A Fluorescent Heteroditopic Hemicryptophane Cage for the Selective Recognition of Choline Phosphate

Dawei Zhang,[a,b] Guohua Gao,*[a] Laure Guy,[b] Vincent Robert,[c] Alexandre Martinez,*[b,d] Jean-Pierre Dutasta*[b]

[a] *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai, 200062, P. R. China. E-mail: ghgao@chem.ecnu.edu.cn*

[b] *Laboratoire de Chimie, CNRS, École Normale Supérieure de Lyon, 46, Allée d'Italie, F-69364 Lyon, France. E-mail: jean-pierre.dutasta@ens-lyon.fr; alexandre.martinez@ens-lyon.fr*

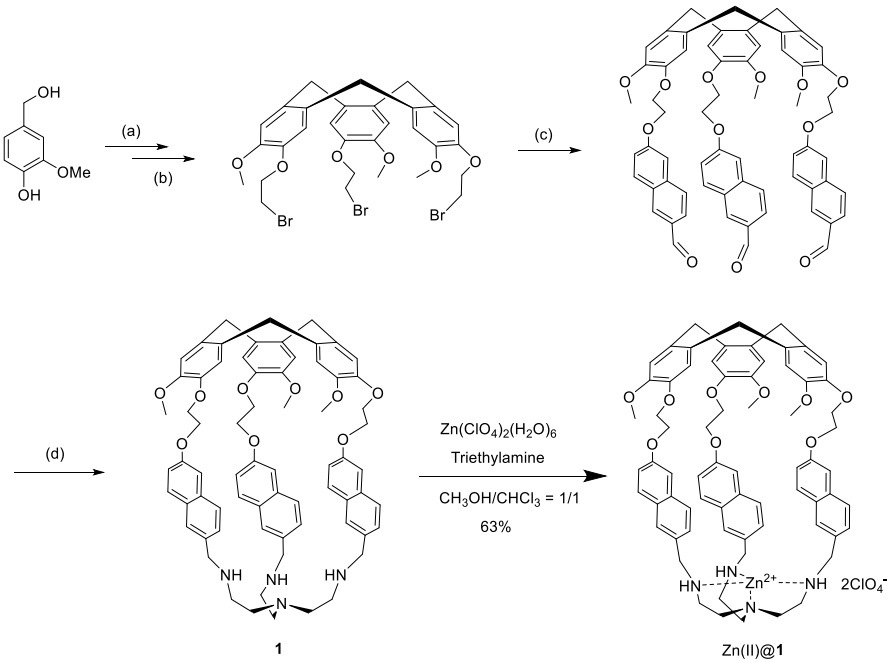
[c] *Laboratoire de Chimie Quantique Institut de Chimie, UMR CNRS 7177, Université de Strasbourg, 4, rue Blaise Pascal, F-67070 Strasbourg, France*

[d] *Equipe Chirosciences, UMR CNRS 7313-iSm2, Aix Marseille Université, Ecole Centrale de Marseille, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20 (France)*

1. Materials and instrumentation

All solvents used were of commercial grade. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer operating at 500.10 MHz and 125.76 MHz for ^{1}H NMR and ^{13}C NMR spectra, respectively. ^{1}H NMR chemical shifts (δ) are reported in ppm and referenced to the protonated residual solvent signal. Fluorescence spectra were carried out with a Horiba-Jobin Yvon spectrofluorimeter. Mass spectra were recorded by the Centre de Spectrométrie de Masse, Institute of Chemistry, Lyon.

2. Synthesis



(a) 1,2-dibromoethane, K_2CO_3, EtOH, 50 °C, 50% (b) $Sc(OTf)_3$, CH_2Cl_2, reflux, 23%, (c) 6-hydroxy-2-naphthaldehyde, Cs_2CO_3, 40 °C, 83%;(d) tris(2-aminoethyl)amine, $CHCl_3$/MeOH, rt., 1 night, $NaBH_4$, 3h, 42%.

Scheme S1. The synthesis of Zn(II)@**1** complex.

