

DTPA - bis(4 - carboxycyclohexyl)amide

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:
: DMF(15 mL) DTPA - bis - anhydride(0.71 g, 2 mmol)
4 - aminomethylcyclohexane carboxylic acid(0.63 g, 4 mmol)
Gd₂O₃(0.18 g, 0.5 mmol) Gd .
3 1 mM 1.5T(64
MHz) . T1
(inversion - recovery) T2 CPMG(Carr - Purcell -
Meiboon - Gill) T1
, R1 , T2 R2 .
: Omniscan(Gadodiamide) R1 = 4.9 mM⁻¹sec⁻¹, R2 =
4.8 mM⁻¹sec⁻¹ R1 SUK090(Gd - C32H74N5O24) 12.46 mM⁻¹sec⁻¹,
SUK091(Gd - C34H78N5O24) 12.77 mM⁻¹sec⁻¹ SUK092(Gd -
C30H56N5O17) 2.09 mM⁻¹sec⁻¹ . R2 SUK090(Gd -
C32H74N5O24) 8.76 mM⁻¹sec⁻¹, SUK091(Gd - C34H78N5O24) 7.60 mM⁻¹sec⁻¹
SUK092(Gd - C30H56N5O17) 1.82 mM⁻¹sec⁻¹ .
: SUK090(Gd - C32H74N5O24) SUK091(Gd -
C34H78N5O24) T1, T2
T1/T2 가 .

500 - 700 (dalton)

가 (3, 4).

T1

T1

가

T1

(1, 2).

가

(Gd)

(Mn)

가 T1

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1

2

3

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(R01 - 2004 - 000 - 10602 - 0)

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: , (700 - 412)

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DTPA-bis(4-carboxycyclohexyl)amide

가 가 . ,
 (rotation) 가
 가 T1
 가
 가 . , 가
 T1
 exchange) 가
 T1 (chemical (1) . DMF(15 mL) DTPA - bis - anhydride (0.71 g, 2 mmol) 4 - aminomethylcyclohexane carboxylic acid(0.63 g, 4 mmol) 65
 T1 4
 10 mL methanol
 silica gel(60 mesh)
 Yield 1.22
 가
 T1 T2
 g(84%) . SUK090 SUK091 -
 COOR 가 SUK092 (-
 COOH) 가 .

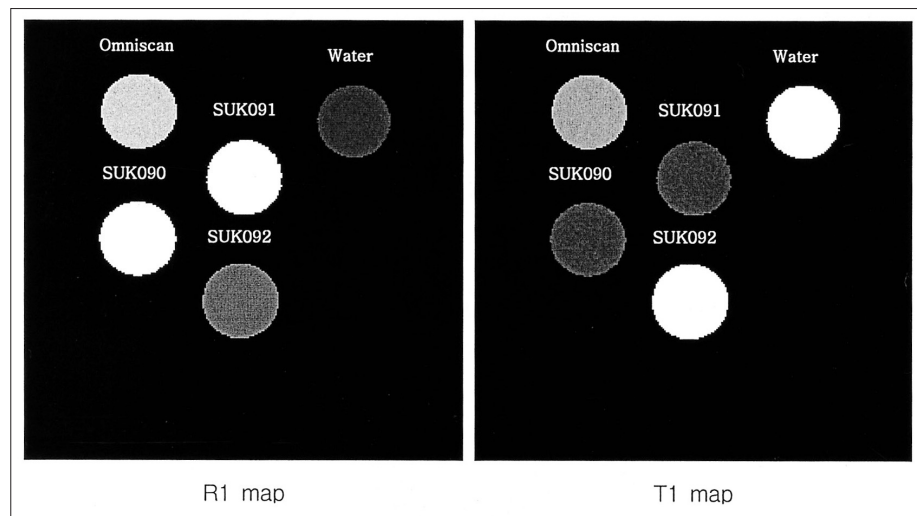
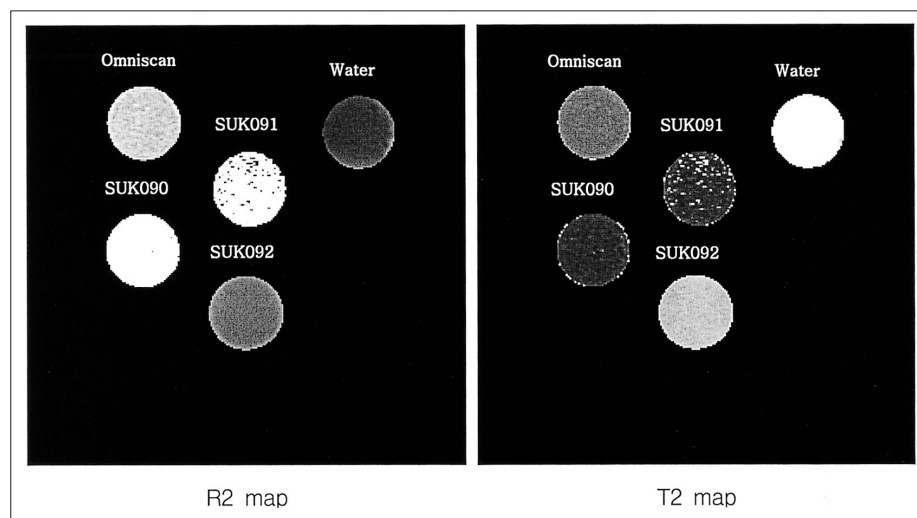


