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Sa Yao, Clement Falaise, Nathalie Leclerc, Catherine Roch-Marchal, Mohamed Haouas, et al.. Improvement of the Hydrolytic Stability of the Keggin Molybdo- and Tungsto-Phosphate Anions by Cyclodextrins. *Inorganic Chemistry*, 2022, 61 (9), pp.4193-4203. 10.1021/acs.inorgchem.2c00095 . hal-03642661

HAL Id: hal-03642661

<https://hal.science/hal-03642661>

Submitted on 30 May 2022

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Improvement of the Hydrolytic Stability of the Keggin Molybdo- and Tungsto-phosphate Anions by Cyclodextrins

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ABSTRACT: Keggin-type molybdo- and tungsto-phosphate polyoxoanions are among the most popular polyoxometalates (POMs), but suffer from their limited stability at low pH in aqueous solution. Their superchaotropic properties generate strong supramolecular complexes with cyclodextrins (CDs) which significantly affect the hydrolytic stability of POM. This chaotropically-driven stabilization effect was systematically monitored by ³¹P NMR spectroscopy covering a wide range of pH (from 0 to 8) and varying the nature of the CD (α -, β -, and γ -form). A shift of ca. two pH units of the stability domains of these POMs were found in the presence of two eq. γ -CD compared to pure water, leading to keep intact the $\text{PW}_{12}\text{O}_{40}^{3-}$ anion without any decomposition up to pH 3.5 (*versus* 1.5 in pure water) and pH 2.5 for $\text{PMO}_{12}\text{O}_{40}^{3-}$ which begins to decompose even at pH 0 in pure water. The effect of the smaller CDs (α - and β -form) is much less pronounced (only 0.5 pH units shift of stability domain) confirming the importance of host-guest size matching to form a sandwich-type inclusion complex, and thus protect the POM structure against basic hydrolysis. Such complexation was further supported by ¹⁸³W and ¹H NMR spectroscopy. Finally, using quantitative ³¹P NMR analyzes, the new speciation and formation constants of phosphomolybdates and phosphotungstates in the presence of cyclodextrins are determined and compared to those previously reported in pure water or in 50:50 water/1,4-dioxane mixture.

INTRODUCTION

The dodecamolybdophosphate and the dodecatungstophosphate are among the most known and studied polyoxometalates (POMs) due to their important properties valuable for many applications in various fields of research such as catalysis,^{1,2} energy,^{3,4} biology,⁵ and environment.^{6,7} This class of highly soluble metal-oxo clusters was first discovered by Berzelius in the early 19th century,⁸ but their structure was not determined until more than 100 years later by Keggin.⁹ The heteropolyanion is composed of a metal-oxo shell containing twelve MO₆ polyhedra (M = Mo^{VI} or W^{VI}) connected together that defined a central tetrahedral cavity in which a phosphorus atom P^V is located (Figure 1a), leading to a general chemical formula PM₁₂O₄₀³⁻, hereafter abbreviated {PM₁₂}. Due to their very low global charge, their stability in aqueous solution is weak and they only exist in strong acidic medium,^{10,11} that greatly limits their use at pH close to neutral or physiological medium. It is crucial that POM integrity should be demonstrated (e.g., by NMR) at pH 7-8 before performing any biomedical studies. There are several reports in the literature in which the POMs is certainly hydrolyzed at the pH conditions and concentrations employed, which raises the question: what is the actual speciation?¹² For instance, the use of Keggin-type polyoxotungstate and -molybdate, H₃PW₁₂O₄₀ and H₃PMo₁₂O₄₀, as disinfectants was reported by Bae et al.,¹³ who found a high photocatalytic inactivation of two different bacterial strains (*Escherichia coli* and *Bacillus subtilis*). In another study,¹⁴ in vitro inhibitory activity of 12-tungstophosphoric acid (H₃PW₁₂O₄₀), on E-NTPDase activity was shown using rat synaptic plasma membranes as a model system. The IC₅₀ value, calculated from concentration dependent sigmoidally-shaped inhibition curve, was in the micromolar range, 1.6 10⁻⁶ mol/L, even though monolacunary Keggin anion was found as the main active molecular species present under physiological conditions (in the enzyme assays, pH 7.4). Hydrolysis of these anions leads to highly charged lacunary Keggin-type POMs like PM₁₁O₃₉⁷⁻ (M = W or Mo) or PMo₉O₃₄⁹⁻ which dominate the phospho-tungstate or -molybdate speciation, respectively.¹¹ Although such a degradation process can be avoided in organic solvents,^{15,16} their utilization in biological systems remains hampered. Therefore, finding chemical additives to stabilize the phosphorus-based Keggin structure in aqueous solution is rather demanding for basic and application purposes.

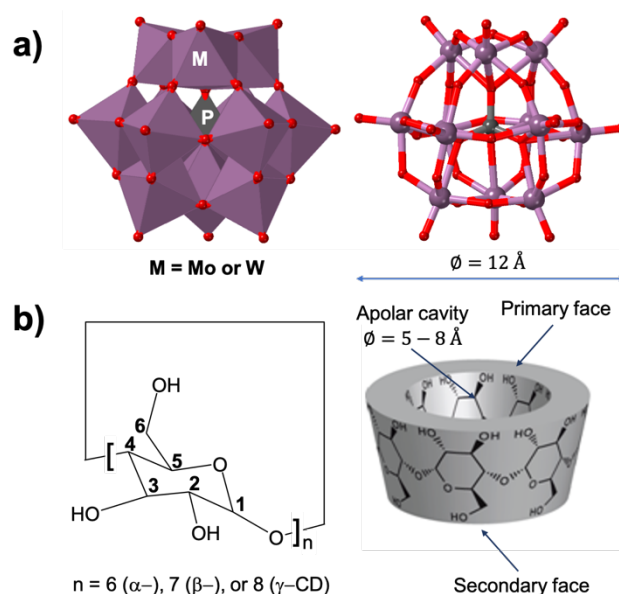


Figure 1. Structural representations of molecular objects used in this study: a) the Keggin-type POM $\{PM_{12}\}$ ($M = Mo$ or W), b) the macromolecular torus α -CD ($C_{36}H_{60}O_{30}$), β -CD ($C_{42}H_{70}O_{35}$), and γ -CD ($C_{48}H_{80}O_{40}$) resulting from condensation of 6, 7, and 8 glucopyranose units, respectively.

POMs have shown a remarkable ability to interact with organic and hybrid moieties to form supramolecular assemblies with specific physicochemical properties.^{17–19} For instance, Keggin-type anions are capable of forming non-covalent complexes in aqueous solution with the toroidal cyclodextrin (CD) macrocycles.^{16,20–26} Some of these CD/Keggin hybrids have shown improved properties in sensor²⁷, or in electrochemical energy storage,²⁸ highlighting the beneficial effects of these supramolecular composites. CDs are natural oligosaccharides made up of 6, 7, or 8 glucopyranose units leading to ring-shaped molecules of different sizes, denoted respectively by α -, β -, and γ -CD (Figure 1b). However, host-guest complexation was only observed with the larger γ -CD molecule which allows a perfect size matching between its inner macrocyclic cavity and the outer surface of the Keggin POM, leading to a 1:2 sandwich assembly with phosphomolybdate, $\{PMo_{12}\}@2\gamma$ -CD,²⁰ or to a 1:1 complex with phosphotungstate, $\{PW_{12}\}@ \gamma$ -CD,²³ while a simple adduct arising from weak mutual interactions was obtained with the smaller α -CD molecule, $\{PW_{12}\} \cdot \alpha$ -CD.²⁸ The crystallographic structures shown in Figure 2 revealed various modes of intermolecular hydrogen bonding, involving not only the outer wall of the CD but also the protons of the internal cavity through the primary or secondary face of the conical cavitaand, depending on

the type of the host-guest association. Indeed, the POM interacts with the larger secondary face in the 1:1 complex $\{PW_{12}\} \cdot \alpha\text{-CD}$, while in the case of the sandwich $\{PMo_{12}\} @ 2\gamma\text{-CD}$, the POM is connected to the CD through its smaller primary rim. In all cases, it is now accepted that the driving force of such supramolecular assemblies lies in the chaotropic effect which consists of a water structure recovery process resulting from the desolvation of the interacting components, namely the POM and organic cavitand.²⁹ Likewise, such an effect has also been observed in other processes involving Keggin POMs where solvation comes into play such as adsorption on micelle surfaces,^{30,31} on temperature-responsive polymer,³² or aggregation with proteins.³³ It has been shown that the chaotropic character of Keggin POMs increases with the decrease in their overall charge according to the Hofmeister series.^{25,29,30} Accordingly, host-guest stabilization of one of the less charged POMs, the Lindqvist anion $M_6O_{19}^{2-}$ with $M = Mo$ or W , was achieved in aqueous solution using $\gamma\text{-CD}$.³⁴ Thus, CDs can be used as trapping or stabilizing agents for elusive and unstable POMs.

