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Hyperpolarized ^{129}Xe MRI Sensor for H_2S

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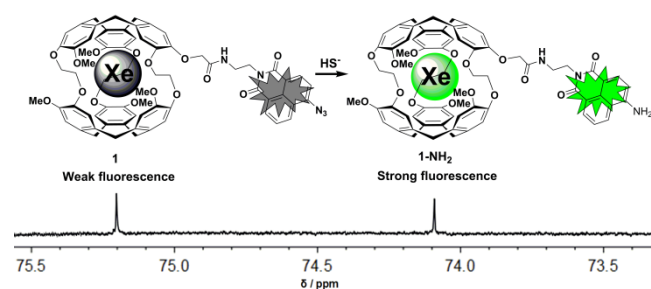
Abstract: A new MRI molecular sensor for hydrogen sulfide detection and imaging using the nuclear spin resonance of hyperpolarized ^{129}Xe is developed. The designed MRI sensor employs cryptophane for NMR sensing together with an azide group serving as a reaction site. It demonstrates a proof-of-concept that fluorescent H_2S probe can be linked to a xenon-binding cryptophane and thereby converted into an MRI probe, which could provide a very generalizable template.

Hydrogen sulfide (H_2S), traditionally known for its characteristic cacodorous odor and toxicity, has recently been shown to be a significant gaseous signaling transmitter in living organisms.^[1] The involvement of endogenous H_2S have been demonstrated in several physiological and pathological processes,^[2] such as regulation of cell growth, cardiovascular protection, modulation of neurotransmission and anti-inflammation action. Moreover, recent studies have shown that any imbalance H_2S levels can lead to health problems,^[3] including the symptoms of Alzheimer's disease, Down's syndrome, and diabetes.

Over the past few decades, several methods have been given to develop H_2S sensors, such as colorimetry,^[4] electrochemical analysis,^[5] and gas chromatography.^[6] Unfortunately, these traditional methods often require complicated post processing and destruction of specimens, and do not provide biodistributions. Recently, fluorescence detection is an attractive approach because fluorescence probes have been instrumental to elucidate the roles of H_2S in biological systems.^[7] These probes are almost always based on the H_2S -mediated specific reactions such as reduction reaction, nucleophilic reaction, and metal-sulfide precipitation.^[8] However, the main drawback of poor penetration depth, light scattering in optically opaque media and associated background noise prevent the use of these fluorescent probes in thick tissues. On the other hand, MRI can generate tomographic images and the penetration depth in tissue is not a limitation. MRI sensors developed to date are mainly based on either ^1H or ^{19}F NMR resonances, which relies on modulation of spin relaxation rates or chemical shifts upon binding.^[9] However, these particular resonances are intrinsically low sensitivity and offer poor chemical specificity. Therefore,

sensitive MRI methods for specific mapping H_2S distribution are highly demanded to understand its biological roles in living systems.

One way for signal enhancement is hyperpolarization and parahydrogen-induced polarization (PHIP) has been used for sensing sulfur-containing compounds.^[10] We propose to enhance the sensitivity with the use of a specific reaction-based hyperpolarized ^{129}Xe MRI sensor. ^{129}Xe nuclei can be hyperpolarized by spin exchange optical pumping (SEOP) to increase the NMR signal by up to four orders of magnitude. In addition, ^{129}Xe has a wide spectral window of more than 200 ppm in biological systems, which renders it highly susceptible to local chemical environment and facilitates the detection of biomolecules or biochemical reactions.^[11] Several biosensors based on hyperpolarized ^{129}Xe NMR have been developed featuring a molecular cage of cryptophane to encapsulate a Xe atom for molecular imaging. Such host molecular systems have been successfully developed for the detection of variety of species, including metal ions,^[12,13] biothiols,^[14] glycans,^[15] proteins,^[16] enzymes,^[17] nucleic acids,^[18] transmembrane receptor targets,^[19] and for the pH measurements.^[20] The sensitivity of ^{129}Xe magnetic resonance could be further enhanced beyond that achieved by hyperpolarization alone if hyperpolarized ^{129}Xe nuclei are detected using the chemical exchange saturation transfer (Hyper-CEST) method,^[17] where the reversible exchange can be used for indirect detection of caged molecules. This Hyper-CEST technique enables the detection of biomolecules and reactions occurring at much lower concentrations. Recently, biosensing studies involving Hyper-CEST have achieved molecular imaging of living cells.^[15,19a,20a,21] Therefore, sensors based on Hyper-CEST now constitute a potential strategy for molecular imaging in living cellular environments.



