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

Thorarinsdottir, A.E. (Northwestern U., Chemistry); Collins, J.H.P. (University of Florida, AMRIS); Harris, T.D. (Northwestern U., Chemistry).

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. We recently demonstrated that dinuclear Co^{II} complexes featuring carboxamide and hydroxyl protons that exhibit CEST peak intensities with opposing pH dependences are promising candidates to achieve high pH sensitivity in the physiological range.[2,3] Herein we report a modified version of these probes, where the ancillary bisphosphonate ligand has been functionalized with an amine group. This Co_2 probe (**1**) exhibits over 4-fold higher pH sensitivity than previous ratiometric PARACEST probes.

Experimental

CEST-NMR and CEST-MRI experiments were carried out at the IMSERC facility at Northwestern U. (500 MHz, 11.7 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 buffer solutions and agar and gelatin gels of **1** at pH 6.40–7.80. A series of MR images using gradient echo FLASH and spin echo images were acquired of a bundle of capillary tubes containing the pH-adjusted gel samples. A train of saturation pulses were applied at a variety of bandwidths and power levels in order to optimize the observed CEST effect.

Results and Discussion

CEST-NMR analysis of **1** reveals highly pH-dependent CEST peak intensities in the pH range 6.2–7.4. The ratios of CEST intensities at 48 and 67 ppm vs H_2O were used to construct a linear pH calibration curve with a pH sensitivity of 8.8(5) pH unit^{-1} (**Fig. 1**), which is over 4-fold greater than for previous probes. The variation in CEST effect at 67 ppm with different pH values, as observed in a FLASH image, is highlighted in **Fig. 2**.

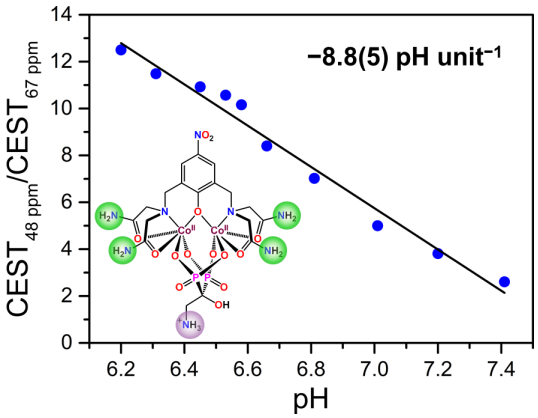

Fig. 1 pH dependence of the ratio of CEST intensities at 48 and 67 ppm for the modified Co_2 pH probe **1** (inset).

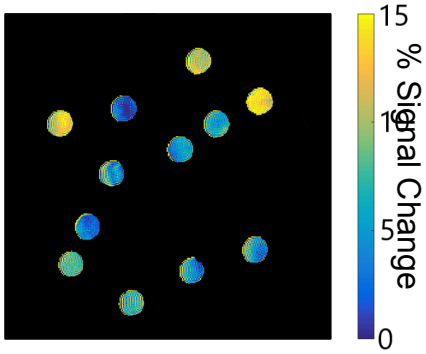

Fig. 2 Change in signal intensity in FLASH images, from pulses at offsets of +67 and −67 ppm.

Conclusions

The CEST effect was observed in NMR and MR images at both 48 and 67 ppm. Work is ongoing to further optimize the imaging and sample preparation protocols in order to optimize the variation in observed signal intensity, while minimizing unwanted image artefacts due to the relatively high rf power deposition.

Acknowledgements

A portion of this work was performed at the National High Magnetic Field Laboratory, which is supported by National Science Foundation Cooperative Agreement No. DMR-1644779 and the State of Florida. Support from Northwestern U. is acknowledged and A.E.T. thanks the Leifur Eiriksson Foundation.

References

[1] Kato, Y., *et al*., Cancer Cell Int., **13**, 89 (2013).
[2] Thorarinsdottir, A.E., *et al*., J. Am. Chem. Soc., **139**, 15836–15847 (2017).
[3] Thorarinsdottir, A.E., *et al*., Inorg. Chem., **57**, 11252–11263 (2018).