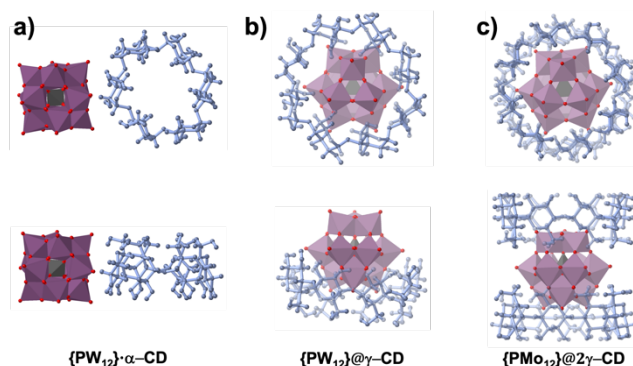


Figure 2. Top and side views of most representative known examples of cyclodextrin- $\{PM_{12}\}$ Keggin-type complexes: a) 1:1 adduct $\{PW_{12}\} \cdot \alpha\text{-CD}$, b) 1:1 host-guest complex $\{PW_{12}\} @ \gamma\text{-CD}$, and c) 1:2 host-guest sandwich-type complex $\{PMo_{12}\} @ 2\gamma\text{-CD}$.

The supramolecular interactions between Keggin POMs and CDs in solution can be studied and followed, primarily by nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry.^{16,22,25,26} However, these studies have rarely been conducted in POM stabilization context and no systematic pH study has been reported so far. The scope of this report will then focus on the

impact of this crucial parameter, namely pH, for the POMs chemistry, hitherto ignored in previous studies about POM-CD systems. Indeed, the acidic polycondensation and basic hydrolysis of metal oxides are processes mainly governed by the pH. In this contribution, we provide a detailed ^{31}P NMR study on the CDs stabilizing effect of Keggin phospho-tungstate and -molybdate POMs over a wide range of pH. The phosphates speciation and the related formation constants are modeled in various systems studied, demonstrating the influence of CDs for expanding the pH domain of the $\text{PW}_{12}\text{O}_{40}^{3-}$ and $\text{PMo}_{12}\text{O}_{40}^{3-}$ anions.

EXPERIMENTAL SECTION

Chemicals and POM syntheses. All reagents were purchased from commercial sources and used without further purification. Solutions were prepared in Milli-Q water. $\text{H}_3[\text{PW}_{12}\text{O}_{40}]\cdot 9\text{H}_2\text{O}$,³⁵ and $\text{H}_3[\text{PMo}_{12}\text{O}_{40}]\cdot 29\text{H}_2\text{O}$,³⁶ were synthesized and purified according to published procedures. The purity and chemical composition of the POMs were confirmed by EDS, TGA, multinuclear NMR (^{31}P and ^{183}W) and FT-IR spectroscopies. For $\text{H}_3[\text{PW}_{12}\text{O}_{40}]\cdot 9\text{H}_2\text{O}$: EDS, obs. W/P: 12/1.4. TGA showed a weight loss of 5.3% in the 30-600 °C temperature range corresponding to 9 water molecules (calculated 5.3%), due to both crystal lattice and hydration water. ^{31}P and ^{183}W NMR (90 mM in D_2O), $\delta_{31\text{P}}$ -14.3 ppm, $\delta_{183\text{W}}$ -97.4 ppm, $^2J_{\text{W-P}}$ 1.1 Hz. FT-IR (Diamond ATR, ATR correction applied) ν (cm^{-1}) 1074 (P-O_a), 974 (W=O_t), 899 (W-O_b-W), 779 (W-O_c-W). For $\text{H}_3[\text{PMo}_{12}\text{O}_{40}]\cdot 29\text{H}_2\text{O}$: EDS, obs. Mo/P: 12/1.1. TGA showed a weight loss of 22% in the 30-600 °C temperature range corresponding to 29 water molecules (calculated 22%). ^{31}P NMR (80 mM in 50:50 D_2O :1,4-dioxane + one drop HCl 6 M), $\delta_{31\text{P}}$ -3.2 ppm. FT-IR (Diamond ATR, ATR correction applied) ν (cm^{-1}) 1076 (P-O_a), 958 (Mo=O_t), 875 (Mo-O_b-Mo), 784 (Mo-O_c-Mo).

Physical methods. Fourier transform infrared (FT-IR) spectra were recorded on a 6700 FT-IR Nicolet spectrophotometer, using the diamond ATR technique. The spectra were recorded on non-diluted compounds and ATR correction was applied. Energy-dispersive X-ray spectroscopy (EDS) measurements were performed using a SEM-FEG (scanning electron microscope enhanced by a field emission gun) equipment (JSM 7001-F, Jeol). The measures were

acquired with a SDD XMax 50 mm² detector and the Aztec (Oxford) system working at 15 kV and 10 mm working distance. The quantification is realized with the standard library provided by the constructor using $L\alpha$ lines. To determine water contents, thermal gravimetric analysis (TGA) measurements were performed using a Mettler Toledo TGA/DSC 1, STAR^o System apparatus under oxygen flow (50 mL min⁻¹) at a heating rate of 5 °C min⁻¹ up to 700 °C.

Nuclear magnetic resonance. NMR spectra were measured in D₂O at 28 °C. ¹H and ³¹P NMR spectra were recorded on a Bruker Avance 400 spectrometer at Larmor frequencies of 400.1 and 162.0 MHz, respectively, using 5 mm standard NMR tubes. The ¹⁸³W NMR spectra were obtained with 10 mm NMR tubes and a Bruker Avance 500 spectrometer operating at a Larmor frequency of 20.8 MHz. The ¹H NMR spectra were recorded with one pulse sequence at 30° flip angle (pulse duration 2.7 μs), using 0.1 s recycle delay, 3 s acquisition time, and 8 number of scans. The ³¹P spectra were recorded in quantitative mode with a 90° pulse of duration 16 μs and a length of free induction decay 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 8 to more than 1000. The duration of an experiment then varied from 30 min to more than 10 h. The ¹⁸³W spectra were performed with a Hahn echo sequence using a 90 ° pulse of 37 μs, a relaxation delay of 2 s and a scan number of over 30,000. Chemical shifts are scaled with respect to standards ($\delta = 0$ ppm): Me₄Si (1% CDCl₃) for ¹H, 85 wt% H₃PO₄ for ³¹P, and Na₂WO₄ (D₂O, 1 M) for ¹⁸³W.

Samples preparation. The solutions were prepared in D₂O. Each sample was prepared from stock solutions of POM (80-100 mM H₃PW₁₂O₄₀ or H₃PMo₁₂O₄₀) and each CD (α -, β -, or γ -CD) which are mixed in known proportions to make 1- or 3-mL final solutions. The volume was adjusted with D₂O to achieve the desired concentrations of POM and CD. Usually, the POM solution was added last. The pH of the solutions is measured systematically and adjusted with concentrated solutions of NaOH (6-12 M). The samples were then transferred into 5 mm (600 μL) NMR tubes for the ¹H and ³¹P analyzes, or 10 mm (2.5 mL) tubes for the ¹⁸³W analyzes. The pH can change over time (especially for tungstate samples). pH measurements were then taken at each start and end of an NMR experiment, which can last several hours. Similar series were also prepared in pure D₂O or in a 50:50 v/v D₂O/1,4-dioxane mixture for comparison.

