

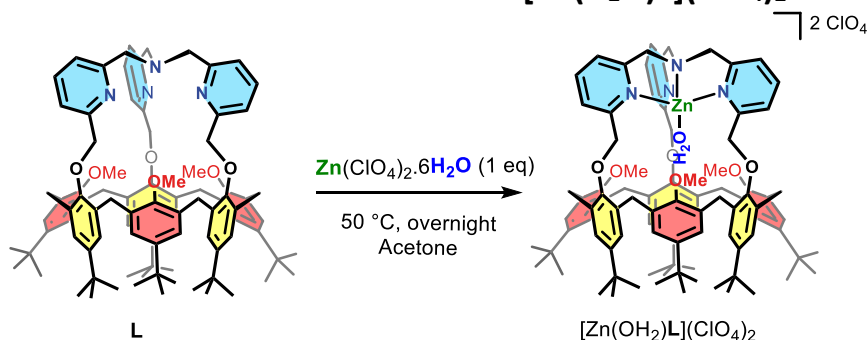
Supplementary Information

Guest exchange in a biomimetic Zn^{II} cavity-complex: kinetic control by a catalytic water, through pore selection, 2nd sphere assistance, and induced-fit processes

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Synthetic procedure and characterization of [Zn(H₂O)L](ClO₄)₂



L (17.5 mg, 1 eq) and Zn(ClO₄)₂·6H₂O (4.9 mg, 1 eq.) were dissolved in acetone (2 mL) under Ar and heated at 50 °C overnight. The complexation was followed by ¹H NMR spectroscopy. The mixture was evaporated, the residue dissolved in CHCl₃ and filtrated through a syringe filter. The filtrate was evaporated and the solid washed with pentane (5 mL) to yield a colorless solid (20.2 mg, 95 %).

¹H NMR (500 MHz, acetone-d₆, 300 K) δ 8.49 (t, $J = 7.8$ Hz, 3H, H_{py}), 8.41 (d, $J = 7.7$ Hz, 3H, H_{py}), 7.90 (d, $J = 7.7$ Hz, 3H, H_{py}), 7.45 (s, 6H, H_{Ar}), 7.31 (s, 6H, H_{Ar}), 5.65 (s, 6H, OCH₂), 4.82 (s, 6H, NCH₂), 4.38 (d, $J = 14.6$ Hz, 6H, ArCH_{ax}), 3.49 (d, $J = 14.6$ Hz, 6H, ArCH_{eq}), 3.12 (s, 9H, OMe), 1.32 (s, 27H, tBu), 1.15 (s, 27H, tBu).

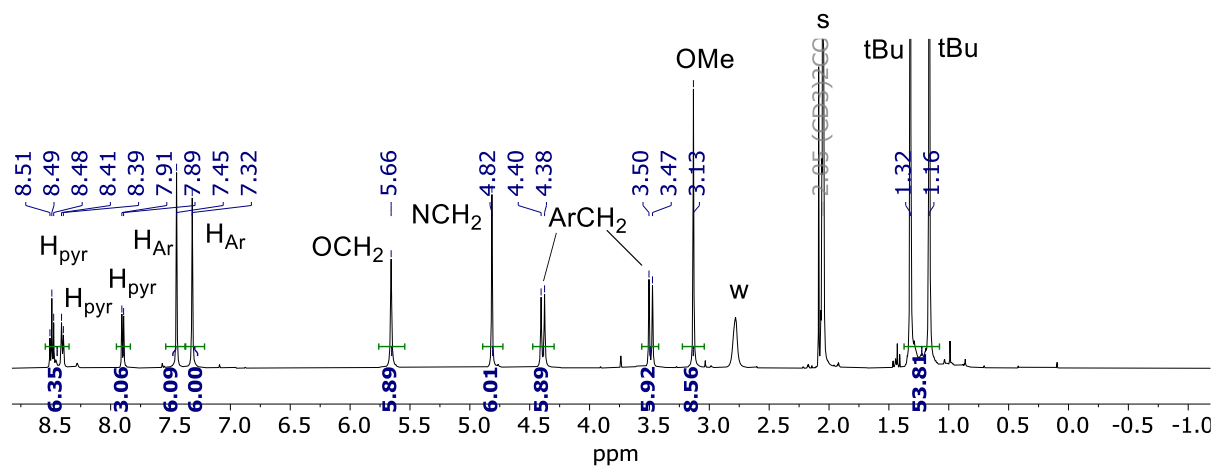


Figure S1. ^1H NMR spectrum (500 MHz, 300 K) of $[\text{Zn}(\text{H}_2\text{O})\text{L}](\text{ClO}_4)_2$ in acetone- d_6 .

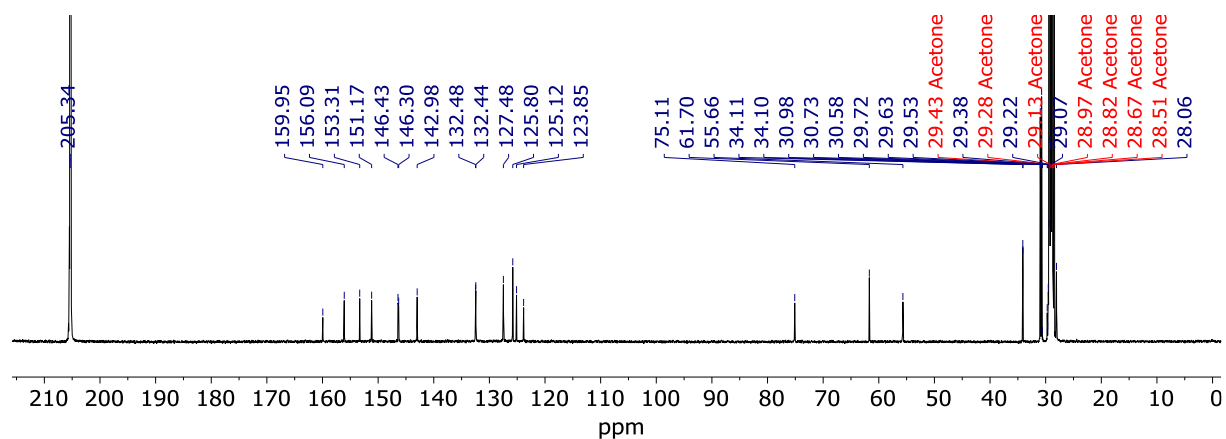


Figure S2. ^{13}C NMR spectrum (126 MHz, 300 K) of $[\text{Zn}(\text{H}_2\text{O})\text{L}](\text{ClO}_4)_2$ in acetone- d_6 .

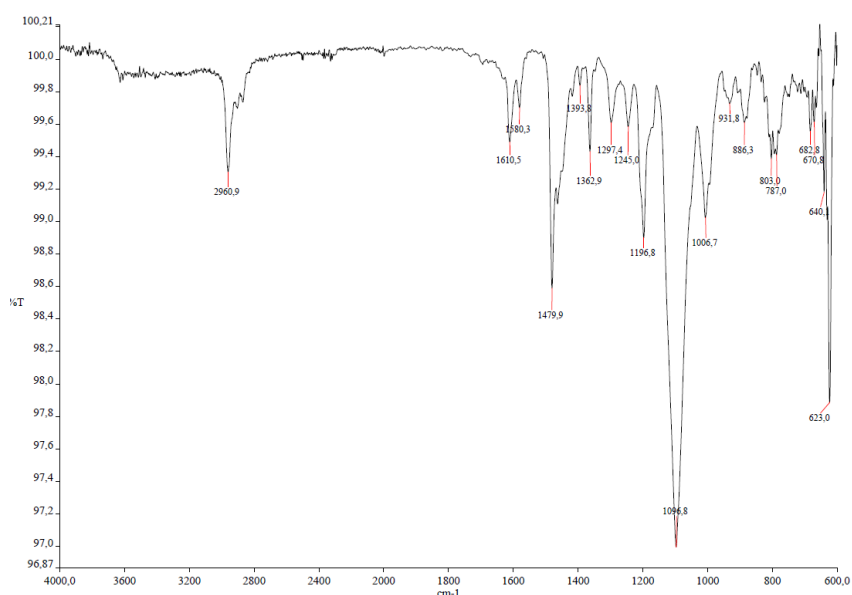


Figure S3. IR spectrum of $[\text{Zn}(\text{H}_2\text{O})\text{L}](\text{ClO}_4)_2$ (solid deposition). The relative integration of the 1363 cm^{-1} (characteristic of the calixarene core) and 623 cm^{-1} (ClO_4^-) bands reveals the presence of 2 ClO_4^- .

