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Relaxivity of Gd-based contrast agents on X nuclei with long intrinsic relaxation times in aqueous solutions

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Abstract

The relaxivity of commercially available gadolinium-based contrast agents was studied for X-nuclei resonances with long intrinsic relaxation times ranging between 6 and several hundred seconds. Omniscan in pure ^{13}C formic acid had a relaxivity of 2.9 mM^{-1} s^{-1}, whereas its relaxivity on glutamate C1 and C5 in aqueous solution was ~0.5 mM^{-1} s^{-1}. Both relaxivities allow the preparation of solutions with a predetermined short T_1 suggest that *in vitro* substantial sensitivity gains in their measurement can be achieved.

^{6}Li has a long intrinsic relaxation time, on the order of several minutes, which was strongly affected by the contrast agents. Relaxivity ranged from ~0.1 mM^{-1} s^{-1} for Omniscan to 0.3 for Magnevist, whereas the relaxivity of Gd-DOTP was at 11 mM^{-1} s^{-1} two orders of magnitude higher. Overall these experiments suggest that the presence of 0.1-10 μM contrast agents should be detectable, provided sufficient sensitivity is available, such as that afforded by hyperpolarization, recently introduced to *in vivo* imaging.

Keywords

gadolinium complexes; carbon-13; lithium-6; relaxivity; contrast agents

Introduction

The measurement of cerebral metabolism using ^{13}C NMR in conjunction with administration of ^{13}C labeled precursor substrate is a powerful tool that allows insight into many metabolic processes *in vivo*, ranging from energy metabolism to neuro-glial compartmentation [1,2]. Assessment of these metabolic reactions depends on the measurement of label incorporation into multiple positions in amino acids such as glutamate [3]. Glutamate ($C_5H_9NO_4$) consists of 3 central carbons flanked by carboxyl groups[4], the labeling of which can provide additional insight into neuro-glial compartmentation. The ^{13}C nuclei of these carboxyl groups have relaxation times on the order of 10 seconds, resulting in poor sensitivity for most NMR experiments. Standard approaches to signal enhancement, such as polarization transfer [5] or

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NOE generation[6], are not available for such carboxyl resonances due to their long intrinsic T_1 (on the order of 10 s) and lack of significant coupling to neighboring protons, leaving as the only option a shortening of the T_1 to improve sensitivity.

Gadolinium-based contrast agents are widely used in magnetic resonance imaging to generate contrast by lowering the spin-lattice relaxation time of water protons [7,8]. Applications of these contrast agents range from the detection of multiple sclerosis[9] to the visualization of brain tumors[10] and tracking of individual cells *in vivo* [11]. However, the effect of contrast agents on the relaxation rate of X nuclei is less well known; in fact we are only aware of a few studies [4,12], which did not report relaxivity as such.

In the aforementioned ^{13}C NMR studies, formic acid (HCOOH), in essence a free carboxyl group, is frequently used to generate a reference signal with which the power levels of various NMR pulse sequences can be conveniently calibrated and adjusted to experimental conditions such as coil loading [13]. However, the T_1 relaxation time of formic acid is on the order of 6 seconds. Consequently, this calibration step requires a substantial effort in time [14]. To demonstrate that Gd-based contrast agents can also be used to predictively shorten the relaxation time of other nuclei we further extended the scope of the study to ^{6}Li, a spin-1 with a very small quadrupolar moment, whose intrinsic longitudinal relaxation has been reported as 170 s in H_2O [15] and 1040 s in D_2O [16]. Lithium is used to treat episodes of mania and depression and to prevent their recurrence[17]. Since ^{6}Li is positively charged, contrast agents with different charges were hypothesized to have a profoundly different effect on T_1 relaxation. Therefore, the aim of this feasibility study was to characterize the relaxivity of commercially available contrast agents in order to shorten long T_1 relaxation times of X nuclei in a predictive manner. Given that unlike water, most compounds discussed above carry one or more charges at neutral pH and are thus likely subject to different interaction with contrast agents (which also differ in charge), a secondary aim of this study was to investigate several different contrast agents.