RESULTS AND DISCUSSION

Before studying the stabilizing role of CDs on $\text{PW}_{12}\text{O}_{40}^{3-}$ and $\text{PMo}_{12}\text{O}_{40}^{3-}$, we must first understand their mutual interaction. Such an interaction should be strong and comparable owing to their similar low charge.^{20,24} Indeed, the main factor affecting the strength of the attractive association of CDs with a given POM of comparable size and shape is its overall charge which is directly related to its solvation properties and its chaotropic character.²⁵ However the size of the cavitand should also be taken under consideration, as this has been reported in similar host-guest systems.^{37,38} In their pioneer work, Stoddart et al. had also shown significant differences in the behavior of $\text{PMo}_{12}\text{O}_{40}^{3-}$ when it reacted with γ - or β -CD.²⁰ Here, we systematically reinvestigate the behavior of these two POMs in the presence of the three types of native CD.

Titration of CDs with POMs. The study of the interaction of Keggin-type POMs with cyclodextrins was carried out by proton NMR through the variation of the chemical shifts of the six types of protons in the molecule, labelled from H1 to H6 (see Figure 1). These experiments consisted of the preparation of aqueous solutions of 4 mM CD to which is added a variable number of equivalents of $\text{PW}_{12}\text{O}_{40}^{3-}$ or $\text{PMo}_{12}\text{O}_{40}^{3-}$ anions. The pH in these solutions was not controlled and varied from ca. 0.5 to 2 depending on the proportion of the POM. The purpose of this titration is to identify the protons that will be most affected and to assess its magnitude as a result of the interaction between the POM and the CD. The anomeric position signal (H1) appears shielded (~5 ppm) and is usually the least sensitive. Protons pointing towards the cavity (H3 and H5) and from the methoxy group (H6) are generally the most subject to interactions with guest molecules. The shape of the spectra and the effects of the presence of POM are different depending on the size of the CD. However, similar results were obtained with the two POMs, i.e., $\text{PW}_{12}\text{O}_{40}^{3-}$ and $\text{PMo}_{12}\text{O}_{40}^{3-}$, confirming that the nature of the metal center does not affect the interaction with the CD. The spectra of molybdenum-based systems are shown in Figure 3, while those of the tungsten-analogues are supplied in Figures S1-S3, in Supporting Information (SI).

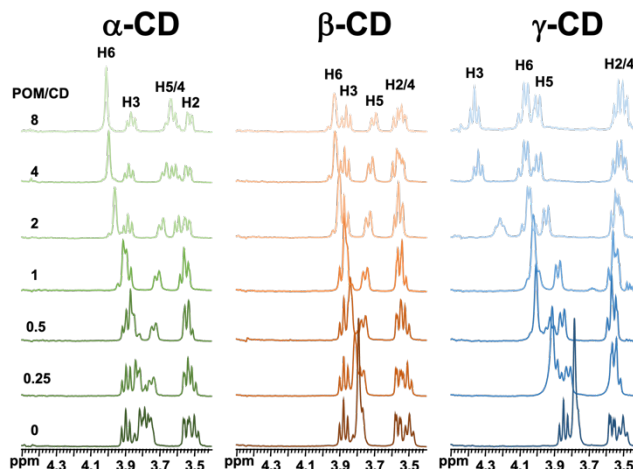


Figure 3. Partial ^1H NMR spectra (from left to right) of 4 mM α -CD, β -CD, and γ -CD after adding increasing amounts of $\text{PMo}_{12}\text{O}_{40}^{3-}$ up to 8 equivalents.

The interaction of γ -CD with $\{\text{PW}_{12}\}$ species has been extensively studied by our group.^{24,25} It has been shown very strong interaction leading to inclusion complexes with association constants of the order of 10^5 M^{-1} . Figure 3 shows the evolution of the ^1H NMR spectra of a 4 mM γ -CD solution with gradual addition of increasing amount of $\{\text{PMo}_{12}\}$ up to 8 equivalents. The evolution of the spectra is very similar to that observed with $\{\text{PW}_{12}\}$ (see Figure S1, in SI),²⁵ but different from that reported by Stoddard et al.,²⁰ probably because of the difference in experimental conditions (our solutions being 4 times more concentrated). As expected, H2 and H4 show negligible effect with only a slight chemical shift variation for H4. However, strong interactions are observed with H5 and H6, undergoing a clear deshielding with a slightly less effect on H5 in the case of $\{\text{PMo}_{12}\}$ compared to $\{\text{PW}_{12}\}$. Nevertheless, H3 is the most interacting hydrogen, as shown by about 0.7 ppm variation for large POM/CD ratio. Thus, γ -CD appears to interact with POM preferentially through H3 and H5 hydrogens when encapsulated in its cavity. The interaction with the primary face of γ -CD is then privileged as shown by the variations observed on H6. This confirms the mode of POM insertion into the γ -CD cavity from the primary rim.

As it has been demonstrated in previous studies,²⁵ the driving force behind such an association arises from the chaotropic nature of POM which facilitates its desolvation and thus promotes inclusion complexation.

The titration of 4 mM β -CD solution by $\{\text{PMo}_{12}\}$ is shown in Figure 3, and compares well with that obtained with $\{\text{PW}_{12}\}$, shown in Figure S2, in SI.²⁶ The six types of protons (H1-H6) of the glucopyranose unit show the same NMR signature as their counterpart in the γ -CD molecule. The six signals are resolved with the exception of those attributed to H5 and H6 which overlap mutually. The introduction of the POM in aqueous solution makes it possible to distinguish perfectly the two signals moving each in the opposite direction of the other. No significant effect can be seen for H2 and H3, while H4 and H5 undergo a slight chemical shift of about 0.1 ppm. The hydrogen which interacts the most is H6 shifting of more than 0.15 ppm from the first POM additions and reaches a plateau for four equivalents of POM. These results indicate that interactions occur mainly with the primary face of the CD, but no deep inclusion within the organic macrocycle was evidenced since the chemical shift of the internal H3 proton appears quite unaffected. Actually, the supramolecular recognition process involving β -CD and Keggin-type anion exhibits weak selectivity due because the host-guest pairing does not allow the desolvation of the POM unit as observed in inclusion complexes built with γ -CD.

In a similar way, a 4 mM solution of α -CD is titrated with the $\{\text{PW}_{12}\}$ or $\{\text{PMo}_{12}\}$ Keggin-type POMs, and the resulting NMR spectra are shown in Figure 3 for $\{\text{PMo}_{12}\}$ and Figure S3, in SI, for $\{\text{PW}_{12}\}$. The six proton types of α -CD are observed as before with a difference in the shape of the H6 signal which changes from a multiplet to a singlet during the titration.

As in the case of β -CD, the signals of the hydrogen H2 and H3 exhibit only slight shifts. The resonances of the H4 and H5 hydrogens change by ca. 0.1 ppm and reach a plateau at around two equivalents of POM. Finally, the H6 hydrogen undergoes the largest shift of its signal from 3.8 to almost 4.0 ppm after adding about four equivalents of POM. Thus, the interactions between α -CD and POM are probably similar to those demonstrated with β -CD, indicating POM-CD interactions mostly occur at the exposed outer wall of the CD and its primary face. It also confirms that like β -CD, α -CD is too small to entirely accommodate POM in its cavity.

In summary, the $\{\text{PMo}_{12}\}$ or $\{\text{PW}_{12}\}$ Keggin-type anions behave similarly toward CD (see the comparison of ^1H chemical shifts in Figure S4, in SI). However, the three CDs interact with the Keggin POM in different ways. The α - and β -CD interact mostly with their outer surface, while γ -CD leads to the usual host-guest inclusion, involving internal

cavity. It then becomes interesting to know whether such contrasted supramolecular behavior could have consequences in the particular context of the hydrolytic stability of POMs in aqueous solution.

Monitoring hydrolytic stability by ^{31}P NMR. The stability of $\text{PW}_{12}\text{O}_{40}^{3-}$ in pure water and in presence of two eq. of the three forms of CD (α -, β -, and γ -CD) was studied over a pH range from 0 to 8.5 by ^{31}P NMR. The concentration of the POM was kept constant and the pH was adjusted using concentrated NaOH solutions. The POM concentration was fixed at 95 mM for the pure water series, and at 60 or 7.5 mM for two eq. γ -CD (120 mM) or β -CD (15 mM) series, taking into account the solubility limits of each CD, respectively. In the case of α -CD series, we observed a white solid precipitate when mixing with phosphotungstic acid in a concentrated system. Such a precipitate would correspond to a CD-POM composite analogous to that reported by Khashab et al.,²⁸ since IR spectroscopy showed the presence of both the characteristic vibration bands of α -CD and $\{\text{PW}_{12}\}$. Then, we had to reduce the concentrations down to 7.5 mM POM and 15 mM α -CD in order to avoid any precipitations. Representative ^{31}P NMR spectra obtained for the pure water system, compared to those contained two equivalents of α - and γ -CD are shown in Figure 4. The overall spectra as well as those of the series with 2 eq. β -CD are given in Figures S5-S8.