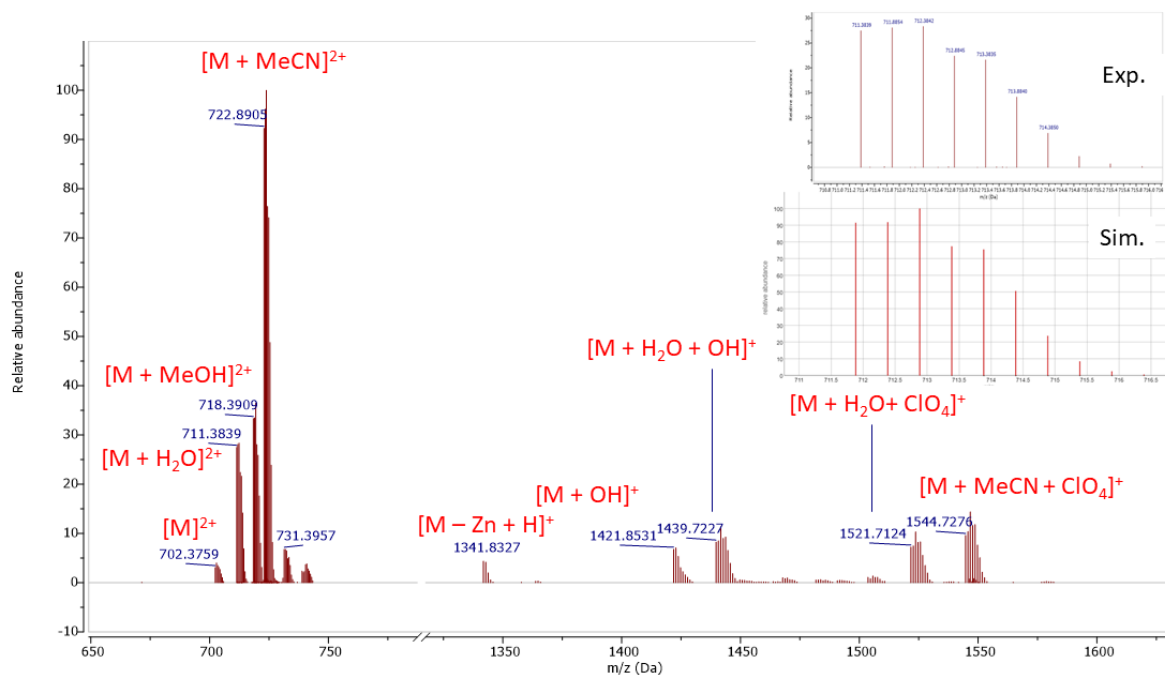
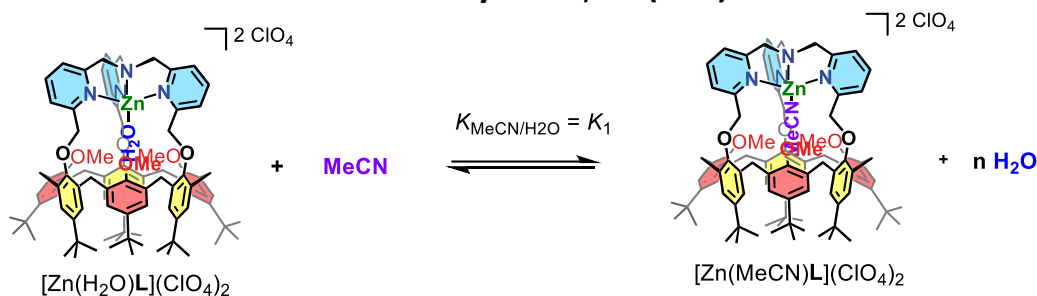


Figure S4. ESI-HRMS of $[\text{Zn}(\text{H}_2\text{O})\text{L}](\text{ClO}_4)_2$ (in acetone): m/z ($M = [\text{Zn L}] = \text{C}_{90}\text{H}_{108}\text{ZnN}_4\text{O}_6 = \text{calc. } 1404.75602$): 711.38392 ($[\text{M}+\text{H}_2\text{O}]^{2+}$ calc. 711.38275), 1421.75822 ($[\text{M}-\text{H}+\text{H}_2\text{O}]^+$ calc. 1421.85307), 1439.7227 ($[\text{M}-\text{H}+2\text{H}_2\text{O}]^+$ calc. 1439.7688), 1521.71242 ($[\text{M}+\text{H}_2\text{O}+\text{ClO}_4]^+$ calc. 1521.71456). Inset: Experimental and simulated isotopic profile of $[\text{M}+\text{H}_2\text{O}]^{2+}$.

Note: the presence of the MeCN complex stems from traces of MeCN inevitably present in the mass spectrometer, even after long washing, and is due to the very high affinity of MeCN for metal complexes based on ligand **L**.

Determination of the relative affinity $K_{\text{MeCN}/\text{H}_2\text{O}} (= K_1)$



$$\text{With: } K_1 = K_{\text{MeCN}/\text{H}_2\text{O}} = \frac{[\text{Zn}(\text{MeCN})\text{L}]^{2+} \times [\text{H}_2\text{O}]^n}{[\text{MeCN}] \times [\text{Zn}(\text{H}_2\text{O})\text{L}]^{2+}}$$

A solution of complex $[\text{Zn}(\text{MeCN})\text{L}](\text{ClO}_4)_2$ in acetone- d_6 was titrated with aliquots of water. The relative amount of each species present in solution was determined by integration of several peaks characteristic of these species, knowing the absolute amount of MeCN added to the solution.

By plotting $\{[\text{MeCN}] \times [\text{Zn}(\text{H}_2\text{O})\text{L}]^{2+}\}$ as a function of $\{[\text{Zn}(\text{MeCN})\text{L}]^{2+} \times [\text{H}_2\text{O}]^n\}$ at different concentrations of water, the linearity is obtained for $n = 1$ whereas for $n = 2$ no fit is obtained (*vide infra*). This shows an exchange process involving only one molecule of water and the corresponding $K_{\text{MeCN}/\text{H}_2\text{O}} = 200 \pm 12$. This value also highlights the higher affinity of the complex for MeCN compared to water.

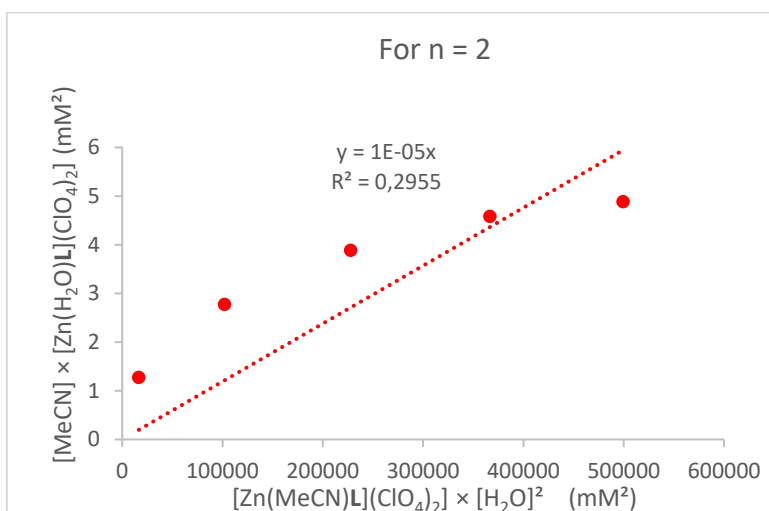
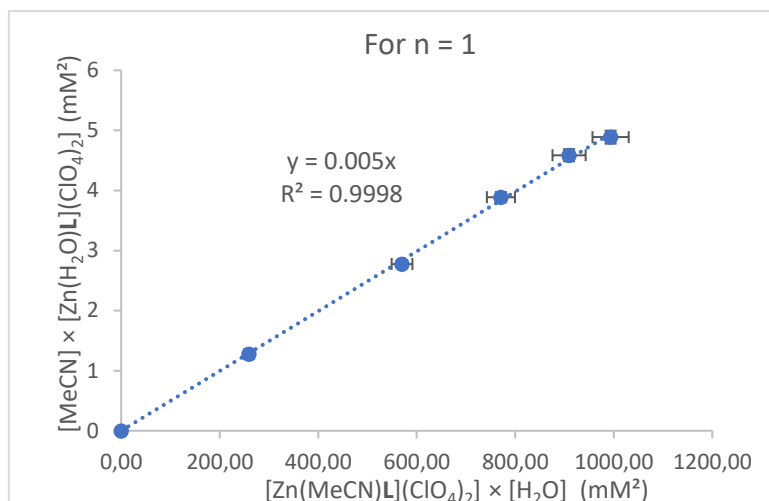


Figure S5. Determination of K_1 at different concentrations of water for $n = 1$ (Top) or $n = 2$ (Bottom).

Kinetic measurements for the MeCN/EtCN guest exchange process inside the cavity of $[Zn(G)L]^{2+}$

The concentration of initial Zn complex is obtained by preparing a stock solution of the complex by weighing the mass of the solid and then the mass of the acetone d-6 in which it is solubilized. A portion of that solution is taken (usually around 500-600 μ L) and put into a pre-weighed NMR tube. The exact volume of liquid into the NMR tube is obtained by weighing the filled NMR tube. The concentrations of water, bound and free EtCN are obtained by integration of the signals and compared to the integration of total Zn complex in solution. The concentration of MeCN is calculated from the known amount of MeCN stock solution added to the NMR tube. A typical guest exchange experiment is shown in Fig. S6

