Synthesis and Characterization of New Polyethyleneoxy Substituted Salicylaldimine Schiff Bases and some corresponding Reduced Tetra- and Penta-aza Ligands and Their Gadolinium(III) Complexes: New Potential Contrast Agents in Magnetic Resonance Imaging

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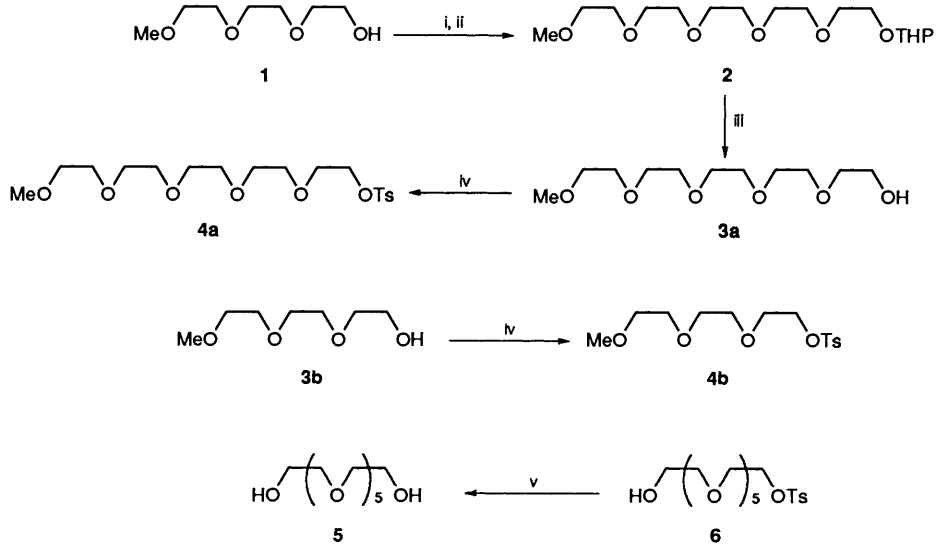
A series of polyether substituted salicylaldehyde derivatives $OHCC_6H_3OH$-2-OR-3 [R = CH_2-$(CH_2OCH_2)_nCH_2OR'$, n = 1, 4 and R' = Me; n = 5 and R' = H] have been synthesised and used to prepare the polydentate ligands $HN[(CH_2CH_2NHCH_2CH_2N{=}CHC_6H_3OH$-2-OR-3$]_2$, $HN[CH_2CH_2NHCH_2CH_2NHCH_2C_6H_3$-OH-2-OR-3$]_2$ and $HN[CH_2CH_2N{=}CHC_6H_3OH$-2-OR-3$]_3$; a preliminary evaluation has been made of the potential use of their gadolinium complexes as contrast agents for diagnostic Magnetic Resonance Imaging.

Complexes of paramagnetic lanthanide ions, particularly Gd^{3+}, are of interest because of their potential use as paramagnetic shift agents in Magnetic Resonance Imaging (MRI).[1] In this context the most commonly used ligands have been amine carboxylates such as diethylenetriaminepentaacetic acid ($DTPAH_5$) or derivatives of tetra-aza macrocycles such as $[CH_2CH_2NCH_2CO_2H]_4$ ($DOTAH_4$).[1-7] These afford complexes which are anionic and in which favourable effects on water relaxation can be obtained if at least one water molecule can enter the first coordination sphere of the paramagnetic metal ion centre.[8] Other ligands offering positively charged complexes have been investigated and recently a hexa-aza macrocyclic Schiff base ligand has been shown to coordinate to Gd^{3+} to give a tricationic complex with a relaxivity comparable to that of free Gd^{3+} in water.[9] Other Schiff base ligands derived from $N(CH_2CH_2NH_2)_3$ and acetylacetone or salicylaldehyde have been used in seeking a ligand system which would form neutral Gd^{3+} complexes[10] and an X-ray crystal structure of a Yb^{3+} complex of this type reveals the presence of coordinated water to give a capped octahedral coordination geometry.[11] In an evaluation of dianionic heptadentate Schiff base ligands which could offer monocationic lanthanide complexes incorporating at least one water molecule in the first coordination sphere we have previously reported the use of linear heptadentate Schiff base ligands such as $[2\text{-}HOC_6H_4CH{=}NCH_2(CH_2NHCH_2)_3CH_2N{=}CHC_6H_4OH\text{-}2']$($LH_2$).[12] An X-ray crystal structure of the complex [LuL(OH_2)]Cl shows that this ligand can form lanthanide complexes in which a water molecule completes eight-coordination around the metal ion. Although the complex $[GdL(H_2O)]^+$ exhibits a relaxivity of 3.91 $dm^3\ mmol^{-1}\ s^{-1}$, which is of similar magnitude to those of 4.23 and 3.98 $dm^3\ mmol^{-1}\ s^{-1}$ found respectively for $[Gd(DTPA)(H_2O)]^{2-}$ ($DPTAH_5$ = diethylenetriaminepentaacetic acid) and $[Gd(DOTA)]^-$ ($DOTAH_4$ = 1,4,7,10-tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetraacetic acid), it lacks the water solubility and osmolality necessary for clinical use. In an attempt to improve these properties we have synthesised a series of polyether substituted derivatives of LH_2 and of $N(CH_2CH_2N{=}CHC_6H_4OH\text{-}2)_3$ which are expected to exhibit improved water solubility. The gadolinium complexes of these ligands have also been prepared and a preliminary assessment of their efficacy as MRI contrast agents has been made.