Fig. 1. R1 and T1 map for Omniscan, water, SUK091, SUK090 and SUK092 (**a**). The darker signal intensity of SUK092 in R1 map shows less T1 relaxation enhancement than that of Omniscan. Fig. 1 (**b**) shows R2 and T2 map for same samples. Again, SUK092 shows least T2 relaxation enhancement.



(2) Gd (0.73 g, 1 mmol) (Relaxation Map)
 (10 mL) Gd₂O₃ (0.18 g, 0.5 mmol) 100 oC 가
 6

MATLAB (Version 7.1)
 MRI (Header)
 methanol 100 mL acetonitrile
 acetonitrile
 70 8 Yield
 0.71 g (78%) MATLAB
 (pixel by pixel) T1
 T2 T1 R1
 T2 R2 R1
 R2 1mM T1 T2 (relaxation rate)

3 1 mM 1.5T (64 MHz)
 T1
 (inversion - recovery)
 T2 CPMG (Carr - Purcell -
 Meiboom - Gill)
 (Inversion time: TI) 50 msec 1750
 msec 35 T2 R2, T2 1(a) Omniscan, R1, T1 1(b)
 (Echo time: TE) 10 msec 1900 2(a) (b)
 msec 34 1.5T (64 MHz)
 GE Bioscience
 Omniscan (Gadodiamide) 1 mM T1 T2
 T1 T2
 T1 T2

$$SI = S_0 \left(1 - 2e^{-\frac{TI}{T_1}} + e^{-\frac{TR}{T_1}} \right) \quad [1]$$

$$SI = S_0 e^{-\frac{TE}{T_2}} \quad [2]$$

SUK090 (Gd - C32H74N5O24) 12.46 mM⁻¹sec⁻¹, SUK091 (Gd - C34H78N5O24) 12.77 mM⁻¹sec⁻¹
 SUK092 (Gd - C30H56N5O17) 2.09 mM⁻¹sec⁻¹
 SUK090 (Gd - C32H74N5O24) 8.76 mM⁻¹sec⁻¹, SUK091 (Gd - C34H78N5O24) 7.60 mM⁻¹sec⁻¹
 SUK092 (Gd - C30H56N5O17) 1.82 mM⁻¹sec⁻¹