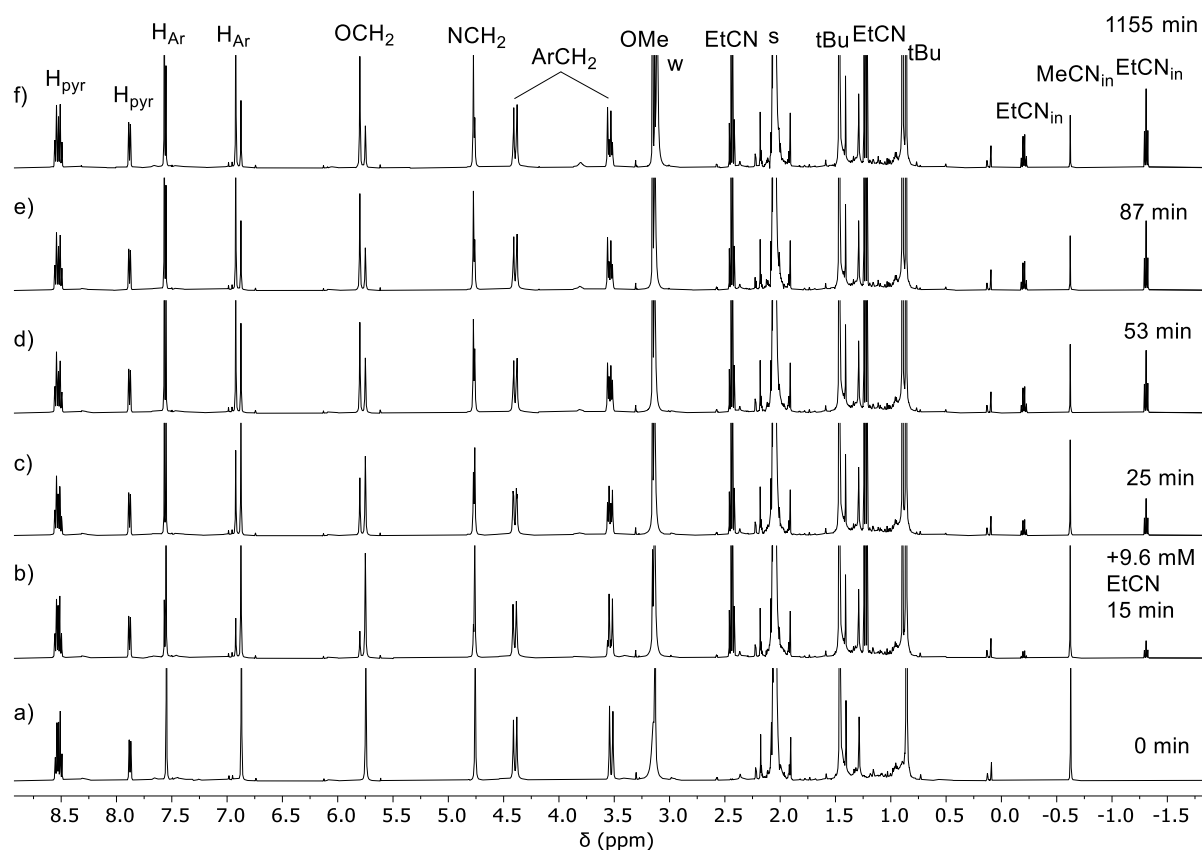


Figure S6. ^1H NMR spectra (300 K, 500 MHz, acetone- d_6) recorded during the titration of $G = \text{MeCN}$ by $G' = \text{EtCN}$. Initial conditions in a) $[\text{Zn}(\text{MeCN})\text{L}] = 3.7 \text{ mM}$, $[\text{Free MeCN}] = 92 \text{ mM}$, $[\text{EtCN}] = 0 \text{ mM}$, $[\text{H}_2\text{O}] = 20 \text{ mM}$. Percentage of propionitrile complex in solution. a) 0%, b) 17%, c) 38%, d) 41%, e) 59%, f) 71%. This experiment is reported as entry A in Table 1. Full conversion corresponds to the maximum amount of EtCN complex formed in the experiments conditions without further addition of EtCN. In this case, full conversion = spectrum f) at 71%. The “50% conversion” is then the time where we have 35.5% of EtCN complex in solution.

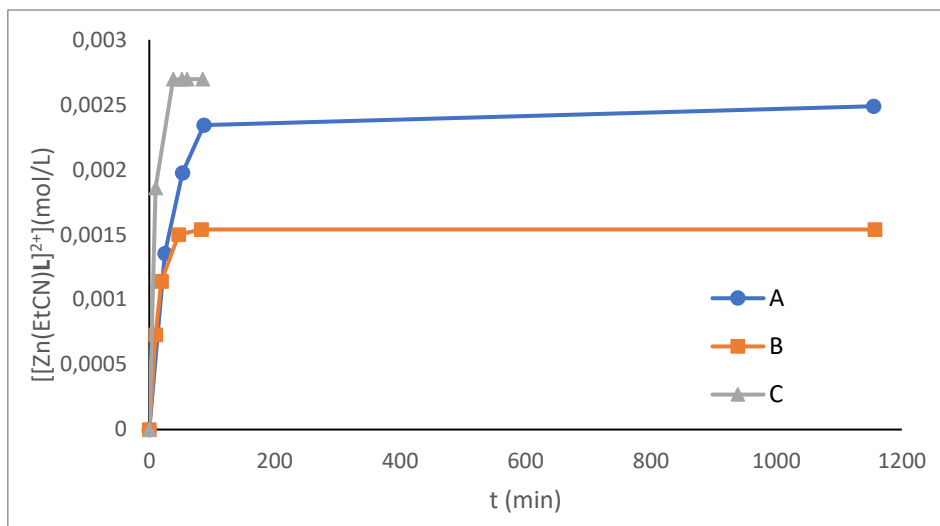


Figure S7. Evolution of $[\text{Zn}(\text{EtCN})\text{L}]^{2+}$ over time. A, B and C correspond to the experiments reported in Table 1 of the main text.

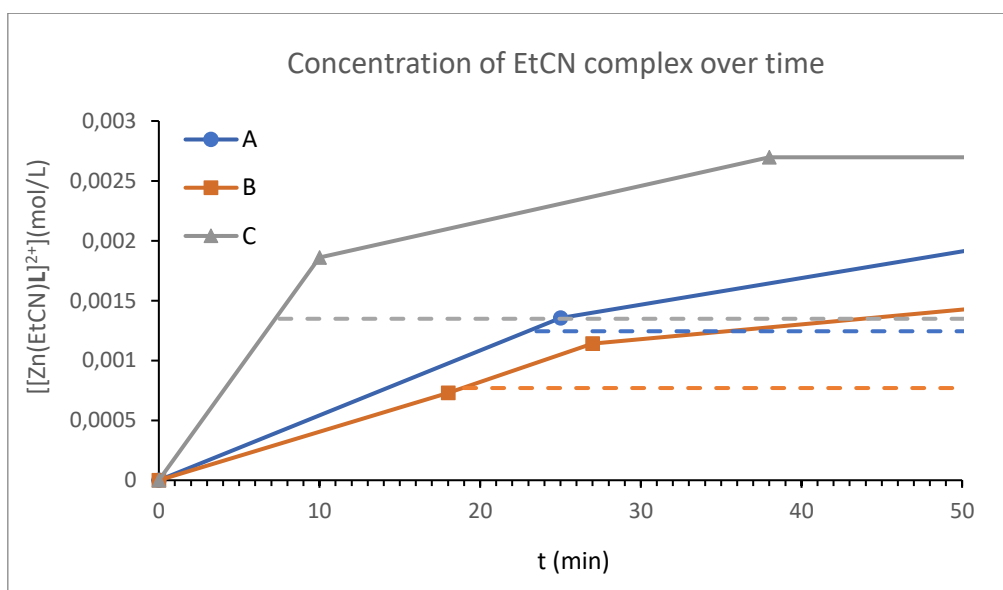


Figure S8. Zoom of Figure S7: Determination of the 50% conversion value. Full conversion corresponds to the maximum amount of EtCN complex formed in the experiments conditions without further addition of EtCN (the plateau reached in all 3 experiments).

Kinetic measurements for the MeCN/H₂O guest exchange process inside the cavity of [Zn(G)L]²⁺

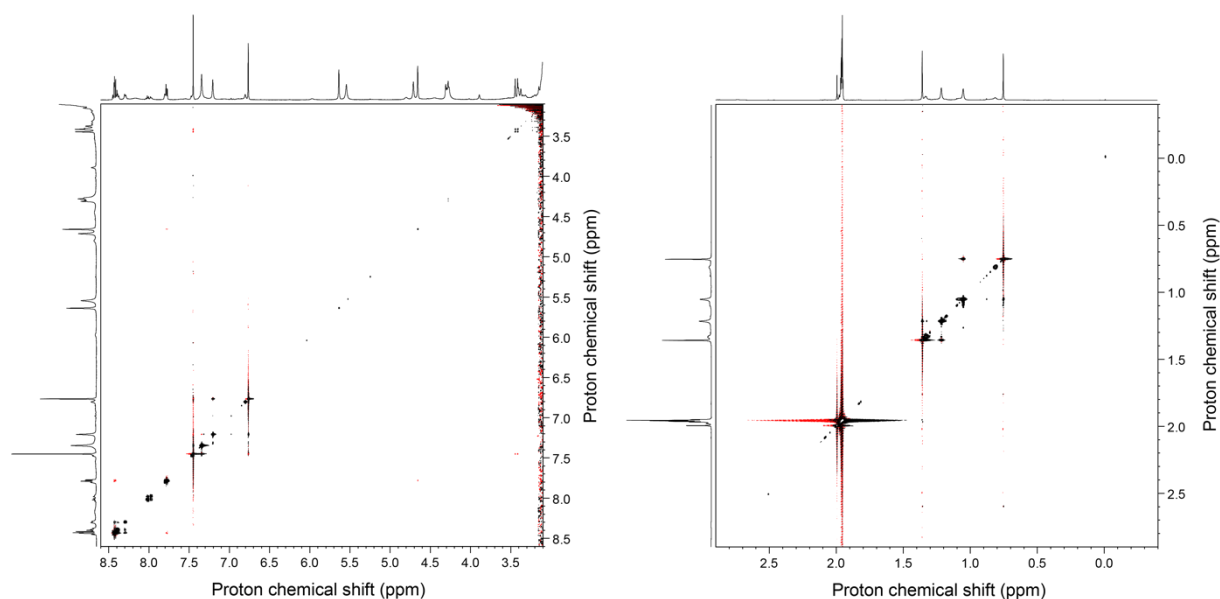


Figure S9. Selected regions of the 2D ¹H-¹H NOESY/EXSY spectrum shown in Figure 4, recorded on a solution containing a mixture of the aqua and MeCN Zn complex [Zn(H₂O)L](ClO₄)₂ in acetone-d₆. This experiment was acquired on a Bruker Avance III NMR spectrometer operating at a proton resonance frequency of 500 MHz, equipped with a dual ¹H/¹³C cryogenically cooled probehead. The standard NOESY pulse sequence was used. For each of the 1024 increments in the indirect time domain, a free induction decay of 4096 points was acquired, with 4 scans and a 3s recycle delay between scans. The mixing time was set to 1500 ms. Non uniform sampling acquisition mode was used, with an amount of sparse sampling of 50% to accelerate the acquisition. The spectral window was set to 9.7 ppm in both dimensions. Data were processed by using zero-filling up to 2048 points in the indirect dimension, and 8192 points in the direct one, apodization of 0.5 Hz and automatic baseline correction in both dimensions.