Scheme 1. Schematic of ^{129}Xe MRI sensor 1 for H_2S detection and imaging.

Continuing our interest in developing hyperpolarized xenon-based sensors,^[13,14] herein we report a new ^{129}Xe MRI sensor for H_2S detection based on a H_2S -specific response reaction (Scheme 1). To investigate the feasibility of this design concept, we chose cryptophane-A as ^{129}Xe NMR moieties, and a known H_2S -mediated specific response group as the reaction site. An azido reduction reaction can selectively detect H_2S because the azide group can be easily converted into amine upon reaction

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with H₂S.^[22] The working hypothesis here is that characteristic changes of the azide group lead to chemical structure conversion and finally, signal modulation via ¹²⁹Xe NMR chemical shift and also the fluorescence. To test this hypothesis, we coupled the cryptophane derivative to the weakly fluorescent molecule 4-azide-1,8-naphthalic anhydride by ethylenediamine. The target sensor 1 was readily obtained in few steps from modified cryptophane-A (used in racemic form) derivative and 4-bromo-1,8-naphthalic anhydride (see Scheme S1). All the synthesized compounds were well characterized by ¹H NMR, ¹³C NMR, and HRMS (see supporting information).

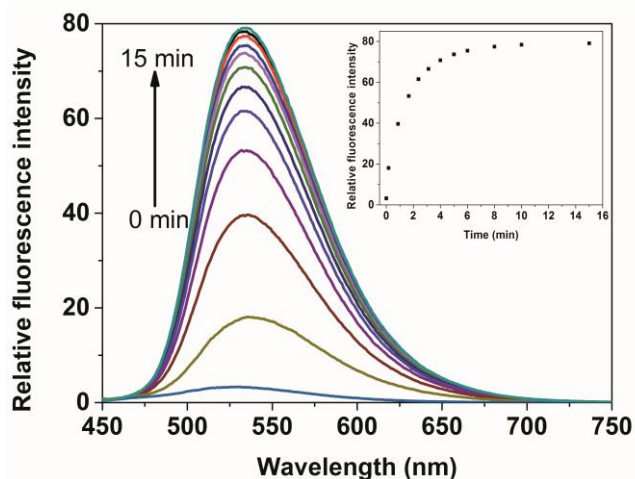


Figure 1. Fluorescence changes of sensor 1 (10 μM) upon addition of 10 equiv. of HS⁻ in HEPES buffer solution (pH 7.4, 20 mM). Spectra were collected for 0 to 15 min at 25 °C with excitation at 435 nm. The inset shows a time course of the fluorescence intensity change.

With sensor 1 in hand, we firstly investigated its optical property under the conditions of 20 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, pH 7.4) buffer with 60% DMSO as cosolvent at 25 °C. Sodium bisulfide (NaHS) was used as H₂S donor in this study. As designed, sensor 1 was found to be colorless in the absence of H₂S (Figure 1) with a major absorption band at 373 nm (see Figure S1). After addition of 10 equiv. HS⁻ to the solution of sensor 1, the colorless solution of sensor 1 rapidly changed to pale yellow, and simultaneously yielded a strong green fluorescence. The UV-vis spectra show that the maximum absorption peak of sensor 1 exhibited a 62 nm red-shift. Fluorescence spectra show the intensity at 534 nm gradually increased along with the time until it reaches emission saturation (about 25-fold) within 10 minutes, which was also indicated by kinetic studies of sensor 1 with 10 equiv. of HS⁻ (see Figure S2). These results suggest that sensor 1 shows fast response towards H₂S.

Encouraged by the above results, the applications of sensor 1 in hyperpolarized ¹²⁹Xe NMR (the level of ¹²⁹Xe hyperpolarization is about 20%) spectroscopy was evaluated. Under the same test conditions, the ¹²⁹Xe NMR spectrum of sensor 1 shows two distinct resonances that are assigned to the signal of free xenon in solution calibrated at $\delta = 240.6$ ppm and the signal of encapsulated xenon in sensor 1 at $\delta = 75.2$ ppm. Notably, a new

signal at $\delta = 74.1$ ppm emerges and meanwhile, the signal at $\delta = 75.2$ ppm disappears after the addition of 10 equiv. HS⁻. Obviously, a chemical shift change of 1.1 ppm between the signals of caged xenon in the absence and presence of HS⁻ was observed (Figure 2). These results reveal that the response of sensor 1 towards HS⁻ lead to the chemical structure transformation, which can be detected and differentiated by hyperpolarized ¹²⁹Xe NMR.

