Disordered Mesoporous Gadolinosilicate Nanoparticles Prepared Using Gadolinium Based Ionic Liquid Emulsions: Potential as Magnetic Resonance Imaging Contrast Agents

Guozhen Liu, Nicholas M.K. Tse, Matthew R. Hill, Danielle F. Kennedy and Calum J. Drummond*

CSIRO Materials Science and Engineering (CMSE), Private Bag 10, Clayton South MDC, VIC 3169, Australia

**To whom correspondence should be addressed. E-mail: calum.drummond@csiro.au*

Abstract

Gadolinium doped mesoporous silica (gadolinosilicate) nanoparticles were synthesised using a novel synthetic approach aimed at incorporating Gd ions into a porous silica network. The ionic liquid gadolinium (Z)-octadec-9-enoate (Gd Oleate) was utilised in a dual role, as a soft template to generate porous silica and also to act as gadolinium source for incorporation into the silicate. The generated silicate materials were structurally characterised for size, structure and composition, confirming that gadolinium was successfully doped into the silicate network in a mesoporous nanoparticulate form. Proton relaxivity results indicated that the gadolinium doped silicates had slightly lower longitudinal relaxivity and much higher transverse relaxivity than the commercial contrast agent Magnevist®, suggesting that the disordered mesoporous nanoparticulate materials have potential as contrast agents for magnetic resonance imaging.

Keywords

Gadolinium oleate, ionic liquid, mesoporous silica, MCM-41, gadolinium silicate, gadolinosilicate, magnetic resonance imaging, MRI, contrast agent

Introduction

Magnetic resonance imaging (MRI) is a commonly used medical diagnostic technique. Its role in medical research and preventive health-care is rapidly evolving.¹ This non-invasive technique is used to map the physiological structures of biological systems. MRI distinguishes between different tissue types based on their water environment.¹⁻³ However, there are many situations where the contrast between adjacent tissues is not strong enough to allow clear distinctions to be made, or to enable the observation of fine structures. This has prompted the development of a new class of non-therapeutic diagnostic compounds known as contrast agents (CAs). CAs frequently incorporate a paramagnetic metal, which modifies the nuclear relaxation of surrounding protons, for example Gd chelates and iron oxides.⁴ CAs are used to enhance images by improving the contrast between areas containing the contrast agent and adjacent tissues. CAs are used clinically in a variety of diagnostic applications, such as targeted drug delivery systems (DDS)⁵⁻⁶, cell labelling⁷ and angiography⁸, with up to 30% of MRI screenings performed in conjunction with the administration of contrast agent.⁹

A CA provides image contrast by shortening both the longitudinal (T_1) and transverse (T_2) relaxation times. The potency of a CA can be directly compared by the longitudinal (R_1) and transverse (R_2) relaxivity values. R_1 and R_2 are linearly dependent on the concentration of the contrast agent and inversely proportional to the T_1 and T_2 times respectively. An effective MRI contrast agent will have a relatively large relaxivity value, R_1 (positive CA) or R_2 (negative CA) .

Apart from having high relaxivity, an effective CA must also have a number of physicochemical properties including: strong effect on proton relaxation of water, water stability, low toxicity and high

dispersibility in biological fluid with in the case of particles smaller than one micron in dimension. According to the standard Solomon-Bloembergen-Morgan (SMB) treatment,¹⁰⁻¹¹ there are a number of factors that influence the efficiency of a CA including: the duration and exchange rate of water molecules with the inner water spheres around a paramagnetic centre, the rate of water exchanges in the outer water sphere and the average molecular tumbling of the paramagnetic ion.^{9,12} Commonly used CAs are paramagnetic small metallochelate agents, which have been developed since the 1980s; detailed reviews of this field have been published by Caravan *et al.*^{9,12-13}

