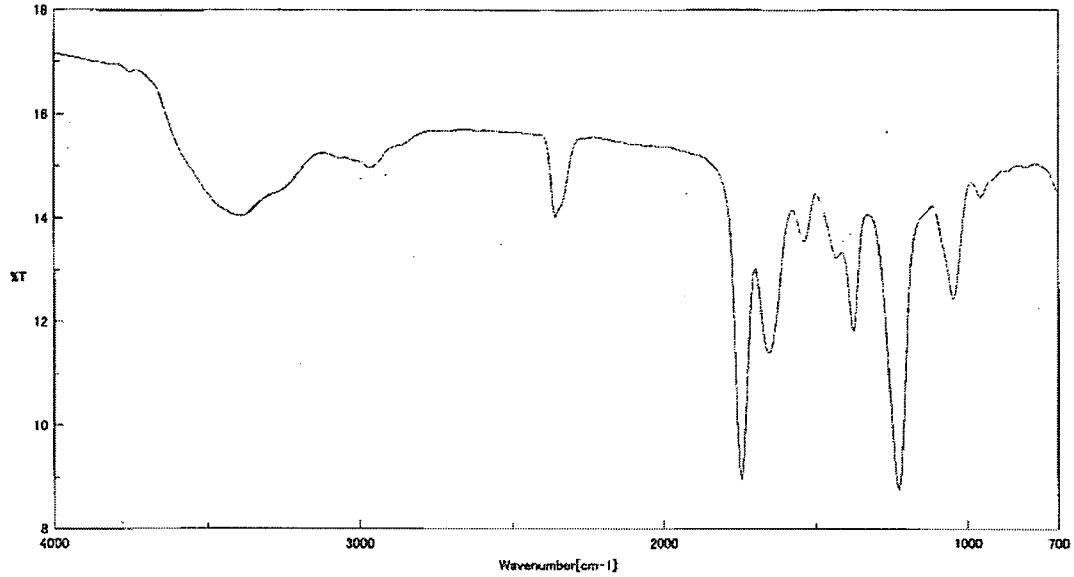


Fig.　２－５－１４　化合物 4 IR スペクトル

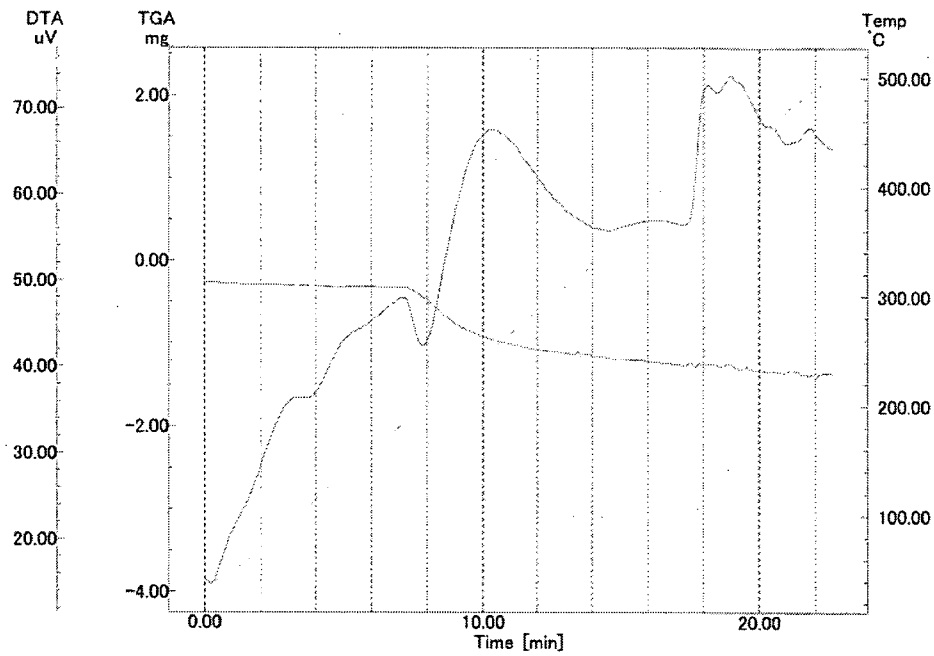


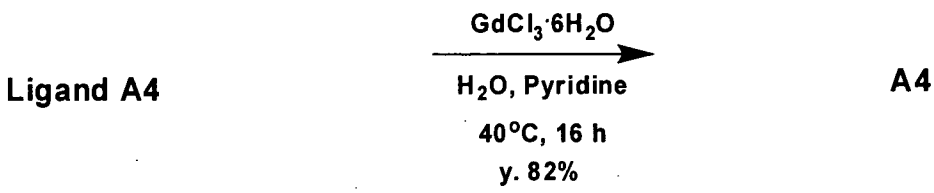
Fig.　２－５－１５　化合物 4 の熱分析

^{1}H-NMR スペクトルより 1.97-2.13 ppm にアセチル基由来のピークを、3.00-3.84ppm にヒドロキシル基由来のピークをそれぞれ確認し、それらのプロトン数とメチン及びメチレンのプロトン数を比較した。ここで、ヒドロキシル基由来のピークは D_2O 置換することで確認した。MS スペクトルより 1945.61 $[M-3H]^-$のピークを確認した。IR スペクトルより 3440 cm^{-1}に O-H 伸縮による吸収を示すことからヒドロキシル基の存在を、1743 cm^{-1}に C=O 伸縮による吸収と 1226 cm^{-1}に C-O 伸縮による吸収を示すことからエス

テルの存在を、1658 cm^{-1} に C=O 伸縮による吸収と 1542 cm^{-1} に N-H 変角による吸収を示すことからアミド基の存在をそれぞれ確認した。以上から化合物 4 の構造を同定した。

２－５－１－４　A4の合成

・A4 (5) の合成



Scheme　２－５－０５

（特許の関係で A4、Ligand　A４の構造については開示できない。）

Gd-DTPA のガドリニウム源として塩化ガドリニウム（Ⅲ）六水和物を利用した合成方法が報告されている。本研究でも、この合成方法を適用した。水中、ピリジン存在下、40℃で化合物 4 と塩化ガドリニウム（Ⅲ）六水和物を反応させることで A4 (5) を収率 82%で合成した。精製は再結晶（イソプロパノール）により行った。