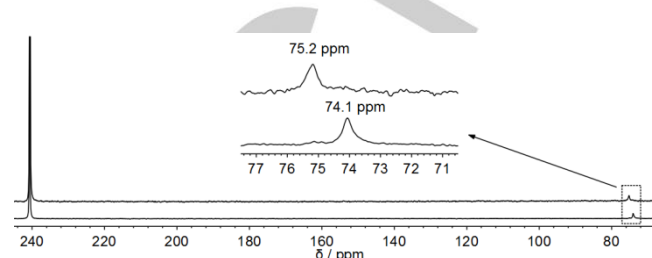


Figure 2. ¹²⁹Xe NMR spectrum change of sensor 1 (100 μM) upon addition of 10 equiv. of HS⁻. The spectra were obtained with two scans under the conditions of 20 mM HEPES (pH 7.4) buffer with 60% DMSO as cosolvent at 25 °C. The inset was the enlarged regional spectra.

The chemical shift changes are likely to be a consequence of azide reduction reaction induced by HS⁻. Azide group is an electron-withdrawing group and can be easily converted to an amino group by electron transfer. This chemical structure conversion alters the electronic density of the NMR moiety, causing a change in the electronic properties of cryptophane, leading to a chemical shift change for the caged xenon. These results clearly demonstrate that ¹²⁹Xe NMR is extremely sensitive to the chemical environment and can sense the structure transformation of sensor 1 induced by HS⁻. Based on the well-established azide reduction mechanism,^[22] the above results can be attributed to the formation of compound 1-NH₂, which is the product of sensor 1 with HS⁻ and also confirmed by HR-MS experiments (see Figure S3).

We then investigated the selectivity of sensor 1 for HS⁻ against various other species such as NO₂⁻, SO₃²⁻, S₂O₃²⁻, Ac⁻, CO₃²⁻, HCO₃⁻, P₂O₇⁴⁻, Cl⁻, SO₄²⁻, H₂PO₄⁻, SiO₃²⁻, OH⁻, HSO₃⁻, Hcy, GSH and Cys. As shown in Figure 3, it was found that only the addition of HS⁻ induced a significant chemical shift change in sensor 1 (see Figure S4). In contrast, addition of other analytes showed almost no significant chemical shift change. These results indicate that sensor 1 exhibits high selectivity for HS⁻ over other test species by hyperpolarized ¹²⁹Xe NMR technique. Furthermore, the selectivity of sensor 1 for H₂S was also probed via fluorescence method which also show high selectivity for HS⁻ (see Figure S5).

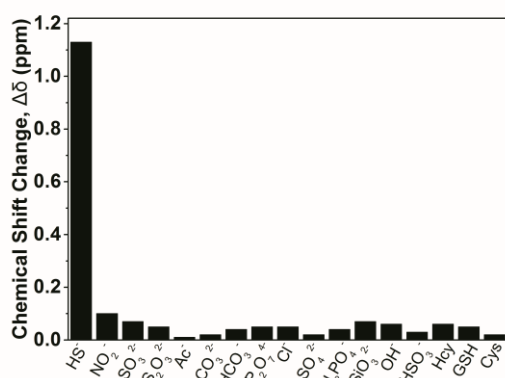


Figure 3. ^{129}Xe NMR chemical shift change of sensor 1 (100 μM) after addition of 10 equiv. various other species (except for Cys, which is 4 equivalent) for 10 min. Bars represent the value of the ^{129}Xe chemical shift in the presence of various other species relative to the ^{129}Xe chemical shift of sensor 1. All the spectra were obtained with two scans under the conditions of 20 mM HEPES (pH 7.4) buffer with 60% DMSO as cosolvent at 25 $^{\circ}\text{C}$.

Following the observation that sensor 1 exhibits high specificity for H_2S , an attempt was made to investigate the ^{129}Xe MRI property using a frequency-selective gradient echo sequence to verify the practical applicability *in vitro* (see Figure 4). A frequency-selective gradient echo sequence centered at 74.1 ppm was used to obtain the images of sensor 1 (A) without and (B) with HS^- . The difference between the two images illustrates that H_2S can be detected and localized by ^{129}Xe MRI.