Hemicryptophane **1** was synthesized according to our previously reported procedure.[1] Zn(II)@**1** complex was prepared as follow: to a solution of **1** (90.3 mg, 0.082 mmol) in 6 mL $CHCl_3$, 20 µL triethylamine was added under argon followed by addition of the solution of $Zn(ClO_4)_2(H_2O)_6$ (30.5 mg, 0.082 mmol, 1.0 equivalent) in 6 mL CH_3OH. After stirring the reaction mixture at room temperature for 2 hours, a large amount of precipitate appeared. The precipitate was collected, washed thoroughly with Et_2O and dried under vacuum to give the

final product as a white solid (70.8 mg, yield 63%). The ligand **1** is soluble in most of the common solvents, for example CH_2Cl_2, $CHCl_3$, acetone and DMSO. However, the Zn(II)@**1** complex is only soluble in DMSO, and moderate soluble in acetone.

Ligand 1:

^{1}H NMR (500.1 MHz, 298 K, $CDCl_3$) δ 7.33 (d, 3H, J = 8.4 Hz); 7.16 (d, 3H, J = 8.3 Hz); 7.13 (s, 3H); 7.07 (s, 3H); 7.00 (d, 3H, J = 9.0 Hz); 6.92 (s, 3H); 6.89 (s, 3H); 6.56 (d, 3H, J = 8.6 Hz); 4.84 (d, 3H, J = 13.8 Hz); 4.58-4.61 (m, 3H); 4.39-4.43 (m, 3H); 4.25 (t, 6H, J = 4.90 Hz); 3.69 (s, 9H); 3.65 (d, 3H, J = 13.3 Hz); 3.63 (d, 3H, J = 13.7 Hz); 3.53 (d, 3H, J = 13.3 Hz); 2.54-2.69 (m, 12H).

^{13}C NMR (125.7 MHz, 298 K, $CDCl_3$) δ 156.8, 148.7, 146.5, 133.6, 133.2, 131.9, 129.3, 128.9, 127.2, 126.9, 126.5, 119.4, 116.7, 113.7, 107.3, 67.6, 67.5, 56.0, 52.9, 47.7, 36.7.

ESI-MS m/z: found 1101.5350 $[M+H]^+$; calcd for $C_{69}H_{73}N_4O_9$: 1101.5372.

IR $\bar{\upsilon}$ = 2931, 1606, 1508, 1263 cm^{-1}.

M.p. > 310 °C (decomp.).

Zn(II)@1 complex:

^{1}H NMR (500.1 MHz, 298 K, DMSO-d_6) δ 7.43-7.63 (broad, 12H); 7.20 (s, 3H); 7.05-7.11 (broad, 9H); 4.66 (d, 3H, J = 13.3 Hz); 4.21-4.43 (broad, 12H); 4.03 (broad, 3H); 3.93 (broad, 3H); 3.69 (s, 9H); 3.47 (d, 3H, J = 13.4 Hz); 2.96-3.18 (broad, 12H).

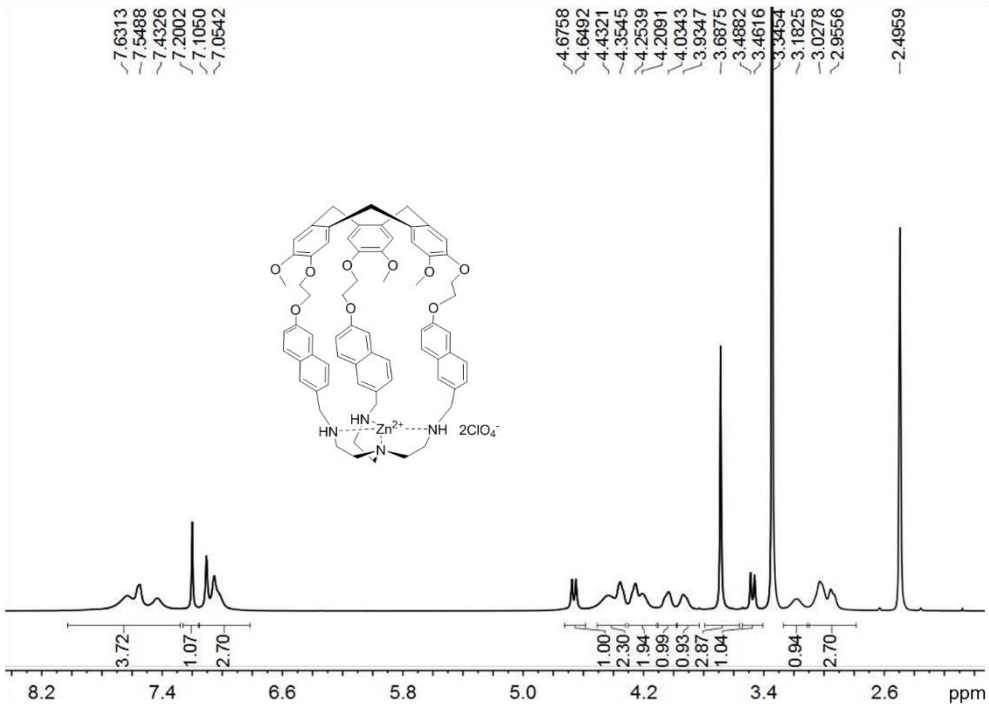
^{1}H NMR (500.1 MHz, 373 K, DMSO-d_6) δ 7.57 (bs, 9H); 7.32 (bs, 3H); 7.03-7.10 (m, 12H); 4.68 (d, 3H, J = 13.5 Hz); 4.28 (bs, 12H); 3.88 (bs, 6H); 3.70 (s, 9H); 3.50 (d, 3H, J = 13.5 Hz); 2.97 (bs, 12H).