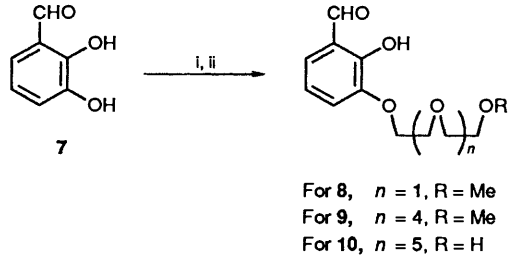
Results and Discussion

The ligands described here may be prepared using a Schiff base condensation between the appropriate polyamine and a salicylaldehyde derivative containing a polyether substituent. These aldehydes **8**–**10** (Scheme 2) were prepared in 42–63% yield by adapting the methodology of Gupta and co-workers[13] which was further developed by Reinhoudt and co-workers.[14-16] This involves reaction of the dianion of 2,3-dihydroxybenzaldehyde **7** with 1-bromo-2-(2-methoxyethoxy)-ethane, pentaethylene glycol monomethyl ether toluene-*p*-sulfonate **4a** or hexaethylene glycol monotoluene-*p*-sulfonate **6**, respectively. The synthesis of pentaethylene glycol monomethyl ether toluene-*p*-sulfonate **4a** (Scheme 1) starts with the preparation of pentaethylene glycol monomethyl ether **3a** by alkoxylation of commercially available triethylene glycol monomethyl ether **1** with 2-(2-chloroethoxy)ethyl tetrahydropyran-2-yl ether[17] in the presence of NaH in THF. This reaction gives **2** which was directly converted, under acidic conditions, into **3a** in 58% yield. Tosylation of **3a** and of triethylene glycol monomethyl ether **3b** was effected in 92 and 96% yield, respectively, using toluene-*p*-sulfonyl chloride and sodium hydroxide under phase-transfer conditions, a method which has been reported previously.[18] Hexaethylene glycol **5** was monotosylated with toluene-*p*-sulfonyl chloride and triethylamine in the presence of 4-dimethylpyridine to give **6** in 69% yield by adapting a procedure which has been recently reported for diethylene and triethylene glycol monotoluene-*p*-sulfonates.[19]

The (2 + 1) condensation of the aldehydes **8**–**10** with tetraethylenepentaamine and the (3 + 1) condensation of the same aldehydes with tris(2-aminoethyl)amine (tren) were carried out by addition of a solution of the corresponding amine to a solution of one of the aldehydes **8**–**10** in methanol. The absence of any absorption due to $\nu(NH_2)$ or $\nu(C{=}O)$ in the IR spectra of compounds **11**–**13** and **15**–**17** together with the presence of medium–strong absorption around 1630 cm^{-1} due to $\nu(C{=}N)$, showed Schiff base condensation to be complete (Table 2). Satisfactory elemental analyses together with the peaks in the FAB mass spectra of **11**–**13** (m/z 813, 1209, 1299) and **15**–**17** (m/z 634, 898, 958) corresponding with the $[M + H]^+$ ions confirmed the formulation of the ligands (Table 1).



Scheme 1 *Reagents and conditions:* i, NaH/THF, N_2, O °C→room temp., 1.5 h; ii, $ClCH_2CH_2OCH_2CH_2OTHP$ **7**, THF, reflux, 24 h; iii, MeOH–CH_2Cl_2, HCl, reflux, 8 h; iv, *p*-TsCl/CH_2Cl_2, 30% aq. NaOH, TEBA (cat), 5 °C→room temp.; v, *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, 5 °C→room temp



Scheme 2 *Reagents and conditions:* i, NaH (2 equiv.), DMSO, 18–20 °C; ii, DMSO, 20–25 °C, R–X (for 8, RX = $BrCH_2CH_2OCH_2CH_2OMe$, for **9**, RX = **4a**, for **10**, RX = 6)

In the ^1H NMR spectra of aldehydes **8–10** and the ligands **11–13**, the phenolic OH protons appear as singlets at 10.8–10.9 and around 14.2 p.p.m, respectively; aldehyde and azomethine protons are observed at 9.89–9.98 and 7.76–7.81 p.p.m (Table 3). There is only a slight difference in chemical shift between the ethereal protons of the aldehydes **8–10** and the ligands **11–13**. ^{13}C NMR shifts also confirm the structures shown for compounds **11–13**. The formation of an azomethine bond causes a shift from 195.4 to 195.8 p.p.m in aldehydes **8–10** to 166.13–166.30 p.p.m in the ligands **11–13** for C-7 (Table 4).

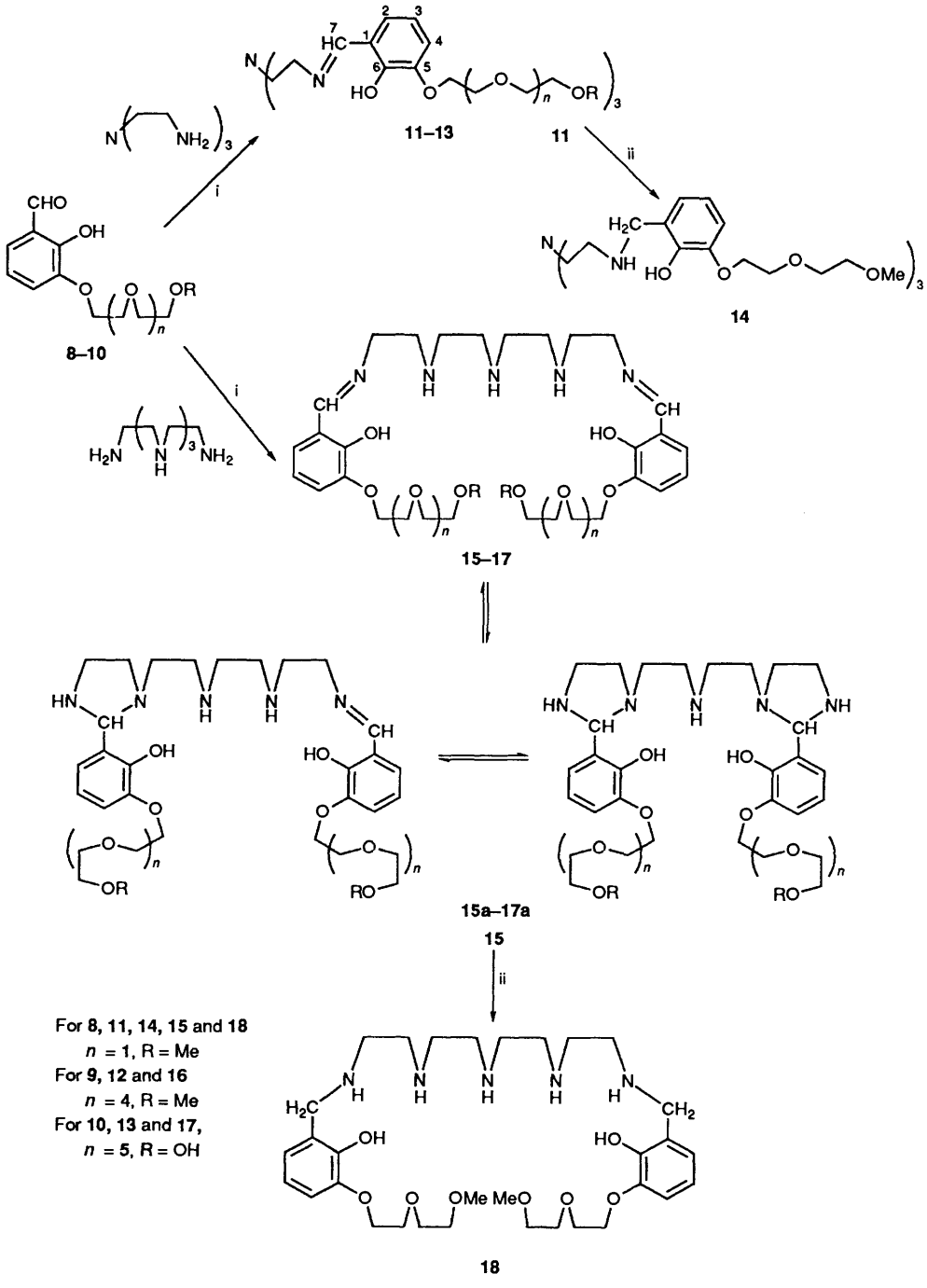
The products **15–17** prepared by the (1 + 2) Schiff base condensation of tetraethylenepentaamine with the aldehydes **8–10** (Scheme 3) gave elemental analyses and FAB mass spectra in satisfactory agreement with their chemical formulae (Table 1). However, the 270 MHz ^1H NMR and ^{13}C NMR spectra in $CDCl_3$ are very complex with broad aliphatic peaks and multiplets for imine protons and carbon, suggesting the presence of isomers of the Schiff base (due to imidazolidine ring formation as a consequence of the nucleophilic addition of the two secondary amine functions of **15–17** across adjacent imine bonds to give **15–17a**). Similar observations have been already reported in the literature.[20–22] Treatment of these condensation products with sodium borohydride (in case **15→18**) or with $GdCl_3$ as a strong Lewis acid (in cases **15–17→23–25**) resulted in the reduction of two imine bonds and/or ring opening of the imidazoline five-membered rings, respectively.

