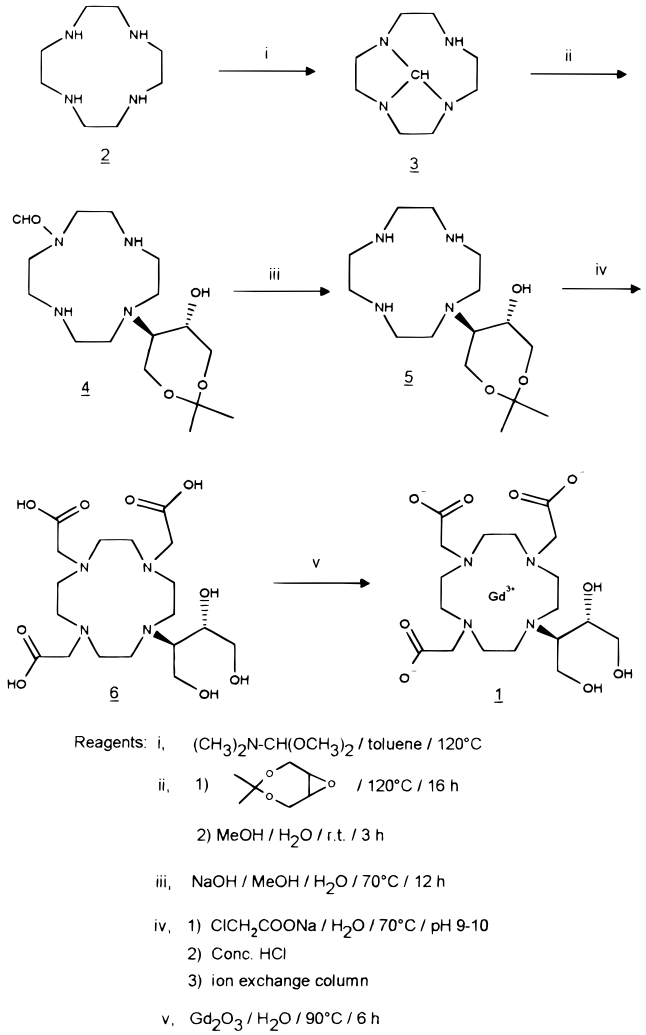
1-Formyl-7-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,-10-tetraazacyclododecane (4) (Scheme 1). To tricyclic **3** was added 98.35 g (683 mmol) of 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane and heated to 120 °C for 16 h. The mixture was cooled to room temperature and then stirred with 1000 mL of methanol/water (3:1) under nitrogen for 3 h and concentrated in vacuo. The residue was purified via flash chromatography (silica gel, methyl *tert*-butyl ether/methanol/25% aqueous NH_4OH: 20/5/1 followed by 3/2/1) to yield 155.9 g (73%) of **4** as a viscous oil.

Mass spectrum (FAB): *m*/*e* 345 [(M + H)$^+$]. ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 3H), 1.32 (s, 3H), 2.20−4.40 (m, 25 H), 8.15 (s, 1H). Infrared spectrum (KBr, cm^{-1}): 3340, 3395, 3290, 3260, 2880, 1680, 1665, 1490, 1460, 1220, 1080, 1055. Anal. Calcd (found) for $C_{16}H_{32}N_4O_4 \cdot 0.71H_2O$: C, 53.79 (53.61); H, 9.03 (9.21); N, 15.68 (15.47); H_2O (3.58).

1-(6-Hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (5) (Scheme 1). To 110 g (319.35 mmol) of 1-formyl-7-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (**4**) dissolved in a mixture of 300 mL of methanol and 100 mL of water was added 110 g (2.75 mol) of sodium hydroxide, and the mixture was stirred at 70 °C for 12 h. The solution was evaporated in vacuo and the residue dissolved in 200 of mL water and extracted 3 times with 400 mL of toluene at 70 °C. The combined toluene layers were dried with KOH and filtered, and the filtrate was evaporated under reduced pressure to yield 94.1 g (93%) of **5** as a viscous oil.

Mass spectrum (FAB): *m*/*e* 317 [(M + H)$^+$]. ^{1}H NMR (D_2O): δ 1.48 (s, 6H), 2.50−2.95 (m, 17H), 3.60−3.80 (m, 25 H). Infrared spectrum (film, cm^{-1}): 3280, 2990, 2940, 2890, 2830, 1460, 1380, 1220, 1160, 1090, 1060. Anal. Calcd (found) for $C_{15}H_{32}N_3O_3$: C, 55.51 (55.32); H, 6.47 (6.69); N, 7.19 (7.05); S, 12.35 (12.21).