The hydrolytic conversions of $\{\text{PW}_{12}\}$ anion have been extensively studied by Maksimovskaya using ^{31}P NMR, and more recently the previously published work in the field, including her research, has been carefully reviewed, providing the most comprehensive hydrolysis scheme, currently existing.^{10,39} The present study allows identifying at least 4 main signals in addition to the signal of the parent Keggin POM $\{\text{PW}_{12}\}$, labelled A, B, C, H and F according to the notation of Maksimovskaya and Maksimov.¹⁰ The assignment of these ^{31}P NMR resonances is reported in Table 1, based on this review,¹⁰ although the authors did not provide a clear assignment for the H and F signals.

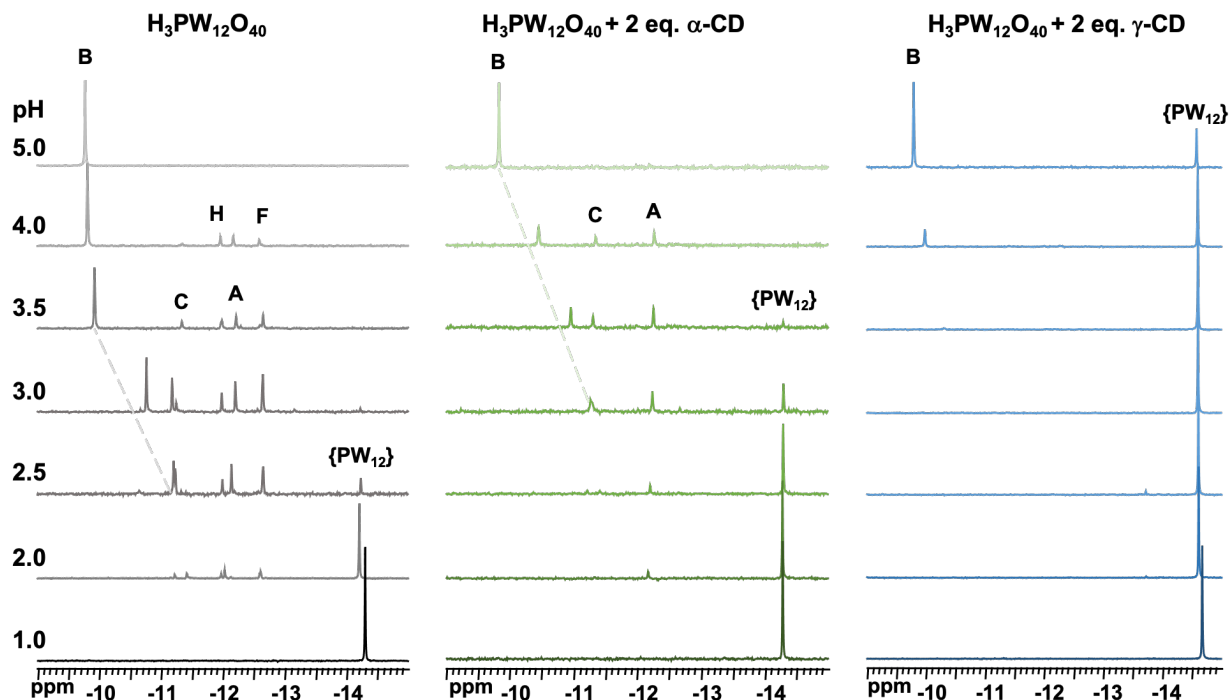


Figure 4. Representative ^{31}P NMR spectra (from left to right) of 95 mM $\text{H}_3\text{PW}_{12}\text{O}_{40}$ in D_2O , 7.5 mM $\text{H}_3\text{PW}_{12}\text{O}_{40}$ in presence of 15 mM $\alpha\text{-CD}$ in D_2O , and 60 mM $\text{H}_3\text{PW}_{12}\text{O}_{40}$ in presence of 120 mM $\gamma\text{-CD}$ in D_2O , at various pH, adjusted with concentrated NaOH.

Table 1. Assignment of Main ^{31}P NMR Signals from Degradation of $\text{H}_3\text{PW}_{12}\text{O}_{40}$.

Label	Species	^{31}P shift (ppm)	Reference
{PW ₁₂ }	$\text{PW}_{12}\text{O}_{40}^{3-}$	-14.3 to -14.2	39
A	$\text{PW}_{11}\text{O}_{39}\cdot\text{WO}_2^{5-}$	-12.3 to -12.0	39
B	$\text{PW}_{11}\text{O}_{39}^{7-}$	-11.4 to -9.8	39
C	$(\text{PW}_{11}\text{O}_{39})_2\text{WO}_2^{12-}$	-11.3 to -11.2	10
H	$\text{P}_2\text{W}_{20}\text{O}_{70}(\text{H}_2\text{O})_2^{10-}$	-12.6 to -12.5	40
F	$\text{P}_2\text{W}_{21}\text{O}_{71}(\text{H}_2\text{O})_5^{6-}$	-12.0	41

At very low pH, the -14.3 ppm resonance is attributed to {PW₁₂}. As shown in Figure S5, the hydrolytic degradation of the {PW₁₂} occurs as soon as pH > 1.5. From a pH 1.8 solution, many new signals in the [-10.5 ; -13.5 ppm] range arise due to the hydrolytic degradation of the {PW₁₂} anion. These species (labelled A, B, C, H, and F) grow as the pH increases to the detriment of the {PW₁₂} anion which disappears at pH 2.5. It is also possible that the monovacant $\text{PW}_{11}\text{O}_{39}^{7-}$ species, labelled B and abbreviated {PW₁₁} hereafter, begins to form in this pH range but remains as minor product. From pH = 3.9, the {PW₁₁} anion becomes predominant, while the other

intermediates have almost entirely disappeared. Furthermore, the signal attributed to $\{PW_{11}\}$ is very pH dependent and stabilizes around -9.7 ppm in the 4-8 pH range. Because the resulting transient cationic species $WO_2(H_2O)_4^{2+}$ and $WO(H_2O)_5^{4+}$ arising from the $\{PW_{12}\}$ hydrolysis would be stabilized in acidic medium, they should be trapped by vacant POMs forming various complexes such as $PW_{11}O_{39}\cdot WO_2^{5-}$ (species A), $(PW_{11}O_{39})_2WO_2^{12-}$ (species C), $P_2W_{20}O_{70}(H_2O)_2^{10-}$ (species H), and $P_2W_{21}O_{71}(H_2O)_3^{6-}$ (species F). These two latter correspond to sandwich-mike POMs resulting from assemblies of two trilacunary Keggin $PW_9O_{34}^{9-}$ linked by two or three W centers, have been isolated by Tourné et al.,^{40,41} and their ^{31}P NMR spectrum is consistent with such assignments.

Similar studies were performed in presence of two eq. α - and β -CDs. The ^{31}P NMR spectra corresponding to the α -CD system (see Figure 4), reveal that the first intermediate, species A ($PW_{11}O_{39}\cdot WO_2^{5-}$) appears at pH 2. This species continues to form accompanied by a second intermediate, the species C ($(PW_{11})_2WO_2$). Nevertheless, the most abundant species that forms corresponds to the monovacant $\{PW_{11}\}$ anion. Furthermore, it can be worth noting that the presence of α - or β -CD reduces the number of intermediates generated from the $\{PW_{12}\}$ degradation. Indeed, the species H ($P_2W_{20}O_{70}(H_2O)_2^{10-}$) and F ($P_2W_{21}O_{71}(H_2O)_3^{6-}$) do not appear here, while the species C ($(PW_{11})_2WO_2$) and A ($PW_{11}\cdot WO_2$) persist over an extended pH range. Similar distribution of species is also observed with β -CD (see Figure S7, in SI), indicating that α - and β -CD produce the same effects upon the hydrolytic behavior of the $\{PW_{12}\}$ anion.