Preparation of the Gd^{III} complex **19** by treating the Schiff base **11** with $GdCl_3$ both in the presence or in the absence of triethylamine failed, only the starting ligand **11** being recovered. However, we have found a new simple route to the Gd^{III} complexes by way of the *in situ* formation of the phenoxide anion of these ligands. Thus, the corresponding ligands **11**, **12**, **14–16** and **18** and the ligands **13** and **17** were successively treated first with stoichiometric quantities of sodium methoxide or with powdered sodium hydroxide in methanol, respectively, and then 1 equiv. of $GdCl_3$. This afforded the corresponding products **19**, **20**, **22–24** and **26** and **21** and **26**, respectively, with a metal : ligand ratio of 1 : 1. In addition, this method allows the preparation of the Gd complexes **19–21** and **23–25** in 'one-pot' reactions starting from the aldehydes **8–10** and the corresponding amine within 5 h in overall yields of over 90%.

The IR spectra of the Gd complexes **19–21** and **23–25** show (Table 1) that the C=N stretch absorption is shifted slightly (15 to 9 cm^{-1}) to lower energy after complex formation (Table 2). A shift in the same way can be seen for $C–O–C_{Ar}$ frequencies, suggesting more restricted conformational mobility of the polyether group in the complexes. There is no shift observed for the Gd complexes **22** and **26** of the reduced ligands **14** and **18**, respectively, suggesting that these compounds are more flexible. When gadolinium was introduced into the ligands **15–18** the ν(NH) stretching absorption in the Gd complexes **23–26** appeared at two distinct frequencies, presumably as a result of different environments for the amino groups in the complex.

The fast atom bombardment mass spectra of the neutral Gd complexes **19** and **22** and **20** and **21** show molecular ion peaks at *m/z* values increased by complexation with sodium or with sodium and potassium, respectively, possibly reflecting differences of cavity size as a consequence of differences in length of the polyethylenoxy chains in the ligands. The parent peaks in the FAB mass spectra of the ionic Gd complexes **23–26** correspond to the molecular ion with loss of chlorine anion.

An important feature affecting the utility of these neutral and ionic Gd complexes **19–26** as potential contrast agents in Magnetic Resonance Imaging (MRI) is their solubility in water. The new gadolinium complexes exhibited improved solubility in water compared to their counterparts which carry no polyether substituents, although the water solubilities of the neutral compounds **19** and **22**, in particular, were still somewhat limited. Compound **23** was sufficiently soluble in water to allow T_1 and T_2 values to be measured on a dilute (1 mmol dm^{-3}) solution. In the cases of complexes **19**, **22** and **26** 1 mmol dm^{-3} solutions were prepared in 10% $EtOH/H_2O$. The T_1/T_2 values

