Nanoconfinement of polyoxometalates in cyclodextrin: computational inspections of the binding affinity and experimental demonstrations of reactivity modulation

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1. Materials and methods

a. Computational details

The optimized coordinates of Keggin-type polyoxometalates, γ -cyclodextrin (γ -CD) and different conformers of the Keggin-(γ -CD) pairs were obtained by optimization using GGA BP86 density functional theory.^[1] Slater type triple-zeta plus polarization basis TZP was selected,^[2] and relativistic effects were considered through the relativistic scalar ZORA approach.^[3] Solvent effects were included using the implicit COSMO model.^[4]

Concerning pair's assemblies, Keggin-(γ -CD) bonding energies were analyzed by bond energy decomposition within the DFT framework. In this step, water is treated implicitly by the COSMO model. In our case, we are interested in the total bonding energy which corresponds to the energy of stabilization by forming the pair.



Molecular simulations considering explicit solvent, water molecules in our case, are the appropriate choice to discuss chaotropic effects. We performed classical molecular dynamics simulations under periodic boundary conditions to model aqueous solutions of several Keggin-type POMs, alkali cations, and explicit water molecules using the GROMACS 5.0.2 program package.^[5] We considered 7 POMs in a cubic box with dimensions of 70 Å. The box is neutralized with the corresponding Na⁺ counter-ions and solved with ca. 11.000 water molecules. Three initial boxes for MD dynamics were built (see figure S1).



Figure S1. Initial periodic simulation box with POMs and γ -CD.

After energy minimization, we performed NVT equilibration runs of 10 nanoseconds and secondly, a production run of 40 ns *NPT* with all positions unconstrained were done. All the simulations were carried out at 300K and 1 atm. The temperature was defined by coupling with the Berendsen thermostat,^[6] with a time constant of 0.1 ps. In the *NPT* simulations, the pressure was coupled to a Berendsen barostat with a relaxation time of 0.3 ps. The Verlet leapfrog algorithm^[7] was used to integrate the equation of motion with a time step of 1 fs. The results were analyzed through a TRAVIS trajectory analyzer.^[8]

Force field parameters consist of atom-typing, bonded, and non-bonded parameters. We define a new systematic atomtyping for Keggin-type POM within an assignment of unique atom type for each atom, the oxygen atoms of POM are classified as terminal, bonding, and central ones and the coordination number of each atom is also included in the atom-typing. For Bonded parameters, a new flexible approach was used, permitting POM intramolecular coordinates of polyoxometalate to adapt to y-cyclodextrin host, in contrast to previous frozen-bonded approaches used in previous MD studies of POMs. At the optimized BP86/def2-TZVP geometry, the cartesian matrix was used to calculate bond and angle force constants by Modified seminario method using Modified Seminario program available at github (https://github.com/aa840/ModSeminario Py). The set of LJ parameters for all-atom types of POM anions were taken from UFF parameters from Rappe et al.^[9] Partial atomic charges were Quadrupolar multipole-derived charges MDC(Q) generated at the BP86/TZP level with of ADF program.^[10,11] Atomic radii used for all atoms were Klamt radius. This charge model was used for large hybrid systems by Segado et al.^[11] In the case of y-CD, the parameters were generated with parachem and taken from the CHARMM general force field (CGenFF). The selection of CHARMM force field was done for several reasons. The charge model of POM used in this work is the same charge model used in previous publication.^[11] The generation of force field for hybrid organic/inorganic POM were done combining CHARMM and this charge model with excellent agreement with experimental results. In addition, force fields such as CHARMM are frequently used in simulations involving cyclodextrin.^[12–14]. In addition, the CHARMM force field is validated by Niels Hansen and co-workers who demonstrated that the CHARMM36 force field show a similar performance as the three recommended GROMOS parameter sets.^[15] Alkali cations were treated with the parameter set reported by Joung and Cheatham for specific water models.^[16] Water molecules were modeled according to SPC(E) and using Settle constraints constraints.^[17] We decided to use SPC(E) for all calculations because we need a water model especially accurate for capturing properties of water such as the diffusion coefficient, coordination number and dielectric constant because and our work relates strongly to these properties and SPC(E) provide better performance on these properties than TIP3P and TIP4P.^[18] Also, Carlos Vega and Jose Abascal^[19] showed that only the nonpolarizable model, the TIP4P/2005 potential, would be better than the SPCE in some water parameters. Moreover, a study of MD using CGEnFF for alkane and several force fields for water, shed lights SPC(E) as the best three-point parametrization model to predict interfacial properties of water.^[20] For LJ parameters, the Lorentz–Berthelot combination rules were used. An atom-based cutoff of 17 Å for non-bonded interactions and particle-particle-mesh Ewald summation method were applied.^[21]