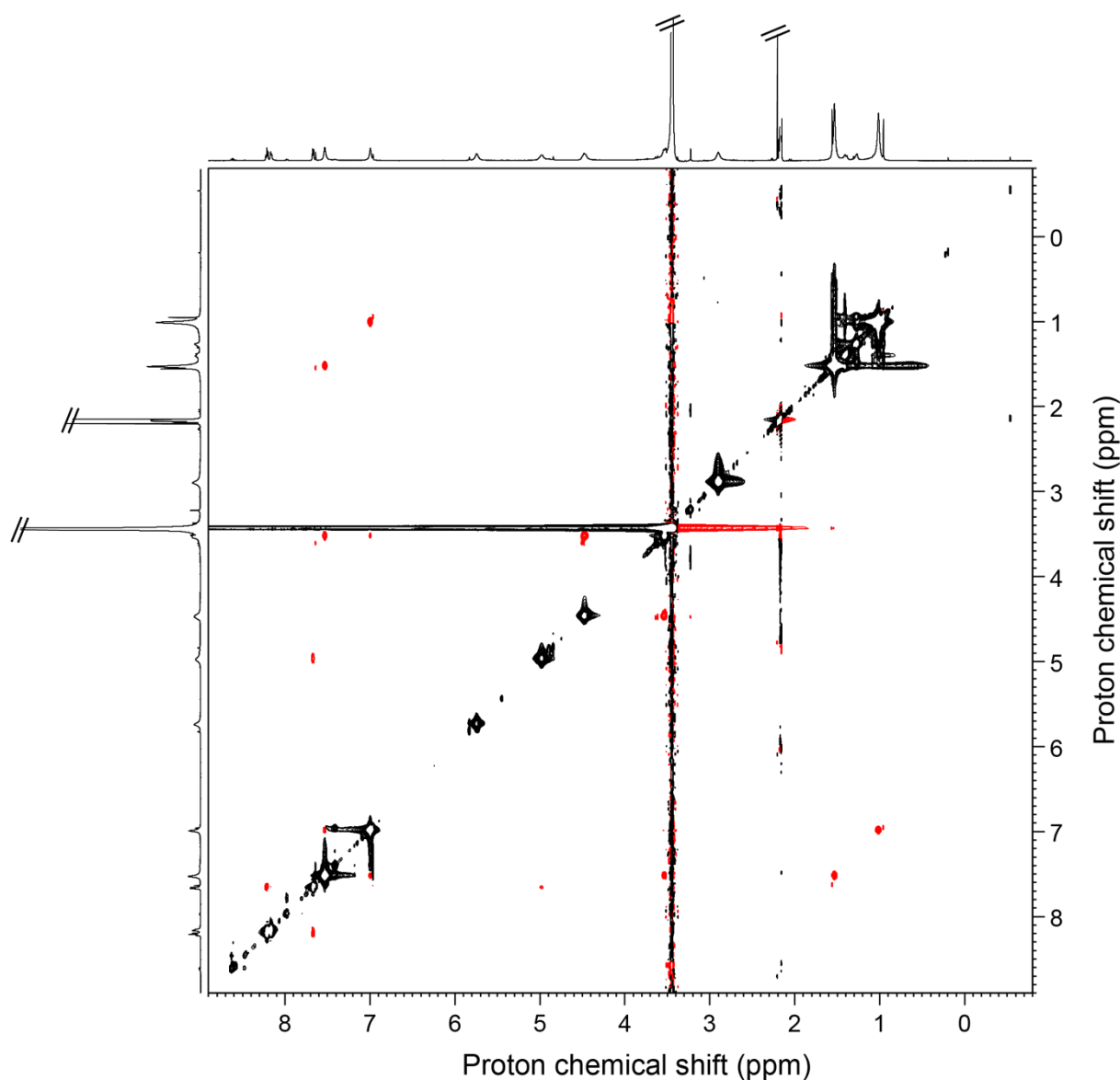


Figure S10. A representative 2D ^1H - ^1H NOESY/EXSY spectrum of a solution containing a mixture of the aqua and MeCN Zn complex $[\text{Zn}(\text{H}_2\text{O})\text{L}](\text{ClO}_4)_2$ in acetone- d_6 , recorded with a mixing time of 800 ms. This spectrum was acquired within a series of six experiments recorded with different mixing times (100, 200, 400, 800, 2000, 5000 ms), on a 600 MHz Bruker Avance IVDr spectrometer equipped with a dual $^1\text{H}/^{13}\text{C}$ probe head, to monitor the exchange processes at play in the investigated complex. This sample was prepared with 1.8 eq. of MeCN and 450 eq. of H_2O to tune the rate of the exchange process to the timescale allowed by the longitudinal relaxation times of the proton sites that were analyzed (see below). The standard NOESY pulse sequence was used. For each of the 1024 increments in the indirect time domain, a free induction decay of 4096 points was acquired, with 4 scans and a 3s recycle delay between scans. Non uniform sampling acquisition mode was used, with an amount of sparse sampling of 50% to accelerate the acquisition. The quantitativity of the resulting data was controlled in a preliminary test by comparing with the same data recorded using the traditional acquisition mode (uniform sampling of the indirect time domain). The spectral window was set to 9.7 ppm. Data were processed by using zero-filling up to 2048 points in the indirect domain, and 8192 points in the direct one, apodization of 0.5 Hz and automatic baseline correction in both dimensions.

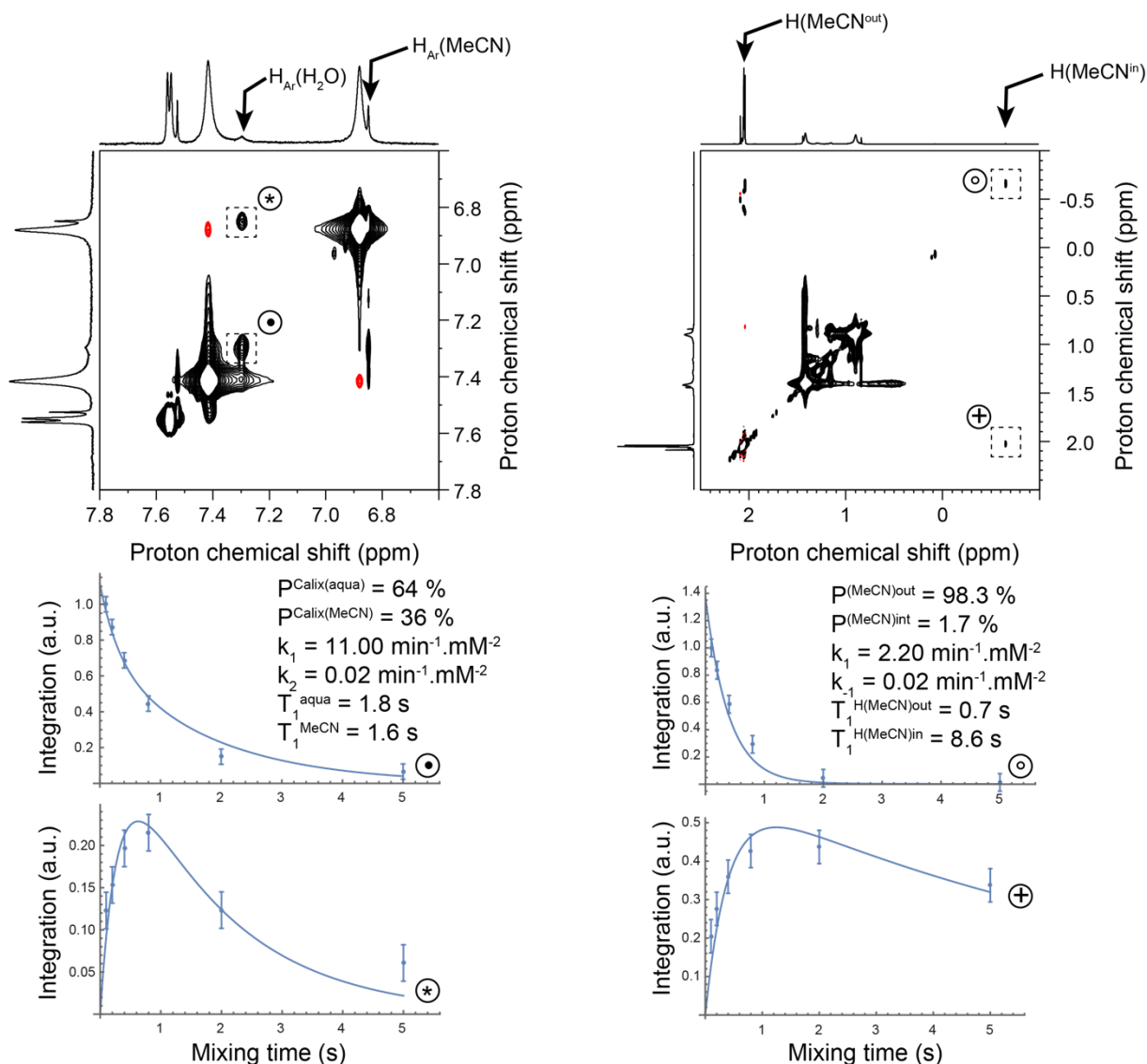


Figure S11. (Top) The regions of interest of the 2D EXSY spectrum showing the correlation patterns assigned to the proton sites that highlight the exchange process between the aqua and MeCN Zn complex (6.85 / 7.3 ppm) on the one hand, and bound and free MeCN (-0.7 / 2.0 ppm) on the other hand. (Bottom) The evolution of the correlation volumes obtained by varying the mixing time from 0.1 s to 5.0 s at 300 K. For each proton site, the evolution of the selected diagonal and cross peaks arising from the exchange process was fitted using modified Bloch equations to model the evolution of the proton longitudinal magnetization during the mixing time, under the effect of longitudinal relaxation and a standard 2-sites exchange process (cross relaxation with other proton sites was neglected). The parameters that were adjusted for each set of signals (respectively H_{Ar} from the complex, and H_{MeCN}) are the rate constants k_1 and k_{-1} (see main text), and the longitudinal relaxation time (T_1) for each proton site. The populations P of the two exchanging proton sites were estimated from the deconvolution and the integration of their respective signals measured on a 1D ^1H spectrum. The following concentration values were used to calculate k_1 and k_{-1} from the apparent rates determined during the fitting of EXSY data: $[\text{MeCN}] = 9.8 \text{ mMol} \cdot \text{L}^{-1}$, $[\text{Zn}(\text{H}_2\text{O})\text{L}]^{2+} = 0.3 \text{ mMol} \cdot \text{L}^{-1}$, $[\text{Zn}(\text{H}_2\text{O})\text{L}]^{2+} = 0.5 \text{ mMol} \cdot \text{L}^{-1}$, and $[\text{H}_2\text{O}] = 2570 \text{ mMol} \cdot \text{L}^{-1}$.