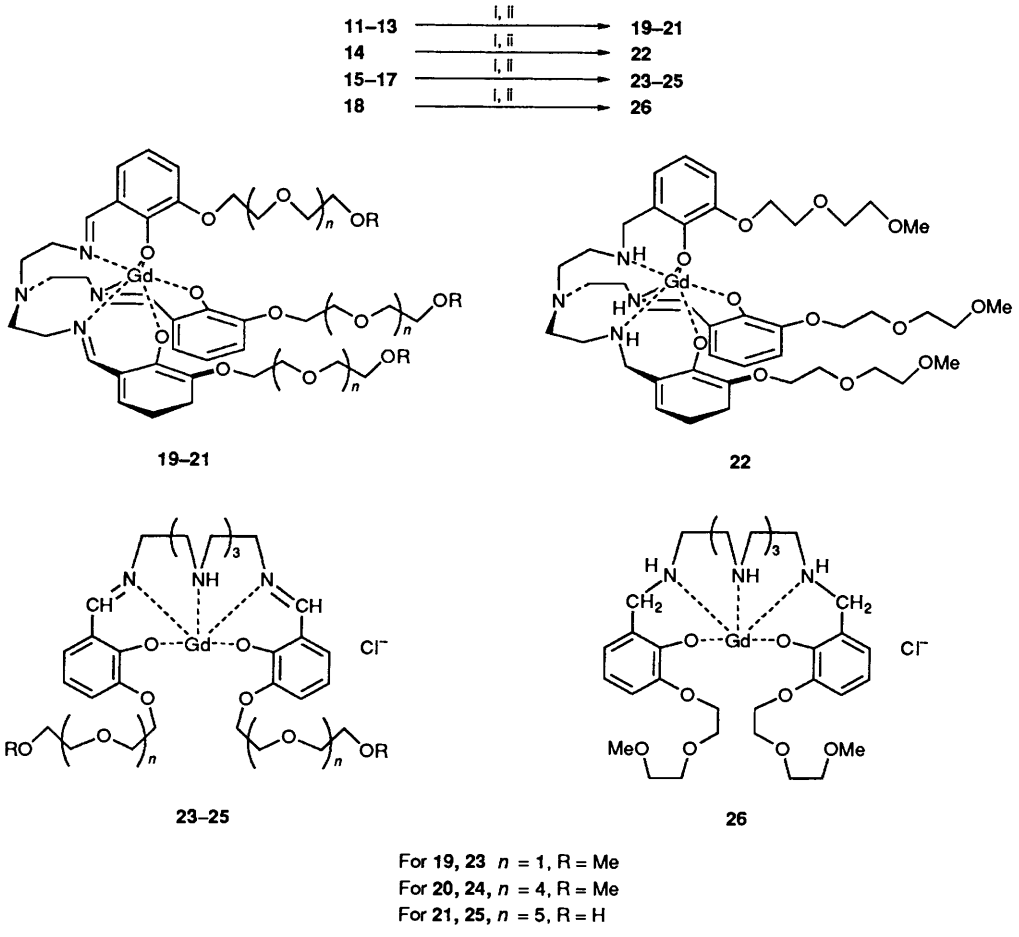


Scheme 3 *Reagents and conditions:* MeOH, reflux, 2 h; ii, $NaBH_4$, MeOH, 5 °C→room temp. 1 h, reflux 2 h

were measured at 37 °C and 20 MHz and the results obtained are presented in Table 5. Compounds **19** and **23** gave results comparable to those obtained for the commercial agents Magnevist and Dotarem while **22** and **26** gave higher relaxivity results, although these may reflect some dissociation of the complex in solution.

In order to further evaluate the potential utility of this class of compound as contrast agents for MRI they were used to obtain images in rats. Compounds **19**, **22** and **26** proved toxic under the conditions used, quite possibly as a result of the ethanol content of the solution. However, 0.6 cm^{-3} (32 mmol dm^{-3}; 60 μmol kg^{-1} of rat) of an aqueous solution of **23** was injected successfully with the rat being alive 3 weeks after injection. The MRI enhancements found in liver, kidney cortex and dorsal muscle after injection of **23** are presented in Fig. 1 as function of time.

These first results show that the signal intensity in the liver, the muscle and the kidney cortex increases immediately after injection to reach a plateau keeping a quasi-constant value up to 1 h after injection. 1 h Post injection, the NMR signal intensity in the liver, dorsal muscle and kidney cortex starts to decrease towards the precontrast value, this being recovered 24 h after contrast product injection. These results show that good contrast enhancement of the liver and kidney cortex was achieved up to 1 h after injection. A 40% liver MR signal intensity enhancement was still observed during this period of



Scheme 4 *Reagents and conditions:* i, **11**, **12**, **14**, **15**, **16** and **18** MeONa/MeOH, room temp. 10 min, for **13** and **17** NaOH/MeOH, room temp., 10 min; ii, $GdCl_3 \cdot 6H_2O$, reflux, 2 h

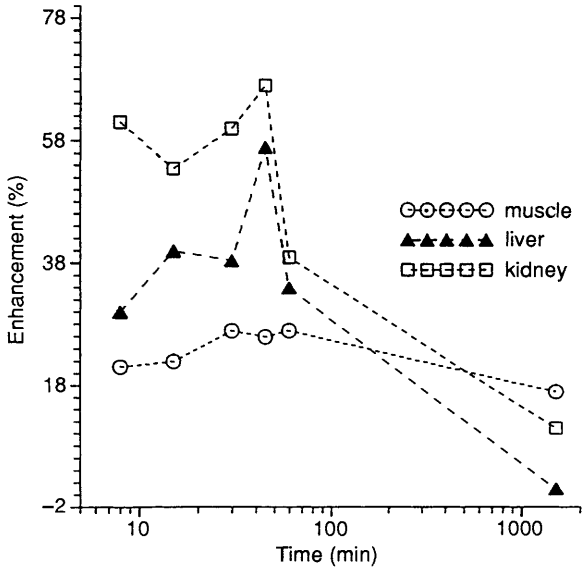


Fig. 1 Time course of the tissue enhancements after i.v. (0.1 mmol kg^{-1}) injection of the complex **23** in different rat tissue (liver, dorsal muscle and kidney cortex). Each point is the average of enhancements observed in three rats.

time in contrast to the results obtained with Magnevist (Schering, Berlin, FRG) which cleared from liver within about 10 min, although this reagent is known to clear rapidly *via* the renal system.

In conclusion, the strategy of using polyether substituents to improve the water solubility of this class of potential MRI contrast agents has met with some success, but solubility limitations and toxicity remain a problem with the neutral systems studied. Although the animal population studied is too small to allow any firm conclusion to be drawn from these preliminary experiments, in the case of compound **23** at least, promising results are obtained. The increase of signal from the liver with the product **23** immediately after contrast injection reflects the enhanced signal from the liver vascular system (arterial + venous) which carries the contrast agent. In addition, the long period of enhancement in liver compared with the enhancement encountered with Gd-DTPA (a pure vascular agent) and the enhancement in the spleen which is not reported in this paper seem to present this product as a potential contrast agent of the reticuloendothelial system.

Experimental

Instrumentation.—^1H NMR and ^{13}C NMR spectra were recorded on a JEOL GX 270 spectrometer (at 270 MHz for ^1H) or on a Bruker AC 300 spectrometer (at 300 MHz for ^1H) at 20 °C using tetramethylsilane as internal reference. IR spectra were obtained as KBr pellets or films on a Perkin-Elmer 1600 spectrophotometer with a Hewlet Packard Color Pro Plotter over the range 4000–500 cm^{-1}. Electron impact (EI, 70 eV) and chemical ionisation (CI) mass spectra were taken on a KRATOS PROFILE machine and fast atom bombardment (FAB) mass spectra on a KRATOS MS 80 RF mass spectrometer with a DS 90 data system. Microanalyses were obtained

by the Micoranalytical service of the School of Chemistry, The University of Birmingham, using a Perkin-Elmer model 1201 automatic analyzer. Analytical samples were dried *in vacuo* (6.5 Pa) at 60–70 °C. M.p.s, uncorrected were taken in glass capillary tubes on a Gallenkamp melting point apparatus.

