Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

A Sensitive Zinc-Activated ^{129}Xe MRI Probe**

Naoko Kotera, Nawal Tassali, Estelle Léonce, Céline Boutin, Patrick Berthault, Thierry Brotin, Jean-Pierre Dutasta, Léa Delacour, Ténin Traoré, David-Alexandre Buisson, Frédéric Taran, Sylvie Coudert, and Bernard Rousseau**

anie_201109194_sm_miscellaneous_information.pdf

Supporting Information

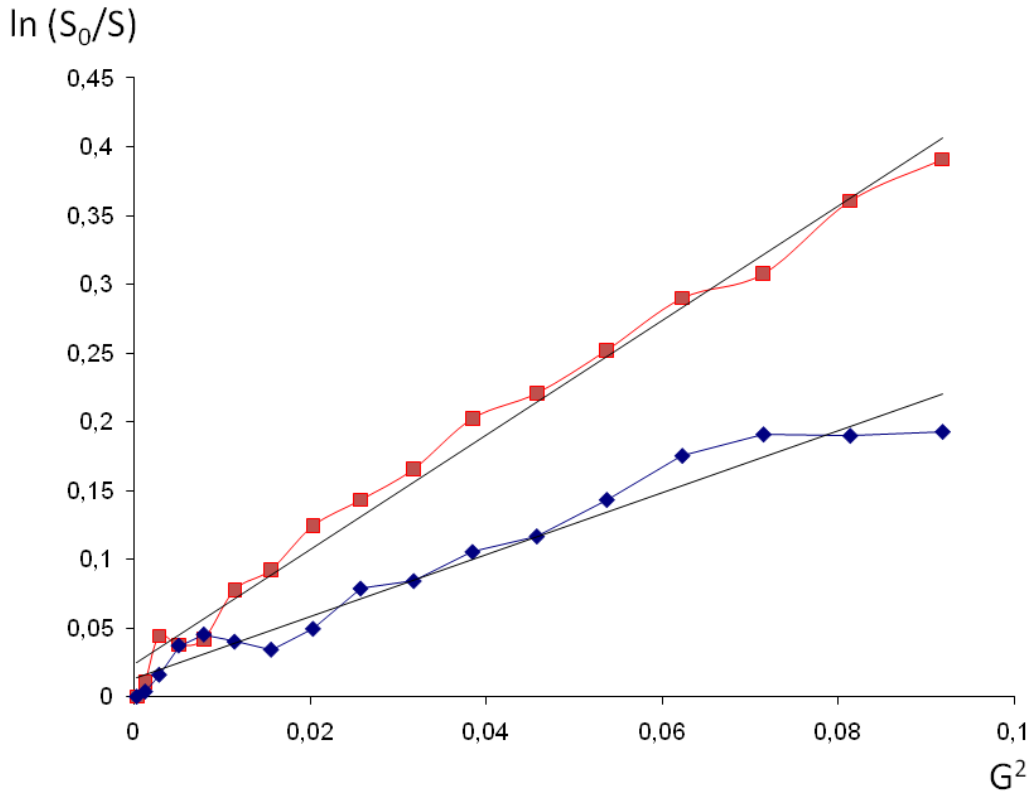


Figure S1: ^{1}H self-diffusion data obtained at 700 MHz, 298K with a stimulated spin echo sequence (sine gradients of duration 1 ms, inter-gradient delay 150 ms). The red squares were obtained for the sensor **1** in the absence of Zn, the blue diamonds for **1** with 50% Zn^{2+}.