^{13}C NMR (125.7 MHz, 298 K, DMSO-d_6) δ 156.6, 148.4, 146.5, 133.9, 133.0, 132.0, 129.4, 128.4, 127.4, 119.3, 116.4, 107.4, 66.9, 66.3, 57.2, 54.6, 51.0, 49.4, 35.4.

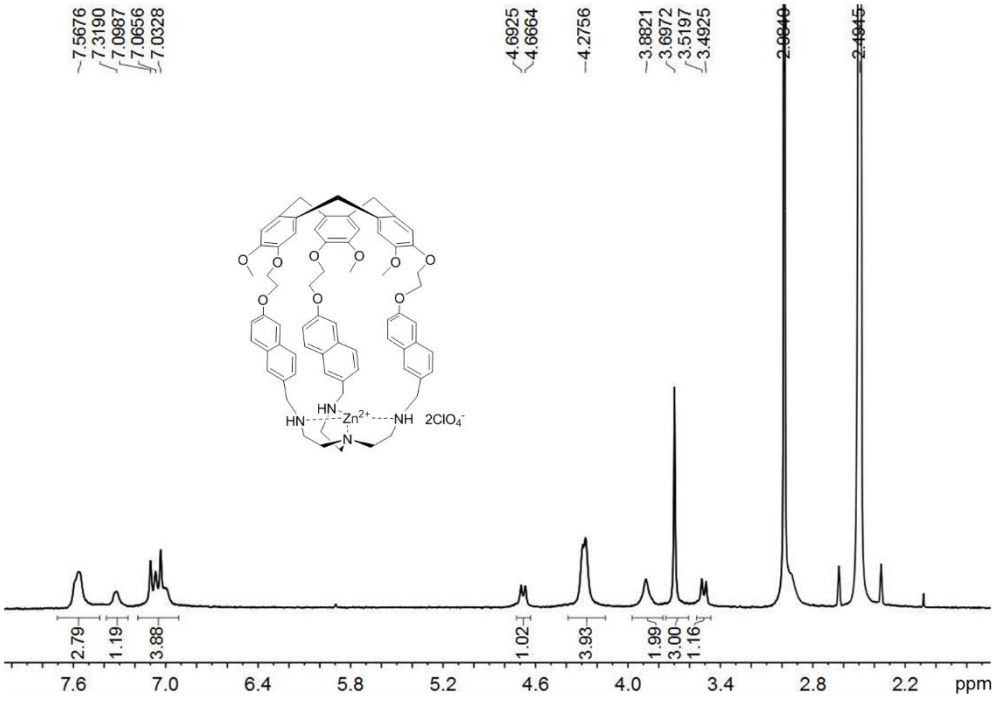
ESI-MS m/z: found 1199.4224 $[M^{2+} + Cl^-]^+$; calcd for $C_{69}H_{73}N_4O_9$: 1199.4274.

IR $\bar{\upsilon}$ = 3237, 2934, 1612, 1507, 1483, 1263, 1218, 1282, 1085 cm^{-1}.