The lanthanide ion, Gd(III), is the most commonly used paramagnetic ion, because of its large magnetic moment with a long electron spin relaxation time.¹⁴ Free Gd(III) ions are highly toxic. Therefore Gd(III) ions are conventionally sequestered by chelation¹² or encapsulation¹⁵⁻¹⁶ in order to reduce toxicity. However, these techniques reduce the number of water molecules coordinated to Gd(III) ions, resulting in compromised effectiveness. Commercial CA are dominated by highly stable gadolinium complexes based on the polyaminocarboxylate ligand, e.g. [Gd(DTPA)(H₂O)]²⁻ (gadolinium(III) diethylene triamine pentaacetate hydrate).¹⁷ However, these small molecule CAs are non-specific, and lack the aspired image contrast ability^{1-2,8,18-20}, additionally they have recently been reported as problematic in patients with pre-existing liver conditions. Hence there is a drive to develop new types of contrast agents with lower toxicity, increased effectiveness, and higher sensitivity.¹⁻² Varied attempts aiming to increase the sensitivity and improve the selective localisation of CAs have been made by developing efficient nanoparticulate carrier systems.²¹

Mesoporous silica nanoparticles have many attractive features, such as stable mesoporous structures forming networks of channels, large surface areas, tunable pore sizes and volumes.²² As optically transparent, biocompatible, and low toxicity materials, this makes them ideal for the hosting of molecules over a wide range of sizes, shapes, and functionalities.²³ In addition, the surface

of silica particles can be easily modified to attach biomolecules such as proteins, antibodies, peptides or oligonucleotides of interest for cell-specific targeting and delivery.²⁴ The porous nature of the network of channels in mesoporous silica nanoparticles permits the movement of water molecules and at the same time maintains the rigidity of the frame, thus offering a strong and penetrable matrix for water exchange. Nanosized porous silica would be an excellent carrier for Gd(III) ions for the development of contrast agents for magnetic resonance imaging. Lin *et al.* have reported the preparation of Gd loaded nanosized mesoporous silica using a long-chain surfactant as a template.²⁵ These Gd loaded silica nanoparticles can have significantly higher r_1 and r_2 relaxivities than $[\text{Gd}(\text{DTPA})(\text{H}_2\text{O})]^{2-}$. Recently we reported the synthesis and investigation of a novel class of metal containing oleate ionic liquids.²⁶ Neat gadolinium (Z)-octadec-9-enoate (Gd Oleate) was found to melt to an ionic liquid at 37 °C.²⁶

Herein we report a new way to synthesise Gd doped silica using Gd oleate as a template to produce a potential MRI contrast agent with improved relaxivities. Such synthesised Gd(III) doped mesoporous silica has an average particle size of 100 nm and an average pore diameter of 2.5 nm. The synthesised mesoporous nanoparticles were found to be monodisperse, and were characterised with a range of analytical techniques to determine their size, structure and elemental composition. Proton relaxivity was also studied to evaluate the potential of these materials as a MRI contrast agents.

Experimental Section

Unless stated otherwise, all chemicals were used as received, without further purification. Tetraethyl orthosilicate (TEOS), cetyltrimethylammonium bromide (CTAB), sodium hydroxide, and 1-pentanol (99.9 %) were all obtained from Sigma-Aldrich.

Synthesis of MCM-41 type silica samples. The control silica samples were synthesised according to the method reported by Cai *et al.*²⁷ A typical preparation of MCM-41 type sample is as following: 1.0 g of CTAB was added dissolved into 470 mL of Milli-Q water, 3.5 mL of 2 M NaOH solution and 10 mL 1-pentanol. The solution was then heated to 80 °C and homogenised by stir agitation. After complete dissolution, 5 mL of TEOS was added dropwise to give a white slurry. The solution was then stirred for 48 h, the resulting product was collected by centrifugation, washed with Milli-Q water, and freeze-dried overnight. The samples collected were then calcined in air at 550 °C for 4 h to remove the templates. The final product is a white powder.

Synthesis of Gd-doped silica samples. Gd doped sample was made in a similar fashion as the MCM-41 type silica. The templating surfactant CTAB was replaced by gadolinium oleate which was synthesised beforehand according to Liu *et al.*²⁶ Different amounts of Gd doping were controlled by the amount of gadolinium oleate added. A list of synthetic composition values are tabulated in Table 1.

Characterisation of samples.

