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Complexation of Monosulfonated Triphenylphosphine with Chemically Modified β-Cyclodextrins: Effect of Substituents on the Stability of Inclusion Complexes

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Abstract

Interactions between the *meta*-substituted monosulfonated triphenylphosphine and chemically modified β-cyclodextrins were investigated in aqueous solution by NMR and UV–vis spectroscopy. Titration and continuous variation plots obtained from ^{31}P NMR data indicate that the monosulfonated triphenylphosphine forms 1:1 inclusion complexes with the 2-hydroxypropylated β-cyclodextrin, the methylated β-cyclodextrin and the (2-hydroxy-3-trimethylammoniopropyl)-β-cyclodextrin chloride. These inclusion complexes are more stable that those formed with native β-cyclodextrin, confirming that poisoning of the chemically modified β-cyclodextrins by the hydrosoluble phosphine occurs when modified cyclodextrins are used as mass transfer promoters in aqueous-phase organometallic catalysis.

Introduction

Cyclodextrins (CD) are water-soluble oligosaccharides which form inclusion complexes with a large number of organic and inorganic molecules [1]. The ability of CDs to accommodate guest molecules of the appropriate size in their cavity has been utilized in aqueous organometallic catalysis to increase the water solubility of the organic substrate [2–10]. Indeed, by forming inclusion complexes, the cyclodextrins increase the concentration of organic substrate in the aqueous phase and consequently, the reaction rate. The best rate enhancements were always obtained with the 2-hydroxypropylated β-CD (HP-β-CD) and the randomly methylated β-CD (RAME-β-CD) [11]. For instance, the cleavage rate of the water-insoluble allyl undecyl carbonate in the presence of a catalytic system composed of palladium and trisulfonated triphenylphosphine (TPPTS) can be enhanced by a factor of 300 and 220 in the presence of RAME-β-CD and HP-β-CD, respectively and only by a factor of 20 in the presence of native β-CD [12]. Similar results were obtained in other reactions such as hydrogenation of aldehydes [13], Wacker oxidation [14], hydrocarboxylation [15] or hydroformylation [16] of higher olefins. Nevertheless, a decrease in the selectivity during rhodium catalyzed hydroformylation reaction [17], a modification of the catalyst structure [18] and a drop in cyclodextrin activity [19] can be observed with these modified CDs in particular conditions. These unexpected and rather disappointing results were attributed to the formation of inclusion complexes between the modified CD and the hydrosoluble phosphine used to dissolved the organometallic catalyst in water. Until now, the behavior of these modified CDs towards water-soluble phosphine has only partially been studied. Indeed, no data on the HP-β-CD is available in the literature and the association constant at 298 K between RAME-β-CD and the TPPTS ligand is the only data reported for this methylated compound [17, 18].

To fill this gap, we have examined in detail the effects of substituents attached to the CD on the complexation of the potassium salt of *meta*-substituted monosulfonated triphenylphosphine (TPPMS), a ligand currently used in biphasic catalysis. This study has been performed with three chemically modified CDs: the RAME-β-CD, the HP-β-CD and the mono[2-*O*-(2-hydroxy-3-trimethylammoniopropyl)]-β-cyclodextrin chloride (HTMAP-β-CD) (Table 1). This last chemically modified CD was chosen for its unusual behavior in catalysis. Indeed, although this CD was highly soluble in water and can form inclusion complexes with reactants, this compound has never enabled to increase significantly the rate reactions (H. Bricout and E. Monflier: unpublished results). Formation of inclusion complexes between these modified CDs and the TPPMS was investigated in aqueous solution by $^{31}P\{^{1}H\}$ NMR and UV–visible spectroscopy. The stoichiometry and the association constants at various temperatures were also

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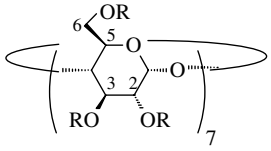
Table 1. Cyclodextrins used in this work

Chemically modified β-cyclodextrin



Abbreviations	Group(s) attached to the cyclodextrin	Number of OH group substituted per glucopyranose unit
β-CD	(–)	0
RAME-β-CD	$-CH_3$	1.8
HP-β-CD	$-CH_2-CH(OH)-CH_3$	0.8
HTMAP-β-CD	$-CH_2-CH(OH)-CH_2-N^+(CH_3)_3$; Cl^-	0.15

determinated. For the HTMAP-β-CD, ^{13}C NMR and a two-dimensional ^1H NMR experiment were also performed to propose a three dimensional structure for this inclusion complex.

