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One and Two-dimensional NMR Investigations of the Inclusion of the Monosulfonated Triphenylphosphine in the β-cyclodextrin

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The interaction between the sodium salt of the monosulfonated triphenylphosphine and the β-cyclodextrin has been investigated in aqueous solution by high field nuclear magnetic resonance and UV–Vis spectroscopies. Continuous variation and titration plots obtained from NMR and UV–Vis data indicate formation of a 1:1 inclusion complex and allow to calculate an association constant of 12,000 M^{-1} at 25°C. The T-ROESY NMR experiments complemented by molecular modelling suggest that one of non-sulfonated aromatic rings is included into the hydrophobic cavity of the β-cyclodextrin from the side of secondary hydroxyl groups. Formation of inclusion complex with the α- and γ-cyclodextrin is also briefly discussed.

Keywords: Inclusion complex; β-Cyclodextrin; Monosulfonated triphenylphosphine; NMR spectroscopy

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six(α-), seven(β-), or eight(γ-) D-glucopyranose residues linked by α-(1,4) bonds. These compounds are truncated cone-shaped molecules with a hydrophobic cavity (Scheme 1) [1,2]. Secondary hydroxyl groups (2-OH and 3-OH) of the respective glucose units are located at the wider rim, and primary 6-CH_2OH groups at the narrower rim. The large internal diameter of CDs cavities allows the formation of inclusion compounds in which the CDs act as molecular receptors that bind organic compounds, forming host–guest complexes [3]. In particular, we have recently reported that β-CD forms inclusion complexes with the sodium salt of trisulfonated triphenylphosphine (TPPTS—$P(m\text{-}C_6H_4SO_3Na)_3$), a well-known standard water-soluble ligand in aqueous-phase organometallic catalysis [4,5]. A geometry for this inclusion complex in which one aromatic ring of the TPPTS is inserted into the hydrophobic cavity from the secondary side of the CD has been proposed using NMR experiments and molecular mechanics calculations [5]. It was also assumed that these inclusion complexes promote the dissociation of TPPTS from the $HRhCO(TPPTS)_3$ species, inducing a decreased selectivity in the rhodium catalyzed hydroformylation reaction [6]. As the sodium salt of the monosulfonated triphenylphosphine (TPPMS—$P(m\text{-}C_6H_4SO_3Na)(C_6H_5)_2$)—Scheme 2) is a water-soluble ligand often used instead of the TPPTS, it was of great interest to study the interaction of this ligand with β-CD [7]. Indeed, evidence of such interactions would make it possible to predict the catalytic performances of TPPMS/β-CD based systems.

In the present study, we report that β-CD forms a 1:1 inclusion complex with TPPMS. The inclusion process was investigated at 25°C in D_2O using ^1H and ^{31}P NMR and in H_2O using UV–Vis spectroscopies. The intermolecular proximity and the

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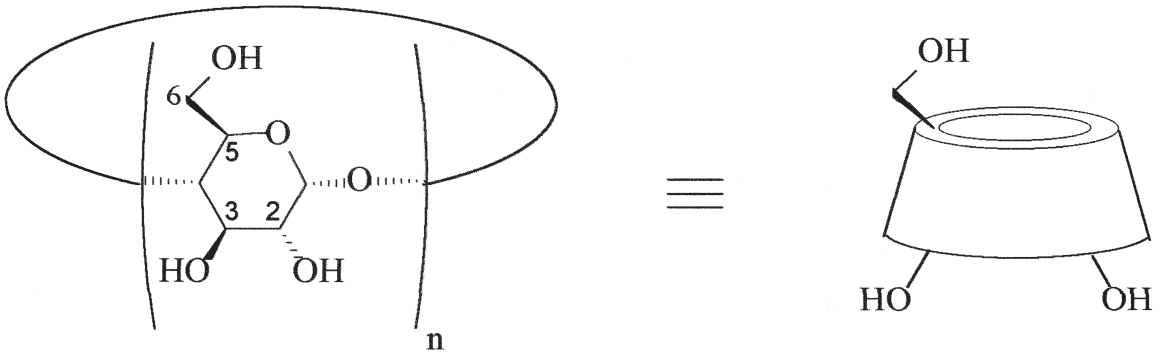


n = 6 α-cyclodextrin
n = 7 β-cyclodextrin
n = 8 γ-cyclodextrin

SCHEME 1 Schematic representation of the shape of α-, β- and γ-CD. The protons H-3 and H-5 are situated inside the host cavity, whereas protons H-1, H-2 and H-4 point outwards.

orientation of TPPMS in the host cavity of β-CD were discussed from two-dimensional T-ROESY experiments and molecular modelling studies. The formation of inclusion complex with the α- and γ-cyclodextrin is also briefly discussed.

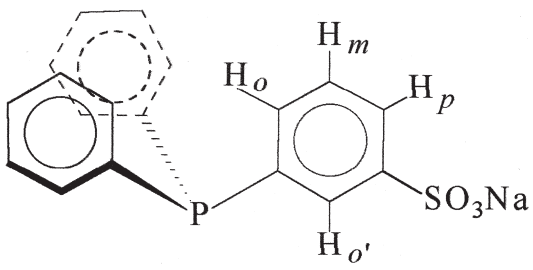
MATERIALS AND METHODS

Materials

The sodium salt of the monosulfonated triphenylphosphine (TPPMS) was synthesized as reported by Chatt *et al.* [13]. The α-, β- and γ-CD were purchased from Aldrich and were carefully dried before use. D_2O (99.95% isotopic purity) was obtained from Merck. Methyl orange (MO) >99% purity were purchased from Acros.