Materials and Methods

Unless stated otherwise, all chemicals of analytical grade were purchased from Sigma-Aldrich (St. Louis, MO) and used without further purification. Omniscan ([Gd(DTPA-BMA)(H_2O)], where DTPA-BMA is 1,7-bis[(*N*-ethylcarbonyl)methyl]-1,4,7-triazaheptane-1,4,7-triacetic acid) was purchased from Amersham Health (Buckinghamshire, UK). Magnevist ([Gd(DTPA)(H_2O)]$^{2-}$) was prepared by mixing equimolar amounts of $Gd(ClO_4)_3$ and DTPA (diethylenetriamine-*N*,*N*,*N*',*N*'',*N*''-pentaacetic acid, Fluka); the absence of free metal ions was verified by performing a xylenol orange test at pH around 6 [18]. [Gd(DOTP)(H_2O)$_{2.75}$]$^{5-}$ (Gd(III)-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra (methylenephosphonate))) was purchased from Macrocyclics (Dallas, TX). All experiments were performed on an actively shielded 9.4T 31 cm bore Varian spectrometer with high-performance gradients (400 mT/m in 130 μs). A home-built surface coil consisting of two ^{1}H coils (operating in quadrature, 14 mm diameter) with a double-turn 10 mm inner ^{13}C coil was used for both excitation and detection [19]. An equivalent surface coil with the inner coil tuned to ^{6}Li was constructed for the lithium-6 measurements. FASTMAP [20] was used for shimming.

All signals were measured as the peak integrals obtained from an inversion recovery sequence (predelay - 180_x- τ - 90_x). A hyperbolic secant (HS) 180° RF pulse [21] was used for inversion, while an adiabatic half-passage (AHP) 90° pulse [22] was used for excitation, which was immediately followed by acquisition of the FID. The inversion time τ was varied logarithmically from 0.01 to 40 s for ^{13}C, and from 0.01 to 400 s for ^{6}Li. To minimize experimental times, several long or short inversion times were omitted if the T_1 was estimated

to be short or long respectively. The resulting curve was fitted with $I=I_0(1-\alpha\cdot\exp(-\tau/T_1))$ to determine T_1. The relaxivity r_1 was then calculated from the slope of a linear regression of R_1 ($=1/T_1$) against the concentration of the contrast agent.

Omniscan was dissolved in 99% pure natural abundance formic acid at concentrations of 0, 0.05, 0.1, 0.2 and 0.5 mM. Omniscan was chosen as a relaxation agent because of its neutral charge and being less prone to complexation. The signal was averaged 16 times and the relaxation delay was set to 25 seconds.

Natural abundance glutamate (1 M) was dissolved in phosphate buffered saline at physiological pH. Omniscan concentrations of 0, 0.2 and 0.5 mM were added. The predelay was 25 s and the signal was averaged 32 times.

150 mM LiCl (^{6}Li is 7.4% naturally abundant) was dissolved in both H_2O and D_2O. Magnevist (0.05, 0.1 and 1 mM) was added to the H_2O. Omniscan was added to a separate LiCl/H_2O solution at 0.4, 0.8 and 1.2 mM, and to the D_2O solution at 0.1, 0.2 and 1 mM. Lastly, 5, 10 and 20 μM Gd-DOTP was added to a third LiCl/H_2O solution to demonstrate the influence of the contrast agent charge on ^{6}Li relaxivity. The signal was averaged 16 times. The predelay was 150s for contrast agent concentrations up to 0.8 mM, while a predelay of 25s was used for the higher concentrations.

