Ratiometric pH Imaging with a Co^{II}_2 MRI Probe via CEST Effects of Opposing pH Dependences

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Introduction

Acidic extracellular pH is a characteristic feature of many pathological conditions, including cancer, ischemia, and inflammation.[1] As such, the ability to spatially map tissue pH is of value for improving the diagnosis and treatment of diseases. Toward this end, magnetic resonance imaging (MRI) techniques are ideal, owing to high spatiotemporal image resolution and tissue penetration depth. In particular, concentration-independent ratiometric pH mapping by means of paramagnetic chemical exchange saturation transfer (PARACEST) is especially attractive. Here, the ratio of the intensities of two CEST signals from a paramagnetic probe that show different pH dependences can be correlated with pH. Nevertheless, current probes suffer from low sensitivity as the changes in CEST intensity with pH are too similar for the two peaks. In efforts to improve the pH sensitivity of ratiometric PARACEST MRI probes, we develop dinuclear Co^{II} complexes featuring two types of CEST-active protons that exhibit CEST intensities with opposing pH dependences. Herein we report a Co^{II}_2 complex (**1**) bearing carboxamide and hydroxyl groups that exhibits remarkably high pH sensitivity in the physiological range, as verified by NMR and phantom MRI experiments, and displays excellent stability in physiological environments.

Experimental

CEST-NMR and CEST-MRI experiments were carried out at the IMSERC facility at Northwestern U. (400 MHz, 9.4 T) and in the McKnight Brain Institute at the NHMFL's AMRIS facility (750 MHz, 17.6 T, 89 mm bore), respectively. All measurements were performed at 37 °C using aqueous solutions of **1** buffered at pH 6.40–8.14.

Results and Discussion

CEST-NMR analysis of **1** reveals highly pH-dependent CEST peak intensities in the pH range 6.5–7.6. The ratios of CEST intensities at 104 and 64 ppm vs H_2O were used to construct a linear calibration curve of $\log_{10}(CEST_{104\ ppm}/CEST_{64\ ppm})$ vs pH, providing a pH sensitivity of 0.99(7) per pH unit (**Fig. 1**), which is over 2-fold greater than for related probes.[2] The pH calibration curve is independent of the concentration of **1** and phantom images reveal analogous linear pH behavior (**Fig. 2**).[3]

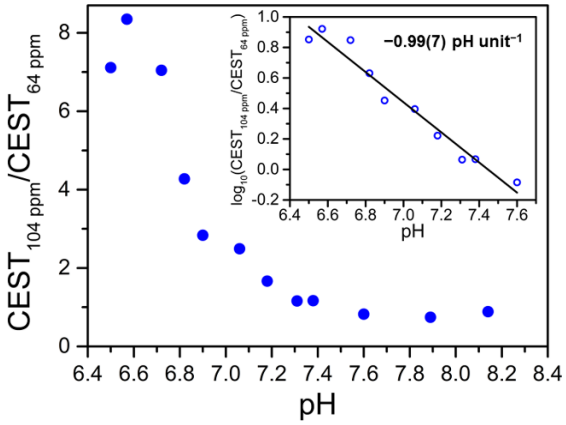

Fig. 1 pH dependence of the ratio of CEST intensities at 104 and 64 ppm for **1**. Inset: Semilog form of the plot, providing pH sensitivity of 0.99(7) per pH unit.

Conclusions

We have demonstrated the ability of Co^{II}_2 complexes to provide a concentration-independent measure of pH in a range relevant for detecting physiological abnormalities through ratiometric PARACEST imaging. The high pH sensitivity and stability of **1** in physiological environments underscore the potential suitability of this and related complexes for pH mapping *in vivo*.

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References

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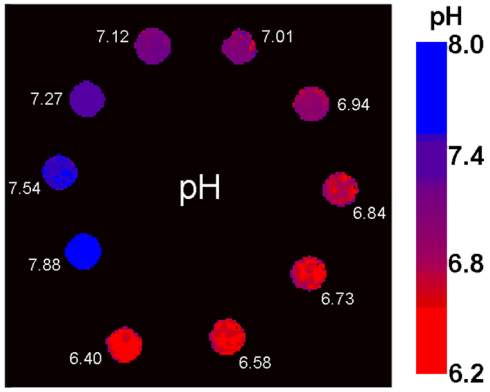

Fig. 2 pH map of phantoms of **1** obtained from CEST-MRI, demonstrating the good agreement with pH measured by an electrode (white numbers).