以下に MS スペクトルのデータを示す。

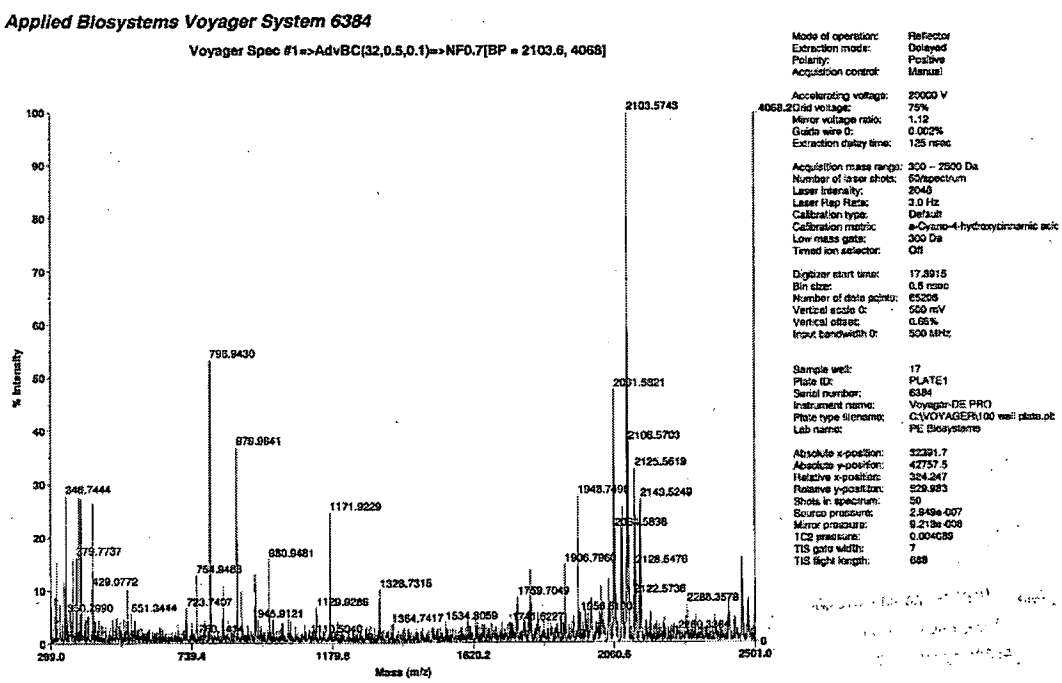


Fig.　２－５－１６　化合物 5 の MS スペクトル

MS スペクトルより 2103.57 $[M+H]^+$のピークを確認した。

２－５－２　実験項

２－５－２－１　使用試薬及び分析機器

全ての試薬類及び溶媒類は、和光純薬工業株式会社・シグマ アルドリッチ・東京化成工業株式会社・関東化学株式会社からの市販品を使用した。

^{1}H-NMR (300 MHz)スペクトルは、JEOL JNM-AL300 核磁気共鳴分光計を用いて測定した。このとき、重溶媒としては重クロロホルム (chloroform-*d*)、重水 (D_2O)、重ジメチルスルホキシド (DMSO-d_6) を使用し、内部標準としては TMS を使用した。

ATR-FTIR スペクトルは、JASCO FT/IR-410 赤外分光計を用いて測定した。

融点測定は、島津製作所 DTG-60A50AH 測定器を用いて測定した。

MALDI-TOF-MS による質量分析は、α-Cyano-4-hydroxycinnamic acid,99% をマトリックスとし、GL Science 社 Voyager-DE Porimerix を用いて測定した。

カラムクロマトグラフィーの固定相は、ワコーゲル C-200 を用いた。

２－５－２－２　実験操作

１）末端(Terminal)部の合成

・2,3,4,6-テトラ-*O*-アセチル-D(+)-グルコノ-1,5-ラクトンの (1) 合成

アルゴン雰囲気下、ナスフラスコに D(+)-グルコノ-1,5-ラクトン (5.00 g, 28.1 mmol) 、無水酢酸 (30 ml)、トリフルオロ酢酸 (2.5 ml) を入れ、室温で 3 時間撹拌した。減圧下で溶媒を除去し、クロロホルムに溶解させ、有機相を飽和炭酸水素ナトリウム水溶液 (20 ml×2) で中和し、飽和塩化ナトリウム水溶液 (20 ml×2) で洗浄した後、無水硫酸ナトリウムで乾燥させた。ろ過、濃縮後、粗生成物をシリカゲルカラムクロマトグラフィー ($CHCl_3$: methanol = 20 : 1) にて単離精製し、目的化合物である無色油状物質 2,3,4,6-テトラ-*O*-アセチル-D(+)-グルコノ-1,5-ラクトン **1** (8.10 g, 23.4 mmol) を収率 85%で得た。

分子式 : $C_{14}H_{18}O_{10}$; M.W. : 346.29

MALDI-TOF-MS (+) :

m.p. : 224℃

IR (岩塩)

ν (cm^{-1}) : 1751 (C=O), 1218 (C-O)

^{1}HNMR ($CDCl_3$)

δ (ppm) : 2.08, 2.12, 2.17, 2.22 (s×4, 12H , $CH_3C(=O)O$×4), 4.24-4.43 (dd, 2H, H-6, 6'), 4.62 (m, 1H, H-5), 5.13 (d, 1H, H-2), 5.36 (t, 1H, H-4), 5.56

(t, 1H, H-3)

・DETA-Sugar (2) の合成

アルゴン雰囲気下、ナスフラスコに 2,3,4,6-テトラ-*O*-アセチル-D(+)-グルコノ-1,5-ラクトン **1** を入れ、ピリジンに溶解させ、氷水浴中で撹拌しながらジエチレントリアミンをゆっくり滴下した。減圧下で溶媒を除去し、クロロホルムに溶解させ、有機相を飽和炭酸水素ナトリウム水溶液 (5 ml)、飽和塩化ナトリウム水溶液 (5 ml) の順で洗浄した後、無水硫酸ナトリウムで乾燥させた。ろ過、濃縮後、目的化合物である黄色結晶 **2** (2.06 g, 2.59 mmol) を粗収率 90%で得た。

分子式 : $C_{32}H_{49}N_3O_{20}$; M.W. : 795.74

MALDI-TOF-MS (+) : 796.44 $[M+H]^+$

m.p. : 225℃

IR (KBr)

ν (cm^{-1}) : 3463 (O-H), 1743 (C=O of ester), 1658 (C=O of amide), 1542 (N-H of amide), 1234 (C-O of ester)

^{1}HNMR ($CDCl_3$)

δ (ppm) : 2.07, 2.14, 2.19, 2.23 (s×4, 24H, CH_3C=O×8), 2.74-3.70 (m, 10H, OH×2, CH_2NH×2, CH_2NHC=O×2), 3.98-4.45 (m, 6H, CH_2×2, CH×2 (sugar hydrogens)), 4.97- 5.55 (m, 6H, CH×6 (sugar hydrogens))

2) コア(Core)部の合成

・DTPA dianhydride (3) の合成

アルゴン雰囲気下、ナスフラスコに DTPA (5.00 g, 12.7 mmol) を入れ、乾燥ピリジン (10 ml) に溶解させ、撹拌しながら無水酢酸 (4.8 ml, 5.08 mmol) を加え、50℃で 24 時間撹拌した。沈殿物を減圧ろ過し、無水酢酸 (10 ml×3)、アセトニトリル (10 ml×3) の順で洗浄した後、真空乾燥することで目的化合物である白色結晶 DTPA dianhydride **3** (4.46 g, 12.4 mmol) を粗収率 90%で得た。

IR (KBr)

ν (cm^{-1}) : 1820 (C=O of carboxylic anhydride), 1774 (C=O of carboxylic anhydride), 1643 (C=O of carboxylic acid anion), 1118 (C-CO-O-CO-C), 949 (C-CO-O-CO-C)