X-ray powder diffraction (XRD) was undertaken on a Bruker D8 Advance X-ray Diffractometer with CuK α radiation (40kV, 40mA) fitted with a graphite monochromator. Each sample was scanned over the 2 θ range 1 to 62° with a step size of 0.02° and a count time of 4 seconds per step. Analyses were performed on the collected XRD data for each sample using the Bruker XRD search match program

EVA™. Crystalline phases were identified using the ICDD-JCPDS powder diffraction database. X-ray photoelectron spectroscopy (XPS) analysis was performed using an AXIS-HSi spectrometer (Kratos Analytical Inc., Manchester, UK) with a monochromated Al K α source at a power of 144 W (12 kV $\times$ 12 mA), a hemispherical analyser operating in the fixed analyser transmission mode and the standard aperture (1 mm $\times$ 0.5 mm). The total pressure in the main vacuum chamber during analysis was of the order of 10^{-8} mbar. Each specimen was analysed at an emission angle of 0° as measured from the surface normal. A circular area with a diameter of approximately 1 mm was analysed on each sample. All elements present were identified from survey spectra (acquired at a pass energy of 320 eV). High-resolution spectra were recorded from individual peaks at 40 eV pass energy. The atomic concentrations of the detected elements were calculated using integral peak intensities and the sensitivity factors supplied by the manufacturer. Fourier transfer infrared spectroscopy (FT-IR) was performed using a BOMEN MB 101 from Extech Equipment Pty. Ltd. Spectra of the crystalline samples as KBr pellets were obtained at room temperature in the 4000–400 cm $^{-1}$ range and were accumulated for 32 scans at a resolution of 8 cm $^{-1}$. Solid state ^{29}Si MAS NMR spectra were recorded at 79.46 MHz, using a Bruker Advance 400 spectrometer. Sample morphology and microstructure were examined by Philips XL30 field emission scanning electron microscopy (FE-SEM). The accelerating voltage used was 2 KV. The nitrogen adsorption-desorption experiments were performed on a Quantachrome Autosorb 1 at 77 K over the partial pressure range $0.005 < P/P_0 < 0.975$. Prior to analysis, samples were degassed at 200 °C/ 5×10^{-3} Torr for 24 hours. Specific surface area values were obtained using the Brunauer-Emmett-Teller (BET) equation and pore sizes by the Barrett-Joyner-Halenda (BJH) method.²⁸ Parameters including BET surface area, total pore volume, and BJH pore size distribution were determined using the 'Autosorb 1 for Windows' ver 1.55 Software, © 2001. The amount of gadolinium in the product was determined using a Varian Vista inductively coupled plasma atomic emission spectroscopy (ICP-AES). The longitudinal and transverse relaxation time, T_1 and T_2 , were measured at 20 MHz (0.47 T) with a MINISPEC from Bruker at room

temperature. For T_1 measurements, the standard inversion-recovery (IR) method was used as the pulse sequence. The recycle delay time was set to five times the T_1 value. Typically 20 points were taken for each T_1 measurement. For T_2 measurements, the Carr-Pucell-Meiboom-Gill (CPMG) method was used.²⁹ The longitudinal relaxivity and transverse relaxivity were then determined from the slope of the linear regression fits of $1/T_1$ and $1/T_2$ vs. the Gd concentration, respectively.

Results

The various templated silica materials synthesised according to the above methodology were characterised by using a range of techniques. Using scanning electron microscopy (SEM), the particle size, morphology and aggregation were analysed for both the silica reference sample, *MCM-41*, and representative gadolinium doped samples. Figure 1 shows SEM micrographs of a *MCM-41* sample and a representative sample template with Gd oleate, *GdSi_C*. The particles were found to be spherical in shape with an average particle size of 150 nm and 80 nm for *MCM-41* and *GdSi_C* respectively. The SEM also showed small degrees of particle aggregation for *MCM-41*.

Figure 1: Representative SEM micrographs of (a) *MCM-41* and (b) *GdSi_C* samples.