Measurements

The ^1H and ^{31}P NMR spectra were recorded at 300.13 and 121.49 MHz on Bruker Avance DRX, respectively. Chemical shifts are given in parts per million (ppm) relative to 3-(trimethylsilyl)propionic acid D4 2,2,3,3 sodium salt (98% atom D) in D_2O using internal capillary. The 2D T-ROESY experiments were run using the software supplied by Bruker. Best results were obtained with a 200 ms mixing time. The data matrix for the T-ROESY was made of 512 free induction decays, 1 K points each, resulting from the co-addition of 32 scans. The real resolution was 1.5–6.0 Hz/point in F2 and F1 dimension, respectively. They were transformed in the phase—sensitive mode after QSINE window processing.



SCHEME 2 Representation of the sodium salt of monosulfonated triphenylphosphine (TPPMS). Protons of the sulfonated aromatic ring have been annotated (H-*m*, H-*p*, H-*o*′ and H-*o*).

Calculation of Association Constants by NMR Spectroscopy

The phosphorus atom, the *para*- and *ortho*′-protons of the TPPMS was used for the determination of the association constant as the overlap does not impede a reliable determination of the chemical shift. Assuming a 1:1 inclusion mechanism, the observed chemical shift of the phosphorus atom or proton (δ_{OBS}) and the complex concentration [COMP] are described as follows:

$$\delta_{OBS} = (\delta_{TPPMS} \times [TPPMS] + \delta_{COMP} \times [COMP])/[TPPMS]_T, \quad (1)$$

$$[COMP] = -\frac{1}{2}\left[\left(\frac{1}{K_f} + [CD]_T + [TPPMS]_T\right)^2 - 4[CD]_T \times [TPPMS]_T\right]^{1/2} - + \frac{1}{2}\left(\frac{1}{K_f} + [CD]_T + [TPPMS]_T\right) \quad (2)$$

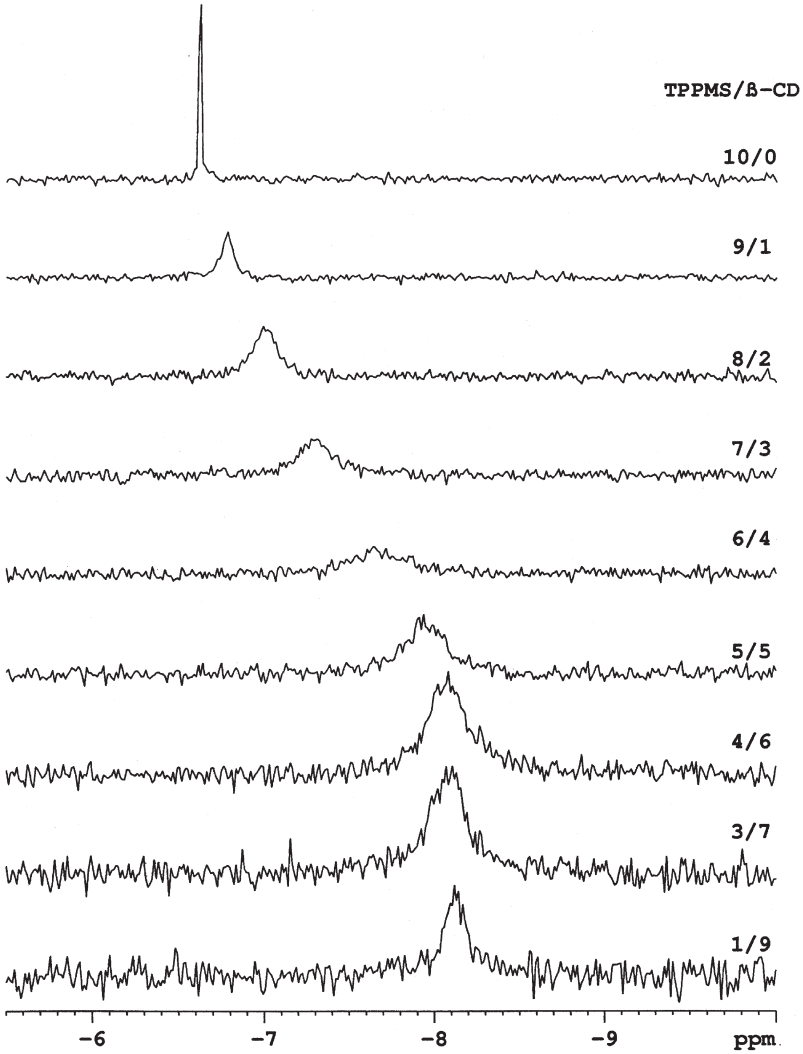


FIGURE 1 Partial 121 MHz ^{31}P NMR spectra of TPPMS/β-CD mixtures in D_2O at 298 K. The total concentration of species is 10 mM. The TPPMS to β-CD ratios are given on the right of spectra.

where K_f and $[\,]_T$ stand for binding constant and total, respectively. For a given value of K_f, [COMP] is known and δ_{COMP} may be calculated from Eq. (1) for each $[CD]_T$. Standard deviation over δ_{COMP} is minimized relative to K_f to obtain the 1:1 association constant.

Calculation of Association Constants by UV–Vis Spectroscopy

The determination of the association constant by UV–Vis spectroscopy was realised in two different ways.