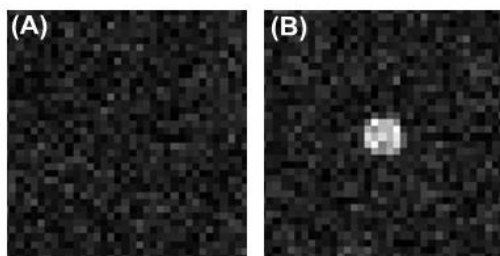


Figure 4. ^{129}Xe axial gradient-echo MRI images of a 10 mm tube containing (A) 100 μM sensor 1 and (B) 100 μM sensor 1 treated with 10 equiv. HS^- for 10 min under the test conditions. Images were acquired with a soft radiofrequency pulse centered at $\delta = 74.1$ ppm.

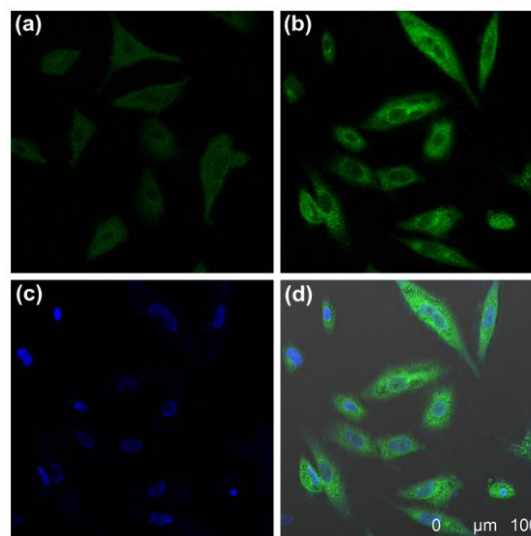


Figure 5. Confocal laser scanning microscope images of A549 cells incubated with sensor 1 (10 μM) for 2 h. (a) control experiment, A549 cells incubated with sensor 1 (10 μM) for 2 h; (b-d) NaHS (100 μM) pre-treated (0.5 h) A549 cells incubated with sensor 1 (10 μM) for another 2 h. (a,b) green channel, Emission was collected at 500. 650 nm upon excitation at 488 nm. (c) blue channel: nuclear staining (DAPI), Emission was collected at 408. 500 nm upon excitation at 405 nm. (d) merged images of (b) and (c). Scale bar = 100 μm .

Finally, we sought to explore the magnetic resonance imaging ability of sensor 1 for H_2S in living cells. The confocal laser scanning microscope was used to image H_2S and localize the sensor due to its high sensitivity and subcellular resolution. Strong fluorescence in A549 cells was observed after pretreatment with HS^- (100 μM) for 30 min and further incubation with sensor 1 (10 μM) for another 2 h (Figure 5). As a control, confocal microscope images of A549 cells incubated with sensor 1 (10 μM) in culture medium for 2 h at 37 $^{\circ}\text{C}$ showed weak fluorescence. As indicated by the strong intracellular green fluorescence, sensor 1 was found to be rapidly internalized by A549 cells and situated mainly in the cytoplasmic compartments. This result demonstrates that sensor 1 can respond to HS^- through azide reduction reaction in living cells. By way of the fluorescence method, H_2S in living cells assays were originally established and sensor 1 was confirmed to localize in the cytoplasm. We then used hyperpolarized ^{129}Xe NMR to detect H_2S and image the living cells at a concentration of 1×10^7 cells mL^{-1} . As shown in Figure 6a, no significant signal of caged xenon in living cells could be detected after pretreatment with HS^- (200 μM) for 0.5 h and further incubation with sensor 1 (25 μM) for another 2 h via direct acquisition of ^{129}Xe NMR signal (4096 signal averages). On the other hand, the same experiment of caged xenon detection in living cells using ^{129}Xe Hyper-CEST method in a direct bubbling phantom yielded a Hyper-CEST response centered at around 74.0 ppm (Figure 6b), a characteristic signal of cryptophane caged xenon. This signal was then used for imaging by using Hyper-CEST MRI (see Figure 6c and Figure S6). However, a Hyper-CEST response of caged xenon in A549 cells at around 74.0 ppm was also detected after incubation with sensor 1 (25 μM) for 2 h (see Figure S7a), while the blank experiment found no obvious

signals (see Figure S7b). This result indicates that the chemical shift of sensor 1 without H₂S in A549 cells is almost the same as that of sensor 1 with H₂S. It could be concluded that the chemical shift of sensor 1 with and without H₂S in living cells is hardly differentiated by Hyper-CEST spectrum presently.