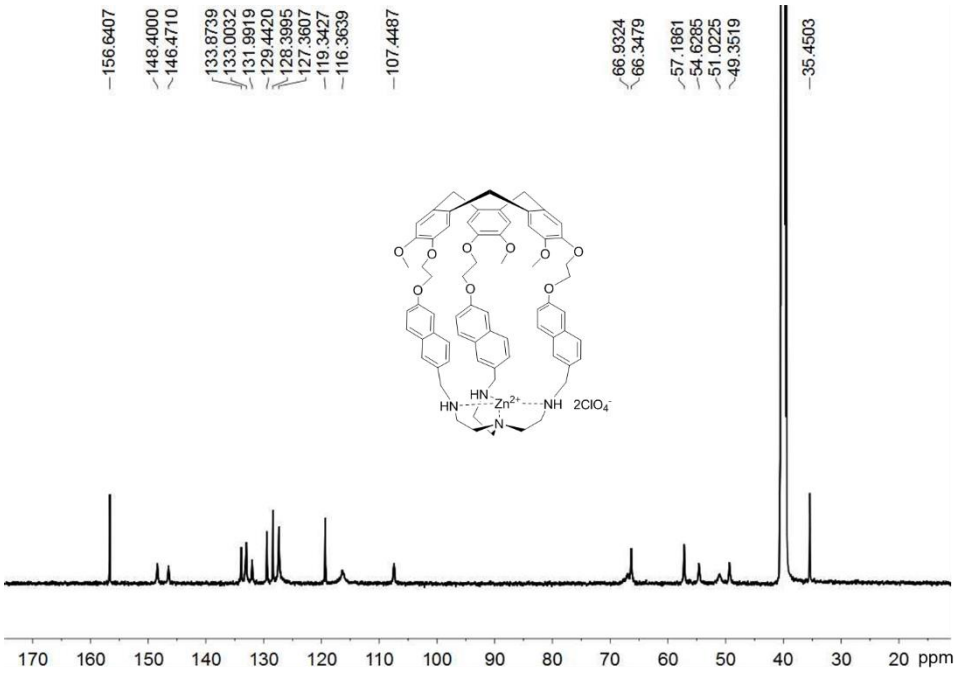
M.p. > 350 °C (decomp.).



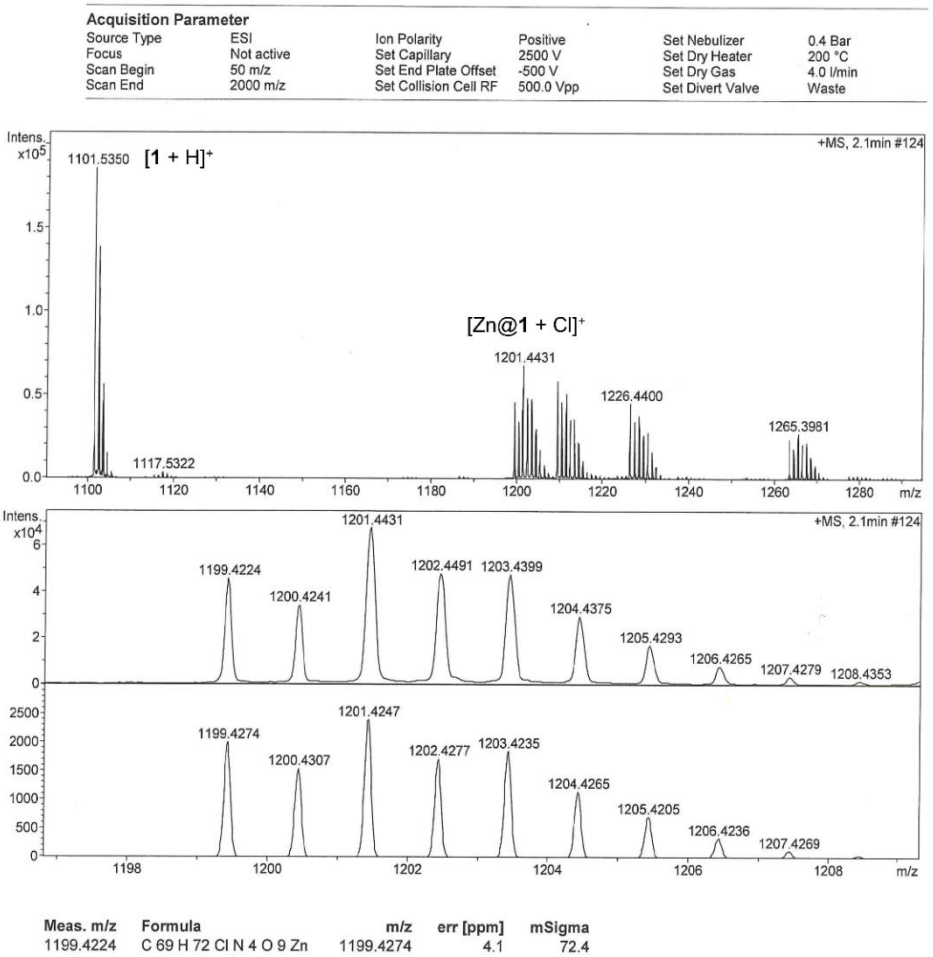
^{1}H NMR spectrum (DMSO-d_6, 500.1 MHz, 298K) of the Zn(II)@**1** complex.