Results

When the concentration of Omniscan was increased up to 1 mM a substantial effect on the line width of ^{13}C formic acid was not detected, even though a profound effect on the inversion recovery signal was clearly discernible (Fig. 1a). At 0.5 mM Omniscan, the relaxation rate R_1 of formic acid was increased by an order of magnitude from 0.15 to 1.54 s^{-1} (Fig. 1b). Consequently, the relaxivity r_1 of Omniscan in formic acid was ~ 3 $mM^{-1}s^{-1}$ (Table 1, first row), roughly two-thirds of its proton relaxivity, which has been reported to be on the order of 4.5 $mM^{-1}s^{-1}$ at comparable field strengths [7].

The T_1 of the glutamate carboxyl resonances C1 and C5 without contrast agents added was within experimental error identical and on the order of 10s as judged from the inversion recovery signal (Fig. 2a), i.e. $T_{1,C1}=10.2\pm0.8$ s and $T_{1,C5}=10.3\pm0.8$ s. After adding Omniscan at 0.2 and 0.5 mM, T_1 was shortened to about 5 and 3 s respectively, resulting in similar relaxivities of ~0.50 $mM^{-1}s^{-1}$ (Fig. 2b and Table 1, 2nd and 3rd row).

The longitudinal relaxation time of ^{6}Li was substantially longer, even in the presence of Omniscan (Fig. 3). For Omniscan the derived relaxivities in both H_2O and D_2O were on the order of 0.1 mM^{-1} s^{-1} (rows 4 and 5 in Table 1). Since the standard deviation values of the T_1 measurements scale with relative value, it decreased with relaxation time. When using Magnevist a three-fold higher relaxivity of ~0.3 mM^{-1} s^{-1} was obtained (row 6 in Table 1). The effect of contast agents on nuclei in charged particles is expected to be different depending on the charge of the contrast agent; we therefore measured the relaxivity of the highly charged Gd-DOTP on ^{6}Li, which was two order of magnitude higher than those for Omniscan (last row in Table 1).

Discussion

The present study reports the relaxivities of several contrast agents on two non-proton nuclei with intrinsically long relaxation times, namely ^{13}C and ^{6}Li. Even though the effect of commercially available contrast agents varied by two orders of magnitude, substantial T_1 shortening can be accomplished in vitro and thus experimental measurement times can be shortened, such as those for ^{13}C NMR calibrations using formic acid signal in an external

reference. Despite the fact that under the acidic conditions of pure formic acid solutions, Gd (III) is free and most likely not complexed with the ligand, r_1 is lower than observed for water ^{1}H (~4 mM^{-1} s^{-1}). One cause might be that the ^{13}C nucleus in formic acid primarily experiences second and/or outer sphere relaxation; this is possible due to the fact that the attached atoms hinder it from reaching the inner sphere of the contrast agent complex. On the other hand the relaxivity is also expected to be reduced compared to protons due to the fourfold lower nuclear gyromagnetic ratio, which affects relaxivity in an almost quadratic fashion according to the Solomon-Bloembergen-Morgan equations [7,8].

The relaxivity being lower for glutamate at physiological pH than for formic acid at low pH was explained by the presence of the complex around the Gd^{3+} ion. According to the structure of Magnevist (which has one hydration site), one can directly exclude any inner-sphere coordination of glutamate to the paramagnetic center due to steric hindrance around the bound water molecule. The replacement of a water molecule in the first coordination sphere is however a common phenomenon that is well established for the proton relaxivity of some bishydrated chelates like [Gd(DO3A)(H_2O)$_2$] by small organic molecules as lactate, malonate or citrate [23-25] or proteins [26]. For Magnevist, the absence of coordination of glutamate ^{13}C to the inner-sphere of the paramagnetic center induces an increase of the distance between the nuclei of interest and the Gd(III), thus resulting in a lower relaxivity.

Despite that inner sphere effects are less dominant and that the reduced gyromagnetic ratio further hampers the relaxivity, a concentration of 2 mM of Omniscan is predicted to shorten T_1 of glutamate carboxyl carbons to ~1 s, which can be exploited with an increased repetition rate to achieve an approximately threefold sensitivity gain. Preliminary measurement of brain extract obtained from a rat infused with 1-^{13}C glucose for several hours indicated that a repetition time of 3 seconds was close to full relaxation for the carboxyl resonances of glutamate (data not shown).