Experimental

General methods

The ^1H, ^{13}C and ^{31}P NMR spectra were recorded at 300.13, 75.47 and 121.49 MHz, respectively, on a Bruker DRX instrument. ^1H and $^{31}P\{^1H\}$ chemical shifts are given in ppm relative to external references: sodium [D_4]3-(trimethylsilyl)propionate (98% atom D) in D_2O for ^1H NMR and H_3PO_4 in H_2O for $^{31}P\{^1H\}$ NMR. The notation used in NMR assignments of HTMAP-β-CD and TPPMS is indicated in Figure 3 and 4, respectively. T-ROESY experiments were carried out as previously reported [20]. UV–vis spectroscopy was performed on a Perkin-Elmer Lamba 19 spectrometer. The cell used was placed in a cuvette holder and the temperature was kept constant at 298 K ± 0.1 by means of a thermostated bath.

Materials

D_2O (99.95% isotopic purity) was obtained from Merck. β-CD, RAME-β-CD and HP-β-CD were purchased from Aldrich and carefully dried before use. The RAME-β-CD was a native β-CD partially *O*-methylated with statistically 1.8 OH groups modified per glucopyranose unit. Moreover, OH groups in C-6 position were fully methylated whereas those in C-2 and C-3 positions were partially methylated (2-*O*: 60%; 3-*O*: 40%). The HP-β-CD was a native β-CD partially *O*-2-hydroxypropylated with statistically 0.8 OH groups modified per glucopyranose unit. The HTMAP-β-CD was synthesized as reported by Deratani *et al.* [21]. This CD contains one 2-hydroxy-3-trimethylammoniopropyl group at the C-2 position. The potassium salt of *meta*-substituted monosulfonated triphenylphosphine (TPPMS) was synthesized as described earlier [20].

Determination of stoichiometry by NMR spectroscopy

The continuous variation method was adopted to determine the stoichiometry of the complex. For each CD, a series of sample containing variable ratio (from 0 to 1) of modified β-CD and TPPMS was prepared keeping the total concentration of species constant (10 mM in this present case). The differences of chemical shift in $^{31}P\{^1H\}$ NMR were measured in function of molar ratio.

Calculation of association constants by NMR spectroscopy

The phosphorous atom was chosen for evaluating the association constant. Assuming a 1:1 inclusion mechanism, the observed chemical shift of the phosphorus atom (δ_{OBS}) and the complex concentration [COMP] are described as follows:

$$\delta_{OBS} = (\delta_{Phos.}[Phos.] + \delta_{COMP}[COMP])/[Phos.]_T \quad (1)$$

$$[COMP] = -1/2[(1/K + [CD]_T + [Phos.]_T)^2 - 4[CD]_T[Phos.]_T]^{1/2} + 1/2(1/K + [CD]_T + [Phos.]_T) \quad (2)$$

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

Calculation of association constants by UV–vis spectroscopy

The titration method was applied for a fixed concentration of TPPMS (0.075 mM) and varying concentration

of CD. The concentrations used for each CD have been chosen in order to obtain 0%, 25%, 50%, 75% and 95% of complex form (an approximate knowledge of the constant is necessary). For example, the concentrations are equal to 0.0045, 0.011, 0.028 and 0.15 mM in the case of the RAME-β-CD. An algorithmic treatment similar to one described above for NMR was used to calculate the association constant. The algorithmic treatment was applied to UV spectra's derivatives (recorded in the range 230–250 nm for TPPMS), so that no effect from the refractive index relative to the CD was observed [22].

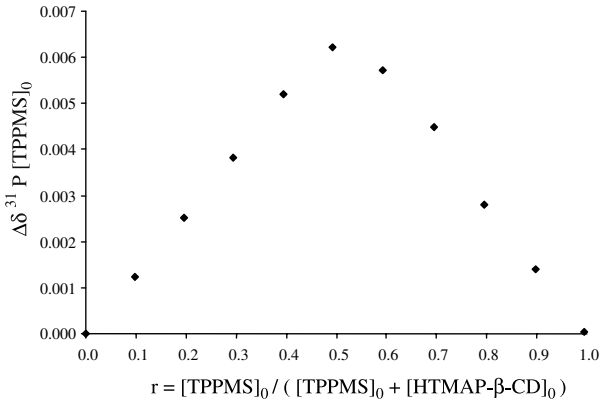


Figure 1. Continuous variation plots (Job's plot) derived from the $^{31}P\{^1H\}$ NMR data for HTMAP-β-CD and TPPMS system.