^{1}H NMR spectrum (DMSO-d_6, 500.1 MHz, 373K) of the Zn(II)@**1** complex.



^{13}C NMR spectrum (DMSO-d_6, 125.7 MHz, 298K) of the Zn(II)@**1** complex.



ESI-MS spectrum of the Zn(II)@**1** complex.

3. Fluorescence Job plot

The continuous variation method was used for determining the binding stoichiometry.[2] In this method, solutions of the host and guest at the same concentration (5μM) were prepared in DMSO containing 2% H_2O. Then the two solutions were mixed in different proportions maintaining a total volume of 3 mL and a total concentration of 5 μM. After incubating the mixture for 30 s, the spectra of the solutions for different compositions were recorded.

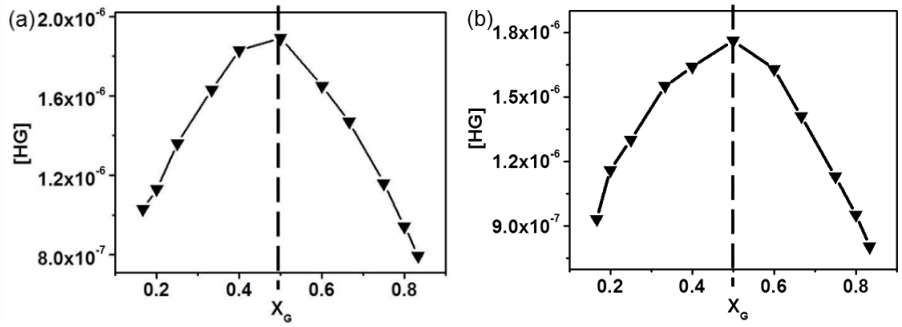


Fig. S1 Fluorescence Job plot of Zn(II)@**1** with choline phosphate **2** (a) and choline **3** (b).

4. Fluorescence spectroscopic titration

2 mL Zn(II)@**1** complex solution (5μM) was taken into the cuvette, and then certain equivalents of a concentrated guest solution (0.5 mM or 5 mM) were added stepwise with a syringe. As a very small volume of guest solution was added, the final amount of the solution was almost unchanged (2 mL). The mixed solution was incubated for 30 s and then irradiated at 300 nm. The corresponding emission values at 350 nm during titration were then recorded.

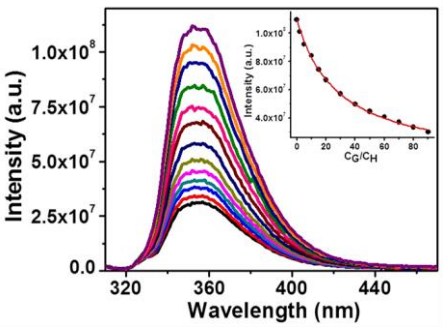


Fig. S2 Fluorescence titrations of 5 μM Zn(II)@**1** with choline **3** excited at 300 nm in DMSO containing 2% water. Inset: the intensity at 350 nm as a function of the added choline **3**.

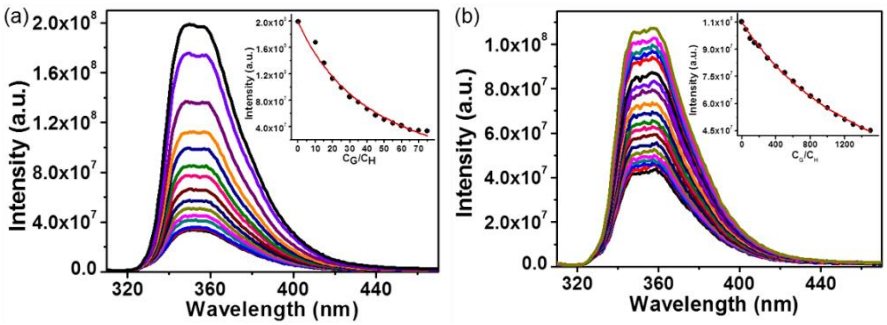


Fig. S3 Fluorescence titrations of 5 μM Zn(II)@**1** with choline phosphate **2** (a) and choline **3** (b) excited at 300 nm in DMSO/H_2O (80/20, v/v). Inset: the intensity at 350 nm as a function of the guest.