XRD was used to investigate the porous structure of the two synthesised silica samples, Figure 2. The porosity of *MCM-41* was found to be an ordered two dimension (2D) hexagonal array, consistent

with previous reports²⁷. The four Bragg peaks with a d-spacing of 36.39, 21.40, 18.71, and 14.14 Å were indexed as the (100), (110), (200), and (210) reflections of the P6mm space group, respectively. For the Gd-doped samples (e.g. *GdSi_C* in Figure 2b) the diffractograms showed no distinguishable sharp peaks. A broad peak at approximately 21° ($d \approx 4.2\text{Å}$), indicates that the silica sample is amorphous in nature. The lack of sharp Bragg peaks suggests that any templated pores are disordered in the Gd-doped silica samples. Such disordered porosity may be due to the following reasons. First, the low concentration of Gd oleate used during the templating process; the amount of template agent was varied in order to achieve the necessary level of doping. Second, at the synthetic temperature, the gadolinium oleate exists as an ionic liquid emulsion.

Figure 2: Representative Powder X-ray diffraction patterns for a) MCM-41 and b) *GdSi_C* samples.

Using the nitrogen gas sorption technique, the surface area and the porosity were determined for all the synthesised silica based samples. Representative N₂ adsorption-desorption isotherms are shown in Figure 3 and a summary of the pore size distribution (PSD), particle size and total pore volume is provided in Table 1. It was found that the various Gd doped silica samples exhibited a much lower BET surface area than the non-doped *MCM-41* reference sample. The pore size distributions of the doped samples were also much larger than that obtained for the *MCM-41* reference sample. The decrease in measured surface area could be due to the accessibility of the pores by the N₂ gas

probe.³⁰ When examining the PSD, Figure 4, it can be seen that the distribution of pore sizes in these mesoporous materials is very broad, spanning *ca.* 25 nm. This range of pore sizes also suggests that the pores are disordered in packing which is consistence with the XRD results. The typical BET surface areas for the various Gd oleate derived samples were in the range of 150–200 m²g⁻¹.

Figure 3: Representative Nitrogen adsorption-desorption isotherms of various silica based samples: (a) *MCM-41*, (b) *GdSi_A*, (c) *GdSi_B*, (d) *GdSi_C*, (e) *GdSi_D* and (f) *GdSi_E* samples. The isotherms for samples *GdSi_D*, *GdSi_C*, *GdSi_B*, *GdSi_A*, and *MCM-41* were vertically offset for clarity.

Figure 4: Pore size distribution of a GdSi_B sample, calculated from the adsorption branch of the N_2 isotherm using the BJH equation. This distribution is typical for the series.

Table 1: Synthetic composition values and measured particle size, specific surface area and pore size distribution for the silicate samples.

Sample	CTAB (g)	Gd oleate (g)	Intended Doping (wt %)	Particle size (nm) ^a	BET Surface area (m ² g ⁻¹) ^b	Mean pore size (nm) ^c	Total pore volume (cm ³ g ⁻¹) ^d
MCM-41	1	-	0	150	960	3.5	0.868
GdSi_A	-	0.26	3	148	172	7.5	0.330
GdSi_B	-	0.80	9	147	141	11.4	0.400
GdSi_C	-	1.00	12	75	150	8.0	0.387
GdSi_D	-	1.20	15	100	170	4.4	0.188
GdSi_E	-	2.00	18	110	144	8.5	0.217

^a Determined from SEM micrographs.

^b Determined from the adsorption branch of the N_2 isotherm using the BJH method.

^c The PDS was calculated from the absorption branch of the N_2 isotherm.

^d Measured at $P/P_0 = 0.995$.

The composition of the synthesised samples were analysed by FTIR, ^{29}Si MAS NMR and XPS. Figure 5 shows the spectra, acquired by FTIR spectroscopy, in the range of 4000–400 cm^{-1} for the various synthesised samples with varying Gd loading. The major features of the FTIR spectra for *MCM-41* are peaks at 1224, 1066, 804 and 450 cm^{-1} (Figure 5a), these peaks are characteristic of the network vibrational modes in a SiO_2 matrix. The 1224 and 1066 cm^{-1} bands are assigned to longitudinal optical (LO) and transversal optical (TO) Si–O–Si asymmetric stretching modes.³¹ The 804 cm^{-1} and 450 cm^{-1} are associated with the stretching/vibration and bending of the Si–O–Si networks structure respectively.³² In addition, The lack of CH_2 vibration, indicated by the 2925 and 2852 cm^{-1} peaks³³, in all the samples, except for possibly *GdSi_B* (Figure 5c), suggests that the templating surfactants are completely removed during the calcination process.

