TmDOTMA$^-$: A sensitive MR thermometry probe for in vivo applications

S. K. Hekmatyar[1], A. Babsky[1], S. K. Pakin[1], N. Bansal[1]
[1]Radiology, Indiana University, Indianapolis, IN, United States

Introduction

Non-invasive temperature monitoring has many direct uses in medicine. MR thermometry techniques based on the chemical shift, relaxation rates and molecular diffusion rate of ^{1}H water signal suffer from poor thermal resolution. Zhu *et al.* [1] and we [2] independently developed a non-invasive MR thermometer based on the temperature dependence of hyperfine shifted ^{1}H signal of the paramagnetic lanthanide complex, TmDOTA$^-$. One potential drawback of TmDOTA$^-$ is low signal-to-noise ratio. In this study, we evaluate the use of lanthanide complexes of a methyl substituted analog of DOTA^{4-}, DOTMA^{4-} for MR thermometry. Aime *et al.* [3] have explored the utility of Yb-DOTMA$^-$ as temperature sensitive imaging probe. DOTMA$^-$ has 12 equivalent protons on the four methyl groups and gives three times more intense signal compared to TmDOTA$^-$. In addition, the methyl proton signals have longer T_2 and narrower line-widths because of fast free rotation of the CH_3^- groups and reduced through-bond paramagnetic contact interaction.

Experimental

LnDOTMA$^-$ were synthesized from Ln_2O_3 (Ln = Pr, Yb, Tb, Dy and Tm) and Na_4DOTMA. ^{1}H spectra of the LnDOTMA$^-$ complexes were acquired in the temperature range 22 to 55°C using a Varian 9.4 T 89 mm vertical bore MR system. ^{1}H spin-lattice (T_1) and spin-spin (T_2) relaxation times of the methyl resonances from the five LnDOTMA$^-$ complexes were measured at 37°C. To determine the effects of pH and Ca^{2+}, on the chemical shift of the methyl resonance of the TmDOTMA$^-$, the experiments were conducted at 37°C at five different pH values (3 to11) and five different Ca^{2+} concentrations (0 to 3 mM). *In vivo* temperature measurements were performed on subcutaneously (sc) implanted RIF-1 tumor in C3H/HeN mice using a 1 cm diameter surface coil placed over the tumor. 1-2 mmole of TmDOTMA$^-$ per kilogram body weight was injected through a tail vein. Animal core body temperature was monitored with a rectal fiber-optic temperature probe. The animal temperature was manipulated over temperature ranging from 35 to 40°C by blowing warm air into the magnet bore.

Results and Discussion

Figure 1 shows the structure and ^{1}H MR spectra of TmDOTA$^-$ and TmDOTMA$^-$ showing H^1 and H^6 or methyl proton signals. The SNR advantage with TmDOTMA$^-$ is clearly apparent in the spectra. Table 1 shows the chemical shifts, temperature coefficients of chemical shift (C_T), line-widths and relaxation times for the methyl resonance from the five complexes. Tb(III), Dy(III), and Tm(III) complexes of DOTMA^{4-} show two resonances because of the presence of two conformational isomers. The relative amount of the minor isomer of TmDOTMA$^-$ is < 4%. The C_T value is the largest for the methyl signal from TmDOTMA$^-$. The ratio of temperature coefficient and resonance full width at half height ($|C_T|$FWHH) is also largest for TmDOTMA$^-$, therefore, this complex was further evaluated. The methyl proton chemical shifts of TmDOTMA$^-$ are independent of the pH, Ca^{2+} concentration or presence of any blood plasma. The proton T_1 and T_2 values for the methyl resonance of TmDOTMA$^-$ at 37°C and 9.4 T are 5.3 and 4.1 ms, respectively. These values are approximately two times more compared to the H_6 signal from TmDOTA$^-$. These data clearly show the advantages of TmDOTMA$^-$ over TmDOTA$^-$. Figure 2 shows representative *in vivo* ^{1}H spectra of TmDOTMA$^-$ from a sc-implanted RIF-1 tumor. The tumor temperature was always lower than the core body temperature. This demonstrates that TmDOTMA$^-$ allows robust measurement of temperature in sc implanted tumors and other tissue in intact animals.