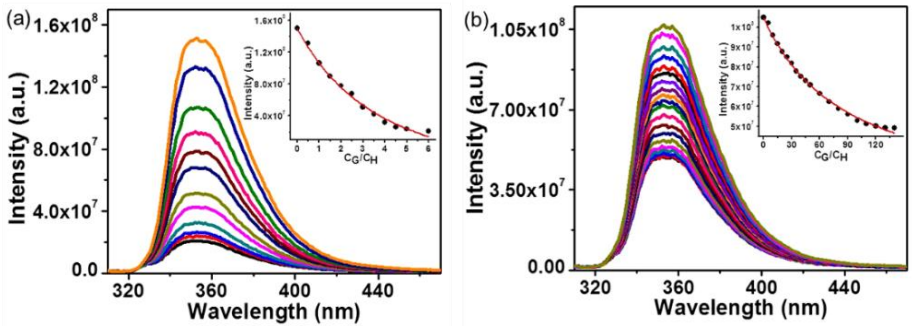


Fig. S4 Fluorescence titrations of 5 μM Zn(II)@**1** excited at 300 nm with guest **4** (a) and guest **5** (b) in DMSO containing 2% water. Insets: the intensity at 350 nm as a function of the guest.

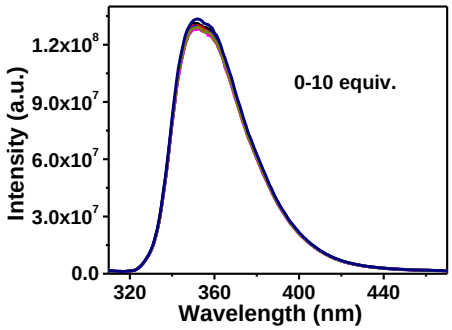


Fig. S5 Fluorescence titrations of 5 μM Zn(II)@**1** excited at 300 nm with taurine **6** in DMSO containing 2% water.

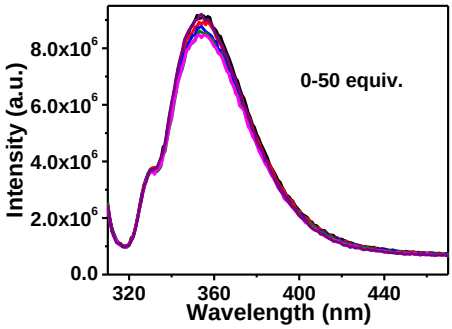


Fig. S6 Fluorescence titrations of 5 μM ligand **1** excited at 300 nm with choline phosphate **2** in DMSO containing 2% water.

5. ^{1}H NMR spectroscopic titration

0.5 mL Zn(II)@**1** complex solution was taken into the NMR spectroscopy tube, and then certain equivalents of a concentrated guest solution were added stepwise with a syringe. As a very small volume of guest solution was added, the final amount of the solution was almost unchanged (0.5 mL). The mixed solution was incubated for 30 s and then the measurement of ^{1}H NMR spectroscopy of the solution was performed.

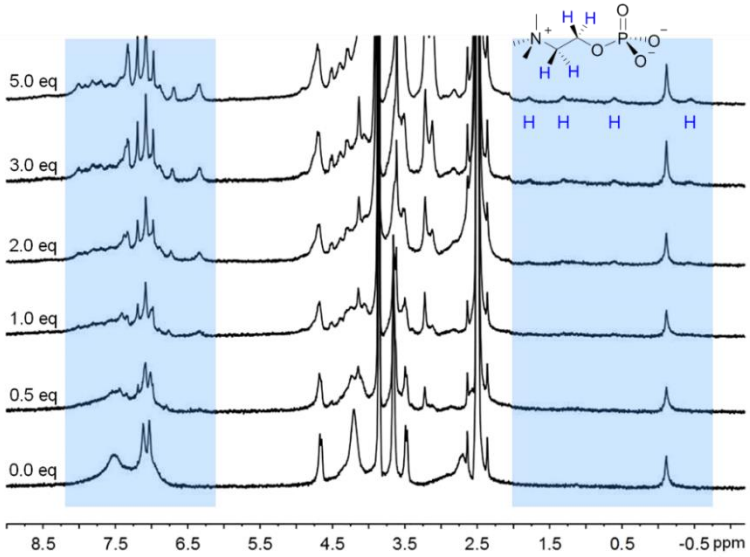


Fig. S7 ^{1}H NMR titrations of 1 mM Zn(II)@**1** with choline phosphate **2** at 298 K in DMSO-d_6/D_2O (80/20, v/v). H atoms in blue are attributed to the four diastereotopic protons of the encaged **2**.