^{13}C NMR(DMSO-d_6),

δ (ppm) : 50.9, 51.9 (2×N-CH_2-CH_2), 52.6 (CH_2-O=C-O-C=O), 54.6 (N-CH_2-CO_2H), 165.6 (O=C-O-C=O), 172.0 (O=C-OH)

3）Ligand A4の合成

・Ligand A4 (4) の合成

アルゴン雰囲気下、ナスフラスコにDTPA dianhydride **3** (0.483 g, 1.35 mmol) と化合物 **2** (2.15 g, 2.70 mmol) を入れ、DMF (10 ml) に溶解させ、50℃で 24 時間撹拌した。減圧下で溶媒を除去し、粗生成物を再結晶（イソプロパノール）にて単離精製し、白色結晶 **4** (1.95 g, 1.00 mmol) を収率 74%で得た。

分子式 : $C_{78}H_{117}N_9O_{48}$; M.W. : 1948.80

MALDI-TOF-MS (-) : 1945.61 $[M-3H]^-$

m.p. : 180℃

IR (KBr)

ν (cm^{-1}) : 3440 (O-H), 1743 (C=O of ester), 1658 (C=O of amide), 1542 (N-H of amide), 1226 (C-O of ester)

^{1}HNMR ($CDCl_3$)

δ (ppm) : （特許の関係で、^{1}H-NMRデータの詳細は開示できない。）

4）A4の合成

・A4 (5) の合成

ナスフラスコにLigand A4 (0.558 g, 0.286 mmol) と塩化ガドリニウム（Ⅲ）六水和物 (0.128 g, 0.344 mmol) を入れ、水 (2 ml) に溶解させ、ピリジン (0.083 ml, 1.03 mmol) を加え40℃で16時間撹拌した。減圧下で溶媒を除去し、粗生成物を再結晶（イソプロパノール）にて単離精製し、白色結晶のA4 **(5)** (0.500 g, 0.236 mmol) を収率82%で得た。

分子式 : $C_{78}H_{114}GdN_9O_{48}$; M.W. : 2103.02

MALDI-TOF-MS (+) : 2103.57 $[M+H]^+$

2－5－3　参考文献

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2) K. Muramatsu, Y. Takehara, H. Sakahara, M. Yamashita, T. Nishikawa, N. Sadatoh, *ISMRM2005*, フロリダ講演ポスター **2005**.

3) M. Yamashita, S. Laurent, L. V. Elst, and R. N. Mullar, *ISMRM2004*, 京都講演ポスター **2004**.

4) C. C. Joseph, H. Regeling, B. Zwanenburg and G. J. F. Chittenden, *Tetrahedron* **2002**, 58, 6910.

5) C. F. Geraldes and A. M. Urbano, *J. Magn. Reson.* **1995**, 13, 401-.

2－6 Synthesis of DTPA amido ester ligands

2－6－1 Introduction

Magnetic resonance imaging (MRI) is a powerful and non-invasive diagnostic technique useful in providing images of the inside of the human body [1]. In recent years, complexes of lanthanides with diethylenetri-amine-N,N,N',N'',N''- pentaacetate (DTPA) and with its amide derivatives have attracted considerable attention as potential contrast agents [2-6]. These paramagnetic complexes contain one water molecule in the first coordination sphere, and fast exchange of this water molecule with the bulk water in the human body provides an efficient mechanism for the enhancement of the relaxation rates of the water protons [7-12]. However, the rapid development of magnetic resonance imaging technique for medical diagnostics has led to an increasing demand for even more effective contrast agent.

As a dendritic DTPA derivative for MRI contrast agent, it contains three parts: core part, linker part and bifurcation part. In our Lab, a novel MRI contrast agent or Gd-DTPA-D1 (Fig.2-6-01) have be prepared by DTPA amide ligands, that displayed a good property on relaxivity and specific in vivo distribution. [13,14] However, the disadvantage is that it cannot be excreted from body timely because its molecular size is too big or its affinity to materials in blood vessel is too high.

The other disadvantage is that its synthesis required a complex, tedious and expensive process. These defects limited the application of this novel MRI contrast agent.

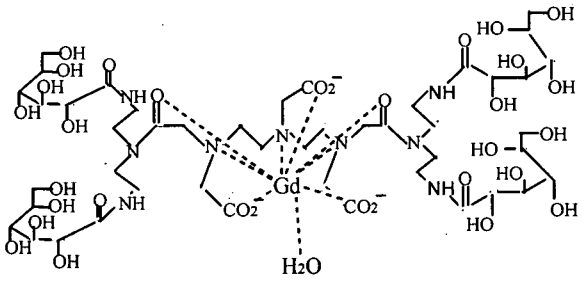


Fig. 2-6-01 The chemical structure of Gd-DTPA-D1

To overcome these disadvantages, we have prepared DTPA amido ester ligand. As we know, C-O bonding is easier to be broken than C-N bonding in body, which make sure that the bigger molecule with ester bonding can be decomposed more easily and excreted faster from

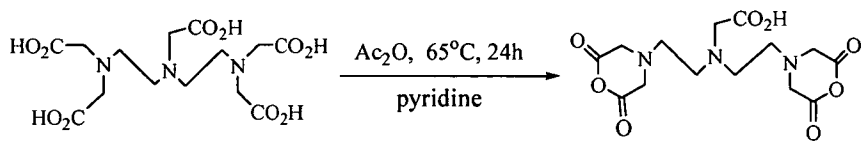
body timely. Maintaining basic chemical structure, the C-O bonding was introduced by using amino alcohol as a linker to connect MR imaging moiety with lactone as a biofunctional group. Also, we can charge different linkers, for example 2-amino-1,3-propanediol or different biofunctional groups, for example glucose to obtain different ligands. The compounds were characterized by IR spectrometry; nuclear magnetic resonance (NMR) spectrometry, mass spectrometry (MS) and the results indicate that only type of species with well-defined structure has been formed.

2－6－2 Results and discussion

In my experiments, The ligand DTPA-bis(amido sugar) was obtained by reaction between D-(+)Glucono-1,5 lactone and DTPA-bis(amido alcohol) which can be prepared by reaction between DTPA bis(anhydride) and 3-amino-1-propanol.

2－6－2－1 Synthesis of DTPA anhydride

The DTPA anhydride was synthesized according to previously reported procedures [15]. DTPA was added with stirring to a mixture of acid anhydride and pyridine for 24 h at 65 degree. After the completion of the reaction, the precipitate was washed by acid anhydride and acetonitrile. After the precipitation heated in vacuum, we can obtain the produce in 90%. The Scheme2-6-01 is the preparation route to DPTA anhydride.



DTPA　　DTPA anhydride; y. 90%

Scheme 2-6-01 The preparation route to DTPA anhydride

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of DTPA anhydride were shown in Fig.2-6-02~ Fig.2-6-04, respectively. From the IR spectrum, we can find the peaks at 1820cm^{-1} (C=O

stretch symmetry), 1774 cm^{-1} (C=O stretch asymmetry) which are characteristic peaks of cyclo-anhydride. Compared with the spectrum of DTPA, we can find four chemical shifts, which appear at 4.0 ppm, 3.6ppm, 3.5ppm, and 3.2 ppm. From these changes of spectra, the structure of produce can be identified.

