In vivo temperature assessment using ^{1}H NMR chemical shifts of NAA-water and TmDOTP^{5-}

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INTRODUCTION. There are several non-invasive methods for temperature imaging *in vivo* [1]. Most of these are based on changes in physical properties of water with temperature, e.g., water proton NMR chemical shift relative to that of NAA, water proton NMR longitudinal relaxation time, water proton diffusion constant. In the last decade, a new non-invasive method was developed, based on the strong dependence on temperature and pH of the proton chemical shifts from the complex between the thulium ion and the macrocyclic chelate 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra (methylene phosphonate) or TmDOTP^{5-}, a shift reagent (**A,** top) [2,3]. Due to high sensitivity of each resonance on temperature and pH, models can be developed [2,3] to determine both temperature and pH simultaneously and with high accuracy. The motivation for the present study was to assess, under *in vivo* experimental conditions, the accuracy of temperature determination using the proton chemical shifts of TmDOTP^{5-} in comparison to the chemical shift difference between water and NAA resonances.

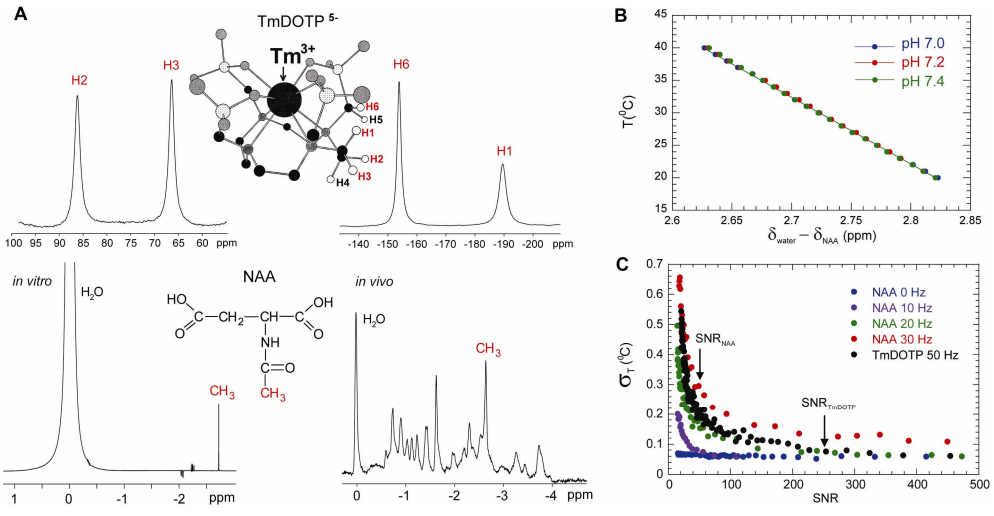
METHODS. ***In vitro:*** The ^{1}H NMR spectrum of TmDOTP^{5-} was obtained using a sample containing 5mM TmDOTP^{5-} and 5mM phosphate buffer at pH 7.4. The spectrum was acquired on a modified 11.7T Bruker spectrometer using a ^{1}H surface coil. The temperature calibration for NAA was obtained using three samples, each containing 20 mM NAA, 20mM phosphate buffer and 1 mM TSP at pH 7.0, 7.2 and 7.4, respectively. The ^{1}H NMR spectra of NAA were acquired at various temperatures in the range from 20 to 40 ^{0}C. ***In vivo:*** The Sprague-Dawley rats (n=4) were prepared as previously described [4]. *In vivo* ^{1}H NMR spectra were acquired on a modified 11.7T Bruker spectrometer using the same ^{1}H surface coil. ***Temperature calculations:*** Spectra of various SNR values were obtained by adding noise to the original FIDs. At each noise figure, 100 calculations were performed so that the standard deviation for temperature estimation (σ_T) could be directly compared with the SNR of the spectra.

RESULTS AND DISCUSSION. The ^{1}H NMR spectrum of TmDOTP^{5-} (**A,** top) reveals a very wide chemical shift difference between four resonances. The temperature-dependent redundancy of three protons (H2, H3 and H6) can be used to increase the accuracy of temperature (and pH) prediction [5]. The H1 proton resonance was not used because it has the lowest SNR for detection (**A,** top). The temperature T and pH values can be calculated from the chemical shift values δX, δY and δZ of three protons by

$$T = a_1 + a_2 pH + a_3\delta X + a_4\delta Y + a_5\delta Z + a_6\delta X^2 + a_7\delta Y^2 + a_8\delta Z^2$$

$$pH = b_1 + b_2 T + b_3\delta X + b_4\delta Y + b_5\delta Z + b_6\delta X^2 + b_7\delta Y^2 + b_8\delta Z^2$$

where nominal values of the parameters (i.e., $a_1 - a_8$, $b_1 - b_8$) can be estimated by linear regression [5]. The ^{1}H NMR spectrum of NAA-water (**A,** bottom left) reveals a much narrower chemical shift difference, where the temperature depends linearly on the chemical shift difference between the water and NAA resonances. The temperature dependence for the NAA-water sample at pH 7.4: $T(^0C) = (-102.7 \pm 0.5)\bullet(\delta_{water} - \delta_{NAA}) + (309.7 \pm 1.3)$ was obtained by linear regression (**B**). The pH dependence data shows that the NAA-water calibration curve does not depend on the pH of the sample, for pH values in the range from 7.0 to 7.4 (**B**). The SNR values as a function of the standard deviation of temperature estimation (σ_T), indicate that the uncertainty in temperature determination is smaller when using NAA calibration *in vitro* without any line broadening (i.e., 0 Hz) than with TmDOTP^{5-} which intrinsically has very broad lines (**C**). Since additional line broadening of TmDOTP^{5-} resonances by as much as 300 Hz has no effect on temperature calculation using TmDOTP^{5-} calibration (data not shown), the calibration using TmDOTP^{5-} protons is independent of *in vivo* line broadening effects. However the NAA-water calibration is very sensitive to line broadening. Since typical line width of NAA *in vivo* may easily exceed 25 Hz at high fields due to inherent inhomogeneities (**A,** bottom right), we estimated the SNR vs. σ_T dependencies at different line broadening values (**C**). The results indicate that σ_T increases by nearly a factor of two from 20 to 30 Hz of line broadening at the same SNR (**C**). Moreover, the typical SNR in a 6x3x6 mm^3 voxel for an *in vivo* ^{1}H NAA signal is $SNR_{NAA} = 50$, which corresponds to σ_T of 0.16 to 0.28 ^{0}C, for NAA linewidths of 20 to 30 Hz (**C**). For a voxel of the same size, the SNR for TmDOTP^{5-} signals are $SNR_{TmDOTP} = 250$, which corresponds to σ_T of 0.08 ^{0}C (**C**). Therefore, σ_T calculated using NAA-water (line broadening >20 Hz) becomes larger than σ_T calculated using TmDOTP^{5-}, under the same *in vivo* experimental conditions. This study demonstrates that TmDOTP^{5-} resonances are independent of line broadening effects whereas NAA-water resonances are not, which in turn corresponds to temperature calibration problems requiring very high SNR spectra for NAA-water. While the TmDOTP^{5-} method is likely to be limited for animal studies at present because of injecting an exogenous agent, the additional advantage of pH determination with TmDOTP^{5-} along with temperature suggests suitability for *in vivo* applications of functional activation [6].



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