The aforementioned experiments demonstrate that the longitudinal relaxation rate can be increased in a predictive fashion using Gd-based contrast agents. Even though the relaxivity was weaker than for water protons, it has a substantial effect that can be exploited to increase the sensitivity in vitro for measuring carboxyl resonances. Contrast agents thus can be used in carbon spectroscopy studies on slowly relaxing resonances such as carboxyl groups to gain substantial time and sensitivity. The calculated r_1 suggests that the T_1 of glutamate carboxyl carbons can effectively be reduced from 10 s to ~1 s at an Omniscan concentration of 2 mM.

The three different contrast agents resulted in ^{6}Li relaxivities that spanned two orders of magnitude, which was attributed to the charge of the contrast agent chelate: at physiological pH Omniscan is neutral and will thus not strongly interact with the ^{6}Li ion's positive charge. Therefore, contrast agents with a different charge were expected to have a different relaxivity. Magnevist is negatively charged (a net charge of -2 at neutral pH) and indeed had a threefold higher relaxivity than Omniscan, whereas Gd-DOTP had a hundredfold higher relaxivity than Omniscan. This can be explained with the net charge of -5 and the presence of four coordination sites for positively charged ions, reducing effectively the distance between the ^{6}Li and the Gd^{3+} center [27]. Overall these experiments indicate that with suitable contrast agents tailored to the nucleus studied (or even compound), potent relaxivities can potentially be achieved. When taking into account that the relaxivity is approximately proportional to the square of the gyromagnetic ratio of the nucleus (for 6Li this is ~2% of protons) and to S(S+1) (2.7fold of protons) a "proton relaxivity equivalent" can be calculated, which was 2 mM^{-1} s^{-1}, about in the same order of magnitude of Magnevist in water. The high relaxivity of DOTP, on the other and, would result in a proton relaxivity equivalent of 185; DOTP thus is clearly a very potent contrast agent.

Aside from the obvious sensitivity gains the long intrinsic relaxation times of X-nuclei offer the prospective of detecting contrast agents at very low concentrations. For example, when assuming that at 10 s a signal reduction by 10% in a ^{13}C is detectable, from solving:

$$\frac{\exp\left[-TR\left(R_{1dia}+\left[CA\right]\cdot r_1\right)\right]}{\exp\left[-TR\cdot R_{1dia}\right]}=\exp\left(-TR\cdot\left[CA\right]\cdot r_1\right)=0.9, \quad (1)$$

the presence of [CA]~20 μM should be detectable with a relaxivity of 0.5 mM^{-1} s^{-1}. Likewise, assuming that a 10% decrease in signal is detectable at 100 s (on the order of T_1 of ^6Li in H_2O) the presence of ~100 nM of Gd-DOTP should be discernible. Given the recent advent of hyperpolarized ^{13}C for *in vivo* imaging [28], it is realistic to consider the potential detection of contrast agents at concentrations well below what is currently being used given that such contrast agents can be custom-synthesized with favorable properties for the nucleus and/or compound to be studied.

We conclude that the determined ^{13}C and ^6Li relaxivity of commercially available contrast agents is strong enough to allow the preparation of solutions with a predetermined and well defined relaxation enhancement, which offers significant sensitivity enhancement and the perspective of detecting contrast agents at potentially very low concentrations.