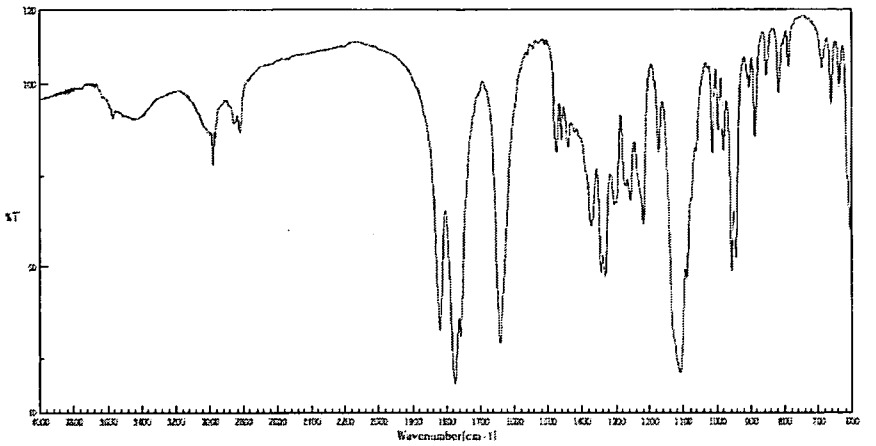


Fig.2-6-02 The IR spectrum of DTPA anhydride

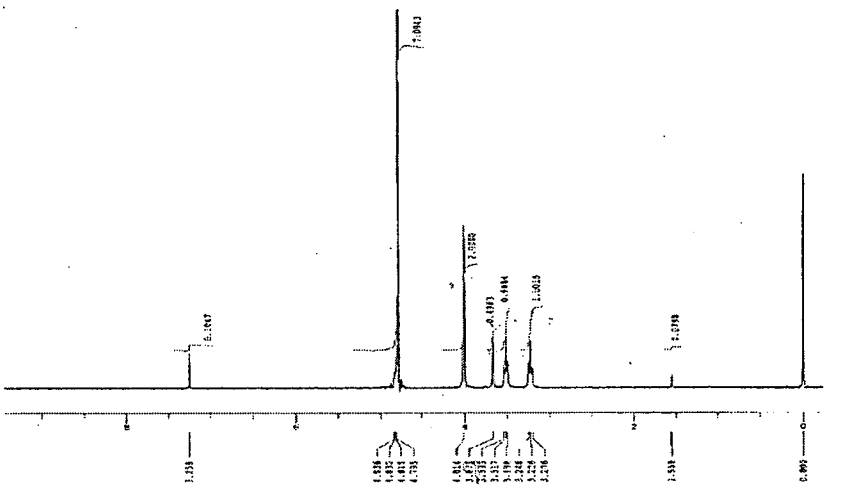


Fig.2-6-03 The ^{1}H-NMR spectrum of DTPA anhydride

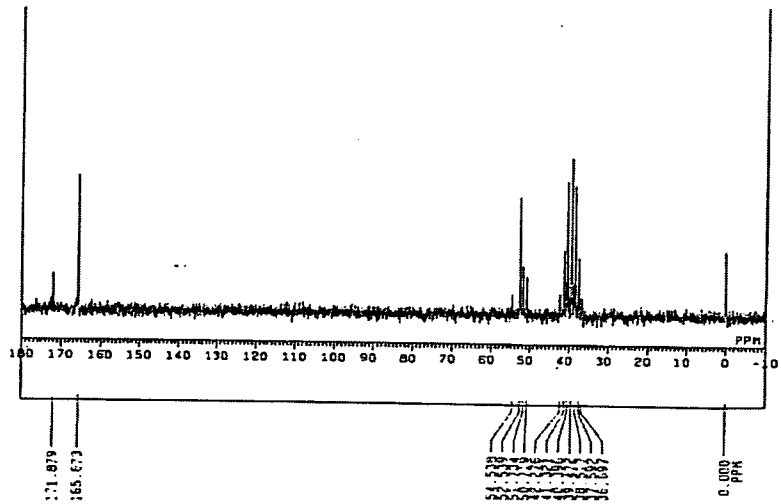
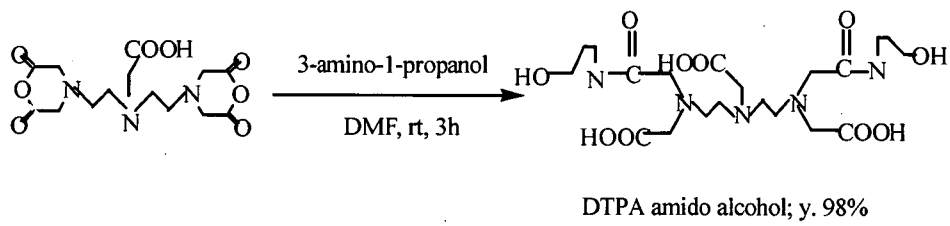


Fig.2-6-04 The ^{13}C-NMR spectrum of DTPA anhydride

2－6－2－2 Synthesis of DTPA amido alcohol

To a solution of DTPA anhydride in dry DMF, 3-amino-1-propanol solution in DMF was dropped into solution at room temperature. After 3 h of stirring, the solvent was evaporated to dryness under reduced pressure. The residue was the product in 98%. The Scheme2-6-02 is the preparation route to DTPA amido alcohol.



DTPA amido alcohol; y. 98%

Scheme 2-6-02 The preparation route to DTPA amido alcohol

Fig.2-6-05 and Fig.2-6-06 are IR and ^{1}H-NMR spectra of DTPA amido alcohol. From the IR spectrum, the peaks at 1820cm^{-1} (C=O stretch symmetry) and 1774 cm^{-1} (C=O stretch asymmetry), which are characteristic peaks of cyclo-anhydride, disappeared. According to the ^{1}H-NMR spectrum of DTPA anhydride, we can find the chemical shifts at 1.79 ppm, 3.64 ppm and 3.89 ppm because of the introduction of amino alcohol. From these changes of spectra, the structure of produce can be identified.