Computational details

Initial structure of the calixarene-MeCN complex

Starting from the $[\text{Cu}^{\text{II}}(\text{NC}(\text{Et})\text{L})(\text{ClO}_4)_2]$ crystal structure,^[1] the Cu^{II} ion was replaced by Zn^{II} . A PM7 semi-empirical optimization was carried out with the program MOPAC2016^[2] after having moved the water molecule so as to avoid any chemical bond with the acetonitrile (MeCN) guest. The default optimization algorithm and parameters were used. The resulting structure suggested a potentially stable complex with both the MeCN and H_2O placed inside the calixarene cavity. The H_2O molecule was further deleted to generate the MD input files.

To study the exchange of water and MeCN through MD simulations, MeCN and the empty calixarene structures were submitted to the Swissparam server^[3] to generate the input coordinates and topology files suitable for the GROMACS2020 MD simulations^[4]. On the whole, the complete coordinate file was built by merging the calixarene, Zn, and MeCN coordinates. Similarly, a full topology file was built to call for calixarene, Zn, and MeCN force field parameters.

To study complexes with propionitrile (EtCN) rather than acetonitrile as the guest, MeCN was replaced by EtCN in the calixarene complex optimized with MOPAC2016. The EtCN structure was retrieved from the free Chemical Entities of Biological Interest (ChEBI) web site^[5] and its coordinates were obtained through a EtCN-MeCN superimposition procedure of the C-C \equiv N moiety. The EtCN topology file that is suitable for GROMACS MD simulations was also obtained using the server Swissparam.^[3] A MeOH topology file was also obtained using the same approach.

MD and SMD simulations of the guest substitution

All MD simulations were carried out with the software GROMACS2020 at 300 K, either in vacuum or in acetone (at 1 bar). In that last case, the initial calixarene-MeCN structure was solvated in acetone whose liquid box coordinates were retrieved from the compound database of the Virtual Chemistry web site.^[6] The initial system size has dimensions of 6.773 x 4.773 x 4.773 nm. Two chloride ions were added to neutralize the system which contains 1184 acetone molecules.

To further allow SMD calculations which require the application of a pulling force on the guest, the initial guest/calixarene structure was oriented along the x-axis of the Cartesian coordinate system.

To avoid too strong a deformation of the calixarene during the MD simulations, distance restraints were applied between the Zn^{II} ion and the four N atoms of the calixarene cap, with lower and upper cut-off values of 0.20 and 0.22-0.23 nm, and a large force constant value of 50,000 $\text{kJ mol}^{-1} \text{nm}^{-2}$. Also, to prevent the calixarene structure from accompanying the guest displacement during the pulling stage, the N atoms of the calixarene cap were held in place using a force constant of 5,000 $\text{kJ mol}^{-1} \text{nm}^{-2}$ in each direction.

The complete systems were optimized to eliminate large forces using a Steepest Descent procedure with a tolerance of $1.0 \text{ kJ mol}^{-1} \text{ nm}^{-1}$ and an initial step size of 0.05 nm . A maximum number of 5,000 iterations was allowed.

The systems were then heated to 50 K through a 10 ps NVT MD, with a time step of 2 fs and LINCS constraints acting on bonds involving H atoms. The trajectory was followed by two successive 20 ps heating stages, at 150 and 300 K under the same conditions. Next, each system was equilibrated during $2,050 \text{ ps}$ in the NVT ensemble in vacuum, and in the NPT ensemble in a solvent, using the thermostat V-rescale and barostat Berendsen algorithms. Snapshots were saved every 50 iterations. Altogether, the MD and SMD calculations build a trajectory of $2,160 \text{ ps}$ ($21,601$ snapshots or frames).

During all MD simulations, the vdW cut-off distance was set equal to 1.2 nm with a force switch set at 1.0 nm . In vacuum, the Coulomb cut-off parameter was set equal to 1.2 nm as well. In solution, a Particle Mesh Ewald (PME) Periodic Boundary Conditions (PBC) scheme was applied to calculate the long-range electrostatic interactions with a cut-off of 1.2 nm too.

The SMD procedure was applied to the last frame of the equilibration stage. It consisted in applying a pulling force to the guest center-of-mass, along the x-axis, while restraining the N atoms of the calixarene cap at their optimized position. The SMD pulling stage was carried out for $30,000$ iterations, with a time step of 2 fs , a harmonic “umbrella” force constant of $1,000 \text{ kJ mol}^{-1} \text{ nm}^{-2}$, and a pulling rate of 0.025 nm ps^{-1} .

Calixarene-MeCN interacting with a water molecule in vacuum at 300 K

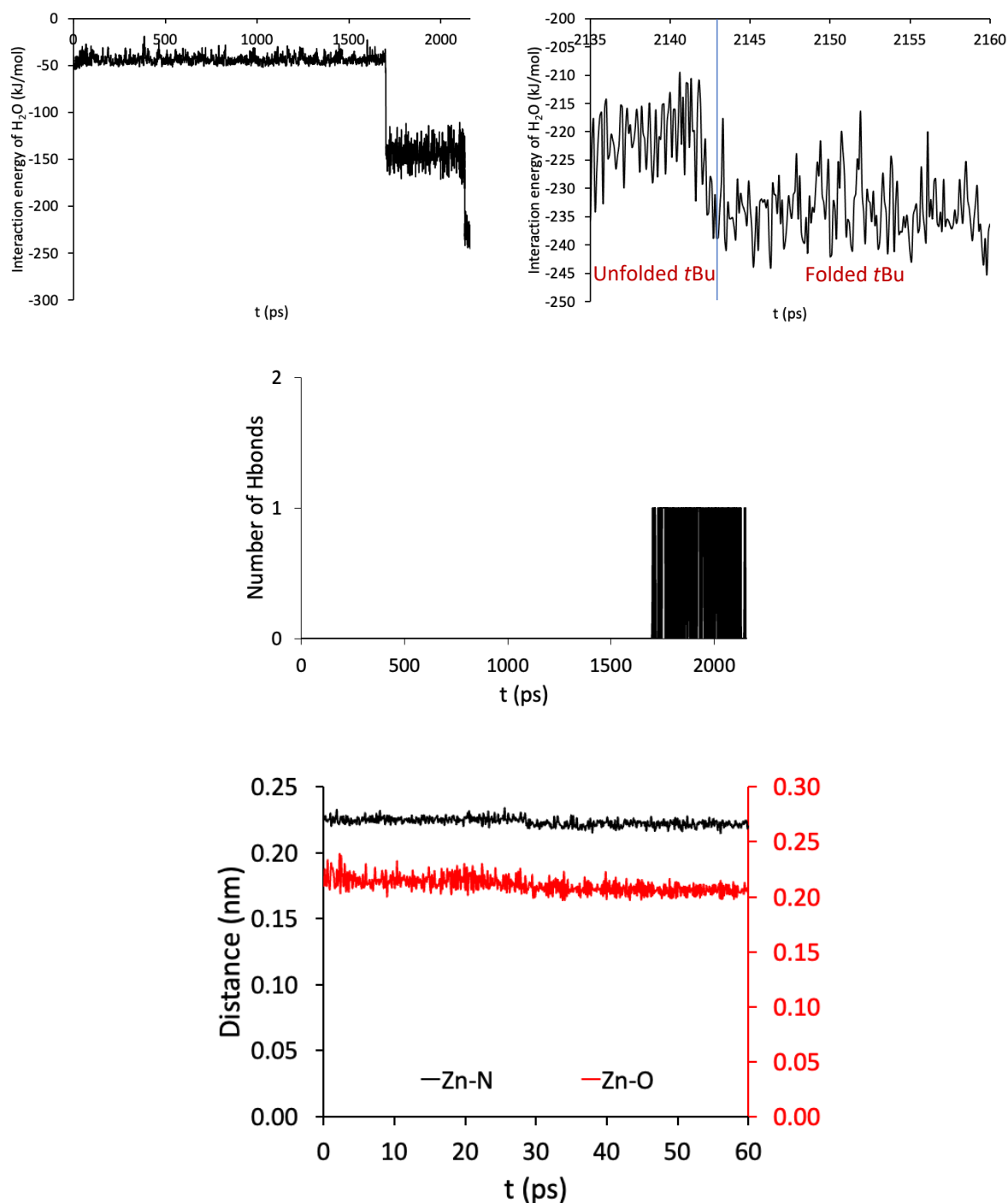


Figure S12. Profiles obtained from the 2,160 ps long simulation of the calixarene-MeCN system interacting with a water molecule, in vacuum at 300 K. (Top Left) Intermolecular interaction energy profile of the water molecule with the calixarene-MeCN complex. (Top Right) Zoom on the interaction energy of water before and after tBu folding during the final steps of the SMD simulation. (Center) Number of water-methoxy hydrogen bonds. GROMACS cut-off values for the hydrogen bonds are: D-A distance = 0.3 nm and H-D-A angle = 30°. (Bottom) Zn^{II}-N_{calix} (black) and Zn^{II}-O_{water} (red) distance profiles during the 60 ps Ion SMD trajectory.