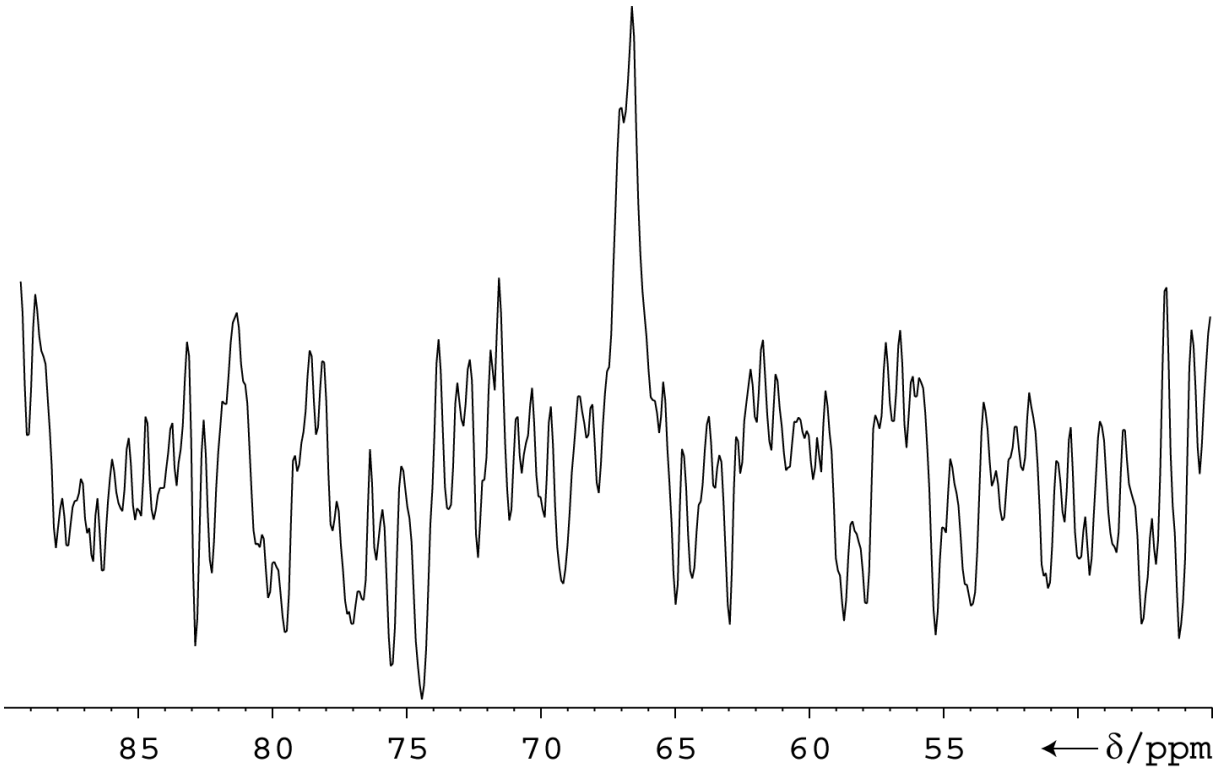


Figure S2: ^{129}Xe NMR spectrum (11.7 Tesla – 293K) of xenon encapsulated in cryptophane **1M** at a concentration of 194 nM in the presence of 50% Zn^{2+}. For this spectrum, the sequence {500 µs Gaussian pulse – Acquisition} has been repeated 3584 times with an interscan delay of 47ms. This experiment, performed with a unique addition of xenon into solution introduced by shaking, required only 2 min 50 s. The xenon polarization was estimated to 0.15.

Cryptophane nomenclature:

Using the *P* or *M* descriptors to characterize each cyclotribenzylene moieties, the two enantiomers of compound **2** and the two diastereomers of biosensor **1** can be named *PP*-**2**, *MM*-**2** and *PP(L)*-**1**, *MM(L)*-**1** respectively, the descriptor *L* being used for the NTA probe. For clarity, the diastereomers *PP(L)*-**1** and *MM(L)*-**1** are noted **1P** and **1M** in the text.

Synthesis of cryptophane 1P: N-hydroxysuccinimide (2.5 mg, 22 µmol) and N'-ethyl-N-dimethylaminopropylcarbodiimide (4.5 mg, 24 µmol) were added under argon atmosphere to a stirred solution of *PP*- **2** (25 mg, 22 µmol) in DMSO (0.5 mL). The mixture was stirred for 5 hours at room temperature. Then a solution of NTA linker (11.0 mg, 43 µmol) dissolved in DMSO (0.1mL) and triethylamine were added. The solution was then stirred for an additional 16 hours at room temperature. The excess of triethylamine was removed under reduced pressure. The solution was then directly injected for purification on preparative HPLC chromatography (Phenomenex Luna column. Size: 150x21.2, flow 21.2 mL/min, gradient: 95/5 to 50/50 H_2O/AcCN + 1%HCOOH) to give **1P** (4.8 mg, 16 %) as a white solid. From this experiment 5.6 mg (22 %) of the starting material *PP*- **2** were also recovered.