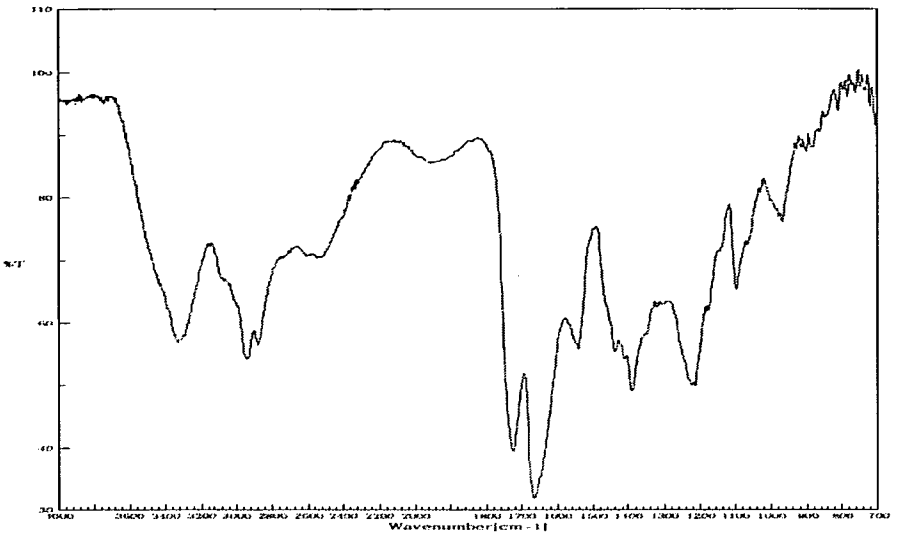


Fig.2-6-05 The IR spectrum of DTPA amido alcohol

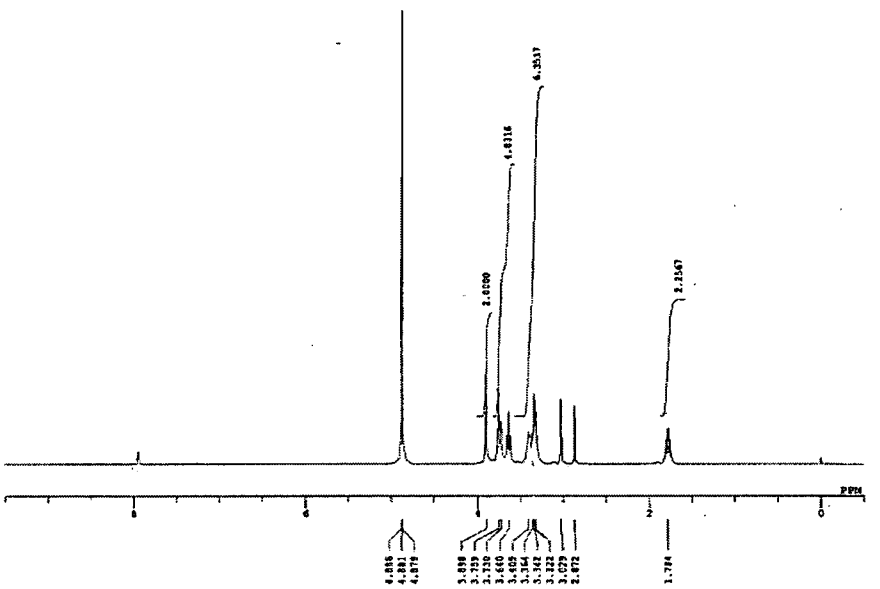


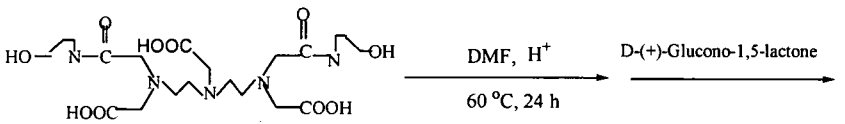
Fig.2-6-06 The ^{1}H-NMR spectrum of DTPA amido alcohol

2－6－2－3 Synthesis of DTPA amido esters

The ligands DTPA-bis(amido sugar) were obtained by reaction between lactones and DTPA-bis(amido alcohol). To a solution of DTPA-bis(amido alcohol) in dry DMF in acid condition, and the lactone was added and the reaction mixture was heated at 60 degree for 24 h .After the completion of reaction, the solvent was removed under reduced pressure and the residue was washed with ethanol and ether and dried in vacuum. The yield of produce is 90%. The Scheme2-6-03 is the preparation route to DTPA amido esters.

The structure of ligands can be identified by IR, MS, and ^{1}H-NMR. The IR, MS and ^{1}H-NMR spectra of ligands were shown in Fig.2-6-07~Fig.2-6-09. From the ^{1}H-NMR spectra, the chemical shift appeared in the regions of 4.3~4.7ppm because of the existence of sugars. In the IR spectra of the ligands, the peaks at 1735 cm^{-1} and 1664cm^{-1} were attributed to C=O (ester).

Further, the evidence for the existence of ligands was obtained from the mass spectrum. From the mass spectra, the peaks at m/z 508, 686, 864 also can be found. The peak at m/z 508 is hydrolyzed ligand DTPA-bis(amido alcohol) without sugar; the peak at m/z 686 is Gd-DTPA derivate containing one sugar; the peak at m/z 864 is Gd-DTPA monohydrolyzed containing two sugars.



DTPA-E1-Glc(OH); y.92%

Scheme 2-6-03 The preparation route to DTPA amido esters

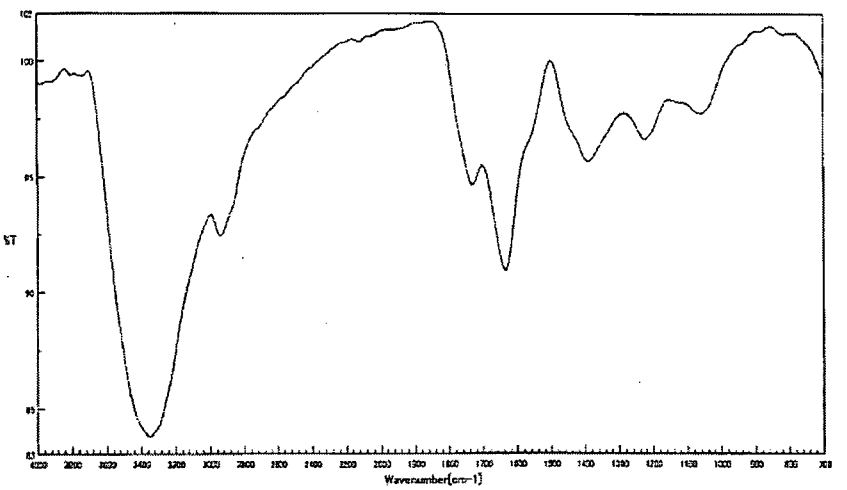


Fig.2-6-07 The IR spectrum of DTPA-E1-Glc(OH)

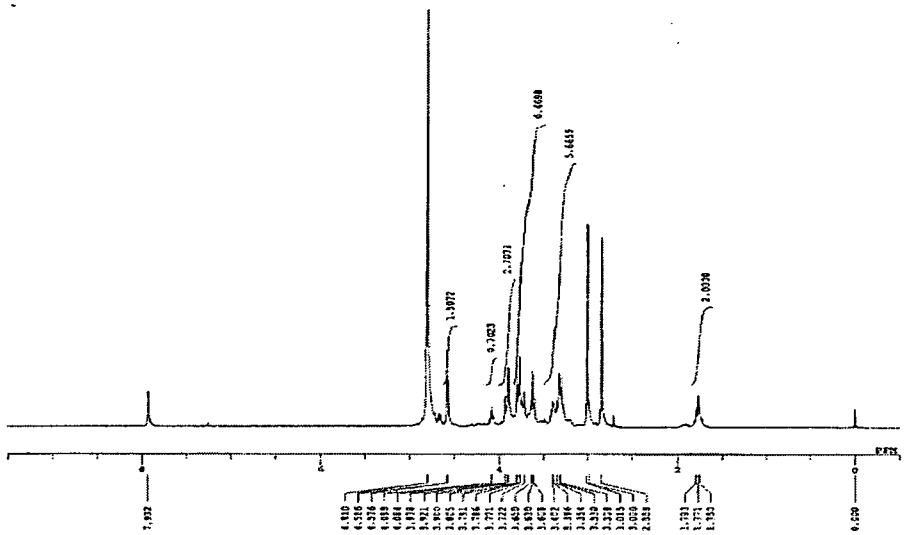


Fig.2-6-08 The ^{1}H-NMR spectrum of DTPA-E1-Glc(OH)