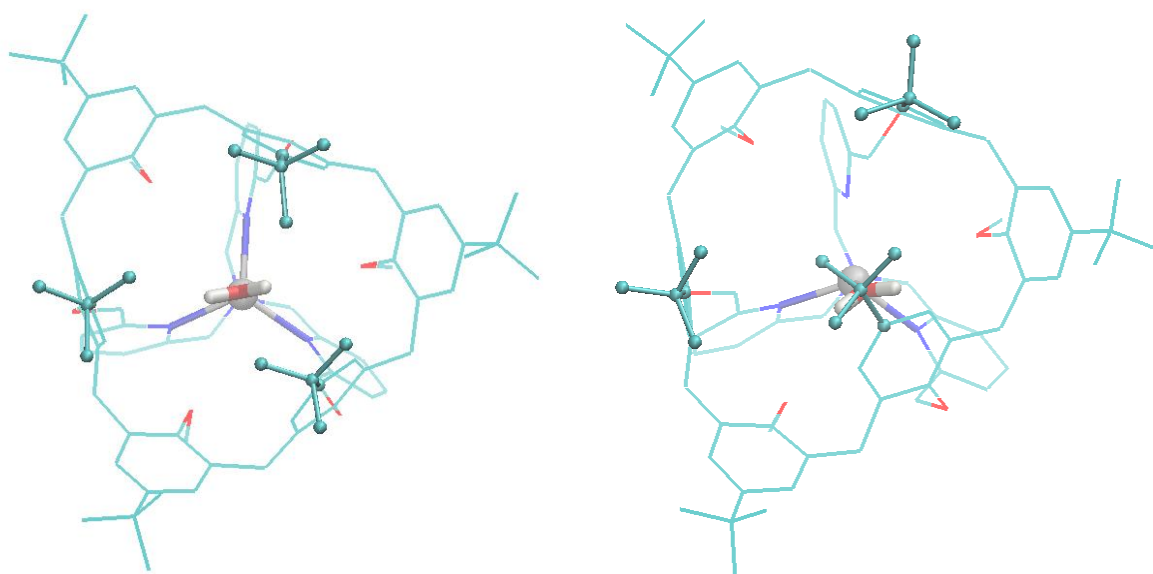


Figure S13. (Left) Snapshot at $t = 42.0$ ps and (Right) final snapshot, obtained from the 60 ps SMD simulation of the calixarene-MeCN system interacting with a water molecule, in vacuum at 300 K. (bottom views). H atoms are not shown for clarity.

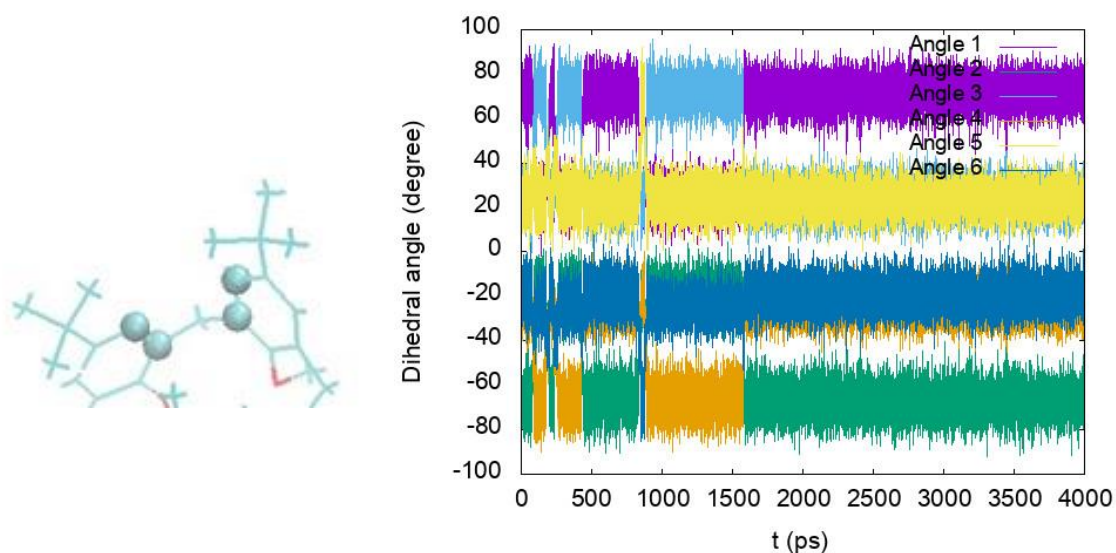


Figure S14. (Left) Atoms used to define a dihedral angle to check the *t*Bu folding during a post SMD simulation. (Right) The six dihedral angle profiles obtained from a post SMD simulation of 4,000 ps, starting from the final SMD atomic coordinates of the calixarene-H₂O system, in vacuum at 300 K.

Calixarene-MeCN interacting with a water molecule in acetone at 300 K and 1 bar

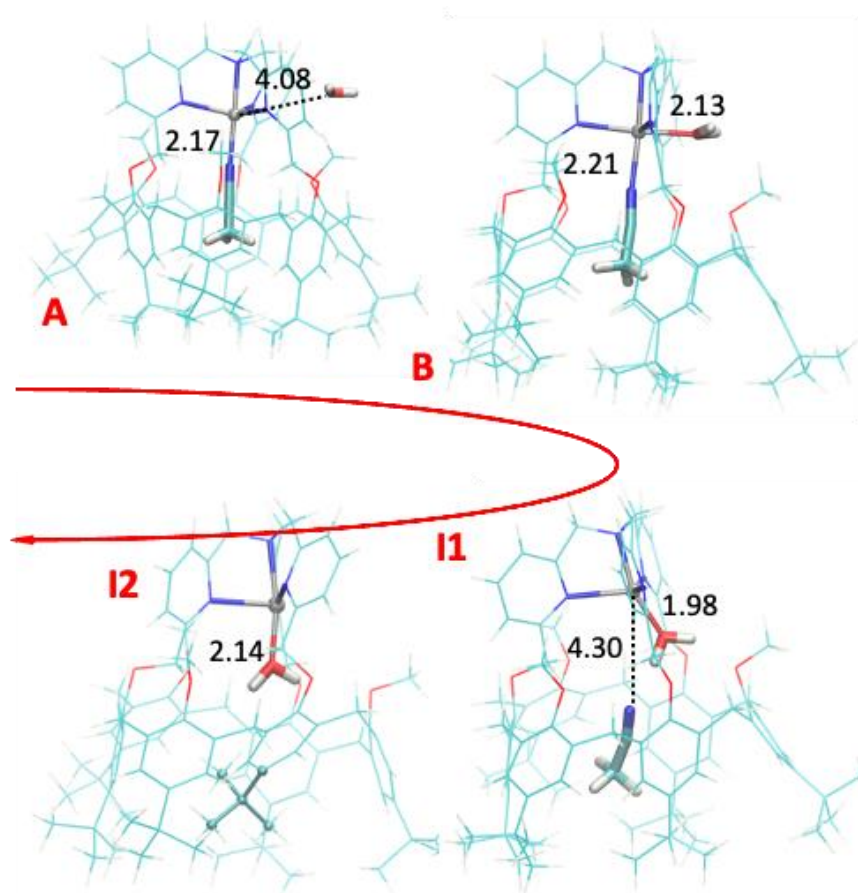


Figure S15. Stepwise substitution of the MeCN guest by a water molecule following an associative pathway, as obtained from the 2,160 ps MD and SMD trajectory in acetone at 300 K and 1 bar. Snapshots at 0 (initial optimized structure - **A**), 870.1 (coordination of H₂O - **B**), 2,109.2 (insertion stage - **I1**), 2,160.0 ps (last snapshot - **I2**). Interaction energy values of the water molecules with the calixarene complex and with the solvent are (-27.44; -31.39), (-106.85; -56.10), (-175.02; -1.45), and (-172.01; -0.61) kJ mol⁻¹, respectively. Distances are in Å. The folded *t*Bu moiety is displayed using ball and stick representations in **I2**.

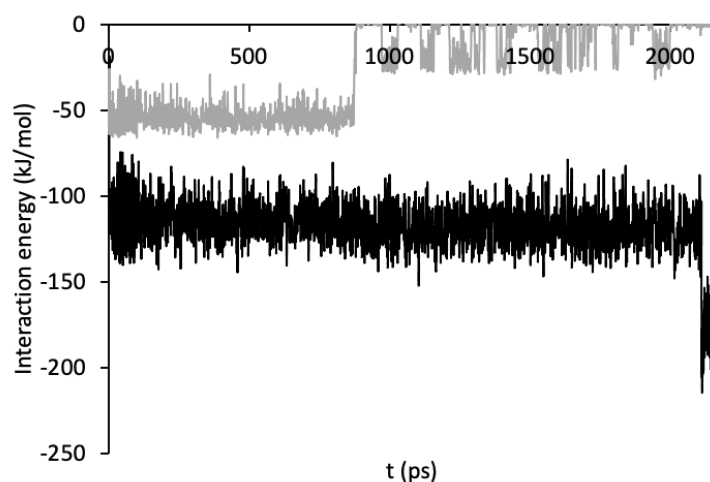


Figure S16. Short-range intermolecular interaction energy profile of the water molecule with the calixarene-acetonitrile complex (black) and with the solvent molecules (gray) as obtained from the 2,160 ps long simulation in acetone, at 300 K and 1 bar.