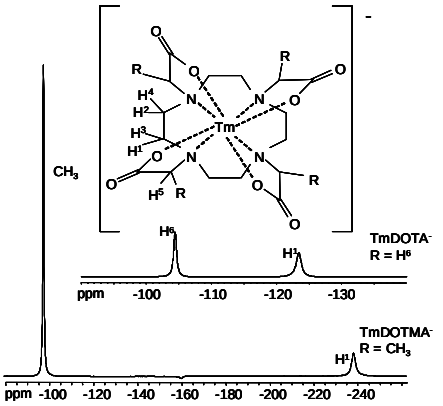

Fig. 1: ^{1}H MR Spectra of TmDOTA$^-$ and TmDOTMA$^-$ showing H^1 and H^6 or methyl proton signals. The H^1 resonances from both the complexes is set to the same signal intensity demonstrating the SNR advantage with the methyl resonance from TmDOTMA$^-$.

Table 1: ^{1}H chemical shifts, temperature coefficients (C_T), full-width at half-height (FWHH), $|C_T|$/FWHH, T_1 and T_2 for ^{1}H methyl signal from Pr(III), Yb(III), Tb(III), Dy(III) and Tm(III) complexes DOTMA$^-$.

Lanthanide complex	[a]Shift ppm	[b]C_T ppm/°C	[a]FWHH ppm	[c]$\frac{|C_T|}{FWHH}$	[a]T_1 ms	[a]T_2 ms
PrDOTMA	6.80	-0.014	0.065	0.210	90	17
YbDOTMA	-13.9	0.058	0.063	0.933	59	29
*TbDOTMA	63.3	-0.269	0.90	0.300	3.0	1.3
	57.5	-0.130	0.48	0.273		
*DyDOTMA	73.3	-0.233	0.59	0.395	2.2	1.7
	78.0	-0.325	0.93	0.351		
TmDOTMA	-99.6	0.586	0.43	1.362	5.3	4.1
	-67.1	0.184	0.39	0.473		

[a] at 35 °C;

[b] Slope of shift vs temperature data from 22-55 °C.

[c] Absolute value of the ratio of temperature coefficient of chemical shift (C_T in ppm/ °C) and the FWHH (full width half height) at 35 °C (in ppm).

*Represents the existence of the isomers for each of the methyl group.

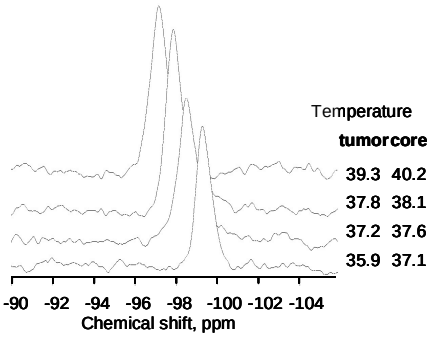

Fig. 2: Representative *in vivo* ^{1}H spectra from methyl resonance of TmDOTMA$^-$ from sc-implanted RIF-1 tumor. The tumor temperature was calculated from the chemical shift of the TmDOTMA$^-$ methyl proton signal with respect to the water proton signal set to 4.7 ppm. The core temperature was measured using a fibre-optic rectal probe.

Conclusion

The major advantages of TmDOTMA$^-$ for MR studies include 1) ~60 times more sensitivity to temperature than water and 15 times more than YbDOTMA$^-$; 2) more intense signal and longer T_2 compared to TmDOTA$^-$ [1,2]; and 3) insensitivity to changes in concentration, pH, [Ca^{2+}] and presence of other ions and macromolecules. These properties should make TmDOTMA$^-$ useful for MR thermometry in a wide range of applications.

References

1. CS Zuo, A Mahmood, AD Sherry. J Mag Res, 151:101-106, 2001.
2. SK Hekmatyar, H Poptani, A Babsky, D Leeper, N Bansal. Int J. Hyperthermia, 18:165-180, 2002.
3. S Aime, M Botta, M Fasano, E Terreno, P Kinchesh, L Calabi, L Paleari, Mag Reson Med 35:648-651, 1996.