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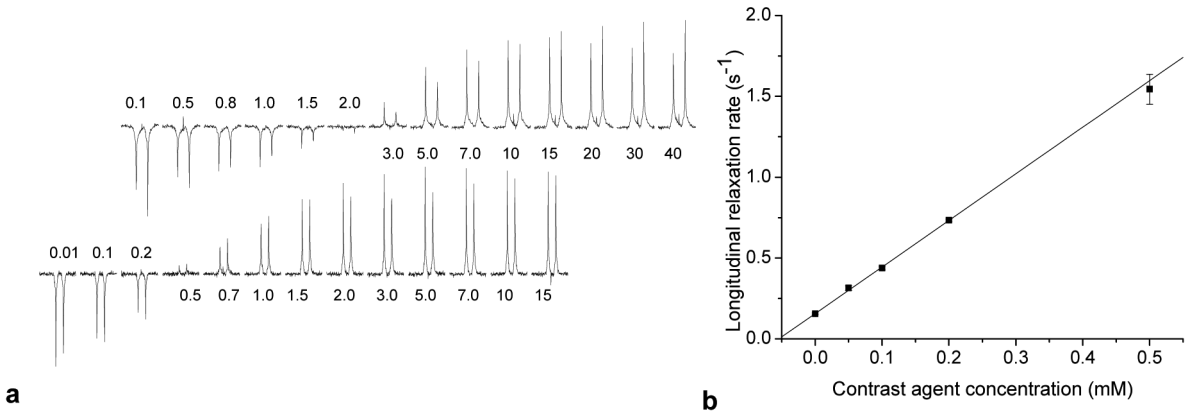

Fig. 1. Effect of Omniscan on formic acid ^{13}C T_1

(a) Series of ^{13}C spectra of formic acid in the presence of 0.05 mM (upper) and 0.5 mM (lower) of the contrast agent Omniscan. The signal is a doublet since no decoupling was used. Inversion times τ (s) are indicated for each trace. The inversion null can be seen at 2.0 and 0.5 seconds respectively.

(b) Linear fit of the relaxation rate R_1 (s) versus the Omniscan concentration [CA] (mM) to determine the relaxivity. Error bars represent the standard deviation of the T_1, and fit are too small to be visible for the lower concentrations.

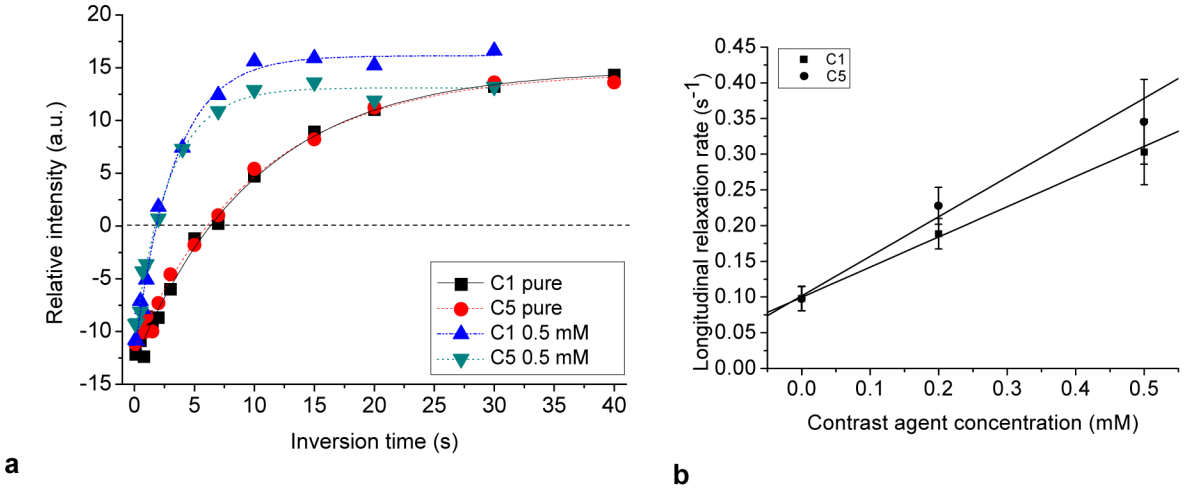

Fig. 2. Effect of Omniscan on the glutamate carboxyl carbon T_1

(a) Inversion recovery curves of the glutamate carboxyl carbons at different concentrations of Omniscan. (b) A linear fit of the relaxation rate R_1 (s^{-1}) vs. the concentration of Omniscan (mM) to determine the relaxivity of the carbons of the carboxyl groups of glutamate. Error bars represent the standard deviation on the inversion recovery fit.