Reagents.—The following solvents were freshly distilled prior to use: tetrahydrofuran (THF) from sodium benzophenone ketyl, methanol (MeOH) from magnesium turnings, methylene dichloride from calcium hydride, dimethylformamide (DMF), pre-dried over 4 Å molecular sieves, from barium oxide. Dimethyl sulfoxide (DMSO) and triethylamine were distilled over calcium hyride and stored under a nitrogen atmosphere. Tetraethylenepentamine (technical grade *ca.* 85%, Aldrich) was purified through the pertosylate salt as described by I. W. Stapleton.[23] 2-(2-Chloroethoxy)ethyl tetrahydropyran-2-yl ether was prepared as described earlier.[17] All other solvents and reagents were of reagent grade quality.

Thin-layer chromatography was carried out either on Merck Kieselgel 60 F_{254} precoated silica gel plates or Polygram Alox N/UV_{254} plastic sheets. Preparative flash column chromatography was performed on Merck TLC-Kieselgel 60H (15 mm) with the solvents specified.

14-*Methoxy*-3,6,9,12-*tetraoxatetradecan*-1-*ol* **3a**.—To an ice cold stirred suspension of sodium hydride (80% in mineral oil; 5.8 g, 0.193 mol) in dry THF (180 cm^3) under nitrogen, was added dropwise 8-methoxy-3,6-dioxaheptan-1-ol (27.6 g, 0.168 mol) in THF (50 cm^3). The mixture was stirred at ambient temperature for 1.5 h and then brought to reflux when a solution of 2-(2-chloroethoxy)ethyl 2-tetrahydropyran-2-yl ether[17] in dry THF (60 cm^3) was added dropwise to it. Stirring was continued for 24 h under reflux after which the reaction was quenched by addition of methanol to the mixture. After evaporation of the mixture under reduced pressure the residue was dissolved in ether and the solution filtered through a pad of Al_2O_3. The combined filtrates were evaporated to give the crude tetrahydropyranyl derivative **2** (47.4 g), which was used without further purification in the next step.

Compound **2** was dissolved in dichloromethane (100 cm^3) and methanol (100 cm^3) containing concentrated hydrochloric acid (3.0 cm^3). The solution was heated under reflux for 3 h and then cooled to room temperature when solid potassium carbonate (30 g) was added to it. The mixture was then stirred for 1 h, filtered and the filtrate was concentrated. The crude product was purified on a silica gel column by flash chromatography with up to 5% gradient elution of methanol in dichloromethane to give pure **3a** (24.6 g, 58%) (Found: C, 52.1; H, 9.8. $C_{11}H_{24}O_6$ requires C, 52.35; H, 9.59%); δ_H(270 MHz, $CDCl_3$) 3.38 (s, 3 H, OCH_3) and 3.53–3.73 (m, 20 H, OCH_2); *m/z* (FAB) 288 ($M + H^+$).

14-*Methoxy*-3,6,9,12-*tetraoxatetradecyl Toluene*-p-*sulfonate* **4a**.—To an ice cold stirred mixture of the alcohol **3a** (21.5 g, 85 mmol), dichloromethane (75 cm^3), triethylbenzylammonium chloride (0.77 g, 3.4 mmol) and 30% aqueous sodium hydroxide (60 cm^3) was added dropwise a solution of toluene-*p*-sulfonyl chloride (17.0 g, 89 mmol) in dichloromethane (75 cm^3). The mixture was stirred at ambient temperature for 3 h and then poured into water (100 cm^3). The organic layer was separated, washed with water, dried ($MgSO_4$) and concentrated.

The crude product was purified by flash column chromatography on silica gel (elution with CH_2Cl_2–MeOH in 99 : 1–99 : 5 gradient) to give **4a** as a colourless oil (31.7 g, 92%) (Found: C, 52.85; H, 7.6. $C_{18}H_{30}O_8S$ requires C, 53.18; H, 7.44%); δ_H(270 MHz, $CDCl_3$) 2.45 (s, 3 H, $ArCH_3$), 3.37 (s, 3 H, OCH_3), 3.52–3.70 (m, 16 H, OCH_2), 4.14–4.18 (m, 2 H, OCH_2), 7.33, 7.36, 7.78 and 7.81 (AB, 4 H, ArH); *m/z* 407 (M^+, 15%), 361 (9), 317 (14), 287 (37), 273 (22), 243 (58), 199 (91) and 155 (78).

8-*Methoxy*-3,6-*dioxaheptyl Toluene*-p-*sulfonate* **4b**.—The title compound was prepared from 8-methoxy-3,6-dioxaheptan-1-ol (24.6 g, 0.150 mol) and toluene-*p*-sulfonyl chloride (30.1 g, 0.158 mol) using the method described above for the compound **4a** (96% yield) (Found: C, 53.1; H, 7.1. $C_{14}H_{22}O_6S$ requires C, 52.81; H, 6.9%); δ_H(270 MHz, $CDCl_3$) 2.45 (s, 3 H, $ArCH_3$), 3.37 (s, 3 H, OCH_3), 3.48–3.55 (m, 2 H, OCH_2), 3.59–3.63 (m, 6 H, OCH_2), 3.69 (t, 2 H, *J* 5, OCH_2), 4.16 (t, 2 H, *J* 5, OCH_2), 7.33, 7.36, 7.78 and 7.81 (AB, 4 H, ArH).

17-*Hydroxy*-3,6,9,12,15-*pentaoxaheptadecyl Toluene*-p-*sulfonate* **6**.—The title compound was prepared by a literature procedure[19] from the corresponding diol in 69% yield as a colourless liquid (Found: C, 52.2; H, 7.3. $C_{19}H_{32}O_9S$ requires C, 52.27; H, 7.39%); δ_H(270 MHz, $CDCl_3$) 2.45 (s, 3 H, CH_3), 3.37 (s, 1 H, OH), 3.58–3.73 (m, 22 H, OCH_2), 4.14–4.17 (m, 2 H, OCH_2), 7.33, 7.36, 7.78, 7.81 (AB, 4 H, ArH); *m/z* 437 (M^+, 8%), 349 (9), 305 (8), 287 (27), 243 (50), 199 (84), 172 (53), 155 (72), 133 (58) and 107 (55).