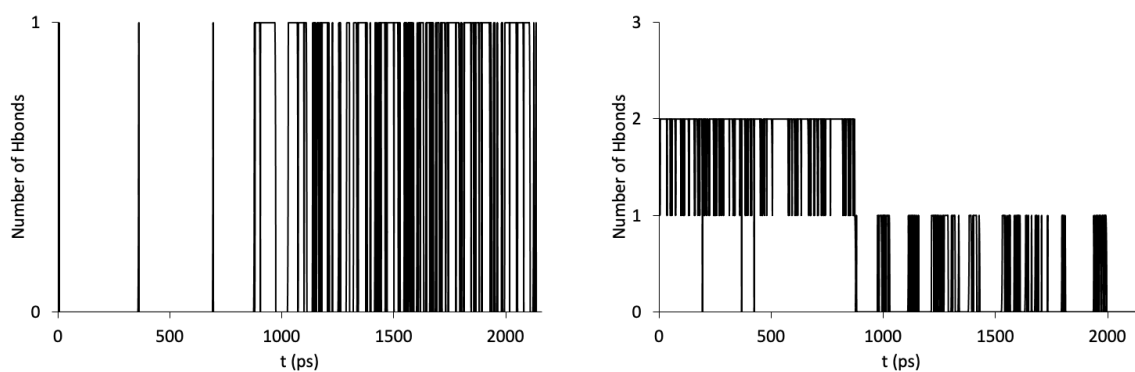


Figure S17. Number of hydrogen bonds occurring between the water molecule and (Left) the calixarene O_{methoxy} atoms, (Right) the acetone molecules, as obtained from the 2,160 ps simulation in acetone, at 300 K and 1 bar. GROMACS cut-off values for the hydrogen bonds are: D-A distance = 0.3 nm and H-D-A angle = 30° .

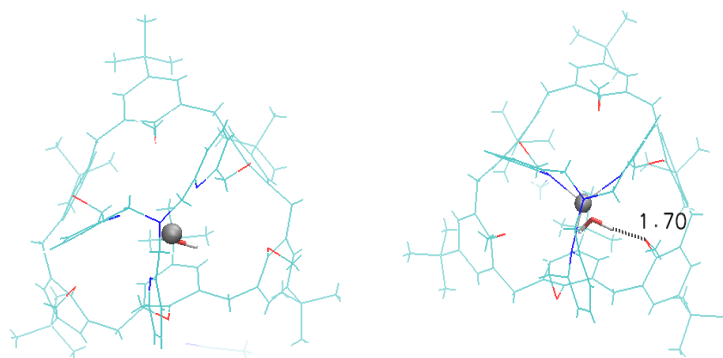


Figure S18. (Left) Final snapshot obtained from the 60 ps SMD simulation of the calixarene-water system in acetone, at 300 K and 1 bar and (Right) its optimized version using MOPAC2016 (top views). Distance in Å.

Calixarene-EtCN interacting with a water molecule in vacuum at 300 K

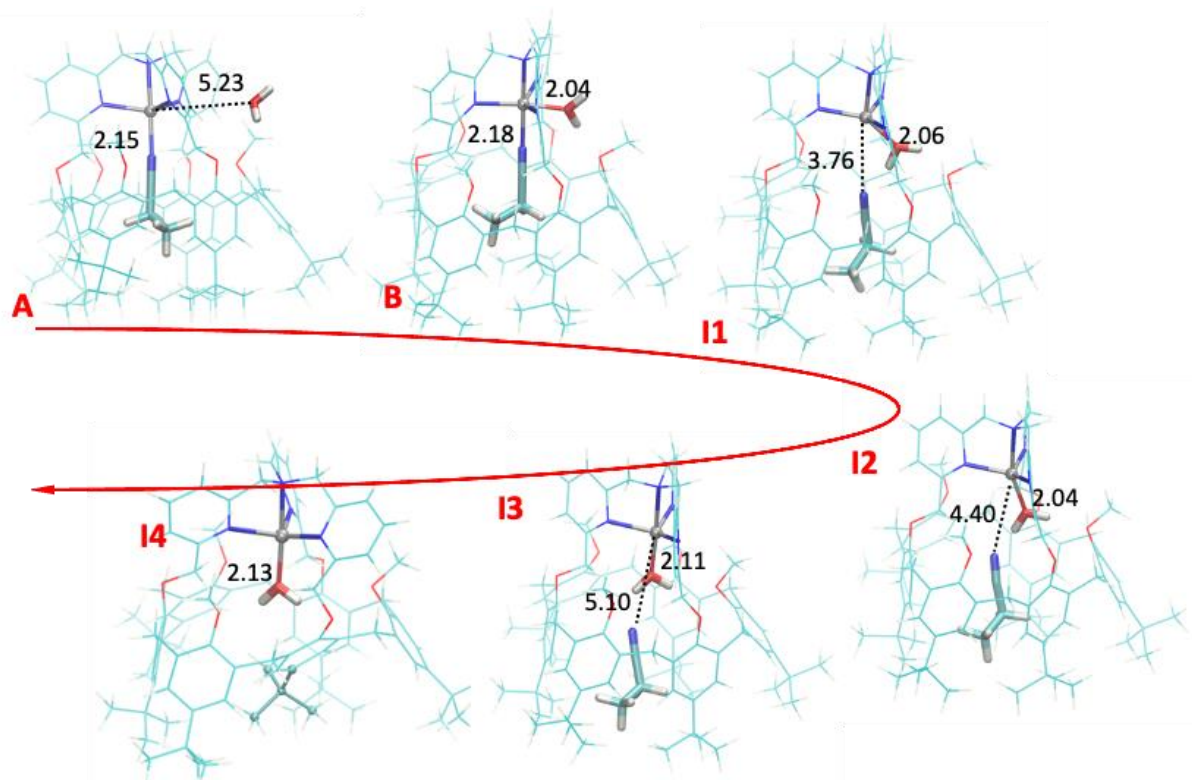


Figure S19. Stepwise substitution of the EtCN guest by a water molecule following an associative pathway, as obtained from the 2,160 ps MD and SMD trajectories in vacuum at 300 K. Snapshots at 0 (optimized structure - **A**), 353.9 (coordination of H₂O - **B**), 2,132.1 (insertion stage - **I1**), 2,132.2 (insertion stage - **I2**), 2,132.3 (insertion stage - **I3**), and 2,160.0 ps (final structure - **I4**). Interaction energy values of the water molecules are -38.71, -117.86, -170.25, -235.63, -235.51, and -236.94 kJ mol⁻¹, respectively. Distances are in Å. The folded *t*Bu moiety is displayed using ball and stick representations in **I4**.

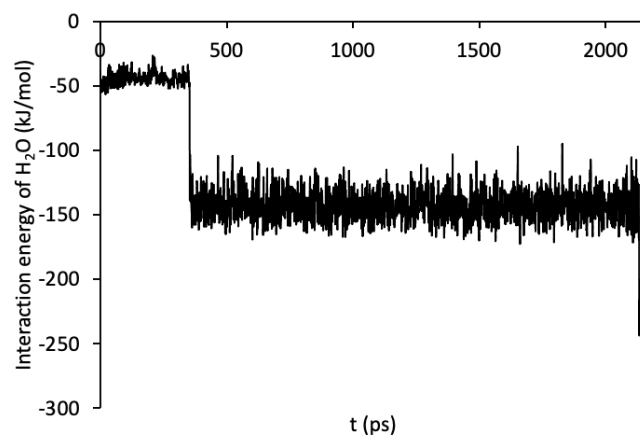


Figure S20. Intermolecular interaction energy profile of the water molecule with the calixarene-EtCN complex as obtained from the 2,160 ps simulation in vacuum, at 300 K.

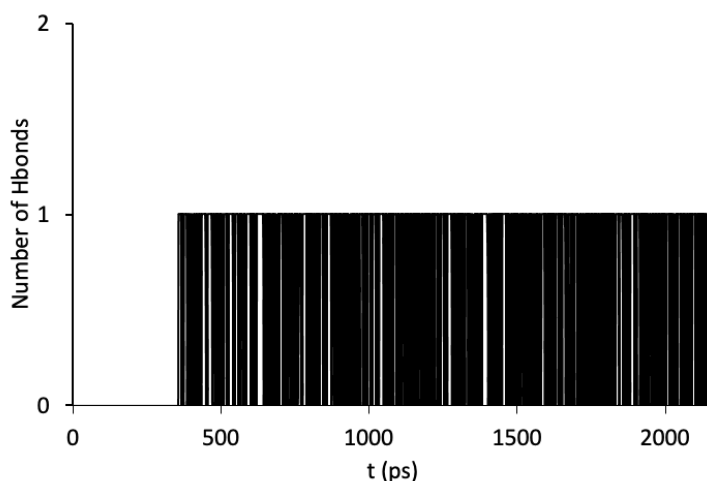


Figure S21. Number of hydrogen bonds occurring between the water molecule and a methoxy group of the calixarene structure as obtained from the 2,160 ps simulation in vacuum, at 300 K. GROMACS cut-off values for the hydrogen bonds are: D-A distance = 0.3 nm and H-D-A angle = 30° .

A hydrogen bond is formed at 354 ps, well before the H bond formation time observed during the MD simulation of the calixarene-MeCN-water case (cf. SI). It has no physical significance since a different starting MD state may have led to a different occurrence time of the H bond.