Results and discussion

^1H NMR spectroscopy furnishes the most relevant informations to study the interactions between the native β-CD and a guest. Indeed, chemical shift variations of protons situated inside the hydrophobic cavity (H-3 and H-5) evidence the inclusion of the guest into the host cavity and a ^1H NMR titration curve allows to calculate the association constant [23]. Unfortunately, with chemically modified CDs such as RAME-β-CD and HP-β-CD, the situation is more complicated as these compounds are mixtures of a number of closely related derivatives with different degrees of substitutions and isomeric forms [24, 25]. So, strong spectral overlaps in ^1H and ^{13}C NMR spectra are observed that impede a reliable determination of the chemical shifts. For this reason, interactions between modified β-CD and TPPMS were investigated by $^{31}P\{^1H\}$ NMR. Indeed, the phosphorous NMR signal cannot be overlapped by any resonance signals. The reality of the inclusion complex and the stoichiometry of these inclusion complexes were provided by the continuous variation technique (Job's method) [26, 27]. For the three modified CDs, the $^{31}P\{^1H\}$ spectra exhibited chemical shift variations for the phosphorous signal and the Job's plots derived show a maximum at $r = 0.5$ and symmetrical shapes as expected for 1:1 inclusion complexes. For example, Figure 1 displays the Job's plot corresponding to the TPPMS/HTMAP-β-CD system.

The association constants of each inclusion complex at various temperatures were evaluated by titration method from $^{31}P\{^1H\}$ NMR spectroscopic data. In order to confirm the value of the association constant derived from $^{31}P\{^1H\}$ NMR data at 298 K, we also performed titrations by the way of UV–vis spectroscopy at 298 K. The values calculated by assuming a 1:1 inclusion complex are listed in Table 2. For comparison, the association constant obtained with the native β-CD is also reported [20].

As in the case of the native β-CD, the value found at 298 K by NMR spectroscopy for the HTMAP-β-CD is in a good agreement with the value calculated from UV–vis data, proving the reliability of the corresponding measures. In the case of the HP-β-CD and RAME-β-CD, the discrepancy observed between the association constant values derived by the two techniques was high, specially in the case of HP-β-CD (91,160 M^{-1} by NMR *versus* 11.860 M^{-1} by UV–vis). With the HP-β-CD, the large decrease in the association constant value when temperature increased from 298 to 318K confirms undoubtedly that the values found by NMR spectroscopy are biased. The lack of agreement could be explained by a broadening of $^{31}P\{^1H\}$ NMR signal during the titration as shown in Figure 2 in the case of the RAME-β-CD.

This large broadering of the $^{31}P\{^1H\}$ NMR signal undoubtedly prevents a good precision for the pick picking and is probably in connection with nature of RAME-β-CD and HP-β-CD that are mixtures of CDs. Indeed, the exchange rate between free and complexed forms on the one hand, and the chemical shifts of the complexed forms on the other hand, are different according to the degree of substitution of the modified

Table 2. Association constant (K, M^{-1}) of TPPMS with native β-CD, RAME-β-CD, HP-β-CD and HTMAP-β-CD

Cyclodextrins	K (298 K)[a]	K (298 K)[b]	K (318 K)[b]	K (328 K)[b]	K (338 K)[b]	K (348 K)[b]
β-CD	7750 ± 50	7110 ± 890	3060 ± 110	2050 ± 70	1550 ± 100	610 ± 40
RAME-β-CD	13,340 ± 140	8040 ± 560	7490 ± 480	7030 ± 780	6040 ± 630	1940 ± 130
HP-β-CD	11,860 ± 80	91,160 ± 22,000	13,140 ± 530	8490 ± 520	4490 ± 210	2680 ± 100
HTMAP-β-CD	111,400 ± 1200	105,500 ± 20,000	56,820 ± 2190	25,450 ± 930	11,080 ± 440	5560 ± 290

[a] Determinated by UV–Vis shift titration.
[b] Determinated by ^{31}P NMR shift titration.

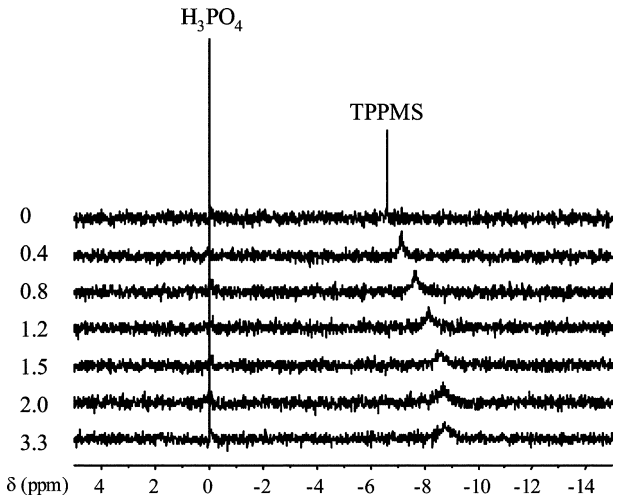


Figure 2. Partial 121 MHz $^{31}P\{^{1}H\}$ NMR spectra of RAME-β-CD/TPPMS mixtures in D_2O at 298 K. The values of the RAME-β-CD to TPPMS ratios are given on the left of spectra. The TPPMS concentration was 3 mM. H_3PO_4 was used as external phosphorous reference.