First, the classical titration method was applied for a fixed concentration of TPPMS (0.1 mM), and varying concentration of β-CD (0.06, 0.1, 0.2 and 1 mM). An algorithmic treatment similar to one described previously was used to calculate the association constant from UV–Vis data (recorded in the range 200–350 nm). The algorithmic treatment was applied to UV spectra's derivatives, so that no effect from the refractive index relative to the β-CD was observed.

The second quantitative determination relies on a spectral displacement method with methyl orange (MO) in its basic form [14]. Indeed, the addition of TPPMS to a solution containing β-CD and MO leads to the formation of the β-CD/TPPMS complex, thus decreasing the concentration of the β-CD/MO complex initially present. The absorbance variation resulting is directly linked to the added concentration of TPPMS, but also to the association constant of β-CD/TPPMS inclusion compound. In practice, spectra were recorded between 520-530 nm for MO, β-CD and TPPMS concentrations fixed at 0.1, 0.5 and 0.5 mM, respectively. The first derivatives of these spectra were used for quantitative analysis by an algorithmic treatment described elsewhere [14].

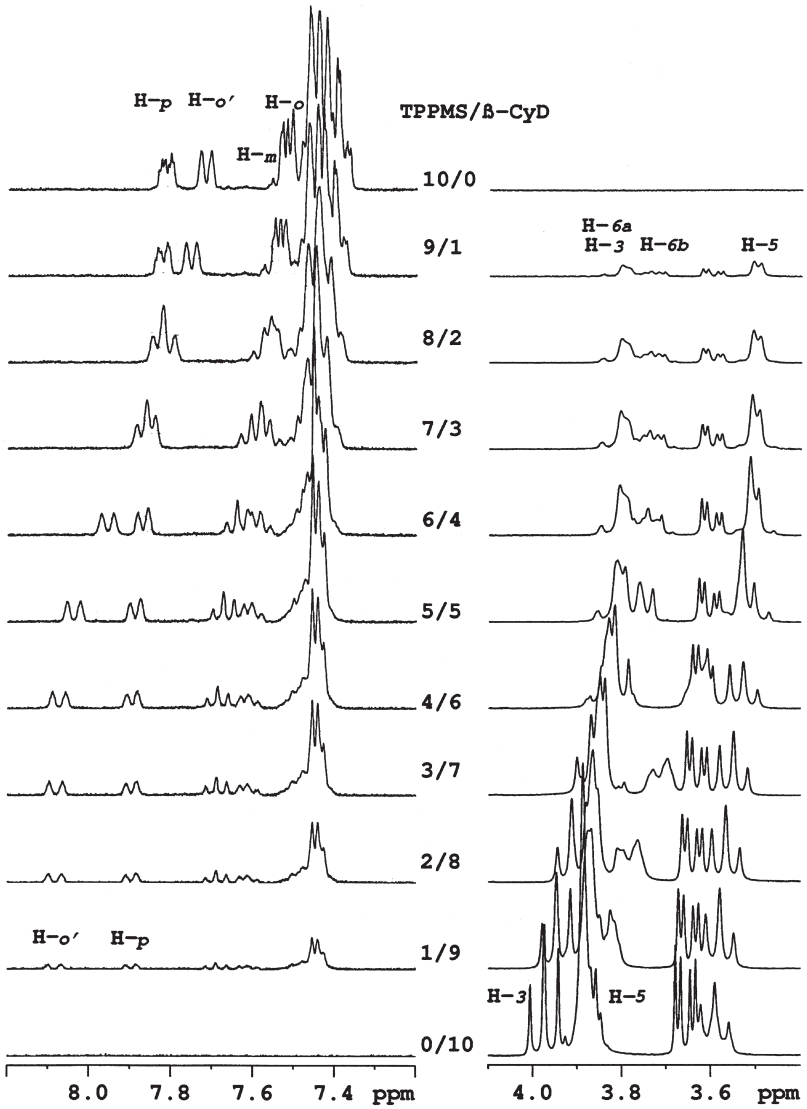


FIGURE 2 Partial 300 MHz ^{1}H NMR spectra of TPPMS/β-CD mixtures in D_2O at 298 K. The total concentration of species is 10 mM. The TPPMS to β-CD ratios are given between the two sets of spectra.

Molecular Modelling

Simulations were carried out using CAChe [15], integrating MM3 force field and AM1 hamiltonian. The partial charge on both host and guest were obtained by using of AM1 (energy determination at fixed geometry). The docking of TPPMS was then investigated on the basis of MM3, by moving the guest along a vector perpendicular to the mean plane of the β-CD linkage oxygens O_4, with a 0,2 Å increment. The depth of penetration is defined as the distance between the centroïd of the seven glycosidic oxygens of βCD and the C ipso of the TPPMS ring which enters the cavity. Each structure was fully energy minimized. All energy minimisations were performed by using successively steepest descent, conjugate gradient and Newton–Raphson algorithm, with final convergence fixed to 0.001 kcal/mol. The final structure was submitted to a SCF energy calculation (AM1) in order to determine the dipolar moment.

RESULTS AND DISCUSSION

Evidence of an inclusion process between TPPMS and β-CD, and determination of the stoichiometry were provided by the continuous variation technique [8]. A series of samples containing variable ratios of β-CD and TPPMS was prepared keeping the total concentration of species constant (10 mM in the present case). The ^{31}P and ^{1}H NMR spectra of the samples are presented in Figs. 1 and 2, respectively.

