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Water-soluble polysaccharides as carriers of paramagnetic contrast agents for magnetic resonance imaging: Synthesis and relaxation properties

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ABSTRACT

Water-soluble, carbohydrate-based, paramagnetic metal chelate derivatives have been investigated as potential organ-selective contrast media for magnetic resonance imaging (m.r.i.). The *in vitro* proton spin–lattice relaxation properties of compounds with different paramagnetic metals, chelating agents, and carbohydrate matrixes have been studied. Typically, these complexes were 60–260% more efficient proton-relaxation agents than the corresponding low-molecular-weight metal chelates at 10 MHz, but less efficient than the corresponding protein derivatives. As expected, carbohydrates that contained manganese or gadolinium were more effective relaxation agents than iron, copper, erbium, or nickel derivatives.

INTRODUCTION

The development of magnetic resonance imaging (m.r.i.) as a clinical diagnostic modality is a major jump in technology in medical imaging after the introduction of computerised tomography approximately twenty years ago. Although m.r.i. provides excellent soft-tissue contrast in unenhanced images, early experiments showed that contrast agents might increase the diagnostic value[1]. The image intensity in m.r.i. is due to the n.m.r. signals of the protons of water, protein, and fat in the human body. The signal intensity is a function of several physical and chemical parameters. However, the main contrast parameters are proton density and the spin-relaxation times T_1 and T_2. In *in vitro* n.m.r. spectroscopy, it is well known that paramagnetic compounds enhance the spin–lattice relaxation rate of water[2–4]; thus, nitroxide radicals and salts and chelates of lanthanides and transition metals have been evaluated as contrast agents[1,5–7]. Most of the clinical experience with paramagnetic contrast today has been gained with gadolinium–diethylenetriaminepenta-acetic acid (Gd–DTPA). This chelate is a general contrast medium with extracellular distribution and rapid renal elimination[6].

There is a need for more tissue-specific compounds. The aims of the study now reported were to synthesise and evaluate the *in vitro* efficacy of water-soluble paramag-

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netic polysaccharides for potential in m.r.i. of vascular space, the lymph system, the liver, and the gastrointestinal tract.

EXPERIMENTAL

General. — Inulin was purchased from Sigma, sodium carboxymethylcellulose from Hercules Inc., and the other polysaccharides from Pharmacia. The mol. wts. are average values obtained by size-exclusion chromatography[5].

The degree of substitution (d.s.) was determined by elemental analysis. Methyl sulfoxide was dried by storage over 4Å molecular sieves.

All products except **4** were purified and isolated as follows. The solution was dialysed against aqueous 0.9% sodium chloride for 5 days. The external solution was exchanged 2–3 times every day until T_1 was >3000 ms (see relaxation measurements). The solution was then dialysed against distilled water and lyophilised, and the residue was dried *in vacuo* at 50°. The metal content (%) in each product was determined by atomic absorption spectroscopy.

Gadolinium(III)–EDTA–hydroxypropylstarch conjugate (**1**). — To a solution of hydroxypropylstarch (2.0 g, mol. wt. 49,000, d.s. 0.75; prepared by hydroxypropylation[9] of maize starch) in dry methyl sulfoxide (100 mL) was added ethylenediaminetetraacetic acid (EDTA) bisanhydride[10] (1.03 g). The mixture was stirred at ambient temperature for 16 h, then cooled, distilled water (100 mL) was added, and the pH was adjusted to 6.2. After stirring at ambient temperature for 6 h, a solution of $GdCl_3 \cdot 6H_2O$ (1.76 g) in distilled water (20 mL) was added, the pH was adjusted to 5.8, and the product was purified and isolated as yellowish flakes (3.4 g) (Gd, 4.7%).

Gadolinium(III)–TTHA–dextran conjugate (**2**). — Triethylenetetra-aminehexaacetic acid (TTHA, 1.0 g) and 4-dimethylaminopyridine (100 mg) were added to a solution of dextran (20 g, mol. wt. 40 000) in dry methyl sulfoxide (200 mL). *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodi-imide hydrochloride (EDCI, 1.9 g) was added. The solution was stirred for 22 h at ambient temperature, then placed in an ice-bath, and distilled water (100 mL) was added. The solution was stirred for 30 min, the pH was adjusted to 6.3, a solution of $GdCl_3 \cdot 6H_2O$ (0.76 g) in distilled water (20 mL) was added, the pH was adjusted to 5.8, and the mixture was stirred for 30 min. The product was purified and isolated as white flakes (2.4 g) (Gd, 1.0%).

