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Rational design of hyperpolarized xenon NMR molecular sensor for the selective and sensitive determination of zinc ions

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ABSTRACT

Although Zn^{2+} ions are involved in large numbers of physiopathological processes, non-invasive detection of Zn^{2+} ions in opaque biological samples remains a huge challenge. Here, we developed a novel zinc-responsive hyperpolarized (HP) ^{129}Xe-based NMR molecular sensor. This HP ^{129}Xe-based NMR molecular sensor was synthesized by attaching 2-(diphenylphosphino) benzenamine as ligand for zinc ions to the xenon-binding supramolecular cage, cryptophane. The ^{129}Xe NMR spectroscopy of such molecular sensor was shifted up to 6.4 ppm in the presence of Zn^{2+} ions, which was nearly four times larger than that of the reported similar sensor. The application of the sensor would benefit low concentration detection by using indirect NMR/MRI method. The response exhibited high sensitivity and selectivity as discriminated from other six potentially competing metal ions. The application of this sensor in the analysis of zinc ions in the rat serum samples was also evaluated. The strategy is generally applicable in developing sensitive and selective sensors for quantitative determination of zinc ions.

1. Introduction

Zinc is an essential trace element in the human body [1] and is the second most abundant transition metal in the living organisms [2]. Zn^{2+} ions not only constitute many enzymes [2] and proteins [3], but also play a key role in various physiological processes [4]. Either a deficiency or excess of Zn^{2+} ions will cause a physiological dysfunction of the organism. Thus, it is of great significance to develop a highly sensitive and specific method for the detection of Zn^{2+} ions.

There are many chemosensors for detection of Zn^{2+}, which are mostly based on quinoline, benzazole or fluorophores. However, the major chemosensors are unsuitable to offer real-time monitoring of the Zn^{2+} distribution in different tissues of the body. Moreover, NMR molecular sensors could provide a potential tool for detecting the Zn^{2+} ions in the living organisms because of its non-invasive and non-destructive their characters. However, the conventional NMR sensors are not as sensitive as most of their peers such as fluorescent sensors [5,6]. The application of NMR molecular sensors has been therefore limited by their intrinsic low sensitivity at thermal equilibrium. In contrast, the use of hyperpolarized ^{129}Xe based NMR molecular sensor suggests a possible solution [7]. The nuclear spin of the xenon atom can be hyperpolarized by a spin-exchange optical pumping (SEOP) technique [8–10], and the resulted nuclear spin polarization could be enhanced by four orders of magnitude in comparison to the Boltzmann polarization [11], leading to an amplification of the NMR sensitivity by a factor of 10,000 [12].

Cryptophanes are an important class of supramolecular hosts that can form stable inclusion complexes with small molecules [13–16], and cyrptophane-A is considered as one of the most suitable host molecules for xenon [17]. A Xe-cryptophane complex can be formed by self-assembly of xenon with a cryptophane, and the ^{129}Xe NMR spectra display two dramatically different chemical shifts for the encapsulated Xe and free Xe in solution [16]. As Xe has large, polarizable electron cloud, the chemical shift of encapsulated Xe was extremely susceptible to the surrounding environment. A Xe-based senso is usually formed by the combination of the cryptophane and a ligand via a molecular linker, and when the ligand interacts with the targeting molecule, it will affect the electron density experienced by the encapsulated Xe, resulting in the change of chemical shift. Therefore, hyperpolarized ^{129}Xe-based NMR molecular sensor could be an exceptional tool for the sensitive detection of targeting molecules. Such Xe-based sensor strategy has already been used for the detection of a variety of biological systems, including proteins [7], enzymes [18], nucleic acids [19], metal ions [20] and in-cell biological targets [21] 2-(diphenylphosphino) benzenamine and its derivatives are a group of ligands [22–24], which are able to chelate with zinc ions [22]. It is widely used as a highly efficient and selective ligand, due to its feasible preparation, stability in air, and great selectivity.