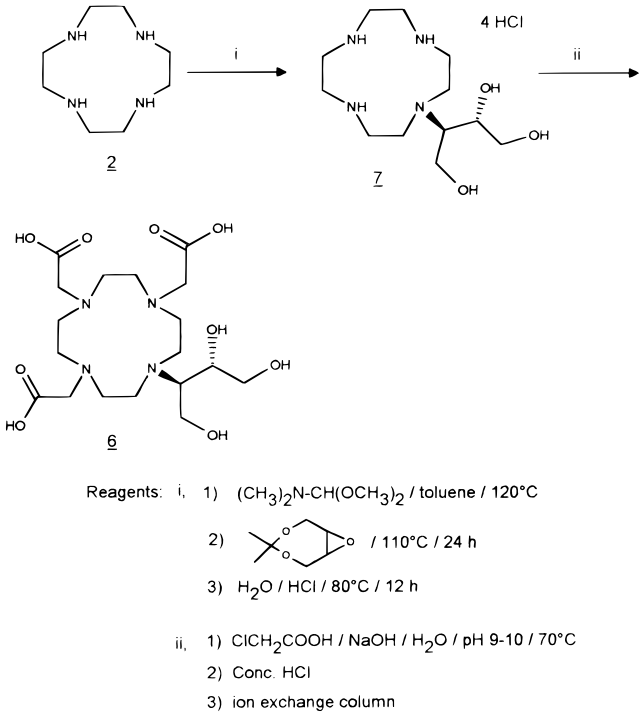
Scheme 1



1,4,7-Tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane (6) (Scheme 1). To a solution of 90 g (284.4 mmol) of 10-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (**5**) in 500 mL of water was added 165.63 g (1.42 mol) of chloroacetic acid sodium salt. The solution was warmed to 70 °C and the pH adjusted to 10 using 40% aqueous NaOH. The pH was adjusted as necessary to maintain a value of 9−10. After 6 h an additional 33.13 g (284.4 mmol) of chloroacetic acid sodium salt was added and stirring was continued for 12 h at pH 9−10. After the solution was cooled to room temperature, the pH was adjusted to 1 using concentrated HCl. The solution was evaporated in vacuo. The residue was dissolved in 1000 mL of methanol, and the solution was stirred for 30 min at room temperature. The solid (NaCl) was collected by filtration, and the filtrate was evaporated under vacuo to yield a glassy solid. The residue was dissolved in water and passed down a cation-exchange column (4 L, IR 120, H$^+$-form). The column was washed well with deionized water, and the ligand **6** eluted from the column with a solution of 2 M NH_4OH. The solvent was removed in vacuo to yield the partially ammonium salt of **6**. The residue was dissolved in 1000 mL of water, and the pH of the solution was adjusted to pH 3.4 by adding cation-exchange resin under stirring. The resin was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The solid was triturated with CH_3OH and dried in a vacuum oven at 50 °C to give 99.94 g (78%) of DO3A-butrol (**6**) as a colorless solid.

Mass spectrum (FAB): *m*/*e* 451 [(M + H)$^+$]. ^{1}H NMR (D_2O): δ 3.60−4.00 (m). ^{13}C NMR (D_2O): δ 46.4 (t), 47.3 (t), 50.5 (t), 50.6 (t), 53.0 (t), 54.1 (t), 57.3 (t), 60.6 (d), 61.2 (t), 61.6 (t), 64.6 (t), 73.5 (d), 184.5 (s), 184.8 (s). Infrared spectrum (KBr, cm^{-1}) : 3420, 1630,

Scheme 2



1600, 1460, 1400, 1330. Anal. Calcd (found) for $C_{18}H_{34}N_4O_9 \cdot 1.53H_2O$: C, 45.22 (45.07); H, 7.20 (7.35); N, 11.72 (11.53); H_2O (5.76).

[1,4,7-Tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecanato]gadolinium (1) (Scheme 1). To a solution of 91.34 g (202.8 mmol) of **6** in 500 mL of water was added 36.75 g (101.4 mmol) of Gd_2O_3, and the suspension was stirred 6 h at 90 °C. After the solution was cooled to room temperature, 120 mL of cation-exchange resin (IR 120/H^+-form) and 120 mL of anion exchange resin (IRA 67/OH^--form) were added and stirring was continued for 30 min. The resin was collected by filtration, and after addition of 5 g of charcoal the mixture was refluxed for 1 h. The hot solution was filtered through a 0.2 μm filter and evaporated to dryness. The residue was dissolved in 200 mL of water, and to the clear solution was added slowly 1800 mL of ethanol. The solution was refluxed for 2 h and then cooled to room temperature. The solid was collected by filtration and dried in a vacuum oven (12 h/60 °C) to yield 106.7 g (87%) of **1** as a white powder.

Mass spectrum (FAB): *m*/*e* 606 [(M + H)$^+$]; *m*/*e* 1211 [(2M + H)$^+$]. Infrared spectrum (KBr, cm^{-1}): 3560, 3280, 2980, 2975, 2940, 2920, 2880, 2870, 1650, 1600, 1380. Anal. Calcd (found) for $C_{18}H_{31}N_4O_9$ Gd·1.07H_2O: C, 34.65 (34.49); H, 5.01 (5.19); N, 8.98 (8.82); Gd, 25.20 (25.11); H_2O (3.09).

1-(1-(Hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane] Tetrahydrochloride (7) (Scheme 2). A solution of 100 g (580.48 mmol) of 1,4,7,10-tetraazacyclododecane (**2**) 100 mL (752.77 mmol) of *N*,*N*-dimethylformamide dimethyl acetal, and 700 mL of toluene was heated to 120 °C under nitrogen while the methanol/toluene azeotrope distilled off over 100 min. Distillation of toluene was continued for additional 60 min. The reaction mixture was concentrated in vacuo at 70 °C and cooled to room temperature. Then 98.35 g (683 mmol) of 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane was added and the mixture was heated to 110 °C over 24 h. The solution was cooled to room temperature, and 600 mL of water was added. The aqueous solution was extracted twice with 250 mL of ethyl acetate. To the aqueous layer was added 500 mL of concentrated hydrochloric acid, and the mixture was stirred for 12 h at 80 °C. The solution was evaporated under reduced pressure, and the residue was dissolved in 400 mL of a mixture of methanol and ethanol (1:1) and evaporated to dryness again. The residue was stirred with 600 mL of methanol at 60 °C for 2 h. After the mixture was cooled to 0 °C, the solid was collected by filtration, washed with methanol and finally with ether, and dried in a vacuum oven at 50 °C for 12 h. Yield 198.5 g (81%) of **7** as a white crystalline powder.

Mass spectrum (FAB): *m*/*e* 277 [(M + H)$^+$]. ^{1}H NMR (DMSO-d_6): δ 2.7−4.0 (m), 9.8 (s). Infrared spectrum (KBr, cm^{-1}): 3420, 3000, 2920, 2815, 2780, 2740, 2680, 1610, 1575, 1440, 1120, 1100, 1070, 1060. Anal. Calcd (found) for $C_{12}H_{32}N_4O_3$ Cl_4·0.21H_2O: C, 33.83 (33.69); H, 7.57 (7.78); N, 13.15 (13.03); Cl, 33.29 (33.01); H_2O (0.89).

1,4,7-Tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane (6) (Scheme 2). To a solution of 50 g (118.42 mmol) of **7** in 200 mL of water was added 55.95 g (592.08 mmol) of chloroacetic acid. The solution was warmed to 70 °C and the pH adjusted to 10 using 40% aqueous NaOH. The pH was adjusted as necessary to maintain it at 9−10. After 6 h further 11.19 g (118.42 mmol) of chloroacetic acid was added and stirring was continued for 12 h (pH 9−10). After the solution was cooled to room temperature the pH was adjusted to pH 1 using concentrated HCl. The solution was evaporated under reduced pressure, the residue dissolved in 300 mL of a mixture of methanol and ethanol (1:1), and evaporated again. The residue was stirred with 400 mL of methanol for 30 min at 50 °C. After the mixture was cooled to 0 °C, the solid (NaCl) was collected by filtration and the filtrate evaporated to dryness. The residue was purified by an ion-exchange column as it was described for the first preparation of **6**, according to Scheme 1. After trituration with methanol the solid was dried in a vacuum oven for 12 h at 50 °C. Yield: 34.68 g (65%) of **6** as a colorless solid.