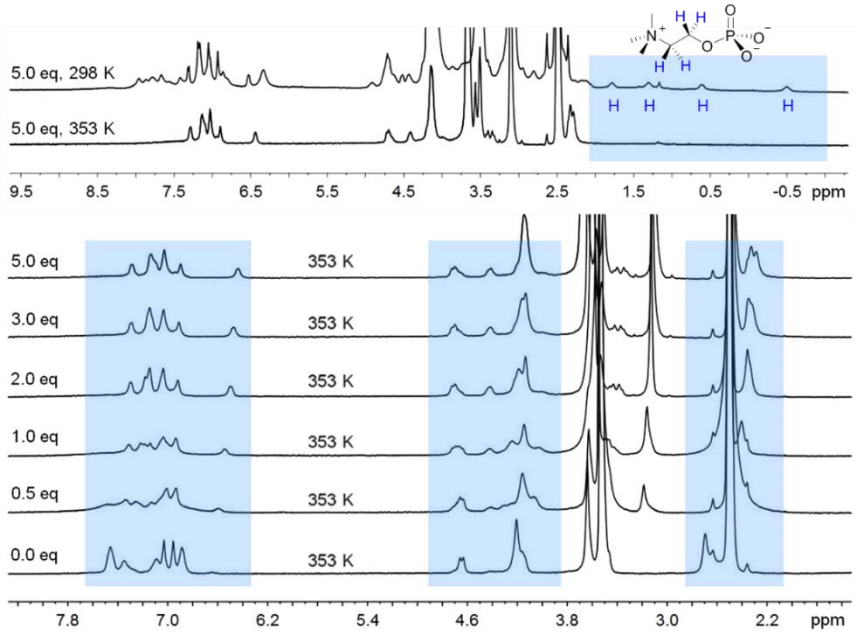


Fig. S8 ^{1}H NMR titrations of 1 mM Zn(II)@**1** with choline phosphate **2** at 353 K and then return to 298 K in DMSO-d_6/D_2O (80/20, v/v).

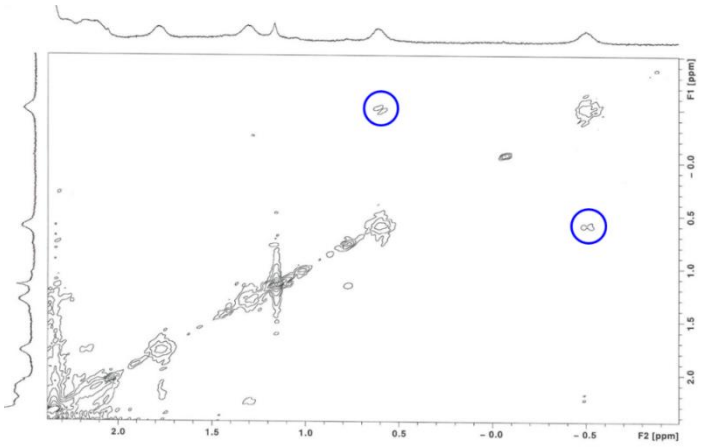


Fig. S9 The up-field region of the 2D COSY NMR spectrum for the mixture of Zn(II)@**1** and 5 equiv. of choline phosphate **2** in DMSO-d_6/D_2O (80/20, v/v).