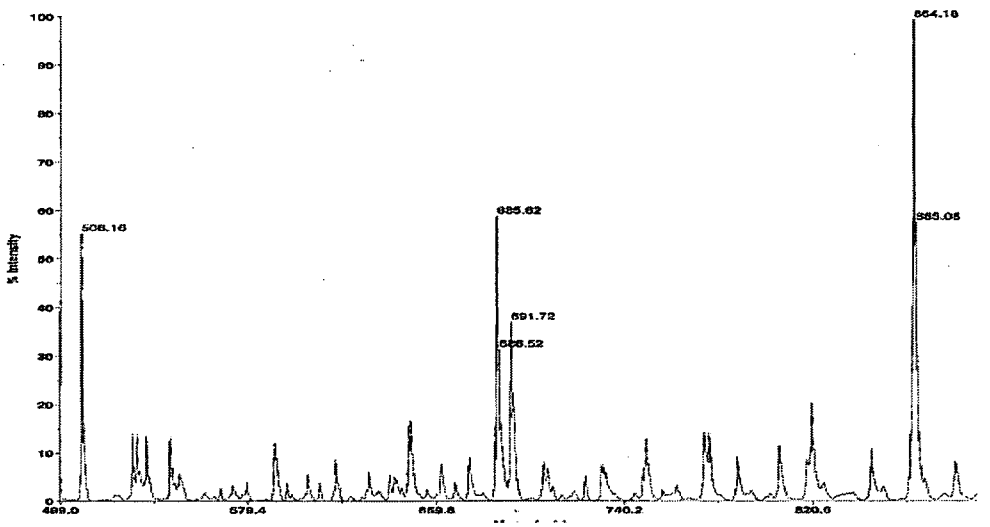
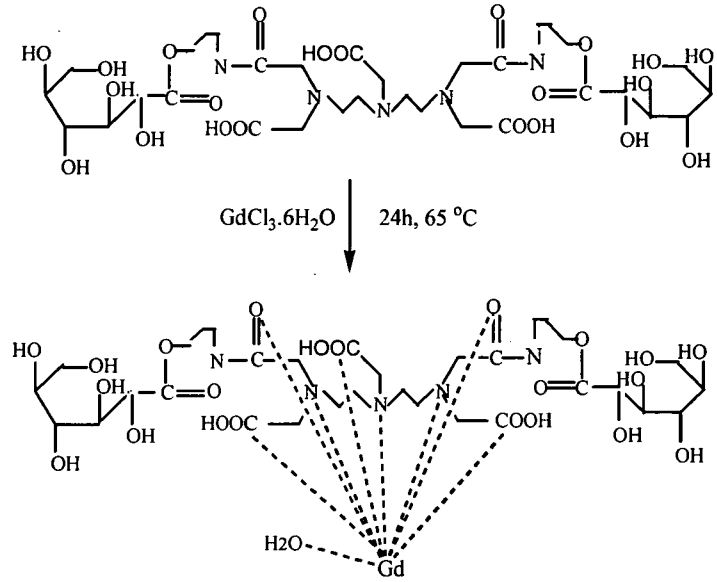


Fig.2-6-09 The MS spectrum of DTPA-E1-Glc(OH)

2－6－2－4 Synthesis of Gd DTPA derivative

The Gd-DTPA derivative was synthesized according to previously reported procedures. To a solution of hydrated $GdCl_3.6H_2O$ (1.1 mmol in 1 ml of H_2O) was added a solution of the ligand DTPA–E1 (1.0 mmol in 10 ml of pyridine), and the mixture was heated at 65 degree for 24h. The solvents were evaporated under reduced pressure and the crude product was then refluxed in ethanol for 1 h. After cooling to room temperature, the complex was filtered off and dried in vacuo. The Scheme2-6-04 is the preparation route to Gd-DTPA-E1-Glc(OH).



Scheme2-6-04 The preparation route to Gd-DTPA-E1-Glc(OH)

2－6－2－5 Physical property of DTPA-E1-Glc(OH)

The MR image intensity in ^{1}H-NMR signal of water protons linked with Gd(III) is dependent on nuclear relaxation times.[16] They have a good correlation to the relaxation rate of the protons. The parameters of relaxation times for DTPA-E1-Glc(OH) was examined. The relaxivity vs. temperature profile is shown in Fig.2-6-10.

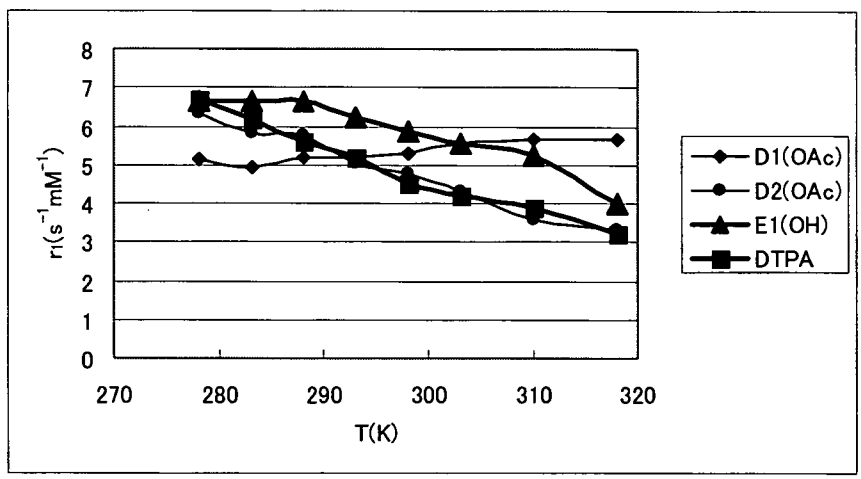


Fig2-6-10 Relaxivity of the Gd-DTPA-E1-Glc(OH) vs. temperature profile.

These results show that relaxivity of Gd-DTPA-E1-Glc(OH)) decreased as temperature risen, that is same with the change of relaxivity of Gd-DTPA. However, at 310K, we can find

the relaxivity of Gd-DTPA-E1-Glc(OH) is higher than Gd-DTPA which indicate Gd-DTPA-E1-Glc(OH) may better than Gd-DTPA as MRI contrast agents.

2－6－3 Conclusions

We have successfully synthesized a new gadolinium conjugated compound by a simple two-step reaction. This complex can be obtained by using DTPA-bis(amido sugar) as the ligand, and using gadolinium(III) as the paramagnetic centers. From the relaxivity of Gd-DTPA-E1-Glc(OH), we think these paramagnetic polymetallic species have a potential as MRI contrast agents.