Gadolinium(III)–DTPA–dextran conjugate (**3**). — Diethylenetriaminepenta-acetic acid (DTPA) bisanhydride[10] (1.4 g) was added to a solution of dextran (2.0 g, mol. wt. 70,000) in dry methyl sulfoxide (100 mL) at ambient temperature. The mixture was stirred for 20 h, then cooled in an ice–water bath, and distilled water (100 mL) was added gradually. The ice–water bath was removed, the reaction mixture was stirred for 7 h, and the pH was adjusted to 6.5. A solution of $GdCl_3 \cdot 6H_2O$ (1.60 g) in distilled water (20 mL) was added, the pH was adjusted to 5.7, and the solution was stirred for 30 min. The product was purified and isolated as colourless flakes (3.2 g) (Gd, 4.7%).

Gadolinium(III)–DTPA–inulin conjugate (**4**). — DTPA bisanhydride[10] (7.0 g) was added to a solution of inulin (10 g) in dry methyl sulfoxide (200 mL) at ambient

temperature. The mixture was stirred at ambient temperature for 20 h, then lyophilised. A solution of the solid residue in distilled water (250 mL) was stirred overnight, the pH was adjusted to 5.0, a solution of $GdCl_3 \cdot 6H_2O$ (8.0 g) in distilled water (75 mL) was added, the pH was adjusted to 5.5, and the solution was stirred for 1 h, then subjected to ultrafiltration with aqueous 0.9% sodium chloride followed by distilled water. The solution was lyophilised and the product was dried *in vacuo* at 50° to give a white solid (13.1 g) (Gd, 9.8%).

Gadolinium(III)–carboxymethyldextran (**5**). — Carboxymethyldextran sodium salt (2.0 g, mol. wt. 65 000, d.s. 0.11) was dissolved in distilled water (100 mL) at pH 5.8, a solution of $GdCl_3 \cdot 6H_2O$ (0.4 g) in distilled water (20 mL) was added, the pH was adjusted to 5.6, and the product was purified and isolated as colourless transparent flakes (1.75 g) (Gd, 2.8%).

Gadolinium(III)–dextran (**6**). — A solution of $GdCl_3 \cdot 6H_2O$ (1.8 g) in water (20 mL) was added to a solution of dextran (2.0 g, mol. wt. 70 000) in distilled water (100 mL) at pH 5.8. The solution was stirred for 30 min, and the product was purified and isolated as colourless transparent flakes (1.7 g) (Gd, 0.7%).

Gadolinium(III)–dextran phosphate (**7**). — Dextran phosphate (2.0 g, mol. wt. 74,800, d.s. 0.13; prepared by phosphorylation of dextran with phosphorus oxychloride[11]) was dissolved in distilled water (200 mL), the pH was adjusted to 6.2, and a solution of $GdCl_3 \cdot 6H_2O$ (0.4 g) in distilled water (20 mL) was added. The pH was adjusted to 5.9, an insoluble by-product was removed by centrifugation, and the water-soluble product was purified and isolated as white flakes (0.55 g) (Gd, 3.1%).

Manganese(II)–EDTA–sucrose–epichlorohydrin copolymer conjugate (**8**). — To a solution of a copolymer of sucrose and epichlorohydrin (2.0 g, mol. wt. 70 000; Ficoll® 70) in dry methyl sulfoxide (200 mL) was added EDTA bisanhydride[10] (1.03 g), and the mixture was stirred at ambient temperature for 16 h. The mixture was placed in an ice–water bath, the pH was adjusted to 5.8, and a solution of $MnCl_2 \cdot 4H_2O$ (0.88 g) in distilled water (20 mL) was added. The pH was adjusted to 5.7, and the product was purified and isolated as white flakes (2.8 g) (Gd, 0.3%).

