

Application note

**NMR relaxometric investigations to improve efficacy of MRI contrast agents.
A versatile system for variable-field NMR relaxometry.
A case study: Nanosized periodic mesoporous silica***

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Introduction

Since the initial experiments, the Magnetic Resonance Imaging technique has rapidly developed into one of the most important diagnostic modalities due to several positive features: lack of ionizing radiation for acquisition of images, non-invasiveness with a high patient acceptability, superb delineation of anatomic structures that derives from a high level of inherent contrast, superb temporal and spatial resolution, ability to apply the technique to virtually every part of the body.

Important achievements have been obtained also thanks to the development of contrast agents that are able to markedly alter the relaxation times of water protons in the tissues where they are distributed, and have led to remarkable improvements in medical diagnosis in terms of higher specificity, better tissue characterization, reduction of image artifacts and functional information.

Over the course of years, very considerable progress was made in the understanding of relevant features of the coordination chemistry of these systems and of the dependence of the various molecular parameters on the relaxivity.

A major boost to these studies was also provided by the use of Fast Field Cycling NMR instruments (relaxometers) that, permit the measurement of the dependence of T_1 or $R_1=1/T_1$ on the magnetic field strength B (NMRD profile), thus allowing a detailed investigation of the interaction between metal-ions and water to obtain fundamental data for evaluating the effectiveness of a contrast agent.

In this application note some NMRD profiles of contrast agents are presented to demonstrate that Fast Field Cycling NMR relaxometry can be highly beneficial for complete characterization of a paramagnetic complex.

Overview

The relaxivity of a contrast agent is the result of a complex interplay between several structural and dynamic parameters [1].

The majority of contrast agents (CA) used in MRI are based on enhancement of the relaxivity of water protons in the tissues where they are distributed. The enhancement of the relaxation rate is the consequence of the dipolar and scalar interactions of the protons with the paramagnetic centres present in the contrast agent.

The phenomena involved in relaxivity have characteristic times from the pico-second to the milli-second range (the fast rotation of paramagnetic complexes, the slow tumbling of macromolecules, the electronic relaxation times, the proton/water exchange between bulk and water coordinated to the paramagnetic complex).

Therefore the investigation of the frequency dependent enhancement makes it possible to draw important conclusions concerning the properties and when evaluating the efficacy of a formulation.

The focus of this document is to show the potential advantages of Fast Field Cycling relaxometry which allows NMR relaxometric measurements to be obtained as function of frequency, and is highly beneficial for discrimination between various molecular dynamics models and for the design and characterization of contrast agents.

Several reviews and books have appeared in the literature on the relaxation mechanism and theory [2-6], nevertheless this note does not attempt any theoretical interpretation of the data collected herein in terms of molecular dynamics.

The method

The Field Cycling instruments provide a reliable and useful method for measuring the R_1 dispersion curve ($R_1=1/T_1$ as a function of the applied magnetic field strength), called Nuclear Magnetic Relaxation Dispersion (NMRD) profile, over several decades of frequency.

A basic field cycling experiment consists of a three step cycle, illustrated in figure1.

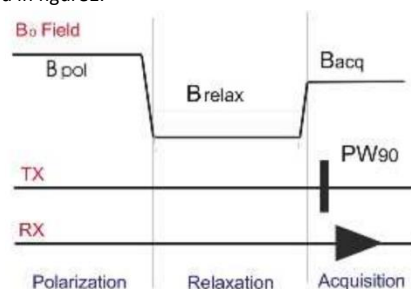


Figure 1. Pulse sequence for a basic NMR field cycling experiment

1. Polarization: The sample is pre-polarized to improve signal Intensity (B_{pol}).
 2. Relaxation: The second field (B_{relax}) allows the sample to relax during a time τ .
 3. Acquisition: The field is set to the detection field (B_{acq}) for signal acquisition.
- At higher magnetic fields, the increase of magnetization after the relaxation field has been switched on is recorded directly as a function of τ .

Examples of the application of Field Cycling for contrast agents are shown as in the following NMRD profiles:

Figure 2 shows a comparison of the NMRD profiles of clinically approved contrast agents. Due to their fast rotation, they have a maximum relaxivity at low magnetic fields.

