

Relaxivity Modulation in Gd-Functionalised Mesoporous Silicas.

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1. Synthesis

NMR spectra were recorded on a on a JEOL Eclipse Plus 400 (operating at 9.4 Tesla).

ESI mass spectra were recorded on a Waters Micromass ZQ.

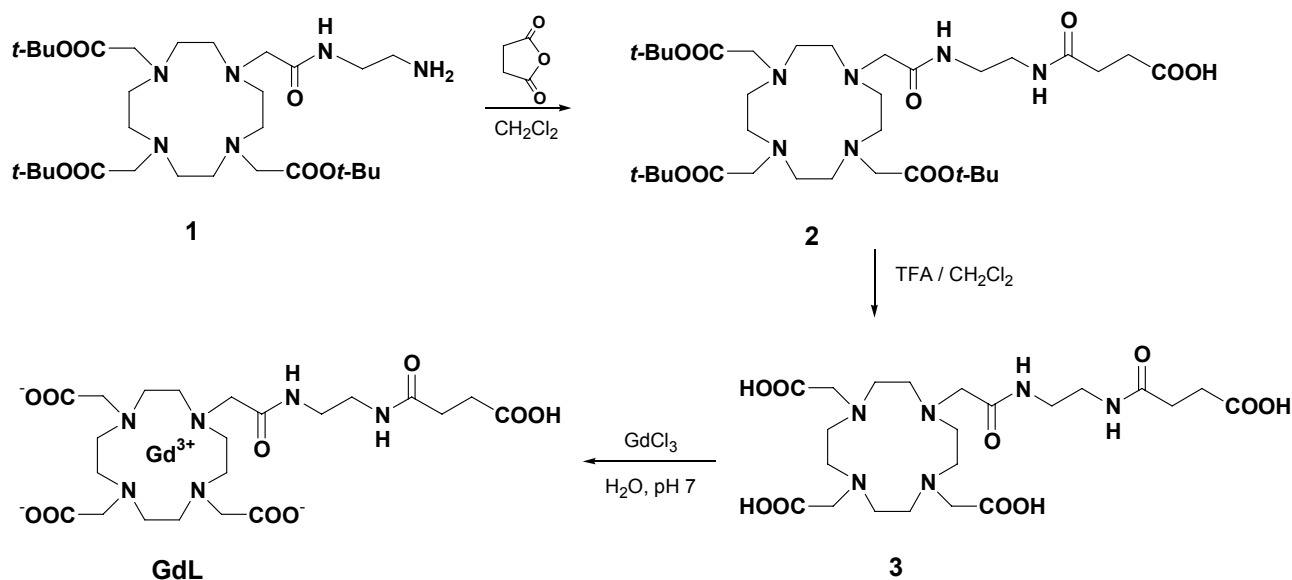
Synthesis of GdL:

- i) **1-(5-amino-3-aza-2-oxopentyl)-4,7,10-tris(*tert*-butyloxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane-DOTAMA(*t*-BuO)₃-en (1):** The synthetic procedure was described in detail by A. Barge et al. in the literature: A. Barge, L. Tei, D. Upadhyaya, F. Fedeli, L. Beltrami, R. Stefania, S. Aime and G. Cravotto, *Org. Biomol. Chem.*, 2008, **6**, 1176–1184.
- ii) **1-(3-aza-9-carboxy-2,5-dioxononyl)-4,7,10-tris(*tert*-butyloxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (2):** DOTAMA(*t*-BuO)₃-en (0,409 g, 0.67 mmol) and succinic anhydride (0,070 g, 0.69 mol) were placed in a roundbottom flask, dissolved in 30 ml of CH₂Cl₂ and stirred 20h at room temperature. The reaction mixture was then washed with water (3 x 20 ml), the organic phase was dried with Na₂SO₄ and the solvent was evaporated under reduced pressure to yield a pale yellow solid (0.383 g, 0.54 mmol, yield 80 %). ¹H NMR (CDCl₃, 400 MHz) δ = 8.18 (s, CONH, 1H); 7.95 (s, CONH, 1H); 4.13, 3.87 (s, NCH₂CO, 8H) 3.70-3.20 (m, CH₂ ring, 16H); 3.00 (b, CH₂NH, 4H), 2.63, 2.56 (s, CH₂CH₂CO, 4H), 1.48, 1.45 (s, C(CH₃), 27H); ¹³C NMR (CDCl₃, 100 MHz) δ = 175.0, 173.9, 171.9, 166.3, 166.0 (Carboxyl and carboxyamide grups, 6C), 82.1 (C(CH₃)₃, 3C), 56.0, 55.8 (NCH₂CO, 4C); 51.6, 48.8 (NCH₂ ring, 8C); 39.5, 39.1 (CONHCH₂, 2C); 37.5, 29.4 (CH₂CH₂COOH, 2C); 28.2, 28.0 (C(CH₃)₃, 9C). ESI-MS (m/z): (calcd. for C₃₄H₆₃N₆O₁₀ 715.9), found 715.5 (M + H⁺).
- iii) **1-(3-aza-9-carboxy-2,5-dioxononyl)-4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (3):** Compound (2) (0.383 g, 0.54 mmol) was dissolved in CH₂Cl₂ (15 mL) and trifluoroacetic acid (15 mL) and stirred at room temperature overnight. The solution was then evaporated in vacuum and the product was precipitated with excess of diethyl ether, isolated by centrifugation, washed thoroughly with diethyl ether and dried in vacuo obtaining pure desired product as amorphous white solid. (0.257 g, 0.47 mmol, yield 87.6%). ¹H NMR (D₂O, 400 MHz): δ = 3.82, 3.73 (s, NCH₂CO, 8H), 3.62-3.27 and 3.20-2.90 (m, CH₂ ring and CH₂NH 20H), 2.63, 2.54 (t, *J* = 7.0 Hz, CH₂CH₂COOH, 4H). ¹³C NMR (D₂O, 100 MHz): δ = 177.8, 170.1, 163.4, 163.0 (Carboxyl and carboxyamide grups, 6C), 56.6, 55.8, 51.7 (NCH₂CO, 4C), 51.0, 48.3 (NCH₂ ring, 8C), 38.9, 38.6 (CONHCH₂, 2C), 31.2, 29.5 (CH₂CH₂COOH, 2C). ESI-MS (m/z): (calcd. for C₂₂H₃₉N₆O₁₀ 547.6), found 547.4 (M + H⁺). The final compound contains, as an impurity, ca. 5 - 10% of the un-functionalized ligand (DOTAMA-En) bearing a primary amino group. We did not purify further the product at this stage since this impurity does

not react during the following steps and can be removed by simple filtration after the grafting procedure on the mesoporous silica particles.

iv) GdL:

Compound (**3**) (0.55 g, 1.0 mmol) was dissolved in 30 ml of H₂O. 0.371 g (1.0 mmol) of GdCl₃·6H₂O was added to the solution. The pH of reaction was corrected to 6.5 by addition of few ml of diluted NaOH solution. The mixture was stirred at room temperature for 20h. Finally, unchelated Gd³⁺ ions were eliminated by precipitation of the hydroxide at basic pH by adding aliquots of a concentrated NaOH solution. The solvent was removed under reduced pressure leading to the formation of the desired product. ESI-MS (m/z): (calcd. for C₂₂H₃₄GdN₆O₁₀ 700.2), found 700.5 (M – H⁺); correct isotopic distribution.