b. Experimental details

i. Nuclear magnetic resonance (NMR)

All solution NMR spectra were measured at 21 °C. ³¹P NMR spectra were recorded on a Bruker Avance 400 spectrometer at Larmor frequencies of 162.0 MHz, using 5 mm standard NMR tubes. The ³¹P spectra were recorded in quantitative mode with a 90° pulse of duration of 16 µs and a length of free induction decay of 1.6 s. A relaxation delay of at least 200 s was necessary to ensure a return to equilibrium of the magnetization. Depending on the concentration of the sample, the number of scans was adjusted and can vary from 2 to more than 1000. The duration of an experiment then varied from 5 min to more than 8 h.

ii. Preparation of Keggin-type precursors

All reagents were purchased from commercial sources and used without further purification. Solutions were prepared in Milli-Q water. $H_3[PM_{12}O_{40}]\cdot 29H_2O$, $H_3[PW_{12}O_{40}]\cdot 9H_2O$ and $K_7[PW_{11}O_{39}]\cdot 14H_2O$ were synthesized and purified according to published procedures.^[22,23] The purity and chemical composition of the POMs were confirmed by EDS, TGA, ³¹P NMR and FT-IR spectroscopies.

iii. Investigation of intermolecular electron transfer of Keggin-type POMs in presence of cyclodextrin

This investigation has been performed on solutions containing 25 mM of $[PW_{12}O_{40}]^{3-}$, $25 \text{ mM} [PW_{12}O_{40}]^{4-}$ and various amount of γ -CD. These mixture have been prepared as At room temperature, an acidic aqueous solution of the oxidized polyanion $[PW_{12}O_{40}]^{3-}$ is prepared using 305 mg of $H_3[PW_{12}O_{40}] \cdot 9H_2O$ (50 mM) and 2 mL of a 0.1M HCl/D₂O (10/1) mixture. Under controlled atmosphere, 6.4 mg sodium dithionite are added to the solution, which instantly turns dark blue. Then, ³¹P NMR spectra were measured after adding various amounts of γ -CD (0 to 150 mM) to solution A, as resumed in the next table.

iv. Investigation of intermolecular metalates transfer in presence of cyclodextrin

Preparation of solution containing 25mM of $[PW_{12}O_{40}]^{3-}$, 25 mM $[PW_{12}O_{40}]^{4-}$ and various amount of γ -CD

At room temperature, an acidic aqueous solution of the oxidized polyanion $[PW_{12}O_{40}]^{3-}$ is prepared using 305 mg of $H_3[PW_{12}O_{40}]\cdot 9H_2O$ (50 mM) and 2 mL of a 0.1M HCl/D₂O (10/1) mixture. Under controlled atmosphere, 6.4 mg sodium dithionite are added to the solution, which instantly turns dark blue. Then, ³¹P NMR spectra were measured after adding various amounts of γ -CD (0 to 150 mM) to solution A, as resumed in the next table.

2. Theoretical studies

a. Supramolecular 1:1 adducts: Keggin-POM $/\gamma$ -CD.

Various types of assembly that have been previously observed in the X-ray crystal structure were found, including the hostguest associations with the primary or secondary face and external interaction. Additionally, two other aggregates, named side-primary and side-secondary assemblies (Figure 1 main text) were identified. To compare the optimized structures with experimental X-ray structures, we focused on the distances between γ -CD and POMs. For simplicity, only the calculated structural patterns of the supramolecular adducts involving PW₁₂O₄₀³⁻ are discussed because no significant difference is observed for SiW₁₂O₄₀⁴⁻ and BW₁₂O₄₀⁵⁻. The most exposed hydrogens of γ -CD to POM are H3 and H5, located inside the cavity, as well as H6, located on the methoxy group outside the ring. However, the most significant hydrogen atoms able to form hydrogen bonds with the Keggin anions are the in-ring and out-ring hydroxo groups, labeled H7 and H8, respectively.