Anal. Calcd (found) for $C_{18}H_{34}N_4O_9 \cdot 1.84H_2O$: C, 44.70 (44.53); H, 7.04 (7.25); N, 11.59 (11.41); H_2O (6.85).

{[4-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)]-1,7-bis[(4-methylphenyl)-sulfonyl]-1,4,7-triazaheptanato}disodium (9) (Scheme 3). A 487.22 g (2.47 mol) amount of *N*-(4-(methylphenyl)sulfonyl)-aziridine[16] was dissolved in 1 L of a mixture of toluene and acetonitrile (1:1) and heated to 50 °C. To this solution was added 178.94 g (1.11 mol) of 5-amino-6-hydroxy-2,2-dimethyl-1,3-dioxepane in small portions over 1 h. The mixture was stirred at 50 °C for 12 h and then evaporated to dryness under reduced pressure. A sample of 1 g was purified via flash chromatography for analytical purposes (silica gel, CH_2Cl_2/ethanol: 20/1). Crystallization from acetone/diethyl ether yielded 680 mg of 1,7-bis[(4-methylphenyl)sulfonyl]-4-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7-triazaheptane as a colorless solid.

Mass spectrum (FAB): *m*/*e* 556 [(M + H)$^+$]. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 3H), 1.27 (s, 3H), 2.15−2.30 (m, 2H), 2.40 (s, 6H), 2.58 (dt (15 Hz, 2 Hz), 2H), 2.64−3.00 (m, 6H), 3.40−3.70 (m, 5H), 3.80 (s, 1H), 6.07 (dd (8 Hz, 3 Hz), 2H), 7.30 (d(9 Hz), 4H), 7.78 (d(9 Hz), 4H). Infrared spectrum (KBr, cm^{-1}): 3475, 3280, 2990, 2945, 2880, 1325, 1220, 1160, 1090, 820, 665, 550.

Anal. Calcd (found) for $C_{25}H_{37}N_3O_7S_2$: C, 54.03 (54.27); H, 6.71 (6.95); N, 7.56 (7.42); S 11.54 (11.38).

The crude residue (about 668 g) was dissolved in 1.3 L of ethanol at 60 °C. To this solution was added a solution of NaOEt (prepared from 61.18 g (2.66 mol) of sodium in 1.2 L of ethanol), and the mixture was refluxed for 5 h. After cooling of the suspension to 0 °C, the solid was collected by filtration, washed twice with 250 mL of ethanol and twice with 800 mL of diethyl ether, and dried in a vacuum oven at 60 °C for 24 h to yield 660 g (quantitative) of **9** as a colorless, hygroscopic powder.

Anal. Calcd (found) for $C_{25}H_{35}N_3O_7S_2Na_2$: C, 50.07 (50.28); H, 5.88 (5.98); N, 7.01 (6.88); S, 10.69 (10.47); Na, 7.67 (7.35).

1-(6-Hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-4,7,10-tris[(4-methylphenyl)sulfonyl]-1,4,7,10-tetraazacyclododecane (10) (Scheme 3). A 300 g (0.5 mol) amount of **9** was dissolved in 3 L of DMF and heated to 100 °C. A solution of 283.85 g (0.5 mol) of *N*,*N*-bis[2-(((4-methylphenyl)sulfonyl)oxy)ethyl]-4-methylbenzenesulfonamide[17] in 1.5 L of DMF was added over a period of 4.5 h. The mixture was stirred at 100 °C for 16.5 h. After being cooled to 80 °C and subsequent addition of 4 L of water, the suspension was cooled to 10 °C, the solid was collected by filtration, washed twice with 1 L of water, and

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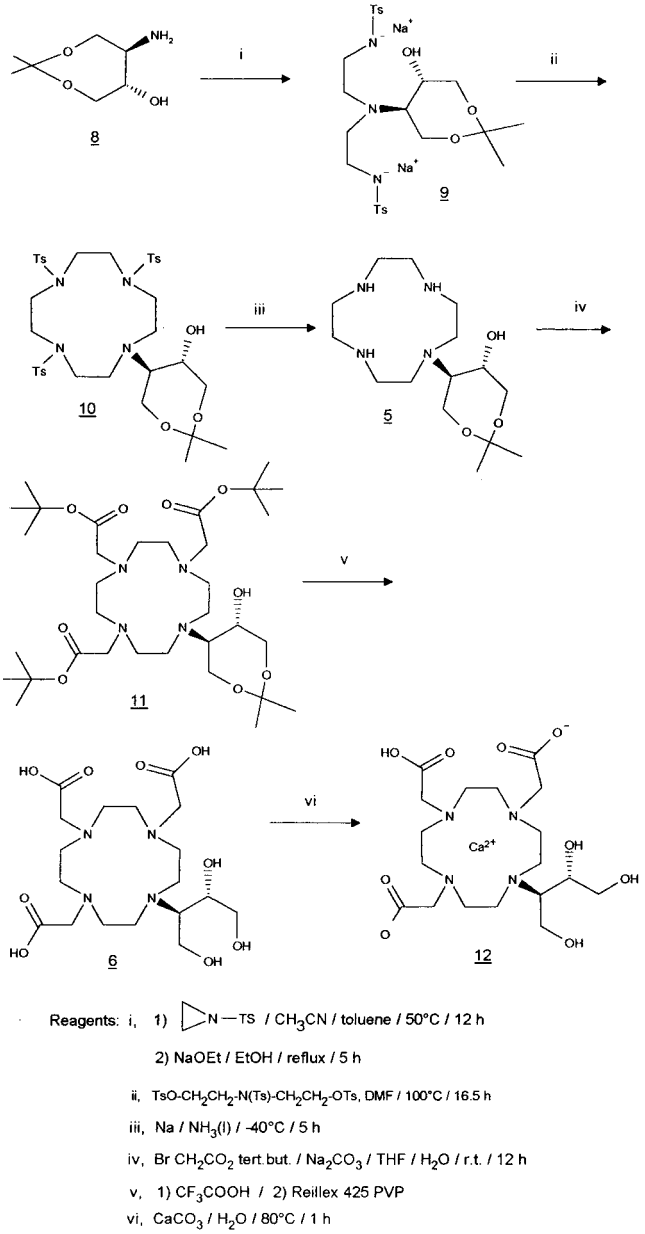
Scheme 3



dissolved in 2 L of CH_2Cl_2, and the solution was extracted twice with 1 L of 5% aqueous NaOH. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from a mixture of methyl *tert*-butyl ether/acetone (10:1) and dried in a vacuum oven at 50 °C for 24 h. Yield: 140 g (35.9 %) of **10** as a white powder. From the mother liquid a second crop of 35 g (9%) of **10** was isolated.