General Procedure for Synthesis of the Aldehydes **8–10**.—The aldehydes **8–10** (Scheme 2) were prepared adapting the methodology of Gupta and co-workers[13] and later developed by Reinhoudt and co-workers.[14–16]

3-(3,6-*Dioxaheptyloxy*)-2-*hydroxybenzaldehyde* **8**.—To a stirred suspension of NaH (80% dispersion in oil; 5.0 g, 0.17 mol) prewashed with hexane, in DMSO (70 cm^3), under a N_2 atmosphere, was added a solution of 2,3-dihydroxybenzaldehyde (9.6 g, 0.069 mol) in DMSO (35 cm^3) at 18–20 °C. The mixture was stirred at room temperature for 1 h after which a solution of 1-bromo-2-(2-methoxyethoxy)ethane (12.7 g, 0.069 mol) in DMSO (15 cm^3) was added to it at 20–25 °C. Stirring was continued for 24 h after which the mixture was poured into water (400 cm^3) and extracted with $CHCl_3$ (2 × 100 cm^3). The aqueous layer was acidified with 6 mol dm^{-3} HCl to adjust the pH to 2 and then extracted with $CHCl_3$ (5 × 100 cm^3). The combined extracts were washed with 4% HCl (2 × 100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure and the residue was subjected to flash column chromatography on silica with up to 2% gradient elution of methanol in dichloromethane to give **8** (7.0 g, 42%), as a yellow liquid.

In a similar way the aldehydes **9** and **10** were prepared. Yields, elemental analyses, mass spectra, ^1H NMR and ^{13}C NMR data are given in Tables 1, 3 and 4.

General Synthesis of Acyclic Tripodal, **11–13**, *and Dipodal,* **15–17** *Ligands.*—A solution of each of the aldehydes **8–10** (2.0 mmol) in methanol (20 cm^3) was added dropwise to a solution of tris(2-aminoethyl)amine (0.67 mmool) or 3,6,9-tetraazaundecane-1,11-diamine (1.0 mmol) in methanol (10 cm^3). The mixture was stirred and heated under reflux and a N_2 atmosphere for 2 h. The solvent was evaporated under reduced pressure and the residue was dried *in vacuo* at 70 °C (0.1 mmHg) for 5 h to give oily products **11–13** and **15–17**, respectively. Yields, elemental analyses and spectral data are summarized in Tables 1–4. The 270 MHz ^1H NMR and the ^{13}C NMR spectra of the products **15–17** are complex, suggesting the presence of isomers of the Schiff bases.

Syntheses of the Reduced Ligands **14** *and* **18**.—To a cooled solution (5–10 °C) of the ligand **11** (820 mg, 1.0 mmol) in methanol (30 cm^3) was added sodium borohydride (100 mg, 2.6 mmol) in one portion. The mixture was stirred at room temperature for 1 h after which additional $NaBH_4$ (100 mg, 2.6

Table 1 Analytical and mass spectral data for the aldehydes **8–10**, the ligands **11–18** and Gd^{III} complexes **19–26**

Compound (formula)	Yield (%) and form	Found (%)/(Required) C	H	N	*m/z* (FAB)
8	42	58.4	7.4		*a*
$(C_{12}H_{16}O_5)$·0.5 MeOH	Oil	(58.58)	(7.08)		
9	63	58.1	7.35		*a*
$(C_{18}H_{28}O_8)$	Oil	(58.04)	(7.58)		
10[b]	51	57.0	7.9		*a*
$(C_{19}H_{30}O_9)$	Oil	(56.69)	(7.52)		
11	94	62.0	7.35	7.2	813 $(M + H)^+$
$(C_{42}H_{60}N_4O_{12})$	Syrup	(62.05)	(7.44)	(6.89)	
12	98	59.9	7.8	5.0	1209 $(M + H)^+$
$(C_{60}H_{96}N_4O_{21})$	Syrup	(59.57)	(8.00)	(4.63)	
13	97	58.5	8.1	4.1	1299 $(M + H)^+$
$(C_{63}H_{102}N_4O_{24})$	Syrup	(58.21)	(7.92)	(4.31)	
14	91	60.5	7.8	6.95	819 $(M + H)^+$
$(C_{42}H_{66}N_4O_{12})$·MeOH	Syrup	(60.68)	(8.29)	(6.58)	
15	96	60.7	7.9	10.7	634 $(M + H)^+$
$(C_{32}H_{51}N_5O_8)$	Syrup	(60.64)	(8.11)	(11.05)	
16	95	58.6	8.3	7.6	898 $(M + H)^+$
$(C_{44}H_{75}N_5O_{14})$	Syrup	(58.83)	(8.42)	(7.80)	
17	96	57.9	8.5	7.2	958 $(M + H)^+$
$(C_{46}H_{79}N_5O_{16})$	Syrup	(57.66)	(8.31)	(7.31)	
18	96	59.2	8.8	10.6	638 $(M + H)^+$
$(C_{32}H_{55}N_5O_8)$·MeOH	Syrup	(59.17)	(8.88)	(10.46)	
19	90	48.7	5.6	5.3	990 $(M + Na)^+$
$(C_{42}H_{57}GdN_4O_{12}\cdot CH_2Cl_2$	Foam	(49.08)	(5.65)	(5.32)	
20	99	52.0	7.0	4.1	1402 $(M + K)^+$
$(C_{60}H_{93}GdN_4O_{21})$·$H_2O$	Glass	(52.16)	(6.93)	(4.06)	1386 $(M + Na)^+$
21	97	51.8	6.7	3.85	1492 $(M + K)^+$
$(C_{63}H_{99}GdN_4O_{24})$	Glass	(52.05)	(6.86)	(3.85)	1476 $(M + Na)^+$
22	92	48.7	6.0	5.6	996 $(M + Na)^+$
$(C_{42}H_{63}GdN_4O_{12})$·$CH_2Cl_2$	Foam	(48.81)	(6.19)	(5.30)	
23	89	46.3	5.9	7.8	789 $(M + H)^+$-Cl
$(C_{32}H_{49}ClGdN_5O_8)$·MeOH	Foam	(46.27)	(6.24)	(8.18)	
24	92	48.2	6.8	6.1	1053 $(M + H)^+$-Cl
$(C_{44}H_{73}ClGdN_5O_{14})$	Glass	(48.51)	(6.76)	(6.43)	
25	98	48.4	6.7	6.1	1113 $(M + H)^+$-Cl
$(C_{46}H_{77}ClGdN_5O_{16})$	Glass	(48.07)	(6.76)	(6.10)	
26	87	43.7	6.0	7.6	793 $(M + H)^+$-Cl
$(C_{32}H_{53}ClGdN_5O_8)$·CH_2Cl_2	Foam	(43.39)	(6.07)	(7.67)	

[a] Mass spectrum, *m/z* found for **8**: 240 (M^+, 28%), 164 (35), 149 (10), 138 (53), 103 (82); for **9**: 372 (M^+, 14%), 226 (20), 209 (26), 182 (30), 165 (68), 137 (65), 103 (70); for **10**: 384 (M^+–H_2O, 32%), 239 (16), 226 (16), 209 (12), 177 (36), 165 (64), 137 (62), 121 (37), 109 (51). [b] Flash chromatography was provided with up to 5% MeOH in CH_2Cl_2.