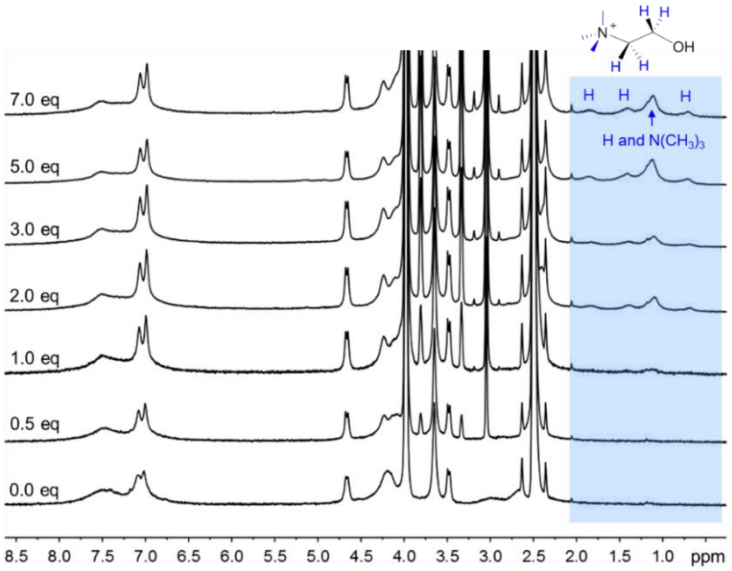


Fig. S10 ^{1}H NMR titrations of 1 mM Zn(II)@**1** with choline **3** at 298 K in DMSO-d_6/D_2O (80/20, v/v). H atoms in blue are attributed to the diastereotopic protons of methylene and $N(CH_3)_3$ of the encaged **3**.

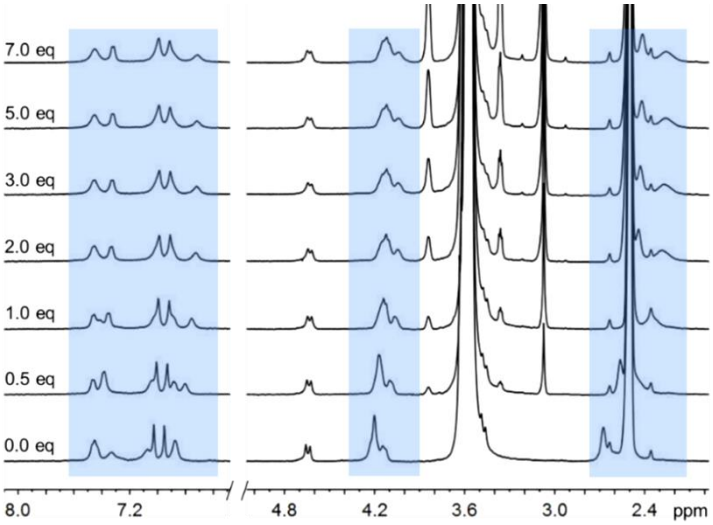


Fig. S11 ^{1}H NMR titrations of 1 mM Zn(II)@**1** with choline **3** at 353 K in DMSO-d_6/D_2O (80/20, v/v).

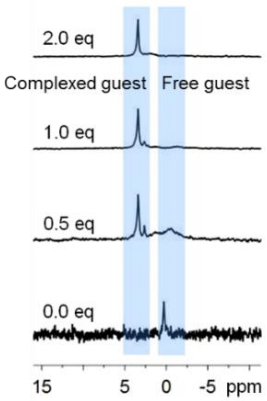


Fig. S12 ^{31}P NMR titrations of 1 mM choline phosphate **2** with Zn(II)@**1** at 298 K in DMSO-d_6/D_2O (80/20, v/v).

6. Computational method

Ab initio evaluations were performed using the Gaussian 03 package17 within a restricted DFT framework.[3] In order to access geometrical information upon the host-guest species, full geometry optimizations were performed using DFT calculations. A combination of BP86 function and an all electron 6-31G* basis set including polarization functions has proven to be very satisfactory for similar issues.[4] We checked using the hybrid B3LYP function that our results do not suffer from the arbitrariness of the exchange correlation function.

7. Reference

[1] (a) B. Chatelet, E. Payet, O. Perraud, P. Dimitrov-Raytchev, L.-L. Chapellet, V. Dufaud, A. Martinez and J.-P. Dutasta, *Org. Lett.*, 2011, **13**, 3706; (b) O. Perraud, J.-B. Tommasino, V. Robert, B. Albela, L. Khrouz, L. Bonneviot, J.-P. Dutasta and A. Martinez, *Dalton Trans.*, 2013, **42**, 1530.

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[3] Gaussian 03: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Jr. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M.

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[4] O. Perraud, V. Robert, A. Martinez and J.-P. Dutasta, *Chem. Eur. J.*, 2011, **17**, 13405.