In the presence of two eq. γ -CD, the chemical system becomes remarkably simple and restricted to the $\{PW_{12}\}$ anion and its hydrolysis product $\{PW_{11}\}$ (see Figure 4). For pH < 3.5, only $\{PW_{12}\}$ is present while for pH 4, its intensity ratio decreases in favor of that of the resonance attributed to $\{PW_{11}\}$ (labelled B). The pH must be increased up to 6.7 to observe the complete disappearance of the $\{PW_{12}\}$ in favor of $\{PW_{11}\}$. Then, no intermediates were observed in this system, and the stability of $\{PW_{12}\}$ was found to be extended at much higher pH.

As already shown, the $\{PW_{12}\}$ anion appears very sensitive to pH and hydrolysis equilibria take place as soon as pH = 1.7. Decomposition leads to numerous degradation products but the monovacant POM $\{PW_{11}\}$ becomes predominant from pH 3.5. In the presence of α -CD or β -CD, much fewer intermediate species were observed and only those based on the $\{PW_{11}\}$ fragment

persist. However, the most dramatic effect is observed with γ -CD which suppresses all intermediate species and improves the stability of $\{PW_{12}\}$ at significantly higher pH up to 6.

The stability of $PMo_{12}O_{40}^{3-}$ in pure D_2O and in the presence of two eq. of γ -CD as well as in a 50:50 v/v D_2O :1,4-dioxane mixture, was studied over a pH range of 0 to 7 by ^{31}P NMR. The concentration of POM was kept constant at 60 mM in all three systems and the pH was adjusted using concentrated NaOH solutions. Figure 5 shows representative ^{31}P NMR spectra obtained from these three systems, while spectra of full series are shown in Figures S9-S11, in SI. The degradation of Keggin POM $\{PMo_{12}\}$ in water with increasing pH have been reported in the literature, and the ^{31}P NMR spectra obtained in this study (see Figure 5) are comparable to those published.⁴²⁻⁴⁵ The four main identified POM species resulting from the $\{PMo_{12}\}$ decomposition in the pH range 0-7 are $PMo_{11}O_{39}^{7-}$ ($\{PMo_{11}\}$), A- $PMo_9O_{31}(H_2O)_3^{3-}$ (A- $\{PMo_9\}$), B- $H_2PMo_9O_{34}^{7-}$ (B- $\{PMo_9\}$), and $P_2Mo_5O_{23}^{6-}$ ($\{P_2Mo_5\}$) (see Table 2).

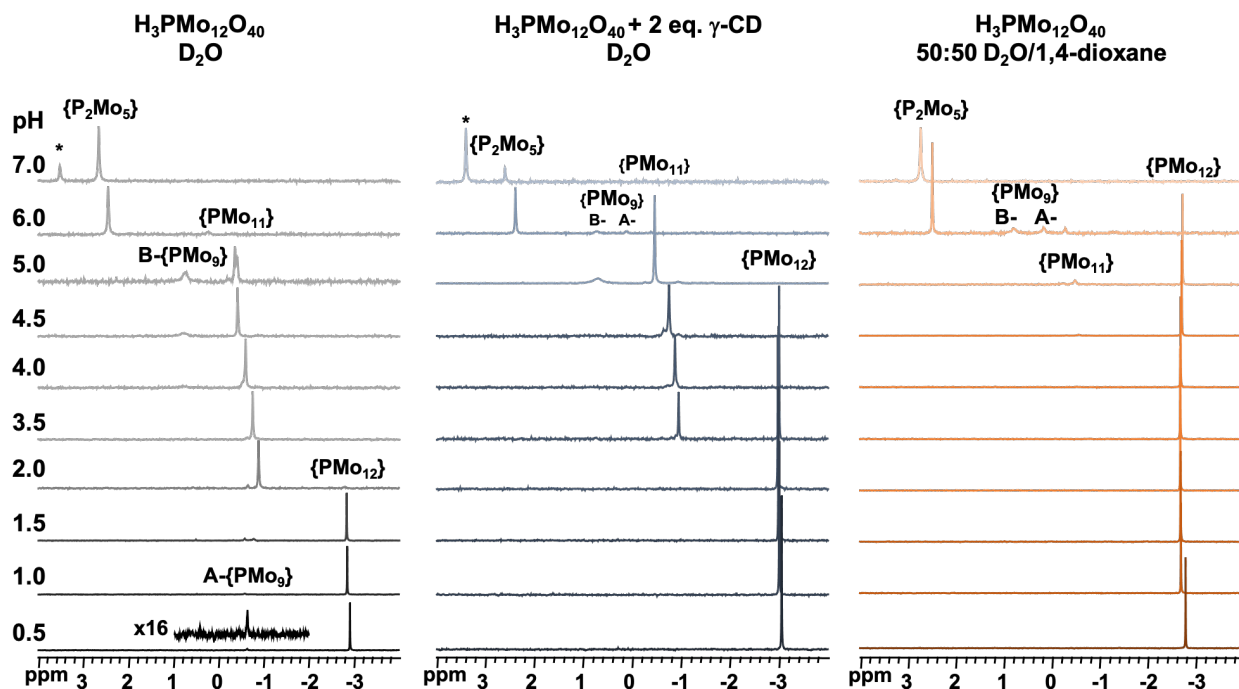


Figure 5. Representative ^{31}P NMR spectra of 60 mM $H_3PMo_{12}O_{40}$ (from left to right) in pure D_2O , in presence of 120 mM γ -CD in D_2O , and in 50:50 v/v D_2O :1,4-dioxane, at various pH, adjusted with concentrated NaOH. Asterisk indicates free phosphate $H_2PO_4^-$.

Table 2. Assignment of Main ^{31}P NMR Signals from Degradation of $\text{H}_3\text{PMo}_{12}\text{O}_{40}$.

Label	Species	^{31}P shift (ppm)	Reference
{PMo ₁₂ }	PMo ₁₂ O ₄₀ ³⁻	-2.9 to -2.8	46
{PMo ₁₁ }	PMo ₁₁ O ₃₉ ⁷⁻	-0.9 to +0.2	46
A-{PMo ₉ }	A-PMo ₉ O ₃₁ (H ₂ O) ₃ ³⁻	-0.8 to -0.6	46
B-{PMo ₉ }	B-H ₂ PMo ₉ O ₃₄ ⁷⁻	+0.7 to +0.8	46
{P ₂ Mo ₅ }	P ₂ Mo ₅ O ₂₃ ⁶⁻	+2.3 to +2.7	47

In pure D₂O system (Figure 5), the ca -3 ppm resonance is attributed to {PMo₁₂} and the two other minor signals at -0.6 and 0.4 ppm are assigned to the A-{PMo₉} species and to free phosphates H₃PO₄/H₂PO₄⁻, respectively. These species are not synthetic impurities but identified as decomposition products since they are absent in the 50/50 v/v mixture of D₂O/1,4-dioxane medium. From pH = 1.6, many new signals begin to appear between -1 and +3.4 ppm due to the decomposition species of {PMo₁₂}. The amount of these species increases with pH to the detriment of {PMo₁₂} which disappears at a pH approximately equal to 2. The {PMo₁₁} anion is formed from pH = 1.6 and becomes predominant until pH = 4.5. For pH = 5, we observe the formation of the trivacant Keggin-type anion B-{PMo₉} identified by the resonance at +0.6 ppm. Above pH = 6, the solution is dominated by the presence of the {P₂Mo₅} species and solvated phosphates H₂PO₄⁻/HPO₄²⁻ observed respectively at +2.4 ppm and +3.4 ppm.

In the presence of two eq. γ -CD, the ^{31}P NMR spectra (Figure 5) show the presence of only {PMo₁₂} for pH < 2.8, but its signal decreases in intensity to the detriment of the signal of {PMo₁₁} when pH increases. The complete disappearance of {PMo₁₂} occurs at approximately pH = 4.2. The formation of the {PMo₁₁} anion occurs until pH = 6 associated with the presence of the A- and B-forms of the lacunar {PMo₉}, as minor species. The stabilizing effect of γ -CD on {PMo₁₂} is evidenced by two observations. The first one lies on the fact that {PMo₁₂} can be dissolved in water without any decomposition as in a mixed hydro-organic medium. The second observation arises from the pH domain of the {PMo₁₂} presence which is extended to more than two pH units. However, no significant change in phosphate speciation could be observed for pH above 5, where highly charged {PMo₁₁} converts into {P₂Mo₅} and free phosphates as observed in pure water. There is almost no action of the γ -CD in this pH range from 5 to 7.