The ^{31}P and ^{1}H NMR spectra denote chemical shift variations for the phophorus and protons of the TPPMS and for most of the β-CD protons. The largest differences in the chemical shifts for the β-CD

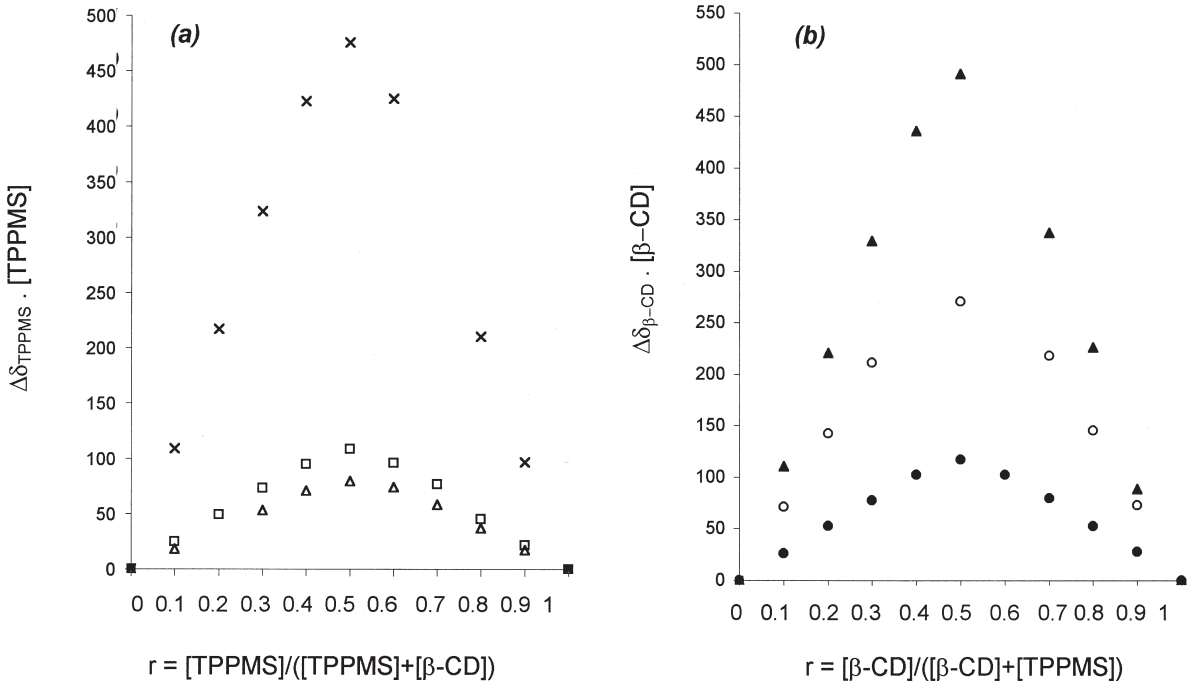


FIGURE 3 (a) Continuous variation plots (Job's plots) derived from experimental data of Figs. 1 and 2 for selected protons of TPPMS (H-*o*′: x; H-*p*: □) and for phosphorus atom of TPPMS (^{31}P: △); (b) Continuous variation plots derived from experimental data of Fig. 2 for selected protons of β-CD (H-1: •; H-3: ○; H-5:▲).

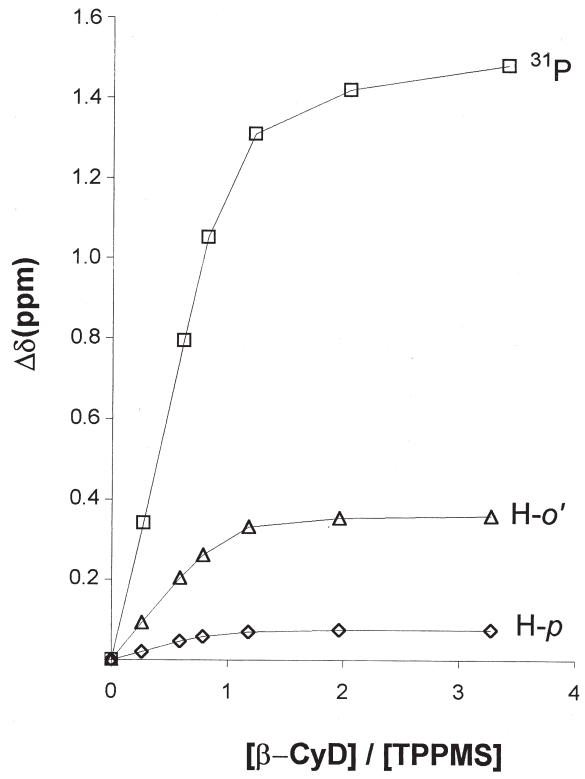


FIGURE 4 Graph of the chemical shifts of phosphorus atom (□), *ortho*′- (△) and *para*- (◇) protons of TPPMS as a function of β-CD/TPPMS mole ratio in aqueous solution at 298 K. The TPPMS concentration was fixed to 3 mM.

protons are observed for the protons situated *inside* the hydrophobic cavity (H-3 and H-5). This observation proves the reality of an inclusion process between TPPMS and β-CD. Indeed, when external interactions phenomena occur between a CD and a guest molecule, no variation of chemical shifts for these inner protons is observed [9].

Under the present conditions, it must be pointed out that only shifts of these signals were observed and no new peak which could be assigned to the pure complex is appeared. This observation implies that the complexation is a dynamic process, the included TPPMS being in fast exchange between free and bound states.

Job's plots suppling the stoichiometry of the inclusion complex were derived from the corresponding ^{1}H and ^{31}P NMR spectra [8,10]. Figure 3 shows the Job's plots for phosphorus atom and for selected protons from β-CD and TPPMS, respectively.