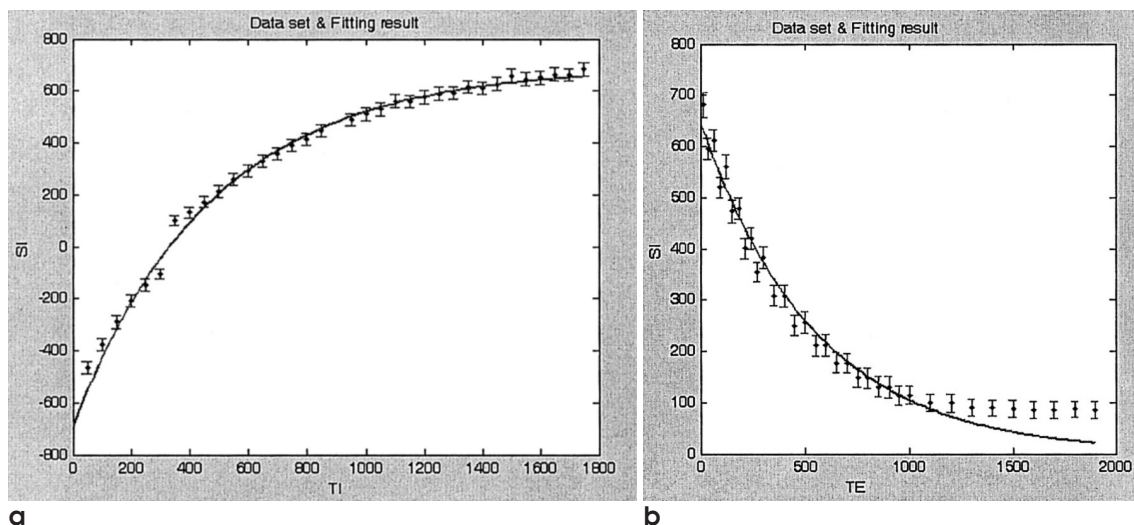


Fig. 2. Typical inversion recovery data set and the corresponding fitting result for T1 measurement (a). The multiple echo CPMG data set and the corresponding fitting result for T2 measurement (b).

DTPA-bis(4-carboxycyclohexyl)amide

$^1\text{sec}^{-1}$	SUK090, SUK091	R1	R2	5000	T1
SUK092	R1	R2			(7, 8).
SUK 092		-COOH 가			(polylysine)
	COO -			(polydextran)	(linear polymer)
	가				GdDTPA
	3(a) (b)				(9, 10).
		R1			T1
mM	1/T1	R2	mM	1/T2	
				(1000)	(587)
				가 T1	가
					Gd
T1, T2		T1, T2	T1	가	가
가		T1	가		
				SUK092(Gd - C30H56N5O17)	916
(rotation correlation time),				SUK090(Gd - C32H74N5O24),	SUK091(Gd -
		(chemical exchange time)		C34H78N5O24)	587
Gd	T1	(6).	Omniscan	R1	R2
	T1		SUK090	SUK091	

Table 1. Molecular weight, T1/R1, T2/R2 values for Omniscan, SUK090, SUK091, SUK092 and pure water. Each values is presented as (mean value \pm SD)

Paramagnetic complex	Molecular Weight (Dalton)	T1 (msec)	R1 ($\text{mM}^{-1}\text{sec}^{-1}$)	T2 (msec)	R2 ($\text{mM}^{-1}\text{sec}^{-1}$)
Omniscan	587	209.8 \pm 5.82	4.9 \pm 0.14	290.8 \pm 21.02	3.4 \pm 0.25
SUK090	1070.1991	79.05 \pm 3.99	12.7 \pm 0.66	113.9 \pm 14.39	8.7 \pm 0.88
SUK091	1098.2522	78.28 \pm 4.68	12.9 \pm 0.84	131.5 \pm 0.002	7.2 \pm 1.9
SUK092	916.0389	477.5 \pm 9.94	2.1 \pm 0.05	550.9 \pm 22.05	1.8 \pm 0.07
Water		842.5 \pm 46.38	1.1 \pm 0.06	1220 \pm 167.20	0.82 \pm 0.12