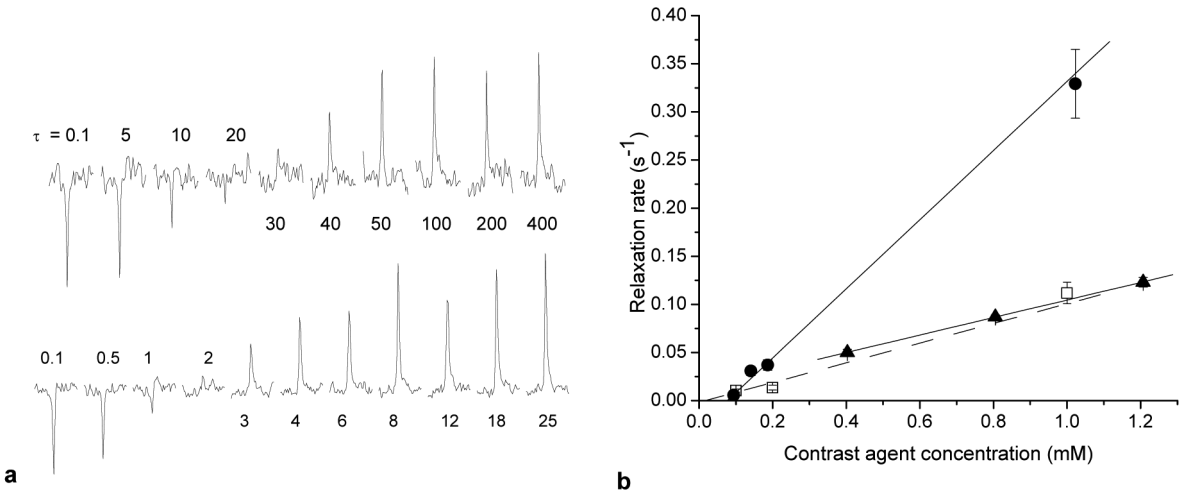

Fig. 3. The effect of contrast agents on lithium-6 transverse relaxation times

(a). Series of inversion recovery spectra for a LiCl solution in H_2O with 0.05 mM (upper) and 1 mM (lower) of Omniscan. Inversion times are mentioned for each individual spectrum. (b) Determination of the relaxivity for the Magnevist in H_2O (●), Omniscan in H_2O (▲) and Omniscan in D_2O (□) solutions. Error bars represent standard deviations of the inversion recovery curve fits.

Table 1

Overview of the determined contrast agent relaxivities by resonance.

The fitted equation is $R_1 = R_{1,dia} + r_1[CA]$, where $R_{1,dia}$ is the diamagnetic relaxation rate or relaxation rate without contrast agent present . Errors are standard deviations from the fits.

Substance	Contrast Agent	r_1 (mM^{-1} s^{-1})	$R_{1,dia}$ (s^{-1})	R^2
Formic acid	Omniscan	2.88 ± 0.05	0.156 ± 0.005	0.9996
Glutamate C1	Omniscan	0.42 ± 0.08	0.10 ± 0.02	0.996
Glutamate C5	Omniscan	0.55 ± 0.10	0.10 ± 0.02	0.976
^6Li in D_2O	Omniscan	0.10 ± 0.01	-0.001 ± 0.002	0.917
^6Li in H_2O	Omniscan	0.091 ± 0.007	0.014 ± 0.006	0.99996
^6Li in H_2O	Magnevist	0.33 ± 0.03	0.006 ± 0.002	0.976
^6Li in H_2O	Gd-DOTP	11 ± 1	-0.015 ± 0.007	0.951