Conversion to Carbon Nano Dots: A Possible Remedy Towards Low Efficiency of diaCEST Contrast Agents

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INTRODUCTION:

Chemical Exchange Saturation Transfer (CEST) contrast agents (CAs) are promising safer alternatives to metal-containing relaxation-based traditional MRI CAs. That is of course only if diaCEST CAs can be made equally efficient to their relaxation-based or paramagnetic CEST (paraCEST) counterparts. The challenges of diaCEST CAs are two-fold. First, the contrast generating exchangeable protons resonate too close to water (2–10 ppm). Second, a narrow solute-solvent frequency separation ($\Delta\omega$) puts a low ceiling on the exchange rate constant before coalescence kicks in. A small offset and a small exchange constant quite predictably make diaCEST CAs relatively inefficient. Here we propose that conversion to water soluble carbon nano dots has the potential to lift both these constraints.

METHODS:

The contrast efficiency of CEST agents depends heavily on the delicate balance of the solvent-solute exchange rate of the labile protons and $\Delta\omega$. It was observed that conversion of a diaCEST agent to carbon dots appreciably alters the exchange rates as well as $\Delta\omega$. This provided a possibility to tweak the contrast efficiency by altering $\Delta\omega$ and/or contrast rates.

RESULTS AND DISCUSSION:

Lidocain hydrochloride, an approved analgesic drug makes an impractical diaCEST CA with less than 1% contrast at the physiological condition (pH of 7.4, temperature 37 °C). The contrast is, however, higher (20%) at a less convenient acidic pH of 5.5 (Figure 1). Hydrothermal treatment of 5 mg/mL aqueous solution of lidocaine hydrochloride at 200 °C for 24 h converts the compound into ~5 nm blue fluorescent carbon dots that not only shows a perfectly reproducible and meaningful 11% contrast at pH 7.4, the maximum contrast touches 46% at pH 5.5.

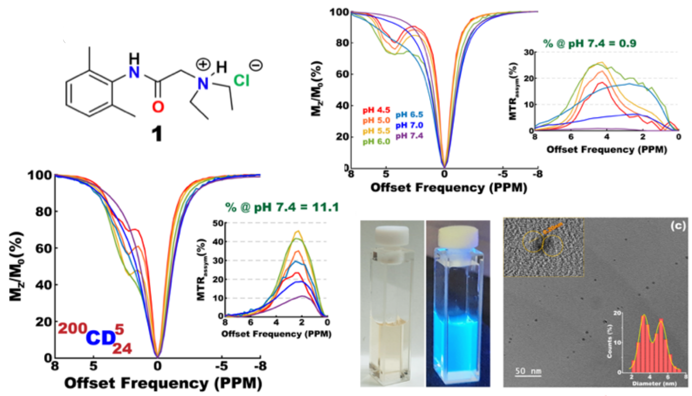

Figure 1. CEST profiles of lidocaine hydrochloride (above) and of its carbon-dots (below) at 37 °C.

Lidocain hydrochloride is not a one-off example. Conversion to hydrothermal carbon dots enhances the CEST contrast of amino-thioamide from a meagre 8% to an excellent 65% at pH 5.5 paving the way for hydrothermal treatment as a possible answer to the long-standing challenge of low efficiency of diaCEST CAs (Figure 2). In fact, the enhancement of the contrast is not limited to the hydrothermal treatment as microwave assisted carbon dots of urea-citric acid mixture showed more than 100% enhancement of contrast efficiency to ~32% at the physiological condition.

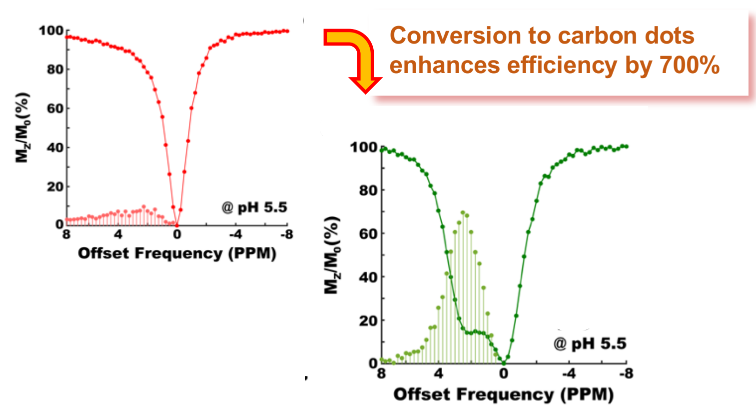

Figure 2. CEST profiles of amino-thioamide (above) and of its carbon-dots (below) at pH 5.5, 37 °C.

CONCLUSION:

We show here that carbon quantum dot preparation can certainly be used as a generic technique that can reliably and reproducibly transform an existing but ordinary diaCEST contrast agent into a super-efficient one. Moreover, it provides an extremely helpful added tunability for pH response.

REFERENCES:

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