Exploring new routes for sensitivity enhanced MRI-CEST agents

S. Aime[1], D. Delli Castelli[1], E. Terreno[1]
[1]Chemistry IFM, University of Torino, Torino, Italy

Introduction

CEST agents (CEST = Chemical Exchange Saturation Transfer) represent a novel and emerging class of diagnostic media for MRI applications. These chemicals act by reducing the signal intensity of the water protons *via* a saturation transfer mediated by chemical exchange.[1] The two main advantages of these agents over the conventional Gd(III) or Fe(III)-based agents are: i) the ability to generate a contrast only following the irradiation of a frequency characteristic of a given CEST agent, and ii) the possibility to design responsive probes whose saturation transfer is not dependent on the absolute concentration of the CEST agent.[2]

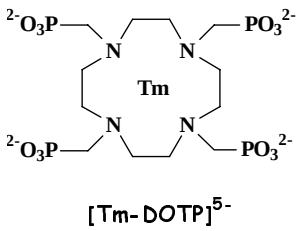
The development of more efficient CEST agents requires the optimization of the parameters involved in the saturation transfer process among which the more relevant are the exchange rate of the mobile protons of the agent, k_{ex}, and their number, n.

The optimal k_{ex} value is mainly related to the difference in the resonance frequency ($\Delta\omega$) between the mobile protons of the CEST molecule and water protons, but it can be also limited by the maximum power of the saturation pulse imposed by SAR.[3]

For this reason, a convenient route for designing high-sensitive CEST probes is to develop systems endowed with a high number of equivalent mobile protons with optimal k_{ex} values. An increase of n can be obtained by exploiting a molecular recognition between a diamagnetic molecule containing a high number of mobile protons and a paramagnetic shift reagent able to considerably enhance $\Delta\omega$.

In this contribution some example of high-sensitive CEST systems based on this approach will be presented.

Results and Discussion



A shift reagent particularly suitable for developing high-sensitive PARACEST agent through its interaction with a proper substrate is represented by the anionic TmDOTP complex whose ability to interact with positively charged compounds is widely documented.[4]

Poly-Arginine was used as model of a diamagnetic compound containing a high number of mobile protons. Figure 1 reports the Z-spectra (7.05 T, pH 7.4 and 312K) of a solution containing poly-arginine (DP = 227) with and without TmDOTP. The broad CEST peak centered at about 25 ppm downfield from water protons is the result of the saturation transfer induced by the irradiation of the guanidine protons of the polymer that are significantly shifted by their interaction with the metal complex.

Figure 2 shows the concentration dependence of the saturation transfer effect (ST%) for a solution containing a [TmDOTP]/[poly-arg] ratio of 24. The great sensitivity displayed by this system is evident by considering that a concentration of only 30 μM of TmDOTP ([poly-arg] = 1.7 μM) is required for detecting a ST% value of 5 % that represents the current lower limit for observing a contrast in a CEST-MR image. The effect of the concentration of the CEST agent on the saturation transfer efficiency has been also assessed in vitro in a CEST-MR image difference (Figure 3).

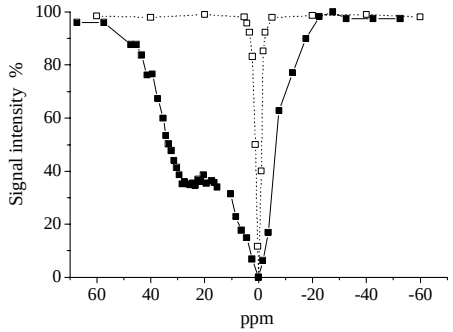


Figure 1: Z-spectra of poly-arginine with (■) and without (□) TmDOTP (pH 7.4, 312 K, 7.05 T).

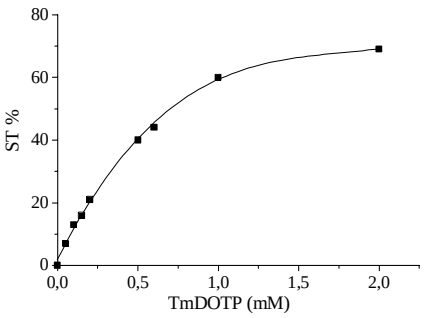


Figure 2: Concentration dependence of ST % for the TmDOTP/poly-arg system (molar ratio 24,(pH 7.4, 312 K, 7.05 T).

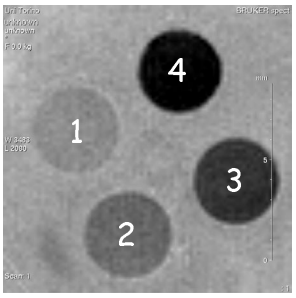
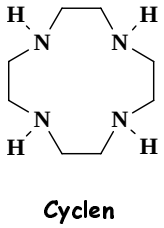


Figure 3: Difference SE-CEST-MR image of a phantom containing 4 solutions with different concentrations of TmDOTP/poly-arg system. (1 = 50μM/2.8μM; 2 = 100 μM/5.5 μM; 3 =200 μM/11.1 μM; 4 =500 μM/27.8 μM) (7.05 T, 312K, pH 7.4)



The use of a shift reagent can significantly widen the array of substrates to be considered as CEST agents at physiological pH and temperature.

As example, the increase of $\Delta\omega$ following the interaction between TmDOTP and Cyclen allows the amine protons of the latter to satisfy the $\Delta\omega > k_{ex}$ condition, fundamental requisite for any CEST agent.

The sensitivity of the TmDOTP/Cyclen system is rather high and the 5 % limit of ST % is reached at a TmDOTP concentration of 60 μM.

To our knowledge, this is the first case in which the CEST system is based on the irradiation of amine protons.

References

[1] Zhang S et al., *Acc. Chem. Res.* 36: 783-790, **2003**.
[2] Aime S et al. *Angew. Chemie Int. Ed.*, 22: 4334-4336, **2002**.
[3] Snoussi K, *Magn. Res. Med.* 49: 998-1005, **2003**.