2－6－4 Experimental

D-(+)Glucono-1,5 lactone, DMF, DTPA, and 3-amino-1-propanol were obtained from Wako Pure Chemical Industries, LTD. The DTPA-bis(anhydride) was synthesized according to previously reported procedures. ^{1}H-NMR spectra were collected on JEOL EX300 (300MHz). IR spectra were measured on a FTIR-spectrometer, using reflection on silicon. Elemental analysis was performed on a FLASH EA1112. The MS measurement was performed on a VOYAGER-DE Porimerix.

2－6－4－1 Synthesis of DTPA anhydride

DTPA (10.0g, 25.4mmol) was added with stirring to a mixture of acid anhydride (10.4g, 102mmol) and pyridine (15mL) for 24 h at 65 degree. After the completion of the reaction, the precipitate was washed 3 times by acid anhydride (50mL) and acetonitrile (50mL). The precipitate was dried in vacuum for 1 h. The product is a white powder: yield, 8.16g, (22.9mmol), 90%.

IR (KBr): ν (cm^{-1}) = 3445 (O=C<u>OH</u>), 1816(O=COC=O), 1761(<u>O=C</u>OH)

^{13}C-NMR (DMSO-d_6);

δ (ppm) = 50.7, 51.7 (N<u>CH_2</u>CH_2×2)

= 52.5 ($\underline{CH_2}O=COC=O$)

= 54.5 ($N\underline{CH_2}CO_2H$)

= 165.7 (O=COC=O)

= 171.9 (O=COH)

2－6－4－2 Synthesis of DTPA amido alcohol

To a solution of DTPA anhydride 0.2500g (0.700mmol) in dry DMF (10mL), 3-amino-1-propanol 0.1051g (1.400mmol) was dropped into solution at room temperature. After 3 h of stirring, the solvent was evaporated to dryness under reduced pressure. The residues were the product as a yellow mass: yield, 0.3515g (0.693mmol), 98%.

IR (reflection on silicon): $\upsilon(cm^{-1})$=3309 (O-H), 1738(O=C), 1654, 1539 (N-C), 1065(C-O).

^{1}H-NMR (300MHz, D_2O),

δ(ppm): = 1.79 (t, 4H; CH_2-$\underline{CH_2}$×2)

= 3.32~3.41 (m, 12H; CH_2-N×6)

= 3.64 (t, 4H; CH_2-OH)

= 3.73 (s, 4H; CH_2-COOH×2)

= 3.75 (s, 2H, CH_2-COOH)

= 3.89 (s, 4H, NCH_2CO×2)

2－6－4－3 Synthesis of DTPA-E1-Glc(OH)

To a solution of DTPA-bis(amido alcohol) 0.3515g (0.693mmol) in dry DMF (10mL) containing 1ml of ether saturated with hydrogen chloride , and the D-(+)Glucono-1,5 lactone 0.2469g (1.39mmol) was added and the reaction mixture was heated at 60 degree for 24 h. The solvent was removed under reduced pressure and the compound was washed with ethanol and ether and dried in vacuo 3 h. The residues were the product as a yellow crystal: yield, 0.5512 g (0.624 mmol), 95%.

IR (reflection on silicon): $\upsilon(cm^{-1})$=3320 (O-H), 1735 (O=C), 1648, 1543 (N-C), 1203, 1089(C-O-C)

^{1}H-NMR (300MHz, D_2O),

δ(ppm): = 1.79 (t, 4H; CH_2-CH_2×2)

= 3.32~3.41 (m, 12H; CH_2-N×6)

= 3.64 (s, 2H; CH_2-COOH)

= 3.73 (s, 4H; CH_2-COOH×2)

= 3.77 (s, 4H, CH_2-CO-NH×2)

= 3.87 (d, 4H, CH(OH)-OH)

= 3.92 (t, 4H; CH_2-O×2)

= 4.37 (t, 6H, CH(OH)-CH×6)

= 4.65 (d, 2H, CH(OH)-CO-O×2)

MS: 863

2－6－4－4 Synthesis of Gd-DTPA-E1-Glc(OH)

DTPA-E1-Glc(OH) (0.5562 g, 0.644 mmol) was dissolved in pyridine (10 mL), and the solution of $GdCl_3.6H_2O$ (0.2549g, 0.137mmol) in water (1 ml) was added. After 24 h of stirring at 65 degree, the solvent were removed and the crude product was then refluxed in ethanol for 1 h. After cooling to room temperature, the complex was filtered off and dried in vacuo at room temperature. The product was a light yellow solid, yield: 0.6423g (0.618mmol), 96%.

Elem. Anal. Calcd.: (found): $C_{33}H_{57}N_5O_{22}.H_2O$: C, 36.34 (34.19), H, 5.78 (5.62), N, 6.69 (6.62).

IR (KBr): υ(cm^{-1})=3361 (υOH), 1664 (O=C), 1538 (N-C=O), 1226 (C-N).

MS: 1039.

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3　*in vitro* 評価

3－1　緩和率

平成19年度から使用が可能となったBURUKER社製の永久磁石NMR分光計Minispeck（0.47T）により当該の開発研究に対して各Gd-DTPA錯体のT1緩和率を測定した。

3－1－1　超純水中でのT1緩和速度測定

Gd錯体であるGd-DTPA（マグネビスト）、およびGd-DTPA-糖誘導体のGd錯体であるGd-DTPA-DETA-D2-4Glc(OH)、あるいは、平成19年度に調製した新規なMRI造影剤（特許出願関係のために、本研究報告書では非公開）のW、X、Y、Zについて、T1緩和速度（単位は[$s^{-1}\cdot M^{-1}$]）を測定し、造影剤としての効果を見積もった。各サンプルの1mM濃度水溶液(超純水に溶解)の緩和速度を計測した(37℃)。また、同様の濃度のGd-DTPA水溶液(マグネビスト、日本シェーリング社製)も測定し、比較した(Fig. 3-01)。

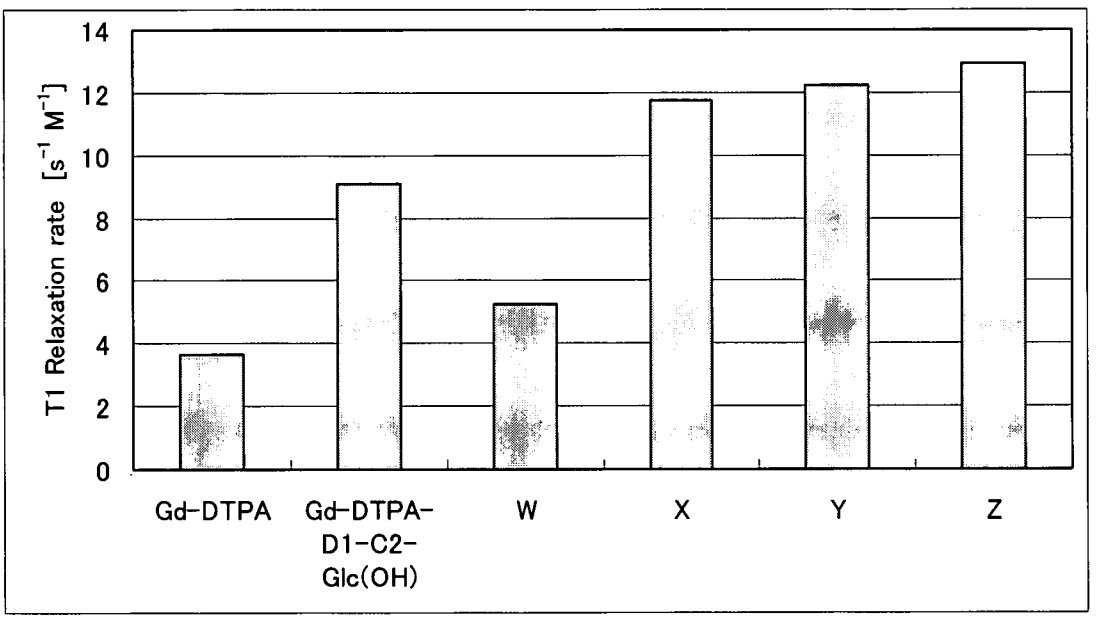

Fig.　3－01　T1 relaxartion rate for Gd complexes in ultra pure water.