All plots show a maximum at $r = 0.5$ and highly symmetrical shapes, suggesting that a 1:1 complex is formed [8,10]. This stoichiometry was also confirmed by monitoring the chemical shift of phosphorus atom, *para*- and *ortho*′-protons of TPPMS (other protons were not used due to strong spectral overlaps which impede a reliable determination of the chemical shift). Figure 4 shows plots of the chemical shift value of phosphorus atom, *para*- and *ortho*′-protons versus the β-CD/TPPMS molar ratio.

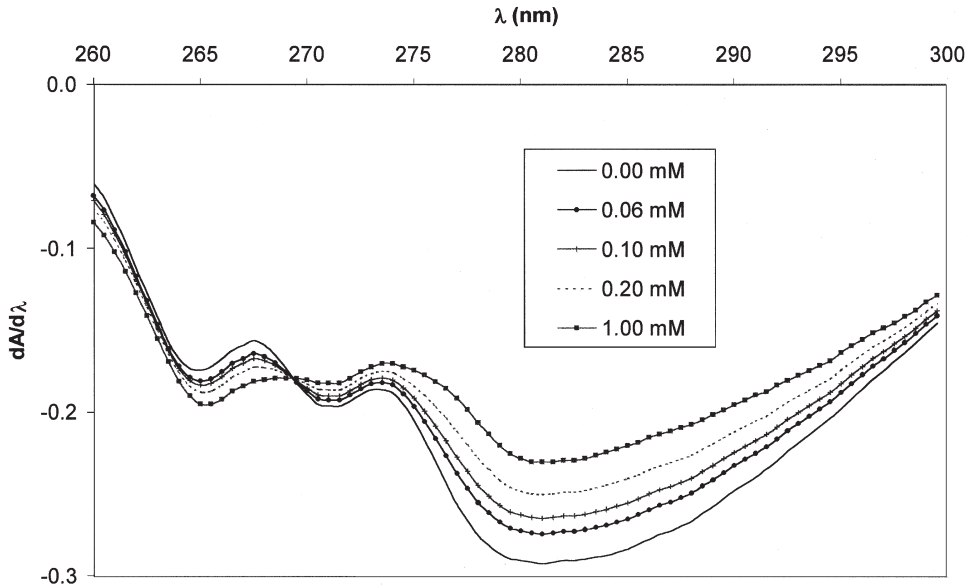


FIGURE 5 First derivatives of the absorption spectra of TPPMS (0.1 mM) in presence of varying concentrations of β-CD (0, 0.06, 0.1, 0.2 and 1 mM) at 298 K.

In all cases, the chemical shift values increase linearly up a ratio equal to 1 and level off markedly beyond this ratio, confirming the stoichiometry 1:1. The association constants of $11{,}600\,M^{-1} \pm 8\%$, $12{,}000\,M^{-1} \pm 10\%$, and $22{,}100\,M^{-1} \pm 30\%$ for this 1:1 complex were calculated by computer fitting of the phosphorus atom, *ortho*′- and *para*-protons NMR data, respectively. The reliability of these calculated binding constants depends highly on the chemical shift difference between free and bound state of TPPMS ($\Delta\delta_{max}$). Indeed, it has been clearly demonstrated that a $\Delta\delta_{max}$ value inferior to 0.25 ppm induces significant error on the association constant, and that the corresponding titration has to be discarded on a quantitative point of view [11]. As the $\Delta\delta_{max}$ value in the case of the *para*-proton is very low (0.073 ppm against 0.341 and 1.467 ppm, for *ortho*′-proton and phosphorus atom, respectively), the *K* value calculated from the *para*-proton is significantly less reliable than the two others and has to be withdrawn.

In order to confirm the value of the association constant derived from NMR, we also performed titrations by the way of UV–Vis spectroscopy (Fig. 5).

The existence of a well defined isobestic point as well as a reproducibility ratio of 1% illustrate the

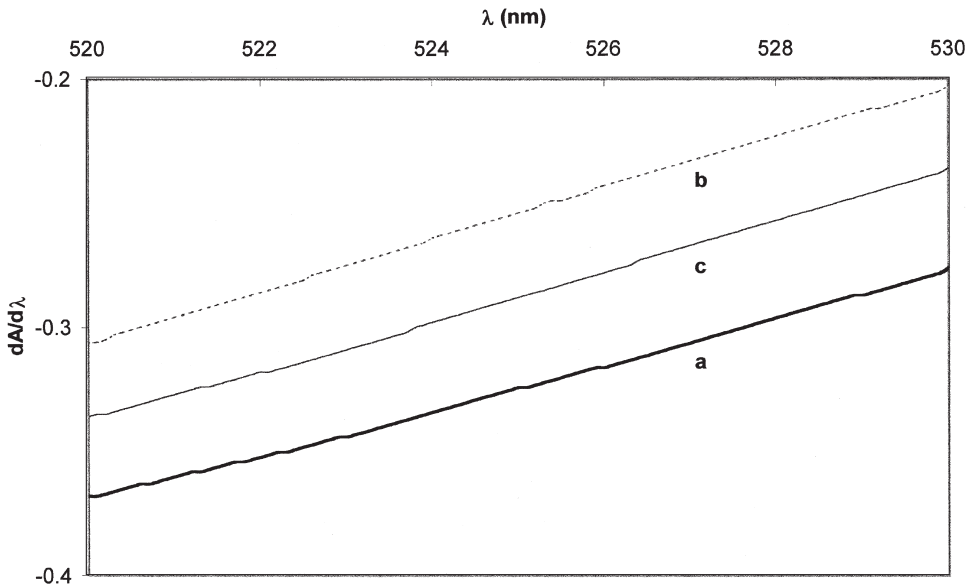


FIGURE 6 First derivatives of the absorption spectra for solutions containing MO 0.1 mM (a); MO 0.1 mM+β-CD 0.5 mM (b); MO 0.1 mM+β-CD 0.5 mM+TPPMS 0.5 mM (c) at 298 K.