Manganese(II)–EDTA–aminoethyldextran conjugate (**9**). — Dextran (100 g, mol. wt. 80 000) was dissolved in a solution of sodium hydroxide (160 g) and sodium borohydride (2 g) in distilled water (500 mL). 2-Chloroethylamine hydrochloride (230 g) was added, and the mixture was boiled and stirred under reflux for 22 h, cooled, and neutralised to pH 7 with conc. hydrochloric acid. The product was precipitated with ethanol, and a solution in distilled water (500 mL) was dialysed, concentrated to 100 mL, and then diluted with ethanol. The product was dried *in vacuo* to yield aminoethyldextran (65 g), mol. wt. 80 000, d.s. 0.35.

To a solution of aminoethyldextran (2.0 g) in dry methyl sulfoxide (200 mL) was added EDTA bisanhydride[10] (1.03 g). The mixture was stirred at ambient temperature for 16 h, then cooled in an ice–water bath; distilled water (200 mL) was added, and the pH was adjusted to 5.8. Stirring was continued at ambient temperature for 6 h, a solution of $MnCl_2 \cdot 4H_2O$ (0.88 g) in distilled water (20 mL) was added, the pH was adjusted to 5.7, and the product was purified and isolated as white flakes (3.8 g) (Mn, 1.7%).

Manganese(II) DTPA dextran conjugate (**10**). DTPA bisanhydride[10] (2.0 g) was added to a solution of dextran (2.0 g, mol. wt. 70 000) in dry methyl sulfoxide (100 mL) with stirring at ambient temperature. The mixture was stirred at ambient temperature for 20 h, then cooled in an ice–water bath, and distilled water (100 mL) was added gradually. The ice–water bath was removed, the mixture was stirred for 7 h, and the pH was adjusted to 6.5. A solution of $MnCl_2 \cdot 4H_2O$ (0.85 g) in distilled water (20 mL) was added, the pH was adjusted to 5.7, and the solution was stirred for 30 min. The product was purified and isolated as white, slightly yellow flakes (3.0 g) (Mn, 4.7%).

Manganese(II)–TTHA–dextran conjugate (**11**). — TTHA (1.0 g) and 4-dimethylaminopyridine (100 mg) were added to a solution of dextran (2.0 g, mol. wt. 40 000) in dry methyl sulfoxide (100 mL), EDCI (1.9 g) was added, the solution was stirred for 22 h at ambient temperature and then cooled in an ice–water bath, and distilled water (100 mL) was added gradually. The solution was stirred for 30 min, the pH was adjusted to 6.3, and a solution of $MnCl_2 \cdot 4H_2O$ (0.40 g) in distilled water (20 mL) was added. The pH was adjusted to 5.8, the mixture was stirred for 30 min, and the product was purified and isolated as white flakes (2.5 g) (Mn, 0.25%).

Iron(III)–DTPA–dextran conjugate (**12**). — A solution of $FeCl_3 \cdot 6H_2O$ (1.16 g) in distilled water (20 mL) was added to a solution of DTPA–dextran (intermediate for **10**) at pH 6.5. After adjustment of the pH to 5.7 and stirring for 30 min, the product was purified and isolated as light-brown transparant flakes (4.0 g) (Fe, 4.6%).

Iron(II)–DTPA–dextran conjugate (**13**). — DTPA–dextran (mol. wt. 2×10^6) was prepared as described for **10** and treated with a solution of $FeCl_2 \cdot 4H_2O$ (0.86 g) in distilled water (20 mL) at pH of 6.5. The pH was adjusted to 5.7, the solution was stirred for 30 min, and the product was purified and isolated as yellow–brown flakes (3.3 g) (Fe, 3.6%).

Iron(III)–EDTA–sucrose–epichlorohydrin copolymer conjugate (**14**). — EDTA was bound to Ficoll 400 as described for **8**, and treated with a solution of $FeCl_3 \cdot 6H_2O$ (1.40 g) in distilled water (20 mL). The pH was adjusted to 5.7, the solution was stirred for 30 min, and the product was purified and isolated as brown flakes (3.2 g) (Fe, 2.7%).

Iron(III)–carboxymethyldextran (**15**). — To a solution of the sodium salt of carboxymethyldextran (2.0 g, mol. wt. 65 000, d.s. 0.11) in distilled water (100 mL) at pH 5.8 was added a solution of $FeCl_3 \cdot 6H_2O$ (0.29 g) in distilled water (20 mL). The pH was adjusted to 5.6, and the product was purified and isolated as brown transparent flakes (1.9 g) (Fe, 3.2%).