Figure 5: FT-IR spectra of Gd loaded silica with different Gd loading a) 0%, b) 2.7%, c) 8.8%, d) 11.9%, e) 14.6%, and f) 19.1%.

XPS surface analysis of the samples was performed and indicated the existence of gadolinium ions in the silica matrix for the Gd doped samples. As expected, the two Gd $3d_{3/2}$ and Gd $3d_{5/2}$ peaks were observed only in the Gd doped samples (e.g. Figure 6a). The silicon-to-oxygen (Si:O) ratio calculated from the XPS analysis in the reference sample, *MCM-41*, was a ratio of 1:2 consistent with SiO_2 . The Si:O ratio for the Gd doped silica samples was lower, suggesting the existence of gadolinium ion in the sample. Furthermore a shift of the O 1s peak (e.g. Figure 6b) and the occurrence of Gd peaks indicated that gadolinium was successfully incorporated. Using *MCM-41* as reference, the normal position of the O 1s peak should be at 530 eV. However in the Gd doped samples, the position of this 530 eV peak was seen to have been shifted to a lower energy. This is the result of the electron affinity of Gd(III) ions compared to Si^{4+} .³⁴⁻³⁵ Since Gd(III) is more electron withdrawing, this shift to a lower energy is expected. In addition, the development of a shoulder peak at 531 eV was observed. This peak was assigned to be a Si–O–Gd bonding which is consistent with literature reports.²⁵

Figure 6: a) Gd 3d XPS spectrum of sample *GdSi_C* (top, blue) and *MCM-41* sample (bottom, green); b) O 1s XPS spectra *MCM-41* (dotted line, red) and *GdSi_C* (solid line, blue) with its fitted peaks (green).

Solid state ^{29}Si MAS NMR was also used as a complementary technique to confirm the presence of gadolinium in the silica matrix (e.g. Figure 7). Three characteristic peaks were observed at positions - 99.7, -102 and -109 ppm in *MCM-41* (Figure 7c) These peaks correspond to the $\text{SiO}_2(\text{OH})_2$, $\text{SiO}_3(\text{OH})$ and SiO_4 environments respectively. The $\text{Q}_4:\text{Q}_3:\text{Q}_2$ ratio indicated that the samples are highly condensed and this value is in good agreement with literature reports.^{31,36}

Figure 7: ^{29}Si MAS NMR Spectra: a) raw spectra of the two measured samples; top trace *MCM-41* and bottom trace *GdSi-C*; b) fitted spectra of the *MCM-41*; c) fitted spectra for *GdSi-C*.

In the ^{29}Si MAS NMR Spectra for the *GdSi-C* sample (Figure 7b), a downfield shift of the native silica peaks along with peak broadening was also observed. This broadening is indicative of the presence

of paramagnetic species.³⁷⁻³⁸ The downfield shift of the silica peaks was attributed to the dipole interaction between the unpaired electrons and the silicon nucleus despite the absence of direct bonds. The hyperfine splitting of the peaks in the presence of the trivalent cation was not resolved at the particular sample rotor frequency, therefore the splitting was observed as a peak broadening effect. In addition, the decrease of the Q₂ and Q₃ peaks suggest that the silica bonding environment has changed. This is consistent with the formation of Gd–O–Si bonds and hence a decrease in the number of Si–O–Si bonds.³⁸⁻⁴⁰

Table 2: Relaxivities of different samples at 0.47 T (20MHz) at 25 °C

	ICP-AES	XPS	XPS	r1	r2	r2/r1
	Gd (wt%)	Gd (at %)	Gd (wt %)	(mM ⁻¹ s ⁻¹)	(mM ⁻¹ s ⁻¹)	
Magnevist®	-	-	-	4.91	6.26	1.74
MCM-41	0.0%	0.0%	0.00%	-	-	-
GdSi_A	2.7%	3.0%	2.2%	1.54	15.77	10.24
GdSi_B	8.8%	9.7%	7.0%	2.01	23.98	11.93
GdSi_C	11.9%	13.1%	9.5%	2.39	41.52	17.37
GdSi_D	14.7%	16.1%	11.6%	1.66	30.89	18.61
GdSi_E	19.1%	20.9%	15.1%	1.29	18.64	14.45

Figure 8: The proton relaxivities determined at 20 MHz at room temperature *GdSi_C*. (a) r_1 for *GdSi_C*, (b) r_2 for *GdSi_C* and (c) r_1 (Top) and r_2 (Bottom) value for the various gadolinium doped samples. Filled circles represents gadolinium doped samples. Line is a visually guide.