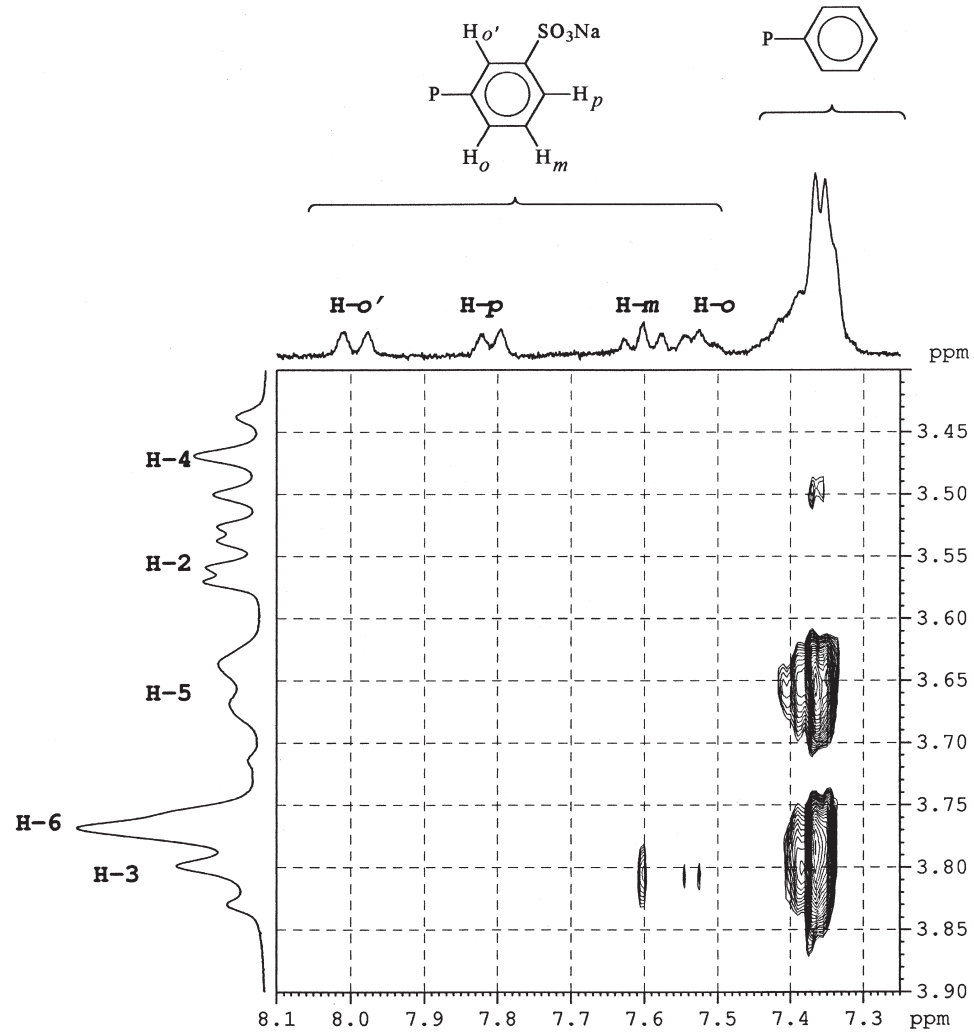


FIGURE 7 Partial contour plot of the T-ROESY spectrum of a solution containing β-CD (7 mM) and TPPMS (3 mM) in D_2O at 298 K with a 200 ms mixing time.

reliability of the corresponding measures. The titrations lead to a *K* value of 11,500 (±10%), which is in good agreement with the phosphorus atom and *ortho*′-proton NMR data. Besides, a spectral displacement method with methyl orange was also applied to the TPPMS complex. The variation of absorbance induced upon addition of TPPMS is described in Fig. 6, and corresponds to a *K* value of 12,600 (±10%).

Thus, the four different affinity estimations are consistent and lead to a mean value of 12,000 (standard deviation equal to 700). It must be noticed that these values were much higher than those found for the TPPTS/β-CD inclusion complex (1200 M^{-1} at 25°C) [4,5], indicating a better affinity of β-CD for TPPMS. This is probably due to a higher contribution of hydrophobic interactions to the complexation thermodynamics. Indeed, contrary to TPPTS, TPPMS possesses hydrophobic parts (apolar aromatic rings) which have a high affinity for the apolar cavity of β-CD.

In order to obtain information upon the geometry and orientation of the guest into the cavity, two-dimensional T-ROESY experiments have been performed. These experiments were preferred to classical ROESY experiments as it was shown that this sequence provides reliable dipolar cross-peaks with a minimal contribution of scalar transfer [12]. Figure 7 displays a partial contour plot of the T-ROESY spectrum of a mixture of TPPMS and β-CD.

