Simultaneous Measurements of Temperature and pH Changes using Two Non-Equivalent Protons in TmDOTP$^-$

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**Purpose**
To develop a method of using two magnetically non-equivalent protons in TmDOTP$^-$ for simultaneous temperature and pH measurements in applications such as hyperthermia.

**Introduction**
MR techniques developed thus far for temperature measurement are mainly based on temperature dependence of T1 relaxation time, chemical shift and diffusion coefficient of water protons (1). While these techniques can provide acceptable thermal mapping for RF ablation and other intervention procedures, their application to hyperthermia, an experimental procedure for cancer treatment, are limited because of the insufficient temperature resolution ($\pm$2°C) resulting from the weak temperature dependence of water protons and their sensitivity to motion.

Recently, paramagnetic complexes have been investigated as potential thermometric substances for MR temperature measurements (2). We have previously demonstrated in phantoms that using a proton and $^{31}$P in TmDOTP$^-$ can provide simultaneous temperature and pH measurements at high field (2). We now extend this two-spin scheme to two magnetically nonequivalent protons in TmDOTP$^-$, one shifted downfield and the other shifted upfield, in animal at 2T. This abstract communicates our preliminary results on using the two proton scheme for simultaneous measurements of temperature and pH changes both in phantoms and in vivo.

**Methods**

**Phantom**
The chemical shift temperature dependencies of TmDOTP$^-$ protons were measured on a 2T Bruker Biospec animal system in a 15mM-TmDOTP$^-$ solution. The phantom temperature was altered in a temperature range of 23°C to 45°C using a hot water bath. The chemical shift dependencies were measured in a 15mM TmDOTP$^-$ plasma phantom in pH range of 6 to 9 by adding 0.1 M NaOH or 0.1 M HCl.

**In vivo**
Measurements were performed in 8 rats weighing ~300g on the 2T system. 15mM TmDOTP$^-$ solution was administered into a thigh at a dosage of 0.02 mmole/45 min. The thigh was heated with ~16°C cw ultrasound irradiation generated by a transducer (diameter 2.5cm) operating at 2.22 MHz. A copper-constantan thermocouple and a micro-electrode were implanted at the heated region to monitor the temperature and pH, respectively. The ultrasonic power was adjusted to make the temperature variations <0.5°C during MR signal acquisitions. MR signals were selectively excited by a 1ms-gaussian pulse using a 2.5 cm surface coil resonating at proton frequency, TR 0.03 sec., averages 1024, and TA 0.5min.

**Data analysis**
The chemical shift of protons and $^{31}$P in TmDOTP$^-$ were linear functions of temperature and pH in the ranges interested to hyperthermia (3). When both temperature and pH may vary simultaneously, chemical shift changes of two nonequivalent spins i and j ($\Delta \delta(i), \Delta \delta(j)$) can be used to calculate $\Delta T$ and $\Delta pH$ changes in temperature and pH.

\[
\Delta \delta(i) = C_{T(i)} \Delta T + C_{pH(i)} \Delta pH \quad [1]
\]
\[
\Delta \delta(j) = C_{T(j)} \Delta T + C_{pH(j)} \Delta pH \quad [2]
\]

where $C_{T(i)}$, $C_{T(j)}$, $C_{pH(i)}$, and $C_{pH(j)}$ are temperature dependence and pH dependence of the chemical shift for i and j in TmDOTP$^-$ respectively.

**Results**

**Phantom**
The chemical shifts of all six TmDOTP$^-$ protons varied linearly with temperature in the range of 23°C to 45°C at 2T. The H1, H5, and H6 peaks were shifted downfield while the H2, H3, and H4 lines were shifted upfield (2). Each proton exhibits the same temperature dependence as that observed at high field within experimental error. For example, H2 and H6 of TmDOTP$^-$ had chemical shift temperature dependencies of 0.6 ppm/°C and 1.0 ppm/°C, respectively. The combination of these two opposite shifted protons provide a higher effective temperature dependence of 1.6 ppm/°C. Similarly, chemical shifts of TmDOTP$^-$ protons had a linear relationship with pH in pH range of 6.5 to 8.5 at a constant temperature. For instance, the pH chemical shift dependencies of H2 and H6 were 3.2 ppm/pH unit and -3.2 ppm/pH unit, respectively.

**In vivo**
Measurements were focused on the chemical shifts of H2 and H6 in TmDOTP$^-$ during a localized hyperthermia in rats (Fig. 1). Temperature and pH values were calculated using Eq. [1] and Eq. [2] with $C_T(2)=-0.6$ ppm/°C, $C_T(6)=1.0$ ppm/°C, $C_{pH(2)}=3.2$ ppm/pH unit, and $C_{pH(6)}=-3.2$ ppm/pH unit. The temperature and pH values measured by NMR and by the thermocouple and micro-electrode in one representative animal are summarized in table 1. The pH values measured by NMR were in good agreement with the values measured by thermocouple and pH meter. The correlation between our noninvasive and invasive temperature measurements was better than 0.5°C and the correlation between the pH measurements was within experiment error.

**Discussion**
The chemical shifts of H2 and H6 in TmDOTP$^-$ are sensitive to temperature and pH, the combination of H2 and H6 in TmDOTP$^-$ appears to be able to achieve a temperature resolution of ~0.5°C and pH measurements within experimental error (Table 1). One benefit of this scheme is that proton spectra of TmDOTP$^-$ can be acquired using clinical MR scanners without extended, broadband frequency capabilities.

In summary, Our experimental results showed that the two TmDOTP$^-$ proton scheme can provide simultaneous measurements of temperature and pH changes in vivo. The pH change measurement may provide important information related to thermal sensitivity of tumor cells (3).

**References**


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<th>Data from Typical Animal Measurements</th>
<th>Calculated T &amp; pH Values</th>
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<tr>
<td>n</td>
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<tr>
<td>---</td>
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</tr>
<tr>
<td>1</td>
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Table 1. Comparison of temperature and pH measured by thermocouple and pH meter and by NMR