Mass spectrum (FAB): *m*/*e* 780 [(M + H)$^+$]. ^{1}H NMR ($CDCl_3$): δ 1.26 (s, 6H), 2.40 (s, 9H), 2.30−2.45 (m, 2H), 3.05−3.80 (m), 7.30−7.40 (m, 6H), 7.60−7.75 (m, 6H). Infrared spectrum (KBr, cm^{-1}): 3520, 2990, 2940, 1600, 1490, 1450, 1340, 1155, 1090, 695, 495. Anal. Calcd (found) for $C_{36}H_{50}N_4O_9S_3$: C, 55.51 (55.78); H, 6.47 (6.70); N, 7.19 (7.03); S, 12.35 (12.15).

1-(6-Hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (5) (Scheme 3). A 600 mL amount of ammonia was condensed into a 2-L three-neck round bottom flask containing 40 g (51.35 mmol) of **10**. The flask was maintained in a dry ice/acetone bath under a N_2 atmosphere. To this solution 16.4 g (713 mmol) of sodium (cut in small pieces) was added over a period of 30 min. The color of the solution turned to dark blue. After being stirred for 5 h at −40 °C, the solution was cooled to −50 °C and quenched by slow addition of 100 mL of methanol. The ammonia was evaporated overnight, and to the residue was added 300 mL of 30% aqueous KOH. The alkaline solution was extracted three times with 200 mL of toluene at 70 °C. The combined organic layers were dried with KOH, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH/25% aqueous NH_4OH: 10/1). The fractions containing the desired product were combined and concentrated in vacuo at 50 °C. The residue was dissolved in 300 mL of toluene and the solution dried with KOH and filtered. The filtrate was evaporated under reduced pressure to yield 5.36 g (33%) of **5** as a slightly yellow viscous oil.

Anal. Calcd (found) for $C_{15}H_{32}N_4O_3$: C, 56.93 (57.18); H, 10.19 (10.32); N, 17.71 (17.52).

1,4,7-Tris(*tert*-butoxycarbonylmethyl)-10-(6-hydroxy-2,2-dimethyl-1,3-dioxepane-5-yl)-1,4,7,10-tetraazacyclododecane (11) (Scheme 3). To a suspension of 19.51 g (38.51 mmol) of **5** and 16.33 g (154.04 mmol) of sodium carbonate in a mixture of 300 mL of THF and 10 mL of water was added 30 g (154 mmol) of bromoacetic acid *tert*-butyl ester over 30 min. After the mixture was stirred at room temperature for 12 h, the solid was collected by filtration and the filtrate concentrated in vacuo. The residue was dissolved in 300 mL of CH_2Cl_2 and the solution extracted twice with 200 mL of a 5% aqueous sodium carbonate solution. The combined organic layers were dried with $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH: 20/1). Yield: 30.87 g (76%) of **11** as a colorless solid foam.

Mass spectrum (FAB): *m*/*e* 660 [(M + H)$^+$]. ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.34 (s, 3H), 1.46 (s, 9H), 1.90−3.10 (m, 11H), 3.20-3.80 (m, 17H). Infrared spectrum (KBr, cm^{-1}): 3350, 2980, 2960, 2860, 2820, 1730, 1455, 1390, 1380, 1370, 1225, 1160, 1110. Anal. Calcd (found) for $C_{33}H_{62}N_4O_9$: C, 60.16 (60.32); H, 9.48 (9.61); N, 8.50 (8.32).

1,4,7-Tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane (6) (Scheme 3). A solution of 30 g (45.53 mmol) of **11** in 150 mL of trifluoroacetic acid was stirred at room temperature for 12 h. The solution was evaporated under reduced pressure. The solid residue was dissolved in 50 mL of water and concentrated in vacuo. This process was repeated three times to remove most of the trifluoroacetic acid. The material was dissolved in 60 mL of water and applied to a 500 g column of Reillex 425 PVP resin. The column was eluted with water, and the fractions containing the desired compound were combined and concentrated in vacuo. The solid was triturated with methanol and dried in a vacuum oven at 50 °C for 12 h to yield 19.07 g (93%) of **6** as a colorless solid.

Anal. Calcd (found) for $C_{18}H_{34}N_4O_9 \cdot 1.91H_2O$: C, 44.59 (44.42); H, 7.07 (7.21); N, 11.56 (11.42); H_2O (7.09).

[1,4,7-Tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecanato]calcium (12) (Scheme 3). To a solution of 3.835 g (8.513 mmol) of **6** in 40 mL of water was added 835 mg (8.343 mmol) of $CaCO_3$. The mixture was stirred at 80 °C for 1 h. The solution was filtered and the filtrate evaporated to dryness under reduced pressure. The residue was suspended in 100 mL of ethanol and stirred at 50 °C for 1 h. After being cooled to 0 °C the solid was collected by filtration, washed twice with 30 mL of ethanol, and dried in a vacuum oven at 60 °C for 24 h to yield 3.91 g (94%) of **12** as a colorless powder.

Mass spectrum (FAB): *m*/*e* 489 [(M + H)$^+$]. ^{1}H NMR (DMSO-d_6): δ 1.90−2.30 (m), 2.40−2.90 (m), 3.00−3.80 (m), 3.91 (d (8Hz)), 4.08−4.20 (br), 4.55 (br), 10.21 (s). ^{13}C NMR (DMSO-d_6): δ 44.70 (t), 45.27 (t), 47.89 (t), 48.22 (t), 48.70 (t), 52.18 (t), 52.95 (t), 56.21 (t), 57.21 (t), 58.56 (t), 58.74 (d), 59.77 (t), 64.27 (t), 70.58 (d), 157.27 (s), 176.56 (s), 178.41 (s). Infrared spectrum (KBr, cm^{-1}): 3400, 2960, 2840, 1600, 1410, 1325, 1275, 1290, 1095. Anal. Calcd (found) for $C_{18}H_{32}N_4O_9$ Ca·1.84H_2O: C, 41.44 (41.65); H, 6.18 (6.32); N, 10.74 (10.65); Ca, 7.68 (7.57); H_2O (6.35).