Table 2 Characteristic IR bands (cm^{-1}) for the ligands **11–18** and Gd^{III} complexes **19–26** (film)

Compounds	NH, OH	$CH_{aliphatic}$	C=N	C–O–C_{Ar}	C–O–C	Others
11	3378	2888	1633	1252	1108	
12	3500	2872	1632	1253	1102	
13	3456	2865	1632	1252	1108	
14	3300	2877		1235	1109	1588 δ(NH)
15	3297	2933	1632	1253	1108	
16	3350	2878	1633	1252	1101	
17	3354	2869	1632	1253	1101	
18	3325	2877		1236	1109	1587 δ(NH)
19[a]	3424	2878	1618	1218	1098	
20	3567	2878	1625	1216	1106	
21	3374	2869	1621	1219	1107	
22[a]	3446	2872		1234	1109	1590 δ(NH), 1311
23[a]	3425, 3225	2864	1623	1219	1102	
24	3430, 3247	2868	1624	1219	1105	
25	3370, 3250	2868	1624	1220	1105	
26[a]	3424, 3243	2862		1235	1090	1590 δ(NH), 1312

[a] (KBr pellets).

mmol) was added to it and the whole heated under reflux for 2 h. After this the mixture was cooled and evaporated under reduced pressure and the residue was dissolved in water (10 cm^3), and the pH of the solution adjusted to 9 with 2.5 mol dm^{-3} HCl. The solution was then evaporated to dryness. Toluene (50 cm^3) was added to the residue and the mixture was distilled azeotropically until no further water was separated. The hot toluene solution was then filtered, and the filtrate evaporated to

Table 3 ^{1}H NMR spectral data for the aldehydes **8**–**10** and the ligands **11**–**14** and **18** in $CDCl_3$

Compound	OH	H–C=O	H–C=N	H_a	$ArOCH_2$	OCH_2	OCH_3	NCH_2
8[a]	10.88 (s, 1 H)	9.96 (s, 1 H)		7.29–7.16 (m, 2 H) 6.93 (t, *J* 7.9, 1 H) 3.58 (t, *J* 5, 2 H)	4.23 (t, *J* 5)	3.90 (t, *J* 5, 2 H) 3.74 (t, *J* 5, 2 H)	3.39 (s, 3 H)	
9[b]	10.85 (s, 1 H)	9.89 (s, 1 H)		7.26–7.12 (m, 2 H) 6.90 (t, *J* 8, 1 H)	4.20 (t, *J* 5)	3.87 (t, *J* 5, 2 H) 3.67–3.58 (m, 14 H) 3.53–3.48 (m, 2 H)	3.34 (s, 3 H)	
10[a,c]	10.83 (s, 1 H)	9.98 (s, 1 H)		7.29–7.16 (m, 2 H) 6.93 (t. *J* 7.8. 1 H)	4.22 (t, *J* 5)	3.90 (t, *J* 5, 2 H) 3.76–3.59 (m, 20 H)		
11[a,c]	14.22 (br s, 3 H)		7.81 (s, 3 H)	6.92 (d, *J* 8, 3 H) 6.57 (t, *J* 8, 3 H) 5.87 (d, *J* 8, 3 H)	4.21 (t, *J*)	3.89 (t, *J* 5, 6 H) 3.72 (t, *J* 5, 6 H)	3.36 (s, 9 H)	2.82 (br s, 6 H)
12[a,c]	14.20 (br s, 3 H)		7.81 (s, 3 H)	6.93 (d, *J* 8, 3 H) 6.50 (t, *J* 8, 3 H) 5.86 (d, *J* 8, 3 H)	4.21 (t, *J* 5)	3.90 (t, *J* 5, 6 H) 3.65 (m, 42 H)	3.37 (s, 9 H)	2.82 (br s, 6 H)
13[b,c]	14.20 (br s)		7.76 (s, 3 H)	6.88 (d, *J* 8, 3 H) 6.45 (t, *J* 8, 3 H) 5.80 (d, *J* 8, 3 H)	4.14 (t, *J* 5)	3.83 (t, *J* 5, 6 H) 3.70–3.63 (m, 12 H) 3.60–3.51 (m, 51 H		2.77 (br s, 6 H)
14[a,c]				6.84–6.81 (m, 3 H) 6.80–6.61 (m, 6 H)	4.17 (t, *J* 6 H)	4.00–3.82 (m, 12 H, and CH_2Ph) 3.80–3.63 (m, 6 H) 3.58–3.52 (m, 6 H)	3.37 (s, 9 H)	2.78–2.43 (m, 12 H)
18[a]				6.85–6.58 (m, 6 H)	4.19 (m, 4 H)	3.97–3.65 (m, 12 H) and CH_2Ph) 3.56 (m, 4 H)	3.36 (s, 6 H)	2.84–2.36 (m, 16 H)

[a] 270 MHz spectrometer. [b] 300 MHz spectrometer. [c] Remaining protons: in **10** 2.86 (s, 1 H, OH); in **11** 3.54 (m, 12 H, OCH_2 and $=NCH_2$); in **12** 3.54 (m, 12 H, OCH_2 and $=NCH_2$); in **13** 3.48 (m, 6 H, $=NCH_2$); in **14** 6.1 (br s, 3 H, NH).