Copper(II)–carboxymethylcellulose (**16**). — The pH of a solution of the sodium salt of carboxymethylcellulose (2.0 g, mol. wt. 90 000, d.s. 0.8) in distilled water (200 mL) was adjusted to 6.0, and a solution of $CuSO_4 \cdot 5H_2O$ (0.41 g) in distilled water (50 mL) was added. After adjustment of the pH to 5.2, the solution was stirred for 1 h, and the product was purified and isolated as blue flakes (1.7 g) (Cu, 2.2%).

Copper(II)–DTPA–dextran conjugate (**17**). — DTPA was bound to dextran (mol. wt. 2×10^6) as described for **10**, and treated with a solution of $CuSO_4 \cdot 5H_2O$ (1.08 g) in distilled water (20 mL) at pH 6.5. The pH was adjusted to 5.7, the solution was stirred for 30 min, and the product was purified and isolated as blue flakes (3.5 g) (Cu, 5.2%).

Copper(II)–mercaptosuccinic acid–dextran conjugate (**18**). — Mercaptosuccinic acid–dextran conjugate (2.0 g, mol. wt. 70 000, d.s. 0.16), prepared by esterification of dextran with *S*-acetylmercaptosuccinic anhydride[12], was dissolved in distilled water (200 mL). After the addition of a solution of $CuSO_4 \cdot 5H_2O$ (0.42 g) in distilled water (50 mL) at pH 6.0, the pH was adjusted to 5.8, and the product was purified and isolated as dark green flakes (1.85 g) (Cu, 1.6%).

Erbium(III)–DTPA–dextran conjugate (**19**). — DTPA was bound to dextran (mol. wt. 2×10^6) as described for **10**, and treated with a solution of $ErCl_3$ (1.6 g, 40% of water) in distilled water (20 mL) at pH 6.5. The pH was adjusted to 5.7, the solution was stirred for 30 min, and the product was purified and isolated as rose-coloured flakes (3.1 g) (Er, 8.4%).

Nickel(II)–DTPA–hydroxyethylstarch (**20**). — Hydroxyethylstarch (2.0 g, mol. wt. 131,000, d.s. 0.52), prepared by hydroxyethylation of starch with ethylene oxide[13], was dissolved in dry methyl sulfoxide (60 mL), and DTPA bisanhydride[10] (1.7 g) was added. The mixture was stirred at ambient temperature for 16 h and then cooled in an ice–water bath. Distilled water (100 mL) was added, the solution was stirred for 30 min, the pH was adjusted to 6.0, a solution of $NiCl_2 \cdot 6H_2O$ (1.23 g) in water (20 mL) was added, and the pH was adjusted to 5.0. The mixture was stirred at ambient temperature for 30 min, and the product was purified and isolated as green flakes (3.4 g) (Ni, 8.5%).

TABLE I

T_1 Relaxivity of paramagnetically labelled polysaccharides in glycerol–water

Conjugate/complex	r_1[a] $(s^{-1}.mmol^{-1}.L)$	M[b] (%)
Gadolinium(III)–EDTA–hydroxypropylstarch conjugate (**1**)	10.5	4.7
Gadolinium(III)–TTHA–dextran conjugate (**2**)	9.0	1.0
Gadolinium(III)–DTPA–dextran conjugate (**3**)	8.3	4.7
Gadolinium(III)–DTPA–inulin conjugate (**4**)	6.6	9.8
Gadolinium(III)–carboxymethyldextran (**5**)	0.2	2.8
Gadolinium(III)–dextran (**6**)	0.2	0.7
Gadolinium(III) dextran phosphate (**7**)	16.0	3.1
Manganese(II)–EDTA–sucrose–epichlorohydrin conjugate (**8**)	19.2	0.3
Manganese(II)–EDTA–aminoethyldextran conjugate (**9**)	12.8	1.7
Manganese(II)–DTPA–dextran conjugate (**10**)	7.7	4.7
Manganese(II)–TTHA–dextran conjugate (**11**)	5.5	0.25
Iron(III)–DTPA–dextran conjugate (**12**)	5.0	4.6
Iron(II)–DTPA–dextran conjugate (**13**)	2.0	3.6
Iron(III)–EDTA–sucrose–epichlorohydrin copolymer conjugate (**14**)	0.5	2.7
Iron(III)–carboxymethyldextran (**15**)	0.07	3.2
Copper(II)–carboxymethylcellulose (**16**)	2.0	2.2
Copper(II)–DTPA–dextran conjugate (**17**)	0.6	5.2
Copper(II)–mercaptosuccinic acid–dextran conjugate (**18**)	0.6	1.6
Erbium(III)–DTPA–dextran conjugate (**19**)	0.05	8.4
Nickel(II)–DTPA–hydroxyethylstarch (**20**)	0.01	8.5