Collection and Reduction of X-ray Diffraction Intensity data for Gadobutrol (1). Crystallization of gadobutrol (**1**) ($C_{18}O_9N_4H_{31}Gd \cdot H_2O$) was made from a mixture of water/ethanol/diethyl ether. The crystal used for the X-ray investigation was cut from a bigger piece and sealed in a thin-walled glass capillary (0.7 mm diameter) together with a droplet of solvent, since it was originally unknown if the crystals were stable outside the solvent. Scans over various reflection profiles indicated only moderate crystal quality, which had to be accepted since

no better specimen could be chosen from the few crystals available. All X-ray work was performed using Nb-filtered Mo Kα radiation with a Siemens four-circle diffractometer controlled by a DEC micro PDP-11 computer.

Cell constants (a = 8.95(2), b = 17.63(2), c = 14.41(2) Å; β = 104.35(9)°; monoclinic, space group $P2_1/n$; one complex molecule per asymmetric unit) and the orientation matrix were obtained by least-squares refinement of 19 centered high-order reflections. A total of 4128 intensity data (3891 unique data) of two octants (*hkl* and $\bar{h}kl$) were recorded by the $\omega-2\theta$ scan technique with variable scan range and variable scan speed up to a resolution of 0.84 Å. Three standard reflections measured every 90 min showed no significant variations. The X-ray data were corrected for Lorentz and polarization effects, but no absorption correction was applied.

Solution and Refinement of the Structure of Gadobutrol (1). The structure was solved with the direct-methods program SHELXS86,[18] while the refinement and related calculations were done with the crystallographic computer program package XTAL.[19] One additional maximum found in the structure determination process having no bond distance to any atom of the complex was interpreted as an oxygen of a water molecule, so that the complex exists as a monohydrate in the crystalline state. First isotropic and later anisotropic displacement coefficients were assigned to all non-hydrogen atoms. Most of the methylene hydrogens and one OH hydrogen (at O14) could be located from difference syntheses and were included in the refinement with isotropic displacement parameters. All further methylene hydrogens were placed in calculated positions. The hydrogens at the remaining oxygens were not located and were not considered in the analysis. After convergence of the refinement, a final R-value of 7.4% (R_w = 8.7%) was obtained using 3465 intensity data with $F_0 > 2\sigma(F_0)$ (data-to-parameter ratio 8.6:1).

Collection and Reduction of X-ray Diffraction Intensity Data for Calcium Complex 12. Crystals of calcium complex **12** ($C_{18}O_9N_4H_{32}$-Ca·1.5H_2O) can easily be obtained from mixtures of water and alcohol. However, for several specimen tested, the qualities of the diffraction patterns were only modest: The intensities of the reflections were low and their profiles often broad or even split. Since recrystallization did not improve the diffraction quality, one of these crystals with a volume of 0.5 × 0.3 × 0.2 mm^3 was used for data collection.

The crystal was glued to a glass fiber and mounted on a Siemens P4 diffractometer. The cell constants (a = 16.697(5), b = 18.393(5), c = 30.97(1) Å; orthorhombic, space group *Pbca*; two complex molecules per asymmetric unit) were derived from the positions of 27 centered reflections. Using monochromated Mo Kα radiation, a total of 12 970 reflections (6204 unique data) were collected up to a resolution of 0.93 Å. A loss of intensity (approximately 15%) of the three periodically measured standard reflections indicated that the crystal decomposed slightly during data collection. The data were scaled according to the loss of intensity. They were corrected for Lorentz and polarization effects, and a semi-empirical absorption correction was applied.

Solution and Refinement of the Structure of Calcium Complex 12. All calculations were performed using the Siemens SHELXTL+ (VMS)[20] program package. The structure was solved by direct methods and subsequent Fourier syntheses. Four additional maxima in the electron density map were interpreted as water positions. Since the parallel refinement of temperature and occupancy factors for these positions gave no reasonable results, occupancy factors were assigned to keep the isotropic displacement coefficient below 0.15 $Å^2$. For the other non-hydrogen atoms, anisotropic displacement coefficients were refined. The methylene hydrogen atoms were included into calculated positions, and some of the remaining OH hydrogens were located from a difference Fourier synthesis. An overall temperature factore was refined for all hydrogen atoms. Convergence of the refinement using 2909 intensity data with $F > 3\sigma(F)$ was achieved at R = 7.7 (R_w = 8.5%, data-to-parameter ratio 4.9:1).

(18) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467−473.
(19) Hall, S. R., Stewart, J. M., Eds. *XTAL 2.2 Users Manual*; University of Western Australia, Nedlands, WA, and University of Maryland, College Park, MD, 1987.
(20) SHELXTL PLUS, Siemens Analytical X-Ray Instruments, Inc.

Results and Discussion

We have developed several approaches to the new macrocyclic ligand DO3A-butrol (**6**). In two of the procedures we started with commercially available 1,4,7,10-tetraazacyclododecane (cyclen, **2**); in the third procedure we established the macrocycle already bearing the butrol side chain by using a modified Richman−Atkins-type synthesis.

According to Scheme 1 cyclen **2** was treated in toluene with dimethylformamide dimethyl acetal to give the known tricyclic compound 1,4,7,10-tetraazatricyclo [5.5.1.0]tridecane (**3**),[27] which without further purification was reacted with 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane at 120 °C, yielding an intermediate which without isolation upon solvolysis with water−methanol (1:3) gave formyl derivative **4** in a 73% yield. ^{1}H-NMR- and ^{13}C-NMR-spectroscopic investigations indicate the formation of the 1,7-disubstituted isomer; the 1,4-substituted product was not observed. Presumably, the steric hindrance imposed by the substituted dioxepanyl ring prevents the formation of the 1,4-isomer. Alkaline treatment of **4** removed the formyl group and resulted in the formation of the monosubstituted cyclen derivative **5** in a 93% yield. Alkylation of **5** with chloroacetic acid sodium salt in water at pH 9−10 and 70 °C gave the ligand DO3A-butrol (**6**). For the purification an acidic solution of **6** was absorbed on a cation-exchange column. Elution with 2 M aqueous ammonia provided the purified ligand, mostly in the form of its ammonium salt, the solution of which was stirred with cation-exchange resin. The material isolated from this solution crystallizes on treatment with methanol.

The complexation of **6** with gadolinium was performed with gadolinium oxide in water at 90 °C. Since the complex **1** does not have any overall charge, all ionic impurities were removed simply by stirring the aqueous solution of **1** with a mixture of anion- and cation-exchange resins. Finally, **1** was crystallized from aqueous ethanol (90%) yielding a material with a purity >99% according to HPLC.

The corresponding calcium complex **12** (see Scheme 3) used for the pharmaceutical formulation of **1** was prepared from the ligand **6** by reaction with calcium carbonate.