The lack of strong interactions between the β-CD protons and the sulfonated aromatic group on the one hand, and the strong dipolar contact observed between the proton H-5 and the aromatic protons of the non-sulfonated aromatic rings on the other hand fully prove that the inclusion occurs by one of the non-sulfonated aromatic ring. The weak cross-peaks between the *ortho*- and *meta*-protons of the sulfonated aromatic group and the H-3 proton led us to assume that (i)the inclusion occurs by the secondary ring of the β-CD and that (ii) the sulfonate group

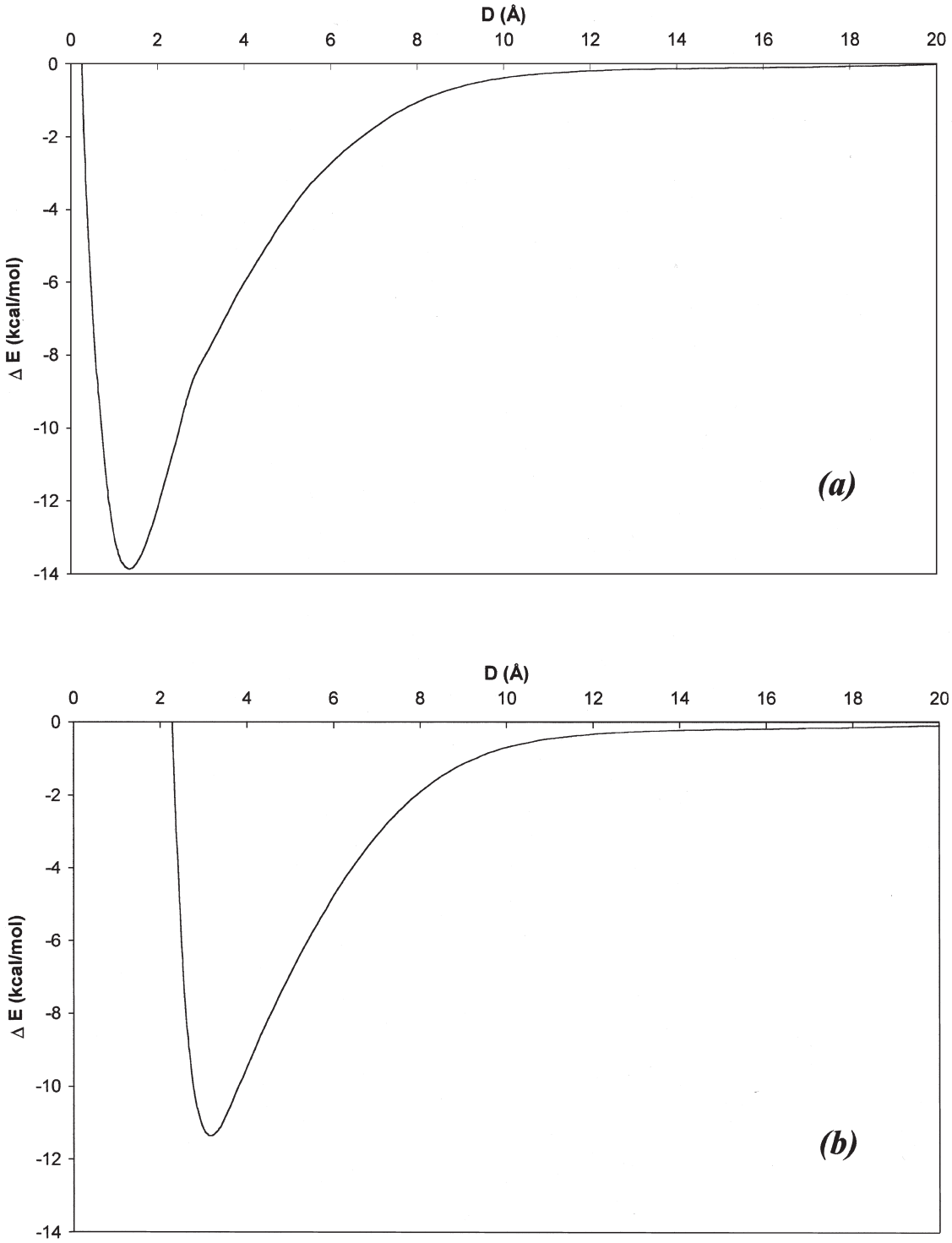
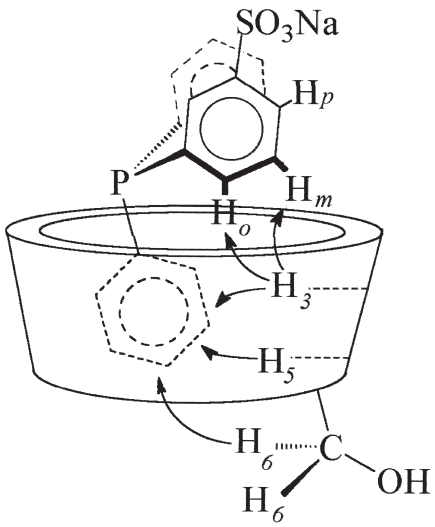


FIGURE 8 Representation of the energy of interaction as a function of the intermolecular distance (distance between the centroïd of the seven glycosidic oxygens of β-CD and the C ipso of the TPPMS ring which enters the cavity), for an inclusion occurring at the secondary side (a), at the primary side (b).

points toward the aqueous phase and remains exposed to the bulk solvent as schematically represented in Scheme 3.

However, from only T-ROESY experiment, it is difficult to prove undoubtedly that the inclusion occurs by the secondary side of the β-CD. Indeed, the partial spectral overlap between protons H-6 and H-3 can easily lead to a wrong interpretation. All attempts to solve this problem with ROESY experiments at different temperatures or different TPPMS/β-CD ratios were unfortunately unsuccessful.