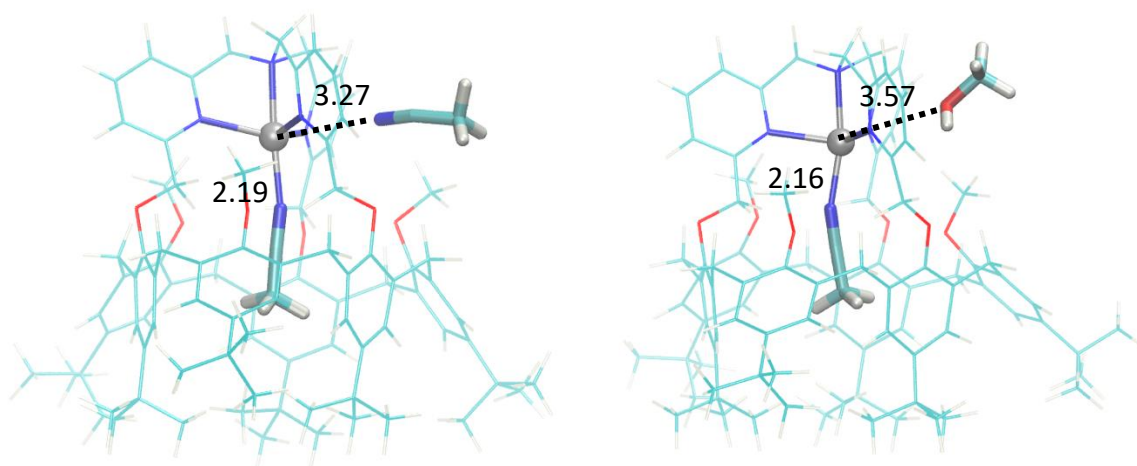


Figure S22. Snapshots obtained from the 2,100 ps long MD simulations of the calixarene-MeCN system in vacuum, at 300 K. The *exo*-ligand is (Left) MeCN at $t = 613.5$ ps, (Right) MeOH at $t = 771.7$ ps. Distances are in Å.

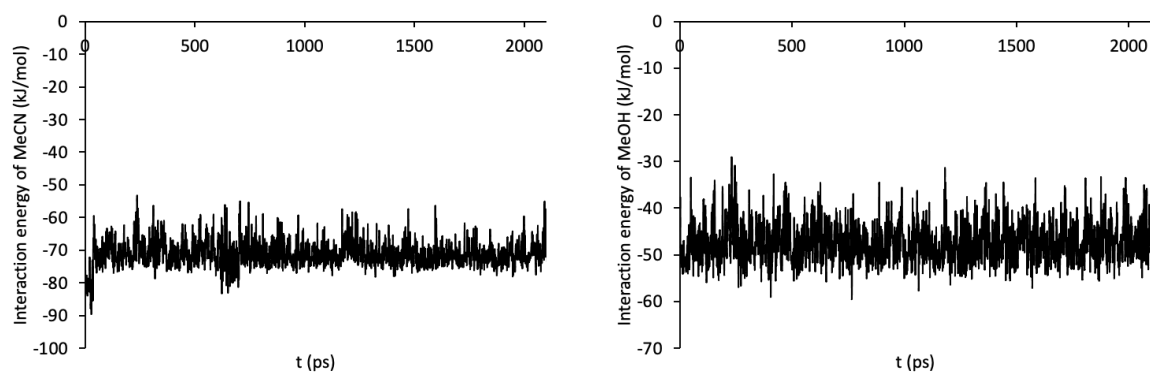


Figure S23. Intermolecular interaction energy profile of the *exo*-ligand molecule with the calixarene-MeCN complex as obtained from the 2,100 ps MD simulation in vacuum, at 300 K. The *exo*-ligand is (Left) MeCN, (Right) MeOH.

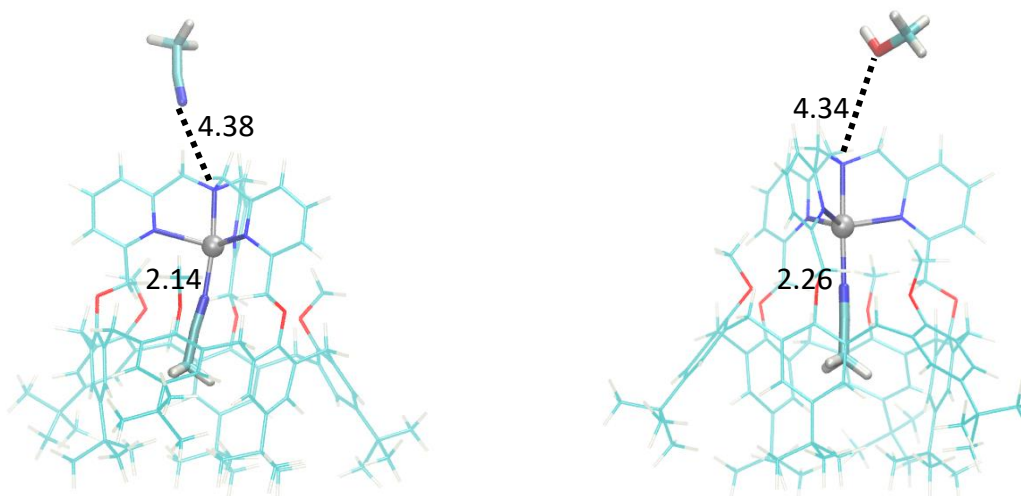


Figure S24. Last frame of the 2,100 ps long MD simulations of the calixarene-MeCN system, in vacuum at 300 K. The *exo*-ligand is (Left) MeCN, (Right) MeOH.

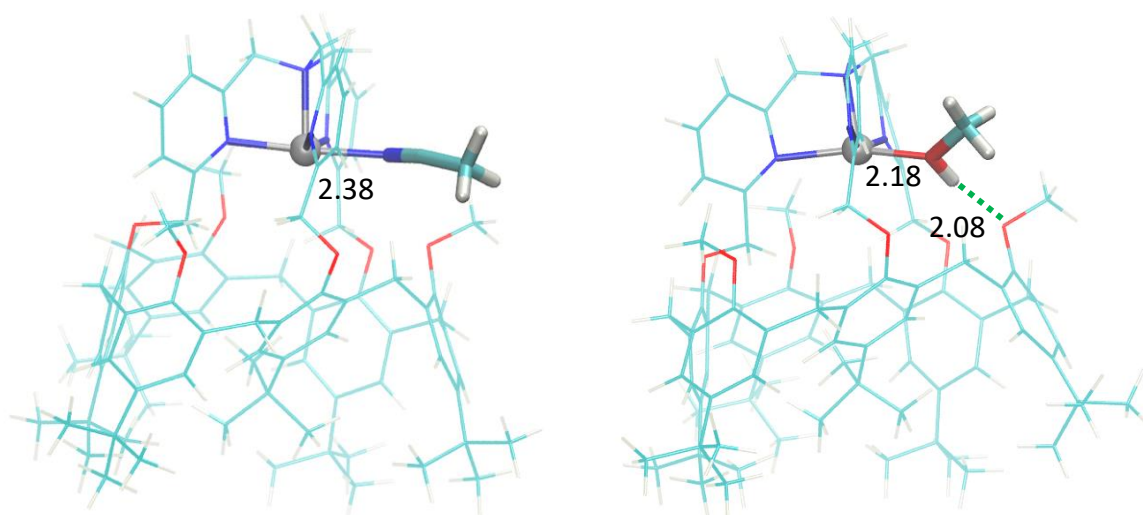


Figure S25. Last frames of the 2,100 ps long MD simulations of calixarene without *endo*-ligand, in vacuum at 300 K. The *exo*-ligand is (Left) MeCN, (Right) MeOH. H bond is displayed with green dotted line.

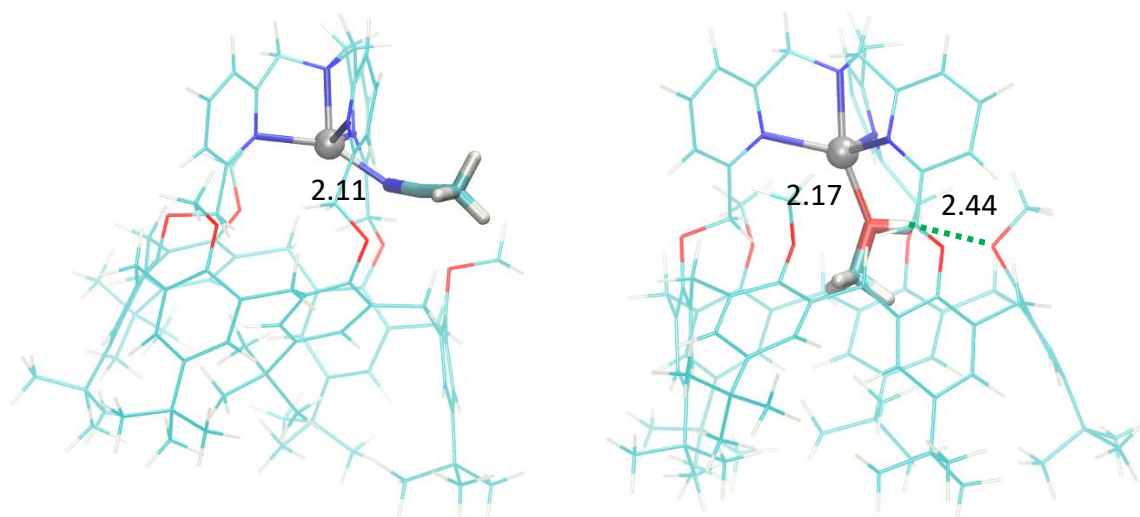


Figure S26. Snapshots obtained from the 60 ps long SMD simulations of calixarene without *endo*-ligand, in vacuum at 300 K. The *exo* ligand is (Left) MeCN at $t = 60$ ps, (Right) MeOH at $t = 41.9$ ps. Distances are in Å. H bond is displayed with green dotted line.

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