For the preparation of Gd-DO3A-butrol on the kilogram scale we prefer the approach described in Scheme 2. Thus, in analogy to the above outlined procedure cyclen **2** was converted to **3** and without isolation reacted with 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane to give the formyl derivative **4**, which also without isolation was treated with aqueous hydrochloric acid at 80 °C. Under these conditions both the formyl group was removed and the dioxepanyl ring gave rise to the free butrol side chain yielding the monosubstituted cyclen derivative in the form of its tetrahydrochloride **7**. The overall yield for this reaction sequence was 81% based on cyclen **2**. Similar to the conversion of **5** to **6** (see Scheme 1), **7** was reacted with chloroacetic acid to give **6** (65%).

A different approach to our key intermediate **5** based on a modified Richman−Atkins procedure is described in Scheme 3. Starting with 5-amino-6-hydroxy-2,2-dimethyl-1,3-dioxepane the reaction with *N*-((4-methylphenyl)sulfonyl)aziridine provided an intermediate which upon treatment with sodium ethoxide yielded **9**, one of the components necessary for the formation of the desired macrocycle. **9** was condensed with *N*,*N*-bis[2-(((4-methylphenyl)sulfonyl)oxy)ethyl]-4-methylbenzenesulfonamide to give **10** in a 45% yield. Removal of the tosyl amide protecting groups was accomplished by reductive cleavage with sodium in liquid ammonia. Although dissolving metal reductions of tosyl amides are not without complications and yields seldom exceed 80%, the observed yields in our hands were disappointing (33%) and prohibited us from using this approach

Table 1. Crystal Data and Structure Refinement for Compounds **1** and **12**

	compound	
	1	**12**
empirical formula	$C_{18}O_9N_4H_{31}Gd\cdot H_2O$	$C_{18}O_9N_4H_{32}Ca\cdot 1.5H_2O$
temp (K)	293	293
wavelength (Å)	0.710 73	0.710 73
cryst system	monoclinic	orthorhombic
space group	$P2_1/n$	*Pbca*
a (Å)	8.953(19)	16.697(5)
b (Å)	17.631(17)	18.393(5)
c (Å)	14.410(17)	30.969(10)
β (deg)	104.35(9)	90
V (Å^3)	2204	9513
Z	4	16
calcd density (g/cm^3)	1.877	1.42
abs coeff (mm^{-1})	3.172	0.324
F(000)	1252	4355
cryst size (mm^3)	1.2 × 0.9 × 0.8	0.5 × 0.3 × 0.2
θ range for data collcn	1.5−25	1.5−22.5
reflcns collcd	4128	12970
indepdt reflcns	3891	6204
data/params	3465/402	2909/594
R value (obsd data) (%)	7.4	7.7

for a large scale production of **1**. For the introduction of the acetic acid side chains **5** was alkylated with *tert*-butyl bromoacetate to give **11**, which after cleavage of the *tert*-butyl esters with trifluoroacetic acid yielded the DO3A-butrol ligand **6**. Purification was performed by passing an aqueous solution of **6** down a column of Reillex 425 PVP resin.

Thermodynamic and Kinetic Stability. DO3A-butrol **6** is an analogue of DOTA missing one of the DOTA carboxylates with three alcoholic hydroxyl groups in one side chain. The complexation properties of DO3A-butrol **6** with a variety of metal ions have been studied in detail.[15] The stability constant obtained for the gadolinium complex **1** (log $K = 21.8$ in 0.1 M KCl) is nearly 2 orders of magnitudes lower when compared with both Gd−DTPA and Gd−DOTA. This is not unexpected since it is generally accepted that the hard lewis acid Gd(III) is more tightly bound to negatively charged atoms rather than to neutral ones. A comparison of the stabilities of **1** and Gd−HP-DO3A (log $K = 23.8$)[5] shows that the introduction of additional hydroxyl groups in one of the side chains decreases the stability. A possible explanation is the formation of intramolecular hydrogen bonds which can reduce the electron density on the metal coordinating hydroxylic oxygen atom. The lower thermodynamic stability is without any consequence for the application in patients, as the complex exhibits excellent kinetic stability. The dissociation rate of the complexes **1** and the clinically used Gd−HP-DO3A[5−8] were studied spectrophotometrically at pH 3.2−5.3 by following the exchange reactions with Eu^{3+}. The rates of the exchange reactions proved to be linearly dependend on the H^+ concentration. The rate constants obtained for the proton-assisted dissociation of **1** and Gd−HP-DO3A are $(2.8 \pm 0.1) \times 10^{-5}$ M^{-1} s^{-1} and $(2.6 \pm 0.1) \times 10^{-4}$ M^{-1} s^{-1}, respectively.[15] Thus, the dissociation rate of **1** is about 10 times lower than that of Gd−HP-DO3A, which might be due to the bulkier 1-(hydroxymethyl)-2,3-dihydroxypropyl side chain of **1** when compared with the 2-hydroxypropyl group of the latter.

Crystal and Solution Structures. The numerical data for the structures **1** and **12** are given in Table 1 (crystal data), Table 2 (selected bond distances), and Table 3 (selected bond angles). A graphical presentation of gadobutrol **1** showing the atomic numbering scheme is given in Figure 1. The nine-coordinated Gd(III) has the four nitrogens of the aza crown, three oxygens of each of the three carboxylic groups, and one oxygen of the 1-(hydroxymethyl)-2,3-dihydroxypropyl side chain in its primary coordination sphere. In related compounds, the ninth coordination atom usually is the oxygen of a water molecule.[21] In this structure, however, the ninth coordination partner surprisingly is a carboxylate oxygen of a symmetry-related (via the crystallographic inversion center) complex molecule (see Figure 2). The geometry of the coordination polyhedron can be approximated by a monocapped square antiprism. The basal plane consists of the nitrogens in the macrocyclic ring; the upper plane next to the cap is formed by the secondary hydroxyl oxygen O14 and three carboxylate oxygens (see Figure 1), while the cap atom is O181 of the centrosymmetrically related complex as mentioned above. The two squares are planar with average displacements of contributing atoms of 0.012 and 0.021 Å, respectively. The planes are almost parallel with an angle of only 2.1(3)°. The Gd(III) cation approaches closer to the oxygen square (0.75 Å) than to the nitrogen square (1.69 Å); the distance of the cap atom O181 to these planes is 1.69 and 4.12 Å.