Finally, we also carried out the same experiments in a mixture 50:50 v/v D₂O:1,4-dioxane 50/50, known to stabilize the {PMo₁₂} POM, with the purpose to compare the influence of the CD with those of the medium (Figure 5). Only the ³¹P NMR {PMo₁₂} signal is visible over a wide pH range from 0.5 to 4.5. It is remarkable to note the presence of the monovacant {PMo₁₁} and trivacant {PMo₉} anions only as minor products. However, the fraction of {PMo₁₂} decreases until disappearance at pH ca. 7 in favor of {P₂Mo₅} as the major end-product. The comparison clearly showed that γ -CD acts as a very good specific stabilizer for the {PMo₁₂} anion. Even if the hydro-organic mixture makes possible to expand the hydrolytic stability of the {PMo₁₂} species until pH = 5-6, it should be worth noting that such a comparison requires activity corrections which were not taken into account in this study.

Phosphate speciation. The previous results showed that distribution of the P-containing species is dependent on the nature of the medium, which can shift the thermodynamic equilibria. From these experimental measurements, the fraction of the phosphate species can be plotted as a function of the pH for the different media such as pure water (D₂O), in the presence of two eq. CD (α -, β -, or γ -form), and in 50:50 v/v D₂O:1,4-dioxane, hydro-organic mixture (Figures 6 and 7). The curves are calculated to best fit our experimental data, making it possible to estimate the formation constants of the various POMs identified during the degradation process of the Keggin-type anion. For this, we use the individual formation equilibria associated to the formation of each species (see section S3 in SI). The formation constants of phosphates, isopolyoxomolybdates, and isopolyoxotungstates are taken from the literature.³⁴ For phospho-molybdates and -tungstates, their constants were optimized as a function of the medium to best fit the experimental data. Tables 3 and 4 gather our results and compare them with data from literature when available.

We did not find in the literature any formation constants related to the formation of phosphotungstates species. Nevertheless, the constant values corresponding to the formation of {PW₁₂} and {PW₁₁} (Table 3) are 40 orders of magnitude higher than their molybdenum analogues, confirming that phosphotungstate POMs are thermodynamically more stable than their molybdenum equivalents. The presence of CDs led to a significant increase in the formation constant of {PW₁₂} by 14 orders of magnitude with α - and β -CD and by 25 orders of magnitude with γ -CD. Such a stabilizing effect of the {PW₁₂} anion takes place at the expense of other less stable POMs such as {P₂W₂₀} and {P₂W₂₁} anions. For phosphomolybdate speciation, our

calculations compare well with published data (see Table 4).⁴⁶ The stability constant of the $\{PMo_{12}\}$ anion increases by 10 orders of magnitudes in the presence of γ -CD, but also remains ca. 10 orders of magnitude lower than the value observed in the mixture 50:50 v/v D_2O :1,4-dioxane. The equilibrium shifts affect mainly the stability domain of $\{PMo_{11}\}$, which disappears almost completely in aquo-organic medium but still persists in water with the presence of γ -CD although considerably reduced (see Figure 7). These results confirm quantitatively the stabilizing influence of CDs.

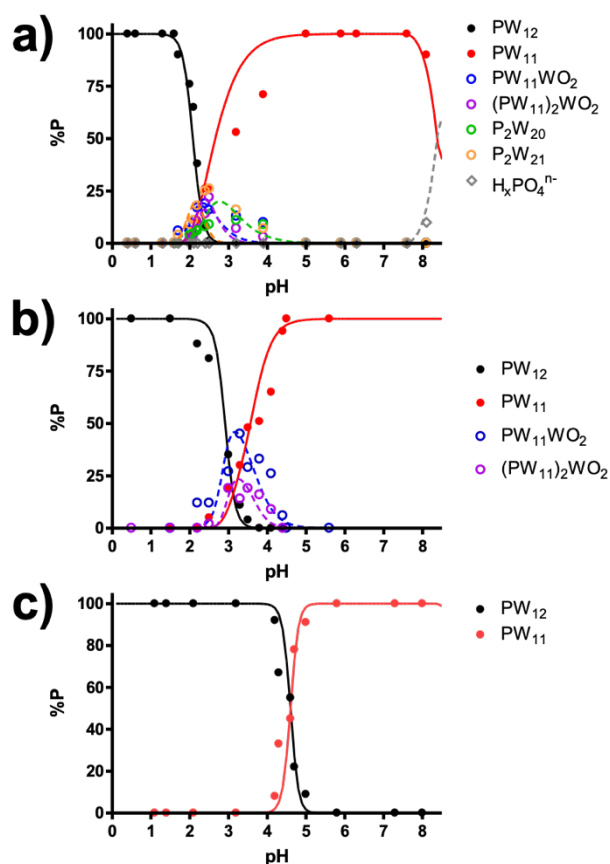


Figure 6. Phosphate species distribution in a) 95 mM $H_3PW_{12}O_{40}$ in D_2O , b) 7.5 mM $H_3PW_{12}O_{40}$ in presence of 15 mM α -CD in D_2O , and c) 60 mM $H_3PW_{12}O_{40}$ in presence of 120 mM γ -CD in D_2O , from ^{31}P NMR spectra. The computed curves correspond to the best fits of experimental data using formation constants reported in Table 3.

Table 3. Formation Constants (Log*K*) at 28 °C of Phosphotungstate Species Calculated from Degradation of H₃PW₁₂O₄₀, in Pure Water (D₂O), and in Presence of two eq. α-, β-, and γ-CD.

species	Protonation state	2 eq. γ-CD in D ₂ O	2 eq. β-CD in D ₂ O	2 eq. α-CD in D ₂ O	D ₂ O
{PW ₁₂ }	PW ₁₂ O ₄₀ ³⁻	208.0	196.6	196.6	183.1
{PW ₁₁ }	PW ₁₁ O ₃₉ ⁷⁻	175.0	170.2	170.5	160.2
{(PW ₁₁)WO ₂ }	PW ₁₁ O ₃₉ WO ₂ (OH) ⁶⁻		187.7	187.7	176.0
{(PW ₁₁) ₂ WO ₂ }	(PW ₁₁ O ₃₉) ₂ WO ₂ ¹²⁻		363.3	363.5	340.0
{P ₂ W ₂₀ }	P ₂ W ₂₀ O ₇₀ (OH) ₂ ¹²⁻				299.3
{P ₂ W ₂₁ }	P ₂ W ₂₁ O ₇₁ (OH) ₃ ⁹⁻				320.2

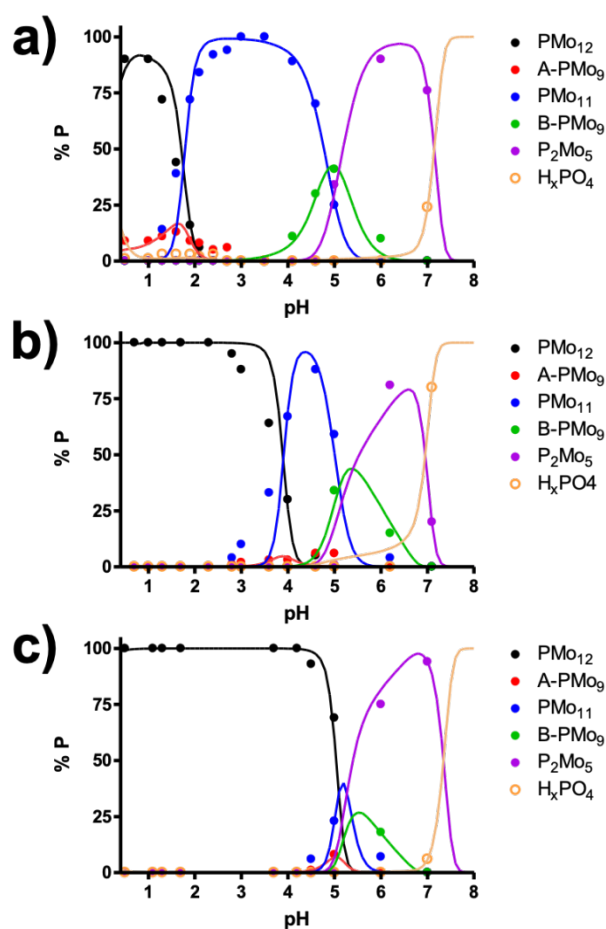


Figure 7. Phosphate species distribution of 60 mM H₃PMo₁₂O₄₀ in a) D₂O, b) presence of 120 mM γ-CD in D₂O, and c) 50:50 v/v D₂O:1,4-dioxane, from ³¹P NMR spectra. The computed curves correspond to the best fits of experimental data using formation constants reported in Table 4.