Scheme of GdL synthesis

Synthesis of mesoporous supports:

i) MCM-41 and SBA-15:

MCM-41 and SBA-15 were synthesised and calcined following the procedure reported in the literature: K. Suzuki, K. Ikari, and H. Imai, *J. Am. Chem. Soc.*, 2004, **126**, 462-463 and D. Zhao, Q. Huo, J. Feng, B.F. Chmelka and G.D. Stucky, *J. Am. Chem. Soc.*, 1998, **120**, 6024-6036, respectively.

ii) NH₂/MCM-41 and NH₂/SBA-15:

1.0 g of calcined SBA-15 and MCM-41 was firstly treated under vacuum at 250°C for 2h in order to remove completely the water adsorbed on the silica surface, then both materials were suspended in toluene (100 ml) under nitrogen flow. 3-Aminopropyltriethoxysilane (99%, Sigma Aldrich) (40

wt%) was added to the suspensions. The reaction was carried on at 50°C under stirring for 20h. Finally, the products were filtered and washed several times with diethyl ether in order to remove the un-reacted silane. The samples were dried at 60°C for 2h.

Synthesis of GdL/SBA-15 and GdL/MCM-41:

Anchoring of GdL on functionalized SBA-15 and MCM-41.

700 mg of NH₂/MCM-41 (or NH₂/SBA-15) were suspended in 50 ml of DMF (Sigma Aldrich) for 30 min. In parallel, **GdL** (0,500 g, 0.7 mmol) and 0.27 g (0.7 mmol) of O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (Sigma Aldrich) were dissolved in 40ml of DMF. The solution was added to the suspensions of NH₂/MCM-41 (or NH₂/SBA-15) and stirred at room temperature. The reactions were carried on under basic conditions, in the presence of N,N-Diisopropylethylamine (124μl) at 50°C for 24h. Finally, the solutions were filtered and washed several times with water. The products were dried at 60°C for 2h to obtain white powders.

Quantification of Gd-loadings per particle of GdL/MCM-41 and GdL/SBA-15.

The determination of Gd-loading per each silica particle was calculated considering the particles as spheres with average diameter 30 nm (for GdL/MCM-41) and 600 nm (for GdL/SBA-15) and considering the densities of GdL/MCM-41 and GdL/SBA-15 around 0.8 g/cm³ (Karen J. Edler, Philip A. Reynolds, John W. White and David Cookson, *J. Chem. Soc., Faraday Trans.*, 1997, **93** (1), 199-202) and, 2.2 g/cm³ (Mietek Jaroniec and Leonid A. Solovyov, *Chem. Commun.*, 2006, 2242–2244), respectively.

2. Characterization

- Infrared (IR) spectra of GdL/SBA-15 and GdL/MCM-41 and the pristine porous supports have been recorded in the range 4000 - 400 cm^{-1} at 4 cm^{-1} resolution using a Bruker Equinox 55 spectrometer. The samples in the form of self-supported pellets have been outgassed (in vacuum (10^{-4} mbar) for 2h.
- High resolution transmission electron microscopy (HRTEM) images were collected on a JEOL 3010 microscope operating at 300 kV. Specimens were prepared by dispersing the sample by sonication in isopropanol and by depositing few drops of the suspension on carbon-coated grids.
- N_2 physisorption measurements were carried out at 77K in the relative pressure range from $1 \cdot 10^{-6}$ to 1 P/P_0 by using a Quantachrome Autosorb 1MP/TCD instrument. Prior to the analysis the samples were outgassed at 373K for 3 h (residual pressure lower than 10^{-6} mbar). Apparent surface areas were determined by using Brunauer-Emmett-Teller equation, in the relative pressure range from 0.01 to 0.1 P/P_0 . Pore size distributions were obtained by applying the NLDFT method (N_2 silica kernel based on a cylindrical pore model applied to the desorption branch).
- Thermogravimetric analyses (TGA) of materials were performed under Argon flow (20 ml/min) with a SETSYS Evolution TGA-DTA/DSC thermobalance, heating from 50 to 800°C at 10 °C/min.
- The observed longitudinal water proton relaxation times (T_{1obs}) were measured on a Stellar Spinmaster spectrometer (Stellar, Mede (PV) Italy) operating at 20 MHz, by means of the standard inversion-recovery technique (16 experiments, 2 scans). The tenor of Gd(III) in the final materials was estimated by elemental analysis (ICP/MS) by the NEOSIS S.A.S Lab. in Turin, Italy.
- MR images were obtained on a 3T Bruker spectrometer equipped with a microimaging probe. The experimental details are reported in the paper.