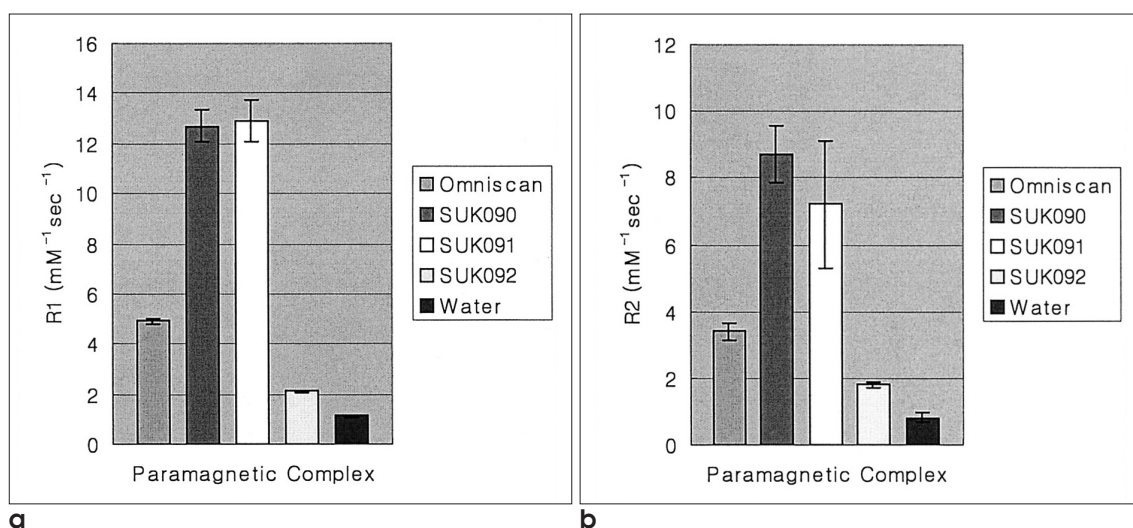


Fig. 3. The comparison of R1 (a) and R2 (b) values at 1.5T. Higher R1 and R2 means more pronounced relaxation shortening effect. Both SUK090 and SUK091 shows better relaxation shortening effect than commercially available MR agent (Omniscan).

(smart agent)	가	(prototype)	가
T1			
<ol style="list-style-type: none"> 1. Mahfouz AE, Hamm B. Contrast agents. <i>MRI Clin North Am</i> 1997;5:223-240 2. Watson AD, Rocklage SM, Carvlin MJ. Contrast agents. In Stark DD, Bradley WG, eds. <i>Magnetic Resonance Imaging</i>. 2nd ed. St. Louis: Mosby-Year Book, 1992: 372-437 3. Heywang SH, Wolf A, Pruss E, Hilbertz T, Eiermann W, Permanetter W. MR imaging of the breast with Gd/DTPA: use and limitations. <i>Radiology</i> 1989;171(1):95 /103 4. Hustvedt SO, Grant D, Southon TE, Zech K. Plasma pharmacokinetics, tissue distribution and excretion of MnDPDP in the rat and dog after intravenous administration. <i>Acta Radiol</i> 1997;38:690-699 5. The detailed synthesis process and characterization are in preparation as a separate manuscript 6. Lauffer RB. Magnetic resonance contrast media: Principles and Progress. <i>Magn Reson Q</i> 1990; 6(2):65-84. 7. Brasch RC. New directions in the development of MR imaging contrast media. <i>Radiology</i> 1992;183:1-11 8. Misselwitz B, Schmitt-Willich H, Ebert W, Frenzel T, Weinmann H. Pharmacokinetics of Gadomer-17, a new dendritic magnetic resonance contrast agent. <i>Magma</i> 2001;12(2/3):128/34 9. Knopp MV, Tengg-Koblick H, Floemer F, et al. Contrast Agents for MRA: Future Directions. <i>JMRI</i> 1999;10:314-316 10. Enochs WS, Weissleder R. Organ- and tissue-directed MRI contrast agents. In RR Edelman, JR Hesselink, MB Zlatkin (eds.), <i>Clinical Magnetic Resonance Imaging</i>, 2nd ed. Philadelphia: W.B. Saunders, 1996: 192-220 11. Konda SD, Aref M, Wang S, Brechbiel M, and Wiener EC. Specific targeting of folate-dendrimer MRI contrast agents to the high affinity folate receptor expressed in ovarian tumor xenografts. <i>Magma</i>, 2001;12:104-113 12. Sipkins DA, Gijbels K, Tropper FD, Bednarski M, Li KC, Steinman L. ICAM-1 expression in autoimmune encephalitis visualized using magnetic resonance imaging. <i>J. Neuroimmunol.</i> 2000;104:1-9 13. Sibson NR, Blamire AM, Bernades-Silva M. MRI detection of early endothelial activation in brain inflammation. <i>Magn Reson Med</i> 2004;51:248-252 14. Josephson L, Lewis J, Jacobs P, Hahn PF, Stark DD, The effects of iron oxides on proton relaxivity. <i>Magn. Reson. Imag.</i> 1988;6:647-653 15. Winter PM, Morawski AM, Caruthers SD, Fuhrhop RW, Zhang H et al. Molecular imaging of angiogenesis in early-stage atherosclerosis with alpha(v)beta3-integrin-targeted nanoparticles. <i>Circulation</i> 2003;108:2270-2274 			