Thus, with a view to confirming the TPPMS binding side, a theoretical docking of the TPPMS



SCHEME 3 Schematic representation of TPPMS/β-CD inclusion complex showing the sulfonate group in the aqueous bulk phase. Cross peaks observed in the ROESY spectrum are indicated on this representation by arrows.

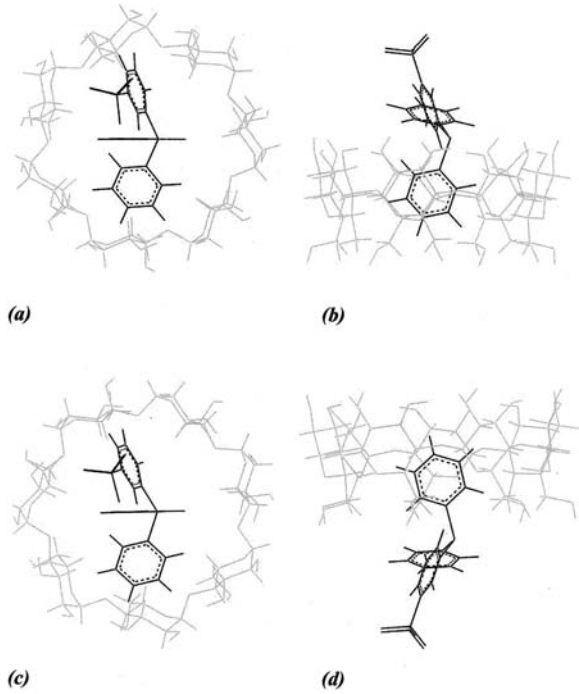


FIGURE 9 Top (a) and side-view (b) of the computer generated structures of the 1:1 inclusion complex obtained by inserting one non-sulfonated ring by the *secondary* side. Top (c) and side-view (d) of the computer generated structures of the 1:1 inclusion complex obtained by inserting one non-sulfonated ring by the *primary* side.

through the β-CD has been performed. As inclusion of more than one aromatic ring is sterically hindered, only the penetration of one non-substituted phenyl ring by the secondary or the primary rim of the β-CD has been investigated. The energy profiles, the side and top-view of the computer generated structures of the 1:1 inclusion complexes are given in Figs. 8 and 9, respectively.

In both cases, favourable interactions take place between the two species as long as no crowding arises from the β-CD periphery and the rings remaining outside the cavity. Thus, an energetic minima is observed for an intermolecular distance of 1.1 Å if the inclusion occurs at the secondary side (complex $C_{secondary}$), while a value of 3.1 Å is obtained for the primary side hypothesis (complex $C_{primary}$). The fact that the secondary side allows a deeper penetration underlines a better fit of the large TPPMS molecule with the wider rim of the β-CD. This is confirmed by an increased van der Waals stabilisation: indeed, the energetic difference between the complexed form and the free species (ΔE) reaches 13.9 kcal/mol for complex $C_{secondary}$, and only 11.3 kcal/mol for complex $C_{primary}$. The steric hindrance which is induced by the narrower primary hydroxyl groups belt may be mainly responsible for such results.

Besides, we have also compared the dipolar moment of the two complexes, since the high permittivity of water (which is not taken into account in the previous simulation) should tend to stabilise the higher polar species. The dipoles values, calculated on the basis of the AM1 method, are respectively equal to 6.5 D for β-CD, 21 D for TPPMS, 40.7 D for complex $C_{secondary}$, 33.4 D for complex $C_{primary}$. So, both complexes lead to a higher dipole moment compared to the sum of TPPMS and β-CD kept separately, especially for the inclusion via the secondary side.

Therefore, both van der Waals and dipolar forces seem to favour the complex $C_{secondary}$, suggesting that the inclusion preferentially occurs via the secondary side of β-CD. It must also be pointed out that the simulated structures of the complex $C_{secondary}$ are in very good agreement with the experimental interactions observed in the T-ROESY spectrum. In particular, the sulfonate group points toward the aqueous phase as mentioned previously.

The formation of inclusion complexes between TPPMS and γ-CD or α-CD has been briefly investigated by ^{1}H NMR spectroscopy. The ^{1}H-NMR spectrum of a 1:1 mixture of γ-CD and TPPMS reveals shifts to lower frequencies for the signal associated with H-3 and H-5, indicating the formation of inclusion complex between the γ-CD and the TPPMS. The stoichiometry and the association constant were determined by monitoring the chemical shift of the *ortho*′-proton of TPPMS versus the γ-CD/TPPMS molar ratio at 25°C. These ^{1}H NMR data were in agreement with an 1:1 equilibrium and led to an association constant of 5300 M^{-1} ± 10% at 25°C. No chemical shift changes were observed in the spectrum of α-CD in the presence of TPPMS, indicating the absence of

inclusion complex. The shape and size of α-CD is likely less suitable to the TPPMS ligand than those of β- and γ-CD.

CONCLUSION

This work has demonstrated that TPPMS can bind to β-CD to form a 1:1 inclusion complex. Moreover, it appears clearly that TPPMS forms a more stable complex with β-CD than TPPTS. This finding led us to conclude that the addition of β-CD to a TPPMS based catalytic system should strongly affect the catalytic behaviour of this system. In particular, the dissociation of phosphine from transition-metal catalyst should be higher with TPPMS than with TPPTS.

Acknowledgements

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