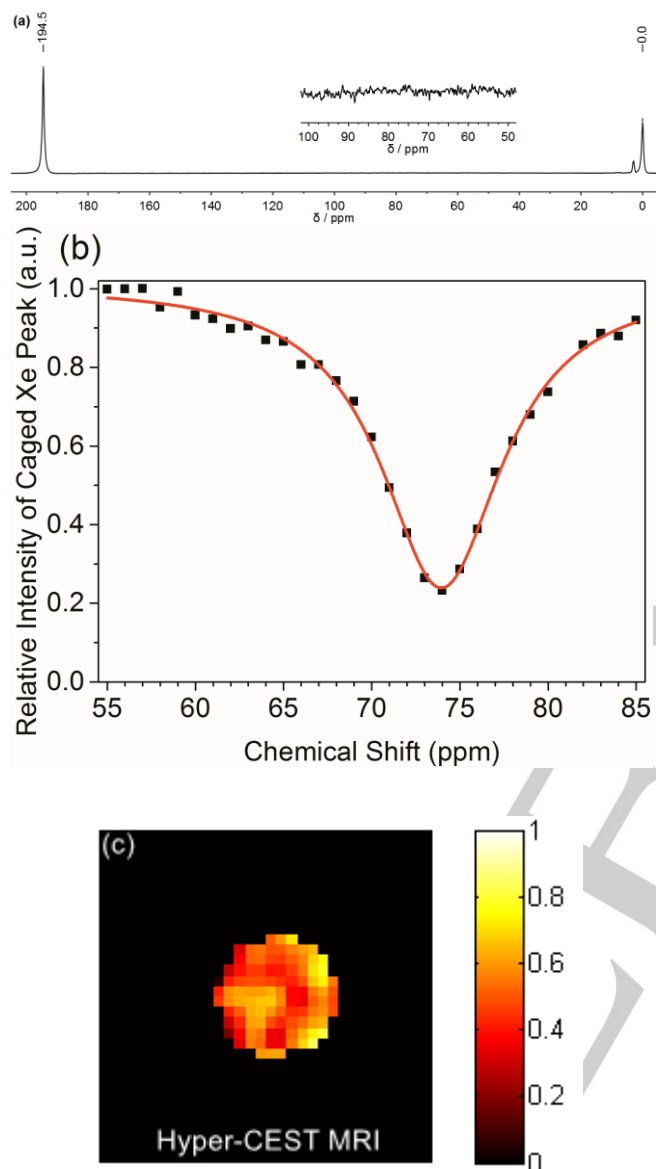


Figure 6. (a) ¹²⁹Xe NMR spectrum of sensor 1 labeled A549 cells (treated with 200 μM NaHS for 0.5 h then incubated with 25 μM sensor 1 for another 2 h) obtained by 4096 signal averages. (b) Hyper-CEST spectra of sensor 1 labeled A549 cells (treated with 200 μM NaHS for 0.5 h then incubated with 25 μM sensor 1 for another 2 h). Exponential fit (red solid line). (c) MRI of Hyper-CEST effect. The Hyper-CEST effect was calculated by using the formula CEST effect = (offRes - onRes) / offRes.

In conclusion, we have presented a ¹²⁹Xe sensor for molecular imaging utilizing hyperpolarized ¹²⁹Xe nuclear spin resonance. We constructed an azide reduction reaction-based ¹²⁹Xe sensor which is composed of modified cryptophane-A

derivative to report chemical information through the ¹²⁹Xe chemical shift. The azide group serves as a reaction site for the H₂S-specific response. This sensor exhibits a chemical shift change of 1.1 ppm (upfield) of caged xenon upon binding to H₂S. The response and cytoplasmic localization in living cells with and without H₂S are well supported by fluorescence and magnetic resonance data. By demonstrating that fluorescent H₂S probe can be converted into an MRI probe by linking to a xenon-binding cryptophane probably offers a universal strategy to analogical sensors.

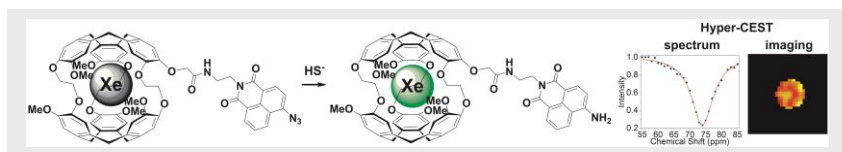
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Keywords: Hyperpolarized ¹²⁹Xe • Magnetic Resonance Imaging • Cryptophane • Hydrogen Sulfide

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Title: Hyperpolarized ^{129}Xe MRI Sensor for H_2S

A hyperpolarized ^{129}Xe magnetic resonance sensor was constructed for H_2S imaging utilizing hyperpolarized ^{129}Xe nuclear spin resonance, which provides a generalizable template for the conversion of fluorescence sensor to MRI sensor.