White solid. ^{1}H NMR (700 MHz, D_2O): δ 6.95-6.70 (m, 12 H), 4.72-4.29 (m, 27 H), 4.29-3.93 (m, 4H), 3.71-3.11 (m, 12 H), 1.86-1.62 (m, 2H), 1.62-1.47 (m, 2 H), 1.47-1.20 (m, 2 H).

HRMS-ES$^+$ (m/z) calcd for $C_{70}H_{71}N_2O_{29}$, 1403.4143 found 1403.4155 ($[M+H]^+$).

Synthesis of cryptophane 1M: Using the same experimental procedure cryptophane **1M** (3.9 mg**,** 12 %) was obtained after purification on HPLC chromatography from cryptophane *MM*-**2**. From this experiment *MM*-**2** (4.2 mg, 16 %) was also recovered.

White solid. ^{1}H NMR (700 MHz, D_2O/NaOD, pD=13): δ 6.96-6.69 (m, 12 H), 4.72-4.30 (m, 26 H), 4.30-3.98 (m, 4H), 3.51-3.35 (m, 6 H), 3.35-3.06 (m, 7 H), 1.64-1.48 (m, 4H), 1.31-1.18 (m, 2 H). ^{13}C DEPT NMR (175 MHz, D_2O): δ 118.4, 71.4, 61.0, 43.7, 39.6, 33.3, 28.2.

HRMS-ES$^+$ (m/z) calcd for $C_{70}H_{71}N_2O_{29}$, 1403.4143 found 1403.4091($[M+H]^+$).

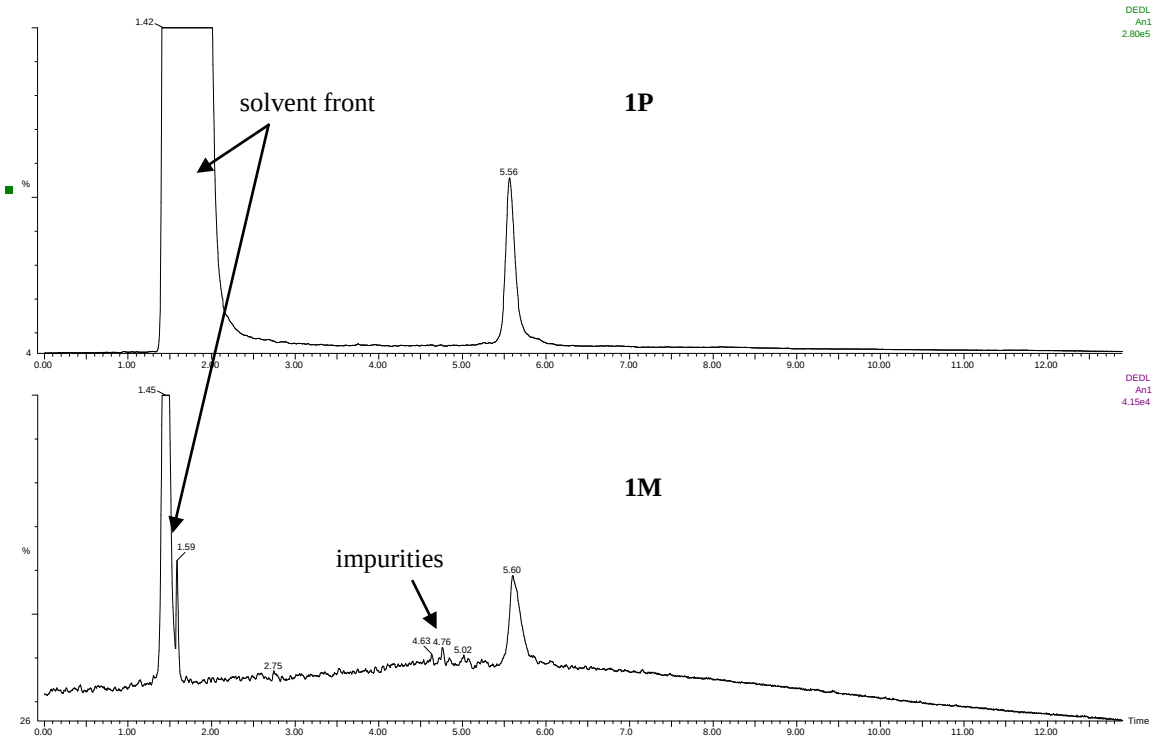
Synthesis of 1: Using the same experimental procedure **1** (3.8 mg**,** 12 %) was obtained after purification on HPLC chromatography from **2**. From this experiment **2** (4.2 mg, 16 %) was also recovered.