Table 4. Formation Constants (LogK) at 28 °C of Phosphomolybdate Species Calculated from the degradation of H₃PMo₁₂O₄₀, in Water (D₂O), with two eq. γ -CD or in 50:50 v/v D₂O/1,4-Dioxane Mixture.

species	Protonation state	50:50 D ₂ O:Dioxane	2 eq. γ -CD in D ₂ O	D ₂ O	Literature ^a
{PMo ₁₂ }	PMo ₁₂ O ₄₀ ³⁻	159.7	152.3	142.7	139.7
{PMo ₁₁ }	PMo ₁₁ O ₃₉ ⁷⁻	127.0	125.2	125.3	118.7
A-{PMo ₉ }	A-PMo ₉ O ₃₁ (H ₂ O) ₃ ³⁻			111.1	107.2
A-{PMo ₉ }	A-PMo ₉ O ₃₁ (OH)(H ₂ O) ₂ ⁴⁻	116.9	112.9		104.7
B-{PMo ₉ }	B-H ₂ PMo ₉ O ₃₄ ⁷⁻			101.1	104.9
B-{PMo ₉ }	B-HPMo ₉ O ₃₄ ⁸⁻	96.6	95.5		102.0
{P ₂ Mo ₅ }	P ₂ Mo ₅ O ₂₃ ⁶⁻	86.1	83.4	84.7	62.0

a) At 25 °C, ionic strength $\mu = 3$ M (NaCl), from reference⁴⁶.

Evidence of the stabilizing role of host-guest complexation. Clearly, the presence of CDs, and particularly the γ -form, improves the stability of the phosphorus-containing Keggin-type POMs. In this section, we will focus on the mechanism of such the stabilizing role. In particular, we will further demonstrate the protective role of supramolecular inclusion complexation against hydrolytic attack of water.

Figure 8 shows the ¹H NMR spectra of a 60 mM solution of {PW₁₂} in the presence of γ -CD at 120 mM at various pH (the same solutions studied by ³¹P NMR and shown in Figure 4). Before addition of the base (6 M NaOH), the spectrum shows a characteristic feature of a solution in the POM/ γ -CD = 0.5 molar ratio observed previously in Figure 3. Such a broadening is characteristic of strong host-guest inclusion complexation. When the pH increases up to 4 only slight shifts in the signals are observed due mostly to the pH effect. From pH 4, the spectrum in the region of H₄/H₂ hydrogens (3.4-3.6 ppm) begins to change. From pH 7, the triplet signal of hydrogen H₃ at ca. 3.9 ppm narrows considerably and the spectra evolve back to the initial signature of free γ -CD. This indicates that cyclodextrin no longer interacts with POMs due to their degradation at neutral pH. According to the ³¹P NMR, the Keggin {PW₁₂} ion disappears completely at pH 6, which corresponds to the change of the ¹H NMR spectrum shape.

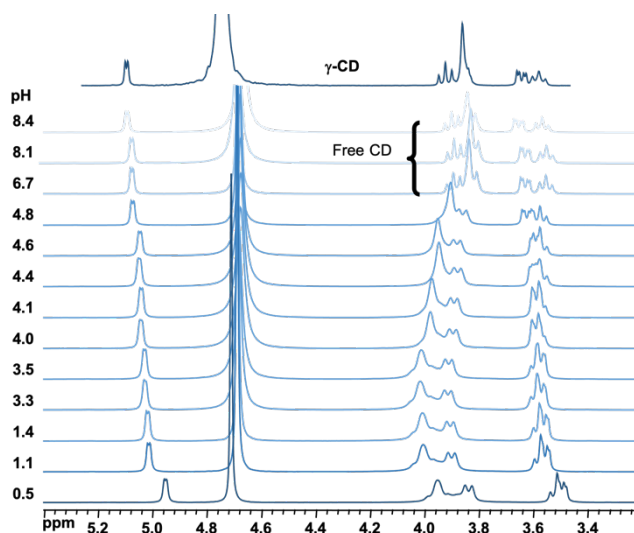


Figure 8. ^1H NMR spectra of 60 mM $\text{H}_3\text{PW}_{12}\text{O}_{40}$ in presence of 120 mM $\gamma\text{-CD}$ in D_2O , at various pH. For comparison, the spectrum of 120 mM $\gamma\text{-CD}$ in D_2O is shown above.

Similar results are also observed with the α - and β -CD systems, where the shape of the ^1H NMR spectrum changes at the pH for which the Keggin POM $\{\text{PW}_{12}\}$ decomposes, around pH = 3 (See Figures S12 and 13, in SI). The same is also obtained with molybdenum-containing POM $\{\text{PMo}_{12}\}$ in the presence of 2 eq. $\gamma\text{-CD}$ (see Figure S14). In this case, the shape change in the ^1H NMR spectra occurs at pH = 5 corresponding to the limit of stability for $\{\text{PMo}_{12}\}$ in this system. All of these data clearly indicate that CDs interact exclusively with the starting saturated Keggin POM, while the less chaotropic vacant POM species show no specific interaction with any type of the three CDs. To provide further information on these interactions, a study by NMR ^{183}W was carried out. The starting $\{\text{PW}_{12}\}$ anion is characterized by a single sharp doublet ($^2J_{\text{W-P}} = 1.1$ Hz) at -95.4 ppm corresponding to the twelve W equivalent nuclei of the POM structure (Figure 9). With the addition of two eq. $\gamma\text{-CD}$, this signal broadens and shifts towards high fields of about 3 ppm (Figure 9). These effects clearly indicate the formation of the inclusion complex with a very strong association which provide a significant shielding on the W nuclei. The line broadening of the ^{183}W signal (guest) like that of the H3 proton (host) results from a strong host-guest contact. These effects are not observed with the other smaller CDs (Figure 9), confirming the unique behavior of $\gamma\text{-CD}$ highlighted by the formation of inclusion complex.

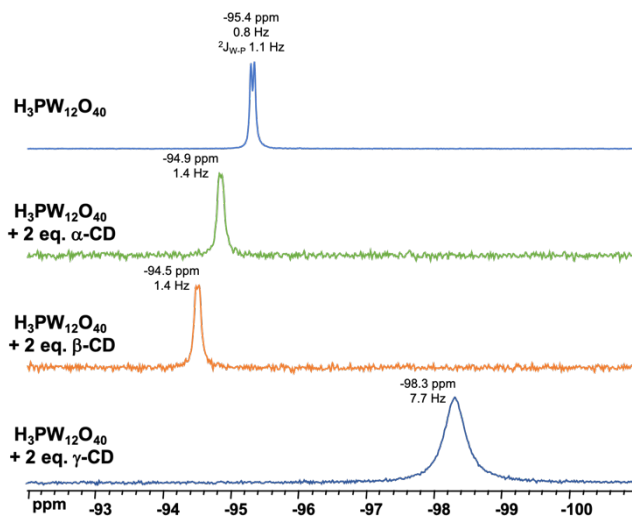


Figure 9. ^{183}W NMR spectra of 7.5 mM $\text{H}_3\text{PW}_{12}\text{O}_{40}$ (from top to bottom) in pure D_2O , in the presence of 15 mM α -CD, β -CD, and γ -CD. The pH was adjusted at ca. 0.5 each time.

All our results obtained so far are in agreement with the conclusion that the host-guest complexation of the Keggin-type anion is at the origin of its exceptional stabilization. However, it is not yet clear whether such a stabilization is dynamic and then reversible. To address such a purpose, we compared the effect of the sequence of addition of γ -CD with respect to $\{\text{PW}_{12}\}$. Figure 10 shows the ^{31}P NMR spectra of the mixture of γ -CD (120 mM) and $\{\text{PW}_{12}\}$ (60 mM) at pH = 3, before and after addition of the CD, for which the sequence of the POM-CD addition has been inverted.