Table 2. Selected Bond Distances (Å) for Compounds **1** and **12**

compd **1**		compd **12** (1)[a]		compd **12** (2)[a]	
Gd−N1	2.741	Ca1−N1	2.711	Ca2−N31	2.657
Gd−N4	2.672	Ca1−N4	2.627	Ca2−N34	2.599
Gd−N7	2.664	Ca1−N7	2.674	Ca2−N37	2.598
Gd−N10	2.648	Ca1−N10	2.615	Ca2−N40	2.631
Gd−O14	2.405	Ca1−O15	2.386	Ca2−O45	2.318
Gd−O182	2.427	Ca1−O19	2.371	Ca2−O49	2.416
Gd−O202	2.360	Ca1−O22	2.395	Ca2−O52	2.403
Gd−O222	2.342	Ca1−O25	2.449	Ca2 -O55	2.345
Gd−O181[b]	2.430				

[a] Two molecules are present in the asymmetric unit. [b] This atom belongs to a centrosymmetrically related complex molecule.

From a structural point of view a number of different isomers could be present. In principle the three different hydroxyl groups in the ligand are able to interact with the central metal ion thus giving rise to three different constitutional isomers. The stereochemistry of the different configurational isomers of **1** is best described in view of the stereochemistry of the parent compound Gd−DOTA.[28] In Gd−DOTA chirality results from the restriction of free rotation around the bonds of the ligand caused by the inclusion of the central metal ion. Thus, four stereoisomers are generated upon complexation of Gd(III) by DOTA.[28]

In **1** the replacement of one of the acetic acid groups of Gd−DOTA by the chiral 1-(hydroxymethyl)-2,3-dihydroxypropyl group gives rise to a diastereomeric differentiation of the four stereoisomers. Therefore, for each of the three possible constitutional isomers of **1** four diastereomers have to be taken into account, thus, generating 12 diastereomers and a total of 24 stereoisomers.

Since the HPLC analysis of an aqueous solution of **1** on a nonchiral stationary phase shows only one narrow peak (>99%) along with some minor ones assumed to be impurities, we believe that the aqueous solution of **1** contains only one diastereomer. But in contrast to the crystalline state, the structure of **1** in aqueous solution is rather a monomer than a dimer in which the ninth coordination site is occupied by a water molecule. This is supported by relaxivity and osmolality measurements.[15]

For the calcium complex **12**, two complex molecules adopting almost identical conformations are present in the asymmetric

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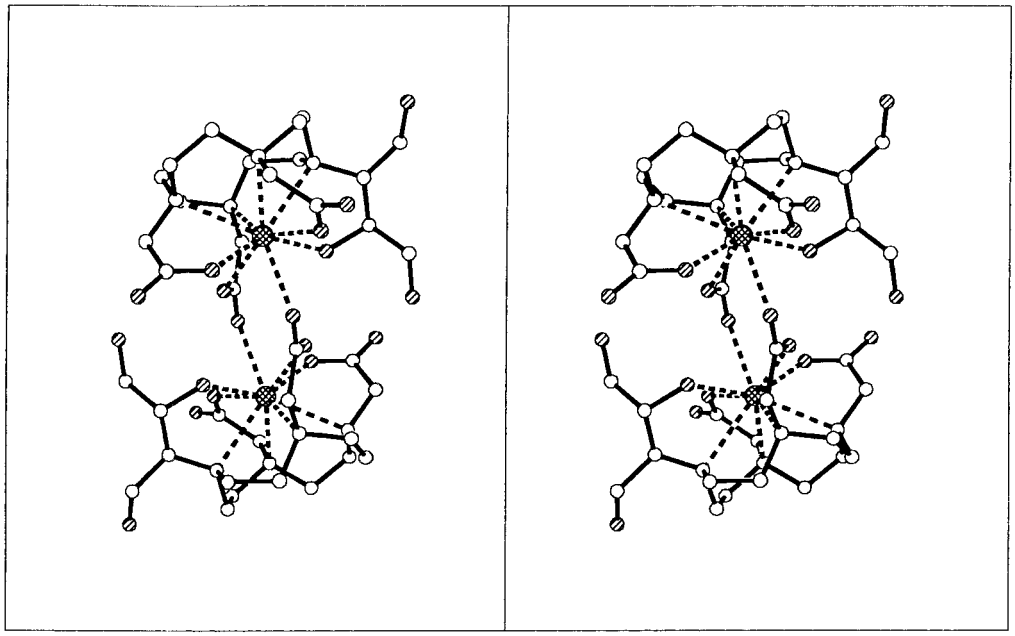

Figure 2. Stereo presentation of a complex dimer of Gadobutrol (**1**). Coordination contacts are drawn as dashed lines, and hydrogens have been omitted.

Table 3. Selected Bond Angles (deg) for Compounds **1** and **12**

compd **1**		compd **12** (1)[a]		compd **12** (2)[a]	
N1−Gd−N4	66.8	N1−Ca1−N4	66.9	N31−Ca2−N34	68.6
N1−Gd−N7	102.0	N1−Ca1−N7	105.4	N31−Ca2−N37	106.1
N1−Gd−N10	67.1	N1−Ca1−N10	69.4	N31−Ca2−N40	68.1
N1−Gd−O14	60.7	N1−Ca1−O15	65.1	N31−Ca2−O45	64.1
N1−Gd−O182	120.9	N1−Ca1−O19	117.8	N31−Ca2−O49	123.6
N1−Gd−O202	151.1	N1−Ca1−O22	158.6	N31−Ca2−O52	158.6
N1−Gd−O222	83.0	N1−Ca1−O25	89.0	N31−Ca2−O55	88.3
N1−Gd−O181[b]	126.4				
N4−Gd−N7	66.4	N4−Ca1−N7	67.8	N34−Ca2−N37	69.7
N4−Gd−N10	102.0	N4−Ca1−N10	103.8	N34−Ca2−N40	106.8
N4−Gd−O14	77.9	N4−Ca1−O15	92.2	N34−Ca2−O45	84.3
N4−Gd−O182	61.5	N4−Ca1−O19	65.3	N34−Ca2−O49	64.8
N4−Gd−O202	122.4	N4−Ca1−O22	120.8	N34−Ca2−O52	122.3
N4−Gd−O222	149.8	N4−Ca1−O25	155.9	N34−Ca2−O55	156.6
N4−Gd−O181[b]	126.7				
N7−Gd−N10	66.4	N7−Ca1−N10	68.1	N37−Ca2−N40	69.5
N7−Gd−O14	144.3	N7−Ca1−O15	160.0	N37−Ca2−O45	154.0
N7−Gd−O182	82.3	N7−Ca1−O19	91.0	N37−Ca2−O49	85.9
N7−Gd−O202	64.3	N7−Ca1−O22	64.6	N37−Ca2−O52	65.9
N7−Gd−O222	123.4	N7−Ca1−O25	120.8	N37−Ca2−O55	123.0
N7−Gd−O181[b]	131.5				
N10−Gd−O14	122.9	N10−Ca1−O15	120.0	N40−Ca2−O45	122.3
N10−Gd−O182	148.6	N10−Ca1−O19	159.0	N40−Ca2−O49	155.2
N10−Gd−O202	84.0	N10−Ca1−O22	89.3	N40−Ca2−O52	90.5
N10−Gd−O222	64.4	N10−Ca1−O25	64.4	N40−Ca2−O55	65.8
N10−Gd−O181[b]	131.3				
O14−Gd−O182	81.7	O15−Ca1−O19	79.4	O45−Ca2−O49	81.2
O14−Gd−O202	144.3	O15−Ca1−O22	130.2	O45−Ca2−O52	131.5
O14−Gd−O222	87.3	O15−Ca1−O25	77.8	O45−Ca2−O55	82.1
O14−Gd−O181[b]	71.7				
O182−Gd−O202	83.9	O19−Ca1−O22	82.3	O49−Ca2−O52	76.8
O182−Gd−O222	142.5	O19−Ca1−O25	132.3	O49−Ca2−O55	131.0
O182−Gd−O181[b]	71.4				
O202−Gd−O222	84.5	O22−Ca1−O25	81.4	O52−Ca2−O55	80.8
O202−Gd−O181[b]	72.8				
O222−Gd−O181[b]	71.1				