全てのGd-DTPA糖錯体について、Gd-DTPAと比べて高い緩和度を得ることが出来た。特にMRI造影剤Zの緩和度は12.9 s^{-1} M^{-1}であり、Gd-DTPAの3.7 s^{-1} M^{-1}の3倍以上の緩和度が得られた。

３－１－２　血清中での T1 緩和速度測定

100 %, 50 %, 0 %の 3 種類の濃度のウシ胎児血清（蛋白 4.5 g/dl）水溶液(超純水に溶解)中での Gd 錯体、Gd-DTPA（マグネビスト、日本シェーリング社製)および Gd-DTPA-糖誘導体の Gd 錯体、Gd-DTPA-DETA-D2-4Glc(OH)、あるいは、平成 19 年度に調製した新規な MRI 造影剤（特許出願関係のために、本研究報告書では非公開）のW、X、Y、Z の 1.0 mM の緩和速度(37 ℃)を計測し比較した。

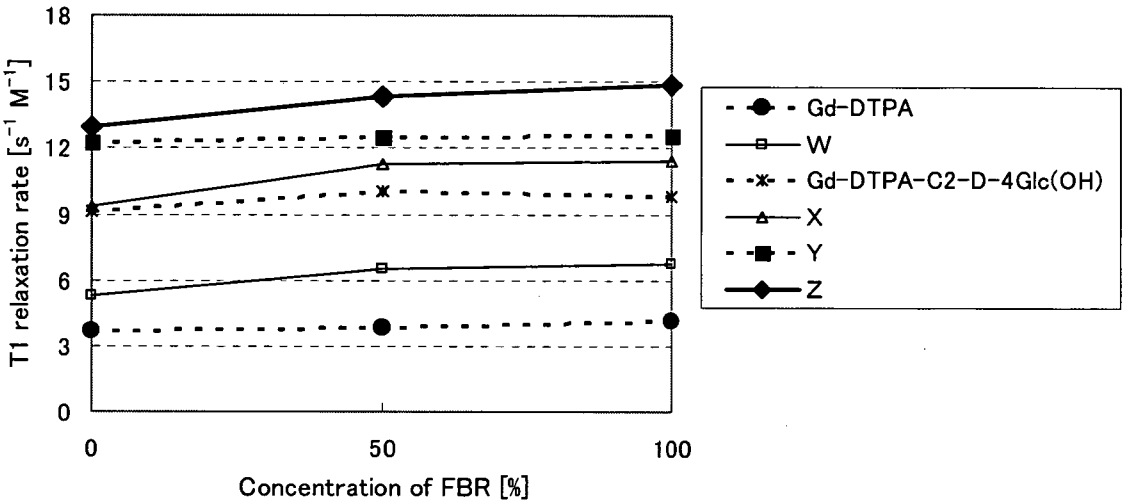

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Fig. ３－０２ T1 relaxation rate for Gd complexes in cow albumin.

Gd-DTPA ではアルブミンの濃度変化による緩和度の変化は見られなかったが、Gd-DTPA 糖錯体では緩和度の上昇が見られた。特に、**Gd 錯体Ｚ** のアルブミンの濃度変化による高い緩和度の上昇率を得ることが出来た。

更に、Gd-DTPAの誘導体Ａ１（ＯＨ)、A2（ＯＨ)、Ａ３（ＯＨ)、Ａ４（ＯＨ)、Ａ５（ＯＨ）あるいはＢ１（Ｒ)、Ｂ２（Ｒ)、Ｂ３（Ｒ）(特許出願関係のために、本研究報告書では非公開)についてもT1緩和速度を測定し、Gd-DTPAのそれと比較した(Fig. 3-03)。また、血清中でのT1緩和速度についても比較検討した。

これらの研究結果から、当該研究により開発を目指す標的分子の設計に対するヒントが得られたと思われる。

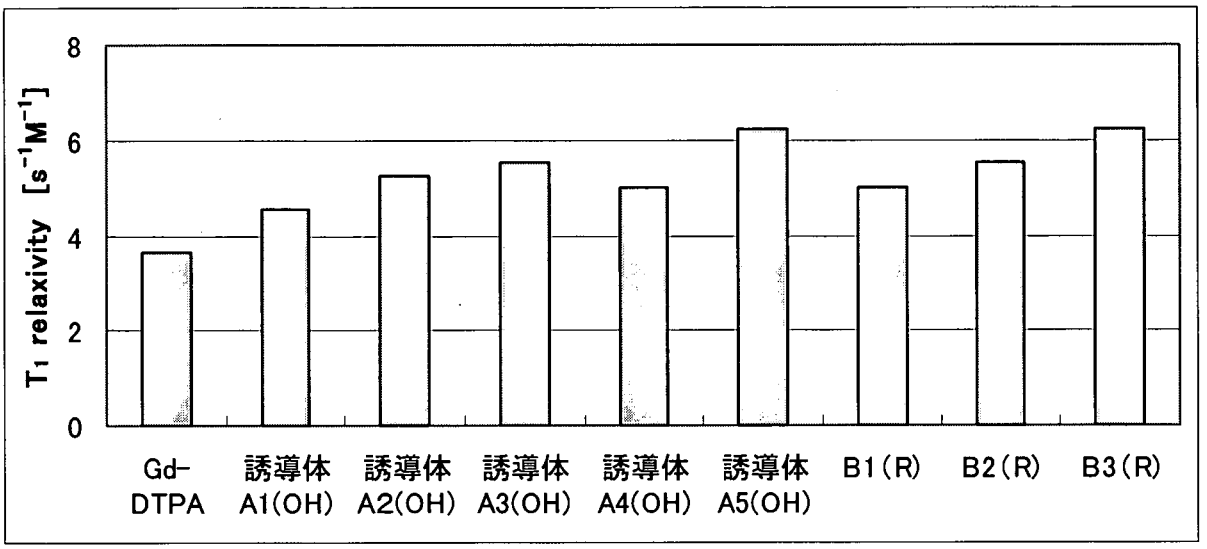

Fig. ３－０３ T1 relaxation rate for Gd complexes A' s and B' s in ultra pure water.