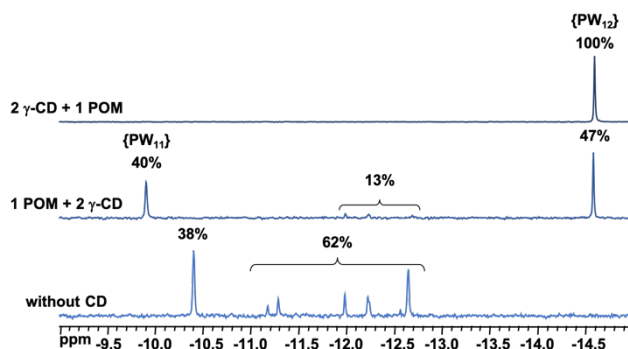


Figure 10. ^{31}P NMR spectra of 60 mM $\text{H}_3\text{PW}_{12}\text{O}_{40}$ (bottom) before and (middle) after addition of 2 eq. γ -CD in D_2O , compared to (top) the spectrum of a mixture of 60 mM $\text{H}_3\text{PW}_{12}\text{O}_{40}$ and 120 mM γ -CD in D_2O for which the POM is added the last. For all the experiments, the pH is adjusted to 3.

As previously shown, at pH = 3, aqueous solution of $\{PW_{12}\}$ anion is unstable giving many intermediate. This decomposition can be fully canceled when the $\{PW_{12}\}$ anion is dissolved in γ -CD-containing aqueous solution. However, when γ -CD is added to an aqueous solution of POM at pH = 3, the restoration of the $\{PW_{12}\}$ anion by shifting the chemical equilibria, is only partial (see Figure 10). Only the intermediate decomposition products exhibit reversible transformation while the most stable decomposition product $\{PW_{11}\}$ appears to be unaffected and retains almost the same fraction as that before the addition of the γ -CD. This result clearly shows that the presence of CD makes it possible to protect $\{PW_{12}\}$ from basic hydrolysis, but also capable of restoring it quasi-quantitatively from the first decomposition products labelled A, C, H and F (see Figure 4). However, it no longer becomes possible to restore $\{PW_{12}\}$ with the CD from the degradation product $\{PW_{11}\}$ anion. The high negative charge the latter makes it poorly chaotrope, and may explain its weak affinity towards the CD. These observations give also information about the equilibrium relationships that link $\{PW_{12}\}$ to its degradation products since these transformations are dynamic and partially reversible.

Highlighting stability domain enhancement of phosphorus-Keggin POMs. Supramolecular associations between Keggin-type POMs and CDs alter significantly the properties of the POM in aqueous solution. Depending on the nature of these interactions, the stability domains of POM can be shifted to a large extent as shown in Figure 11.

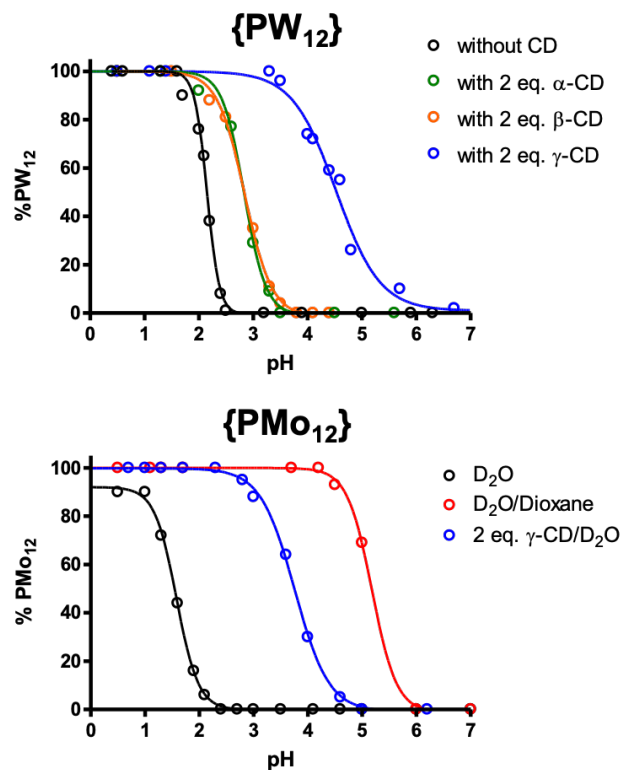


Figure 11. Effect of medium on stability domains of Keggin POM {PW₁₂} and {PMo₁₂}.

The stability of POM in the presence of α- or β-CD is only slightly improved by about one pH unit (Figure 11). These two CDs have shown to behave similarly with the Keggin anion. In fact, the interactions have been identified as non-specific, involving mainly the outer surface of the CDs, leading to very similar and comparable effects. However, γ-CD, acting as a true host molecule for inclusion complexation, its stabilizing effect is much larger. This CD is able to maintain the {PW₁₂} anion intact up to near pH = 4, and to expand its existence in aqueous solution up to pH = 6, a value close to that of the physiological pH. In addition, no intermediate decomposition products are observed during the transformation of {PW₁₂} into {PW₁₁}. Similar behavior was also observed with the less stable {PMo₁₂}, but with one pH unit lower, i.e., maintaining its structure intact up to pH = 3, and its existence up to pH = 5 (Figure 11).

CONCLUSIONS

The stabilizing role of cyclodextrins on $\text{PW}_{12}\text{O}_{40}^{3-}$ and $\text{PMo}_{12}\text{O}_{40}^{3-}$ has been studied by NMR spectroscopy. While degradation of POMs occurs at pH ca. 1.5 and becomes complete until pH = 3, we show that specific supramolecular interactions are able to expand the pH stability scale. The α - and β -CD showed similar interactions in solution, which were identified as non-specific due to small size of the cavities compared to that of the Keggin-type anion. Conversely, the larger γ -CD exhibits specific recognitions with the POM, leading to a stable host-guest inclusion complex involving two γ -CDs and a POM. As a result, α - and β -CD have a limited stabilizing effect on POMs by expanding their pH stability domain by only about one pH unit. Due to the formation of close host-guest assembly, γ -CD acts as a protecting shell for the POM against hydrolytic attack of hydroxide ions. Significant stability improvement has been demonstrated, up to pH = 5 for $\text{PMo}_{12}\text{O}_{40}^{3-}$ and pH = 6 for $\text{PW}_{12}\text{O}_{40}^{3-}$.

It then clearly appears that the presence of CDs modify the thermodynamic properties of POMs in aqueous solutions. A previous report showed that such supramolecular interactions alters significantly their redox properties,^{24,25} while in the same way, we highlight that these supramolecular interactions, driven by the chaotropic effect were strong enough to modify the speciation diagram of metalate ions or increase significantly the rate of the polycondensation processes.^{34,48} This is confirmed by the present study since CDs modify the distribution of the intermediates resulting from the degradation of the Keggin-type anion. Moreover, such an interaction-type, directed by the chaotropic effect reveals important consequences about the solution properties of POMs, that could be one of the important keys for a rational understanding of the POM behavior in complex matrices, such as biological media or aqueous wastes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

Additional ^1H and ^{31}P NMR data.

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ACKNOWLEDGMENTS

M. Lajoie and F. Nagbo are thanked for their technical assistance during their Master internships. Authors gratefully acknowledge financial supports from LabEx CHARMMMAT (grant number ANR-11-LBX-0039), University of Versailles Saint-Quentin, and the Paris Ile-de-France Region – DIM “Respire”. S.Y. thanks the China Scholarship Council (201904910419) for her scholarship.

DEDICATION

In memory of Raisa I. Maksimovskaya.

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Table of Contents Synopsis

The stabilizing role of cyclodextrins (CDs) on Keggin-type molybdo- and tungsto-phosphates, was investigated using ^{31}P NMR spectroscopy. The formation of supramolecular host-guest inclusion complexes observed with γ -CD provides a protective shell on the POM surface against hydrolytic attack which extends the stability domains by more than three pH units. With the smaller CDs (α -, and β -type), the stabilization is only moderate, demonstrating the importance of size matching effect in host-guest complexation and its protective role.

Table of Contents Graphic