[a] Two molecules are present in the asymmetric unit. [b] This atom belongs to a centrosymmetrically related complex molecule.

unit. The only exceptions are the 1-(hydroxymethyl)-2,3-dihydroxypropyl groups which adopt slightly different conformations in the two crystallographically independent molecules. The two Ca(II) cations have only eight coordination partners. Except for the missing cap atoms, the coordination geometries are very similar for Gadobutrol **(1)** and the calcium complex **12** (see Figure 3). This might be due to the stability of the preferred conformation of the macrocycle described below.

The Gd···O coordination distances are in the range from 2.344(9) to 2.437(9) Å (Gd···O_{av} 2.40 Å); they are significantly longer for Gd···N, where they range from 2.65(1) to 2.74 (1) Å (Gd···N_{av} 2.68 Å). Almost identical values were found in a

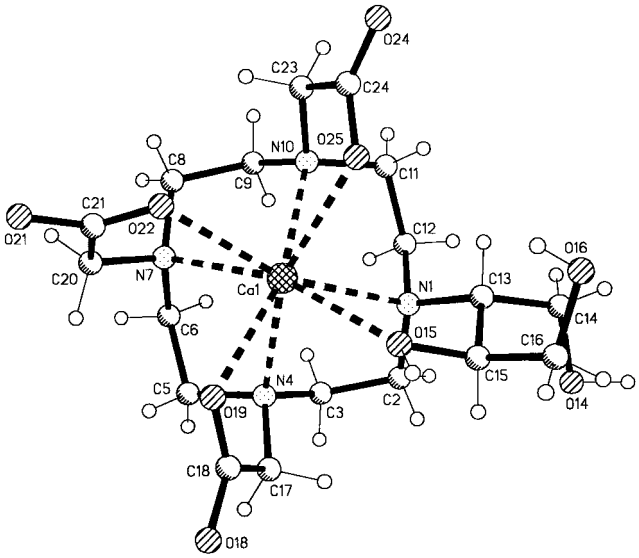

Figure 3. Structure of the calcium complex **12** in the crystal.

previous X-ray investigation of a tetraazacyclododecane−Gd complex.[22] The average Ca···O and Ca···N distances for **12** are almost identical to the corresponding coordination distances in Gadobutrol (1) (Ca···O_{av} 2.39 Å, Ca···N_{av} 2.64 Å).

In both compounds, the complex anion consists of the tetraazacyclododecane macrocycle being asymmetrically substituted in that the four nitrogens carry three carboxymethyl and one 1-(hydroxymethyl)-2,3-dihydroxypropyl group. Bond lengths and angles in this anion (see Supporting Information) do in no case differ from expectations if the high standard deviations for the calcium complex **12** are taken into consideration.

The 12-membered macrocycles adopt the typical square conformation described by Dale[23] as a [3333] form and having been found for cyclodedecane[23] and for crown ethers of the 12-crown-4 type.[24] It is characterized by an endocyclic gauche−trans−gauche conformations being present four times. The averaged numerical values for the corresponding torsion angles are −59, 162, and −79° for Gadobutrol **(1)**, and −60, 163, and −77° for the calcium complex **12**. For comparison, these values are −70, 165, and −70° for cyclododecane[25] and −76, 165, and −64° for a noncoordinated tetraazacyclododecane macrocycle.[26]

Since most O−H hydrogens could not be located in the two crystal structures, the existence of hydrogen bonds is based on O···O contacts only. The water present in the crystal structure of Gadobutrol **(1)** does not contribute to the Gd coordination but is engaged in hydrogen bonds to three different complexes, probably twice as a donor and once as an acceptor. It is interesting to note that the complex dimer described above obtains an additional stabilization by two hydrogen bond pairs. A direct contact is made via O14−H14···O182′, and an indirect connection involves the water molecule via the sequence O15−H···O1W···O201′. For the calcium complex **12**, direct hydrogen bonds between complexes are only observed between the two crystallographically independent molecules which are connected by three direct hydrogen bonds between O15···O49 (2.72 Å), O16···O51 (2.96 Å), and O18···O45 (2.57 Å). The two complex molecules are thus arranged pairwise although no dimers are formed as observed for **12**.

Conclusions

We have prepared a new ligand, 1,4,7-tris(carboxymethyl)-10-(1-(hydroxymethyl)-2,3-dihydroxypropyl)-1,4,7,10-tetraazacyclododecane (**6**) which was converted to a neutral highly hydrophilic and kinetically stable gadolinium chelate (**1**). The synthetic approaches allow the synthesis of **1** on a kilogram scale. **1** is used as a contrast agent in magnetic resonance imaging and is currently in clinical trials. Ligand **6** was also utilized to prepare the calcium complex **12** used as an additive in the pharmaceutical formulation of **1**.

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Supporting Information Available: Tables of crystallographic data, atomic parameters, complete bond lengths and bond angles, anisotropic thermal parameters, and hydrogen atom coordinates (21 pages). Ordering information is given on any current masthead page.

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