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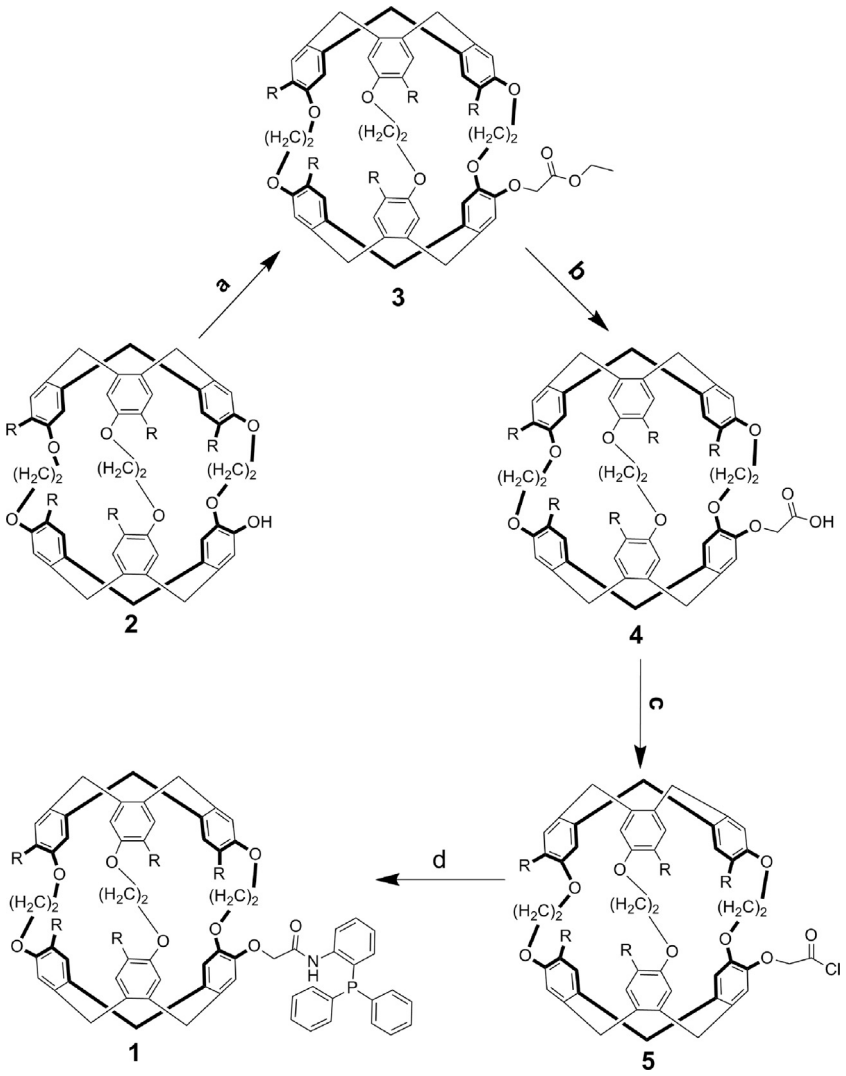

Scheme 1. Synthesis of HP ^{129}Xe-based NMR molecular sensor **1**. R=OCH_3. Conditions and reagents: (a) Br–$CH_2COOC_2H_5$, K_2CO_3, acetone, 56 °C, 5 h, 81%; (b) NaOH, THF, 66 °C, overnight, 95%; (c) $SOCl_2$, Et_3N, DCM, N_2, 39 °C, overnight; (d) $C_{18}H_{16}NP$, N_2, 25 °C, 12 h, 44%.

In this study, a HP ^{129}Xe-based NMR molecular sensor exploiting 2-(diphenylphosphino) benzenamine as a ligand for the capture of zinc ions was synthesized. The synthesized sensor was composed of a cryptophane moiety as a Xe-based NMR signal reporting part, 2-(diphenylphosphino)benzenamine as the chelating moiety, and a molecular linker (Scheme 1). The detection of Zn^{2+} ions by the new HP ^{129}Xe-based NMR molecular sensor was conducted, and the HP ^{129}Xe-based NMR molecular sensor responded to Zn^{2+} ions with a high selectivity. It is worth noting that the chemical shift difference of the encapsulated xenon is nearly four times larger than that of the reported similar sensor, which is important for the low concentration detection by using indirect NMR/MRI method, such as Hyper-CEST [25], and the feasibility of the application of the indirect NMR/MRI method has also been improved because of the largely enhanced chemical shift difference.

2. Experimental

2.1. Materials

2-(Diphenylphosphino) benzenamine was purchased from VsciChem™ Technology (Beijing) CO., Ltd. Thionyl chloride was purchased from Shanghai Jin Shan Ting Xin™ Chemical Reagent Factory. Deuterated toluene-d_8 was obtained from Landisville™ NJ Norell Inc. USA, and 1,1,2,2-tetrachloroethane was commercially available from Sinopharm™ Chemical Reagent Beijing Co., Ltd.

2.2. Apparatus

A tailor-designed xenon hyperpolarizer was used in this study [26]. The high performance liquid chromatographs (HPLC) were produced by the Scientific Software International. Inc. The ^{1}H NMR and ^{129}Xe NMR spectra were obtained with a Bruker™ AVANCE 500 spectrometer and Bruker™ AVANCE III 400 spectrometer, respectively, and the mass spectra were produced by a Bruker™ micrOTOFQ spectrometer.

2.3. Synthesis of sensor 1

2.3.1. Synthesis of compound *3*

To conjugate the alkyl linker to Cryptophane-Cage 2, 881 mg (1 mmol) compound **2** was dissolved in 30 mL acetone. Excess amounts of anhydrous potassium carbonate and ethyl bromoacetate were added to the solution, and the reaction was allowed to initiate and sustained with stirring and refluxing for 5 h, followed by a series of processes including cooling down to room temperature, filtering,