Table 4 Carbon-13 NMR spectral data for the aldehydes **8–10** and the ligands **11–13**

Compound	CHO	C-7	C-2	C-3	C-1	C(4)–C(6)	CH_2-O	OCH_3[a] OCH_2OH[b]	CH_2-N
8[c]	195.8		151.9	147.2	121.0	124.8, 120.7 119.2	71.7, 70.5 69.4, 69.1	58.7[a]	
9[d]	195.6		151.8	147.1	121.0	124.7, 120.6 119.1	71.6, 70.5 70.2, 69.3, 69.0	58.6[a]	
10[c]	195.4		151.7	147.0	121.0	124.3, 120.4 119.0	72.1, 70.4, 70.1 69.9, 69.2, 68.7	61.2[b]	
11[c]		166.13	152.3	147.27	118.42	124.15, 117.32 116.64	71.77, 70.53 69.59, 68.71	58.82[a]	57.20, 55.64
12[d]		166.30	152.86	147.45	118.56	124.32, 117.49 116.79	71.92, 70.80, 70.57 70.49, 69.73, 68.84	58.99[a]	57.35, 55.81
13[d]		166.30	152.99	147.48	118.57	124.33, 117.48 116.88	72.53, 70.78, 70.57 70.55, 70.33, 69.73 68.87	61.68[b]	57.31, 55.80

[a] Methyl carbon. [b] Methylene carbon. [c] 22.5 MHz spectrometer. [d] 75 MHz spectrometer.

Table 5 Relaxivity Data

Compound	T_1/ms	R_1/dm^3 mmol^{-1} s^{-1}	T_2/ms	R_2/dm^3 mmol^{-1} s^{-1}
19	260	3.85	182	5.49
22	116	8.62	107	9.34
23	260	3.85	182	5.49
26	105	9.52	175	5.71
Magnevist {[Gd(DTPA)(H_2O)]$^{2-}$}	238	4.2		
Dotarem {[Gd(DOTA)]$^-$}	251	3.98		
10% EtOH/H_2O	1300			

afford a residue which, after being dried *in vacuo* gave the pure base **14**. Analogously, the ligand **18** was prepared from the ligand **15** (2.0 mmol) and $NaBH_4$ (0.3 g). Characterisation data are given in Tables 1–3.

General Preparation of the Gadolinium(III) *complexes* **19**, **20**, **22–24** *and* **26**.—A stirred solution of the appropriate ligand **11**, **12**, **14** or **15**, **16**, **18** (1.0 mmol) in methanol (20 cm^3), under a N_2 atmosphere was treated with sodium methoxide (6.0 cm^3, 3.0 mmol) or (4.0 cm^3, 2.0 mmol), respectively. After 10 min $GdCl_3$·$6H_2O$ (371 mg, 1.0 mmol) was added in one portion to the mixture which was then heated under reflux for 2 h. After this it was cooled and evaporated under reduced pressure. Dichloromethane was added to the residue and the separated sodium chloride was filtered off. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding product **19**, **20**, **22** and **23**, **24**, **26**, respectively (after drying *in vacuo* at 70 °C at 0.1 mmHg for 5 h). Characterisation data are given in Tables 1–2.

Preparation of Gadolinium(III) Complexes **21** *and* **25**.—The title compounds were synthesized from the ligands **13** and **17**, respectively, under conditions analogous to those described above for compounds **19**, **20**, **22–24** and **26** except that powdered *sodium hydroxide* was used instead of sodium methoxide. Characterisation data are given in Tables 1–2.

The gadolinium(III) complexes **19–21** and **23–25** have been also prepared in a 'one-pot' reaction using the above described procedure for the ligands **11–13** and **15–17** (without their isolation) followed by reaction with $GdCl_3$ under analogous conditions as mentioned above. The products obtained (in similar yield) were identical with those described above.

Imaging Experiments.—The study of contrast enhancements in NMR images was performed in a 4.7 T (200 MHz) superconductive imager (Biospec, Bruker, Karlsruhe, FRG). The rats were imaged in a linearly polarized 'bird cage' transmitter-receiver coil of 7 cm diam. and 6 cm length. Images were acquired using a T_1 weighted multislice spin-echo imaging sequence (TR/TE; 406/13 ms). The corresponding measurement time for 4 acquisitions (averages) of a series of 12 transversal slices was 3 min 28 s. The choice of 406 ms for TR is a compromise between the signal amplitude (signal-to-noise ratio), multiple acquisition (to average out motion artifacts in abdomen), number of slices, sequence duration (to achieve the desired time resolution in the kinetics measurements) and machine dependent constraints.[24]

The image field-of-view (FOV) and slice thickness were respectively 6 cm and 2 mm, the image matrix was 256^2 pixels providing a spatial resolution of 0.235 mm per image pixel. Images were acquired in male WISTAR rats for NMR pharmacokinetics measurements. The rats (n = 3) weighing 300 g were anaesthetized with Rompun (Bayer, FRG) (0.6 cm^3 kg^{-1}) and Ketalar (Parke-Davis, USA) injected intramuscularly. In a first step, images were taken prior to contrast agent injection (pre-contrast imaging). In a second step, animals were pulled out of the magnet and contrast agent was injected (0.1 mmol kg^{-1}) in the penile vein. After contrast agent injection, animals were pulled back into the imager and post-contrast images were acquired. Signal intensities of the liver, the cortex kidney, the dorsal muscle and the reference tubes[25] were measured from NMR images using a home-built image processing software called 'MEDIMAN'[26] implemented on a DEC-AXP 3000-400 (Digital Equipment Co., Maynard, USA) minicomputer. Several circular regions of interest (ROI) were selected in each organ and reference tubes and the average intensity and standard deviation calculated.

The percentage of signal enhancement in each tissue was expressed as:

$$\left[\frac{\left(\frac{\text{Tissue}}{\text{Reference}}\right)_{\text{post}} - \left(\frac{\text{Tissue}}{\text{Reference}}\right)_{\text{pre}}}{\left(\frac{\text{Tissue}}{\text{Reference}}\right)_{\text{pre}}} - 1\right] \times 100\%$$

$\text{Tissue}_{\text{pre/post}}$ is, respectively, the brightness of the signal of each tissue before and after injection of the contrast agent. $\text{Reference}_{\text{pre/post}}$ is the brightness of the signal of a reference compound, respectively, before and after injection of the contrast agent. This reference was used to normalize the brightness of signal against time. It corrects variations induced by uncontrollable hardware fluctuations between 2 image acquisitions.

Six series of transversal slices were acquired 8, 15, 30, 45 and 60 min and 24 h after contrast agent injection to follow up the signal enhancements induced by the contrast product in tissues of interest.

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