HPLC chromatograms of 1P, 1M:

Purity checked on C18 Column Gradient: 95/5 to 0/100 H_2O/AcCN + 1% HCOOH.

Retention time for **1P** : 5.56 min.

Retention time for **1M** : 5.60 min.

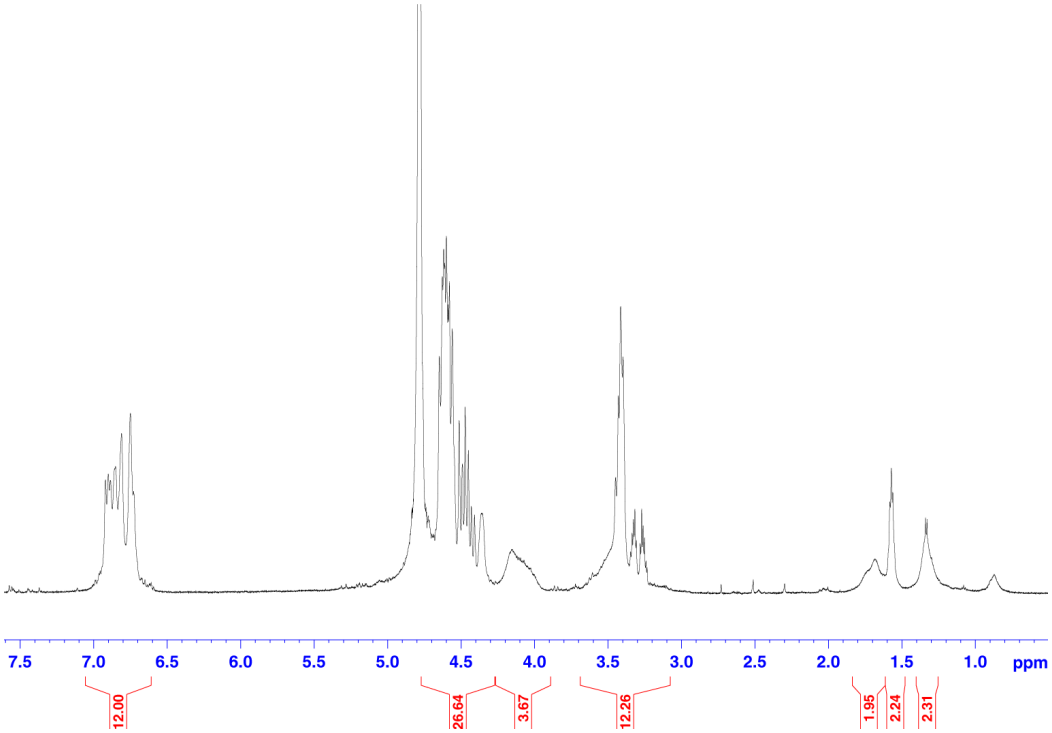


The chromatogram of **1P** shows one defined peak.
The chromatogram of **1M** shows some small peaks at the left of the major peak (in agreement with the hyperpolarized ^{129}Xe NMR spectrum). These impurities could not be removed and seem to correspond to minor conformers of the cryptophane.

NMR Spectra of 1P and 1M

Differences in spectra of **1P** and **1M** can be seen for the ^{1}H and ^{13}C of the NTA linker. The variation of the chemical shifts of the protons can be easily explained by the difference of pH in the two solutions.

^{1}H NMR Spectrum of **1P**



^{1}H NMR Spectrum of **1M**