[a] All relaxivity values are denoted per metal concentration. [b] Metal in the compound.

Relaxation measurements. — The measurements were performed in glycerol water (1:2.13) at 0.24 T and 37° on a Radx n.m.r. spectrometer (Radx Proton Spin Analyzer), using an inversion recovery sequence. The spin–lattice relaxivities (r_1) are listed in Table I.

DISCUSSION

Although there have been few reports[14–20] on the use of polysaccharides in m.r.i., their use has been investigated extensively as carriers for therapeutic drugs[21] and improved pharmacological properties have been obtained. Polysaccharides have been used as carriers in diagnostic imaging other than m.r.i. In ultrasound imaging, gas bubbles encapsulated in polysaccharide have been evaluated as a potential contrast agent for echocardiography[22]. Polysaccharides have been used for the targetting of radiopharmaceuticals, e.g., ^{99m}Tc and ^{113m}In. Radiolabelled dextran has been suggested for lymposcintigraphy[23] and as a blood-pool agent[24], ^{99m}Tc-labelled cellulose has been studied as an agent for the gastrointestinal tract[25], and polydextran microspheres labelled with ^{113m}In have been suggested for perfusion studies[26].

As for proteins, polysaccharides may be labelled with metals directly or by covalent attachment of the chelating agent. Polysaccharides can bind metal ions without any chelating moiety[27], although the stability of the complexes is expected to be somewhat lower. Tc-labelled dextran[23,24] utilises this property, whereas the cellulose product for gastrointestinal scintigraphy[25] and the In-labelled particles[26] include a chelating agent.

Both types of paramagnetic labelling have now been investigated. Dextran binds gadolinium ions (**6**), but the product from direct labelling is probably not stable *in vivo*. Dialysis of this product against citrate buffer extracted the gadolinium[28]. In the other compounds, the paramagnetic metal was associated with functional groups other than sugar alcohols, either in such strong chelating agents as EDTA, DTPA, or TTHA, or with such complexing groups as carboxyl groups or phosphate esters. EDTA and similar compounds were attached directly to the polysaccharide through an ester link (**2–4**, **8**, **10–14**, **17**, and **19**) or *via* a spacer arm that also resulted in an ester link (**1** and **20**), an amide link (**9**), or a thioester link (**18**). Amide and thioester links are probably more stable *in vivo* than are esters. The chelating agents were coupled to the polysaccharides either by direct reaction with bisanhydrides or by carbodi-imide-mediated reactions. The former method resulted in more cross-linking, as was confirmed by determination of average molecular weights of different polysaccharide conjugates[28].

Table I summarises the results of the relaxivity measurements. As expected from the efficacy of the paramagnetic salts[5] used, the gadolinium-, manganese-, and iron-based products generally were more efficient proton relaxers than the corresponding copper-, erbium-, and nickel-based products. However, for the products that contained gadolinium, manganese, and copper, the relaxivity was lower than for the corresponding labelled proteins[29]. The protein derivatives have prolonged rotational correlation times that resulted in more efficient relaxation of bulk-water protons by the partly

