

# NMR Temperature and pH Measurements using a Paramagnetic Lanthanide Complex

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## Purpose

To develop a method for accurate, simultaneous pH and temperature measurements by MR.

## Introduction

Accurately monitoring temperature and pH of heated tissues is critical for the efficacy of hyperthermia. The small temperature difference ( $\sim 2^\circ\text{C}$ ) needed to kill tumor cells without damaging normal tissues requires the development of new techniques for high thermal resolution at clinical field strengths. It is well known that the chemical shifts of nuclear spins in paramagnetic complexes are sensitive to temperature. This phenomenon has recently been exploited for *in vivo* NMR thermometry (1-3). This work was performed to explore further the properties and use of TmDOTP<sup>5-</sup> for MR temperature and pH measurements *in vivo* using two nonequivalent spins in the complex.

## Methods

All studies were performed with 20 mM TmDOTP<sup>5-</sup> solutions in D<sub>2</sub>O. Chemical shifts of <sup>1</sup>H and <sup>31</sup>P in TmDOTP<sup>5-</sup> were measured using a 7.06 T GE spectrometer. T<sub>1</sub>'s of <sup>1</sup>H and <sup>31</sup>P in TmDOTP<sup>5-</sup> were <4 ms in the temperature range of interest. FID's were acquired using TR=26 ms and 20-100 averages, giving SNR of 40:1 to 230:1 for the various peaks in TmDOTP<sup>5-</sup> in less than 3 s. Temperatures were regulated using the GE controller and were accurate to within 1°C.

Chemical shifts were measured for <sup>1</sup>H and <sup>31</sup>P of TmDOTP<sup>5-</sup> in a process where temperature and pH were allowed to change simultaneously within pH 6 to 8 and temperatures of 25 to 45°C. The temperature dependences of chemical shifts for <sup>1</sup>H and <sup>31</sup>P are independent of pH within the linear region of the shift *versus* pH curve from pH 6 to 8 (3). The changes in temperature and pH ( $\Delta T$  &  $\Delta\text{pH}$ ) can be calculated from two independent chemical shifts using the equations (4):

$$\Delta T = \frac{\Delta\delta^H \cdot C_{pH}^P - \Delta\delta^P \cdot C_{pH}^H}{C_T^H \cdot C_{pH}^P - C_T^P \cdot C_{pH}^H} \quad \text{and} \quad [1]$$

$$\Delta\text{pH} = \frac{\Delta\delta^P \cdot C_T^H - \Delta\delta^H \cdot C_T^P}{C_T^H \cdot C_{pH}^P - C_T^P \cdot C_{pH}^H} \quad [2]$$

where H and P represent <sup>1</sup>H and <sup>31</sup>P, respectively. C<sub>T</sub> and C<sub>pH</sub> are temperature and pH dependences of the chemical shifts.

## Results

The complex contains six nonequivalent groups of protons, previously designated as H<sub>1</sub> to H<sub>6</sub>, and one group of equivalent <sup>31</sup>P's. The H<sub>1</sub>, H<sub>5</sub>, and H<sub>6</sub> peaks were shifted upfield (-194, -399, -156 ppm) while the H<sub>2</sub>, H<sub>3</sub>, and H<sub>4</sub> lines were shifted downfield (93, 73, 514 ppm) (4). All proton shifts varied linearly with temperature between 25 and 45°C, with each type of proton exhibiting a unique line width and temperature dependence (+1.08, -0.54, -0.42, -2.88, +2.19, +0.87 ppm/°C from H<sub>1</sub> to H<sub>6</sub>). The <sup>31</sup>P line had a width of 1.05 ppm, a temperature dependence of 2.18 ppm/°C and a shift of -350.7 ppm at 25°C (4).

The linear portion of the <sup>31</sup>P shift *versus* pH curve had a slope of -15.32 ppm/pH unit, and the H<sub>6</sub> shift had a slope of

-3.27 ppm/pH unit. Temperature and pH changes measured using <sup>31</sup>P and H<sub>6</sub> shifts were calculated for five different combinations of temperature and pH settings using C<sub>T</sub><sup>H</sup> = +0.87 ppm/°C, C<sub>T</sub><sup>P</sup> = +2.18 ppm/°C, C<sub>pH</sub><sup>H</sup> = -3.27 ppm/pH unit, and C<sub>pH</sub><sup>P</sup> = -15.32 ppm/pH unit. Results typically agreed with set values to within a few tenths of a degree and 0.1 pH unit. For example, when the sample temperature setting was increased by 10.0°C while the pH was decreased by 0.9 units, <sup>1</sup>H and <sup>31</sup>P chemical shifts changed by +12.1 and +37.5 ppm, respectively. Using these shifts in combination with Eqs. [1] & [2] gave measured changes of +10.1°C and -1.0 pH unit, in good agreement with the set values.

## Discussion

The <sup>31</sup>P and <sup>1</sup>H chemical shifts in TmDOTP<sup>5-</sup> were linearly dependent on pH while their temperature dependences exhibited little sensitivity to pH (< 5%) between pH 6-8, the physiological pH range for hyperthermia. Thus, within the linear portion of the titration curve, the pH effect and temperature contributions could be separated and the chemical shifts of <sup>31</sup>P and <sup>1</sup>H in TmDOTP<sup>5-</sup> could be used to measure temperature and pH simultaneously. The advantages of using TmDOTP<sup>5-</sup> for measuring extracellular pH *in vivo* are that it is rapid, relatively noninvasive, offers adequate pH and temperature resolution, and does not require extra hardware. Although <sup>31</sup>P and H<sub>6</sub> signals were used here for simultaneous pH and temperature measurements, similar results could be obtained by using a pair of <sup>1</sup>H lines.

An alternative method for measuring temperature is to combine the chemical shifts of two nonequivalent TmDOTP<sup>5-</sup> spins, one shifted upfield and the other shifted downfield, to provide a much larger shift temperature dependence than that obtainable from one shift alone. In figure 1, the combination H<sub>6</sub>-H<sub>3</sub> provides a temperature dependence of 1.3 ppm/°C, much higher than the combination of H<sub>6</sub>-H<sub>1</sub>, about one order of magnitude larger than in YbDOTMA (1), and more than two orders of magnitude greater than <sup>1</sup>H in water and <sup>19</sup>F in perfluorocarbons. Another advantage of using a difference between two TmDOTP<sup>5-</sup> shifts is that changes in bulk susceptibility do not invalidate the temperature measurement.

## References

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## Acknowledgments

This research was supported in part by the Whitaker Foundation.