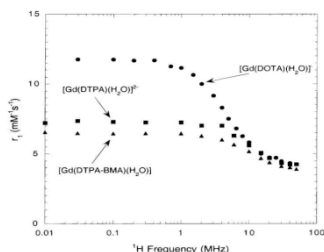


Figure 2. NMRD curves for three clinically approved gadolinium(III) chelates at 25 °C. [7]

A major improvement of relaxivity is often achieved by bonding the paramagnetic ion to a large macromolecule, which may increase the rotational correlation time by orders of magnitude, with a dramatic effect on the NMRD profile (see Figure 3).

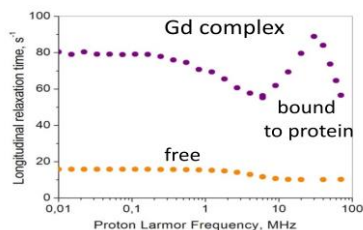


Figure 3. Proton paramagnetic relaxation rate (NMRD) of Gd complex in the bound and free state.

Nanosized periodic mesoporous silica*

Nanosized periodic mesoporous silica (PMS) materials loaded with gadolinium have recently been proposed as potential contrast agents (CA) for Magnetic Resonance Imaging (MRI) due to a particularly high R_1 relaxivity ($R_1 = T_1/[CA]$), maintained also at higher magnetic field strengths.

The mesoporous silicas presented here are hexagonally structured SBA-15 materials with varying pore diameter (figure 4) [7].

The silica materials are reacted with different metal precursors, resulting in a surface loaded with Gd- oxides and -hydroxides (figure 5).

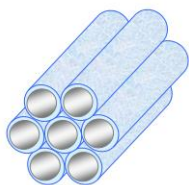
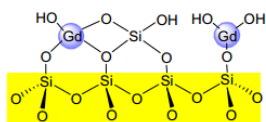


Figure 4. Porous, hexagonal structure of the parent silica material



GdxOy@PMS
Figure 5. Surface modified material

To further understand the potential of gadolinium modified PMS materials as new contrast agents, the focus of the present study was to examine the parameters inducing the improved relaxivity.

For this purpose, Nuclear Magnetic Relaxation Dispersion (NMRD) profiles were acquired.

Knowledge of the field dependence of potential new contrast agents is needed to model their detailed mechanisms of paramagnetic

relaxation, measured over a wide range of magnetic field strengths, from 0.01 MHz up to the range of high field clinical MRI scanners.

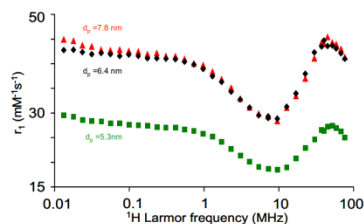


Figure 6. NMRD profiles of three Gd-grafted silica materials with varying pore diameters (dP) at 28 °C. Pore diameters are obtained from N_2 - physisorption

The NMRD profiles of the gadolinium modified silica materials (Figure 6), have the typical shape of a CA with decreased mobility of the metal complex. The maximum relaxivity for the silica samples is at a higher magnetic field strength (50-60 MHz or 1.2- 1.4 T) than normally observed for gadolinium-based contrast agents. The relaxivity for all the samples also stays above 20 mL-1s-1 even at 80 MHz (1.9 T). This type of material therefore shows promising properties as a CA even at high magnetic field strengths.

The relaxivity seems to increase with increasing pore diameter of the parent silica material.

The Instrumentation

The NMRD profiles (0.01 to 80 MHz) were achieved by use of a high field relaxometry system from Stelar/ HTS-110. Two different NMR techniques and instrumentation were used: a dedicated Field Cycling NMR relaxometer (Stelar) for the measurements in the range from 0.01 to 40 MHz and a cryogen-free, superconductive magnet (HTS-110) in the range from 40 to 80 MHz.

The two systems are equipped with a sample variable temperature controller and a 10 mm tunable probe.



Field cycling relaxometer designed to measure the field dependence of T_1 from 0.01MHz to 1 tesla (42.6 MHz) [9]



The 2.2 Tesla, iron-yoked split-pair high temperature superconducting magnet, cooled by a single stage Gifford-McMahon cryorefrigerator.

*Acknowledgement

We thank professor John G. Seland (University of Bergen) for his kind cooperation.

Ref

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