immobilised paramagnetic ions. In larger proteins, the prolonged rotational correlation time no longer dominates the total dipolar correlation time, and the electronic relaxation time, being field dependent, may cause asymmetric variations of the relaxivities with varying fields[30]. Our measurements were performed at 10 MHz, in glycerol–water (1:2.13), a medium that has relaxation properties similar to those of body fluids. The difference in relaxivity of GdDTPA and Fe(III)-DTPA in this medium and distilled water is considerable (Table II), reflecting the difference in viscosity. The gadolinium–carbohydrate derivatives showed a 60–260% increase in relaxivity compared to that of GdDTPA. Gibby *et al.*[18] measured the relaxivity of gadolinium–DTPA–dextran derivatives with various molecular weights at 80 MHz, and found only a ~25% increase in relaxivity compared to that of GdDTPA. These results may indicate that the rotational correlation time of the paramagnetic sites on dextran is short enough to dominate the total dipolar correlation time, which will result in lower relaxivity and less magnetic-field dependence. Lauffer[5] stated that, when metal chelates are attached covalently to the lysine side chains in proteins, the internal flexibility of the methylene side chains may reduce the relaxivity because of an increase in the rotational correlation times of the metal chelate part. The linear character of the polysaccharides used in the present study may allow more independent rotation of parts of the molecule, consequently resulting in a reduced relaxivity.

The chelating agents were connected to the carbohydrates *via* ester bonds, which probably resulted in a higher degree of co-ordinated inner-sphere water (q) on the metal ion. According to the Solomon–Bloembergen theory[3,4], this situation will result in an increased relaxation rate of the bulk water protons.

The gadolinium-labelled derivatives in Table I show some expected trends in r_1. The high-molecular-weight derivative (**3**) of GdDTPA, the low-molecular-weight derivative (**4**) of inulin and GdDTPA, and GdDTPA (Table II) show a corresponding decrease in r_1 from 8.3 to 6.0 $s^{-1}.mmol^{-1}.L$. The EDTA derivative **1** had a higher r_1 than the DTPA derivative **3** with the same molecular weight, reflecting the difference in degree of inner sphere water (q).

TABLE II

T_1 Relaxivity of paramagnetic chelates

Compound	r_1 ($s^{-1}.mmol^{-1}.L$)	*Frequency (MHz)*	*Temp.(°)*	*Medium*[a]	*Ref.*
Gadolinium(III)–DTPA	6.0	10	37	A	28
Gadolinium(III)–EDTA	6.6	20	35	B	31
Gadolinium(III)–DTPA	4.1	20	35	B	31
Manganese(II)–EDTA	2.9	20	35	B	31
Manganese(II)–DTPA	1.3	20	35	B	31
Iron(III)–DTPA	0.72	20	37	B	32
Iron(III)–DTPA	1.3	10	37	A	28
Copper(II)–EDTA	0.21	20	20	B	33
Copper(II)–DTPA	0.12	60	20	B	34

[a] A, Glycerol–water(1:2.13); B, water.

The extremely low r_1 of Gd–dextran **6** indicates that the few paramagnetic ions (0.7%) may be buried in the polymer matrix, thereby making the outer-sphere water inaccessible. This situation is indicated also by the fact that the gadolinium ions were not removed by extensive dialysis.

In contrast, the phosphate ester derivative **7** had an r_1 which was 100-fold larger than that of **6**. The phosphate ester groups have a high affinity for gadolinium and are situated on the "surface" of the carbohydrate matrix. The high r_1 (16 s^{-1}. $mmol^{-1}$.L) of **7** may reflect an excess of co-ordination sites of gadolinum over those for water combined with a somewhat lower tumbling rate of the molecule because of increased ionic character of the surface.

The manganese derivatives also showed some expected trends. The derivatives **9**, **10**, and **11** had similar molecular weights, but the ligands used had an increasing number of donating groups (EDTA, DTPA, and TTHA). This situation resulted in reduced degree of inner-sphere water (q) and reduction of r_1.

The sucrose–epichlorohydrin polymer used in the Mn–EDTA derivative **8** was anticipated to have a matrix which was more cross-linked than that of the dextran-type polymer. Hence, there was some restriction in the internal flexibility of the matrix, which seemed to be expressed in the difference in r_1 between **8** and **9**.

The iron(III) and iron(II) derivatives of DTPA–dextran, **12** and **13**, respectively, had the expected difference in r_1. A feature of iron chemistry is the tendency of ions to form hydroxides and oxides at neutral pH, which results in a large reduction of the relaxation efficacy. In the DTPA derivative, the chelate is stable enough to resist this tendency, but, in **14** and **15**, the formation of hydroxides is the probable cause of the lower r_1.

The relaxivity data for the salts of nickel, and erbium correspond with those of the carbohydrate derivatives **19** and **20** which show low relaxivity[5,28].

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