The proton longitudinal and transverse relaxivities, r_1 and r_2 were determined at 20 MHz (representative plots are in Figure 8a and Figure 8b) and are summarised in Table 2 and Figure 8c.

The longitudinal relaxivity was observed to peak (0.13 atomic fraction) with incorporated gadolinium content. The longitudinal relaxivity is comparable to the standard MRI contrast agent Magnevist®; $r_1 = 2.39 \text{ mM}^{-1} \text{ s}^{-1}$ and $r_1 = 4.91 \text{ mM}^{-1} \text{ s}^{-1}$ for *GdSi_C* and Magnevist® respectively. The seemingly low longitudinal relaxivity, despite the high gadolinium content, may be explained by reduced bound water within the coordination sphere of the gadolinium taken up in Gd-O bonds through their incorporation into the gadolinium-silicate framework.²⁰ The transverse relaxivity was also found to depend on the concentration of gadolinium content. The optimal doping level was also observed to be at 13.0 at% gadolinium doping. Further increase of gadolinium doping resulted in a decrease in transverse relaxivity. A plausible explanation for this phenomenon is a reduction in the outer-sphere hydration contribution upon increasing gadolinium content.⁴¹⁻⁴⁴ The improvement in transverse

relaxivity, over Magnevist®, may be linked to the porous nature of these nanoparticulate materials. Porosity may facilitate water exchange for the outer-hydration sphere and the nanoparticulate nature reduces the rotational coefficient time. Both of these effects can contribute to an improvement in the transverse relaxivity. The total overall contribution of these effects are normalised against the number of existing gadolinium species. The initially observed increase in relaxivity may be due to the increased effect of the outer-sphere relaxation contribution.⁴¹ The distribution of the dopant in the silica matrix is expected to be more homogeneous with increased gadolinium content. This results in higher gadolinium concentration per unit surface area. However upon further increase in doping, the contribution of outer-sphere hydration and rotational effect reaches a maximum. At which point continual increase results in a decrease of the measured relaxivity.⁴⁵⁻⁴⁶ A similar saturation effect has also been observed in previous CA studies.^{25,42}

Conclusions

Gadolinium doped mesoporous silica (gadoliniosilicate) nanoparticles have been successfully synthesised *via* the emulsified ionic liquid templating route. The silicate sample, with varying amount of gadolinium, was controlled by varying the amount of gadolinium oleate; acting as both the template agent and the gadolinium source. The samples synthesised were then characterised in terms of particle size, structure and elemental composition by using SEM, XRD, nitrogen-gas sorption, FTIR, XPS and ^{29}Si MAS NMR. The relaxivity of the final product was also measured and it was found that at low field strengths, longitudinal and transverse reach an optimum value at 13.0 atomic percent gadolinium doping. These optimum relaxivity values are postulated to be the result of the combined effect of the saturation of inner- and outer-sphere hydration and nanoparticulate tumbling effects. The results confirm that Gd doped porous silica nanoparticles have the potential to be used as MRI contrast agents. Further work is needed to elucidate the precise factors governing the observation of maximum relaxivity upon increased doping.

Acknowledgement

We thank Mr Mark Greaves for the SEM microscopy, Dr Thomas R. Gengenbach for help with running XPS samples, Dr Tim Bastow for the ^{29}Si MAS NMR characterisation and the CSIRO Hierarchical Materials Emerging Science Initiative for financial support. G.L. and D.F.K. were the recipients of CSIRO postdoctoral fellowships, N.M.K.T a CSIRO PhD studentship and C.J.D. an Australian Research Council Federation Fellowship during this work.

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