3. Figures and Table

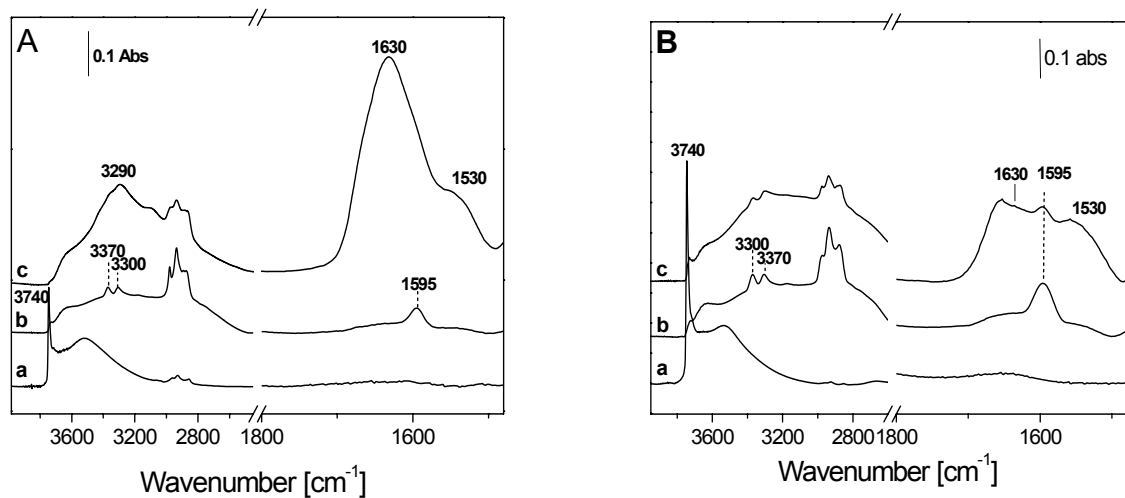


Figure 1: IR spectra in vacuum of A): SBA-15 (a), NH₂/SBA-15 (b) and GdL/SBA-15 (c) and B): MCM-41 (a), NH₂/MCM-41 (b) and GdL/MCM-41 (c).

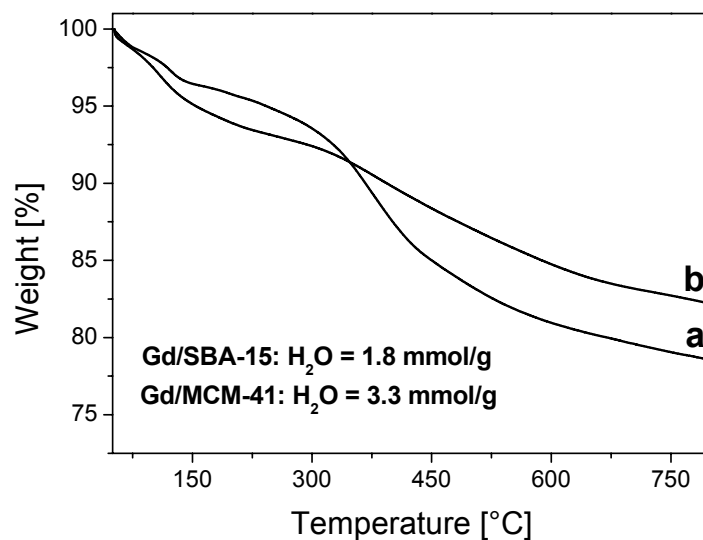


Figure 2: Thermogravimetric analysis (TGA) of GdL/SBA-15 (curve a) and GdL/MCM-41 (curve b) collected under Argon flow at 10°C/min.

Table 1: Textural parameters of mesoporous supports and the hybrid materials.

	SBET m²/g	Pore Volume cm³/g
SBA-15	750	0.94
NH ₂ /SBA-15	535	0.70
GdL/SBA-15	530	0.78
MCM-41	890	1.47
NH ₂ /MCM-41	855	1.24
GdL/MCM-41	625	0.95