The Magnetic Relaxation Properties of DTPA-bis(4-carboxycyclohexyl)amide Paramagnetic Gd-chelates

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Purpose : To evaluate the NMR relaxation properties of newly developed high performance paramagnetic complexes.

Materials and methods : 4-aminomethylcyclohexane carboxylic acid (0.63 g, 4 mmol) was mixed with the suspension solution of DMF (15 mL) and DTPA-bis-anhydride (0.71 g, 2 mmol) to synthesize the ligand. The ligand was then mixed with Gd₂O₃ (0.18 g, 0.5 mmol) to synthesize Gd-chelate. For the measurement of magnetic relaxivity of paramagnetic compounds, the compounds were diluted to 1mM and then the relaxation times were measured at 1.5T(64 MHz). Inversion-recovery pulse sequence was employed for T₁ relaxation measurement and CPMG(Carr-Purcell-Meiboom-Gill) pulse sequence was employed for T₂ relaxation measurement. Using MATLAB(Version 7.1) program, T₁ magnetic relaxation map, R₁ map, T₂ magnetic relaxation map and R₂ map were developed to represent magnetic relaxation time and magnetic relaxivity as image.

Results : Compared to R₁ = 4.9 mM⁻¹sec⁻¹ and R₂ = 4.8 mM⁻¹sec⁻¹ of Omniscan (Gadodiamide), which is commercially available paramagnetic MR agent, R₁ of SUK090(Gd-C₃₂H₇₄N₅O₂₄) was 12.46 mM⁻¹sec⁻¹ and R₁ of SUK091(Gd-C₃₄H₇₈N₅O₂₄) was 12.77 mM⁻¹sec⁻¹. However, R₁ of SUK092(Gd-C₃₀H₅₆N₅O₁₇) was decreased to 2.09 mM⁻¹sec⁻¹. In case of R₂, SUK090(Gd-C₃₂H₇₄N₅O₂₄) was 8.76 mM⁻¹sec⁻¹ and SUK091(Gd-C₃₄H₇₈N₅O₂₄) was 7.60 mM⁻¹sec⁻¹ whereas SUK092(Gd-C₃₀H₅₆N₅O₁₇) was decreased to 1.82 mM⁻¹sec⁻¹.

Conclusion : Among three new paramagnetic complexes, SUK090(Gd-C₃₂H₇₄N₅O₂₄) and SUK091(Gd-C₃₄H₇₈N₅O₂₄) showed higher T₁, T₂ magnetic relaxation rates than that of commercially available paramagnetic MR agent and thus expected to have more contrast enhancement effect.

Index words : Contrast Agent, Relaxation, Paramagnetism

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