In the primary adduct, there are close interactions between the H5 and H6 hydrogen atoms and the oxygen atoms of the Keggin anions. Specifically, the H5-O^{bridging} distances range from 2.53 to 2.65 Å, the H5-O^{terminal} distances range from 2.05 to 2.12 Å, and the H6-O distances range from 2.28 to 2.64 Å. In the case of the secondary adduct, hydrogen bonds are formed between the hydroxo H7 hydrogen atoms (from 1.76 to 2.23 Å), and there are close contacts between the inorganic guest and the H3-O^{bridging} distances (from 2.18 to 2.67 Å) and H3-O^{terminal} distances (from 2.53 to 2.96 Å). Additionally, H5 interacts with the terminal oxygen (from 2.21 to 2.80 Å). On the other hand, the external adduct exhibits fewer specific interactions. However, hydrogen atoms located outside the cavity (H2, H1, H4). All these distances fall within the range of O-H distances observed in X-ray crystal structures for the secondary, primary, and external configurations involving $PW_{12}O_{40}^{3-}$, Si $W_{12}O_{40}^{4-}$, and $BW_{12}O_{40}^{5-}$, respectively.^[24-26].

3. Experimental studies

[γ-CD] (mM)	γ-CD/POM	Exchange regime	k_{et} (L.mol ^{-1.} s ⁻¹)	$\log k_{et}$
0	0	Intermediate fast	6 329 000	6.80
25	0.5	Intermediate fast	687 600	5.84
50	1	Intermediate fast	176 200	5.25
75	1.5	-	-	-
100	2	Intermediate slow	2 500	3.40
125	2.5	Intermediate slow	630	2.80
150	3	Intermediate slow	330	2.51

Table S1. Effect of [γ -CD] on the rate constant k_{et} for self-exchange of PW₁₂O₄₀³⁻/PW₁₂O₄₀⁴⁻ in aqueous solution



Figure S2. Time evolution of the ³¹P NMR spectra of an aqueous solution containing 50 mM of γ -CD and in which PW₁₂O₄₀³⁻ (25 mM) and PMO₁₂O₄₀³⁻ (25 mM) have been introduced. The experiment has been carried out at room temperature (21°C).



Figure S3. Evolution of the species distribution from 3.5 to 175h for an aqueous solution containing 50 mM of γ -CD and in which PW₁₂O₄₀³⁻ (25 mM) and PMO₁₂O₄₀³⁻ (25 mM) have been introduced. The experiment has been carried out at room temperature (21°C). The relative amount of each entity has been determined by integrating the ³¹P NMR resonances.



Figure S4. Top/ Time evolution of homometallic POM $PMo_{12}O_{40}^{3-}$ (left) and $PW_{12}O_{40}^{3-}$ (right) proportion of an aqueous solution containing 50 mM of γ -CD and in which $PW_{12}O_{40}^{3-}$ (25 mM) and $PMo_{12}O_{40}^{3-}$ (25 mM) have been introduced. Bottom/ First-order kinetics fitting of the decrease of the concentration of the homometallic POMs.

[γ–CD] (mM) / T°	k [₩] _{obs} (h⁻¹)	$t^W_{1/2}$	k ^{Mo} _{obs} (h ⁻¹)	$t^W_{1/2}$				
0/21°C	1.736	0.4 h	6.336	0.11 h				
25 / 21°C	0.324	2.1 h	0.786	0.89 h				
50 / 21°C	0.036	19 h	0.101	6.9 h				
75 / 21°C	0.013	53 h	0.036	19 h				
100 / 21°C	0.0009	32 d	0.002	15 d				

Table S2. Effect of $[\gamma-CD]$ on the observed rate constants of decomposition of PMo₁₂O₄₀³⁻ (k_{obs}^{Mo}) and PW₁₂O₄₀³⁻ (k_{obs}^{W}) and their related half-life of a first-order reaction ($t_{1/2}$).

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