CD. In the case of the HP-β-CD, the very small chemical shift differences between the free and complexed form induce also significant error (0.14 ppm for HP-β-CD *versus* 1.4 ppm and 2.13 ppm for β-CD and RAME-β-CD, respectively) [28].

Although the NMR technique appears to be limited to determine the association constants of TPPMS with the RAME-β-CD and the HP-β-CD, it must be pointed out that the values of the association constants are always higher to those found for the native β-CD, suggesting that these modified CDs display higher binding abilities than native β-CD. This is probably due to the presence of a deep hydrophobic host cavity. Indeed, attachment of methyl or hydroxypropyl groups to the β-CD extends the cavity of the β-CD. Thus, these CDs have much more important lipophilic domains and cavity volumes approximately 10–20% larger than native β-CD due to the increase in the height of the CD torus [29–31]. This gives rise to CDs that accommodate more easily a hydrophobic phenyl group of the TPPMS. In the case of HTMAP-β-CD, this explanation is not satisfactory to account for the outstanding enhancement of the TPPMS/HTMAP-β-CD association constant value. Indeed, the presence of only one 2-hydroxy-3-trimethylammoniopropyl group on the CD is insufficient to extend the cavity. Such an increase is probably due to electrostatic interaction between the anionic sulfonate group of TPPMS and cationic ammonium group of HTMAP-β-CD, leading to the formation of an ion pair. It is worth mentionning that coulomb interactions between oppositely charged host/guest molecules have already invoked in the literature to explain drastic enhancement of inclusion complex stability [32, 33].

^{1}H and ^{13}C NMR data fully support our assumption. For instance, the ^{1}H and ^{13}C NMR signals corresponding to methyl groups of 2-hydroxy-3-trimethylammoniopropyl substituent are unusual when one equivalent of TPPMS was added to a HTMAP-β-CD solution. As shown in Figure 3, the singlet at $\delta = 3.12$ ppm corresponding to this group is splitted into three signals ($\delta = 3.08$ ppm) in presence of TPPMS (compare Figure 3a with c).

Similarly, two ^{13}C NMR signals were observed for the methyl groups (C_{10}) in presence of TPPMS instead of one without TPPMS (compare Figure 3b with d). These NMR data demonstrate that the three methyl groups are inequivalent in the presence of TPPMS. Such a phenomenon is generally ascribed to a very strong immobilization of the methyl groups, which is consistent with the formation of an ionic pair between the two entities during the inclusion process.

The three dimensional structure of the 1:1 inclusion complex can be deducted from the ^{13}C NMR data and two-dimensional ^{1}H NMR (T-ROESY) experiments. As shown in Figure 4, all ^{13}C NMR signals corresponding to the non-sulfonated ring of the TPPMS ($C_{7'}$, $C_{8'}$, $C_{9'}$ and $C_{10'}$) splitted into doublet in the presence of HTMAP-β-CD.

This result was interpreted by considering that the non-sulfonated rings are inequivalent. In fact, one of the non-sulfonated group is included in the host cavity of the CD and the other outside the cavity. The T-ROESY spectrum of a 1:1 mixture of HTMAP-β-CD and TPPMS confirms this hypothesis (see Figure 5).

Indeed, the very strong cross-peak observed between H-3 and H-5 protons and the protons of a non-sulfonated aromatic ring on the one hand, and the interaction observed between the methyl groups of the ammonium and some protons of a non-sulfonated aromatic ring on the other hand, could be attributed to a non-sulfonated aromatic ring included in the cavity and to another outside the cavity, respectively. Presence of a non-sulfonated ring near the secondary face of the CD and outside the cavity was also evidenced by the strong cross-peaks observed between H-7, H-8 and H-9 protons and some protons of a non-sulfonated aromatic ring. Lack of strong correlation between the protons of the sulfonated aromatic ring and the H-3 and H-6 protons of CD confirms also that the sulfonated ring is located outside the cavity. Undoubtedly, this position makes easier the formation of an ion pair. A schematic representation for such an inclusion complex is displayed in Figure 6.

For an extensive comprehension of the process leading to TPPMS/HTMAP-β-CD inclusion complex, the thermodynamic quantities were determined from the temperature dependence of the association constant K using the van't Hoff relation. The van't Hoff plots were apparently linear for this cyclodextrin within the temperature range considered (298–348 K – plots not presented), confirming once again the reliability of the measures. Therefore, changes in the heat capacity were neglected. The enthalpies and entropies were determined in the usual manner from the slopes and intercepts of the

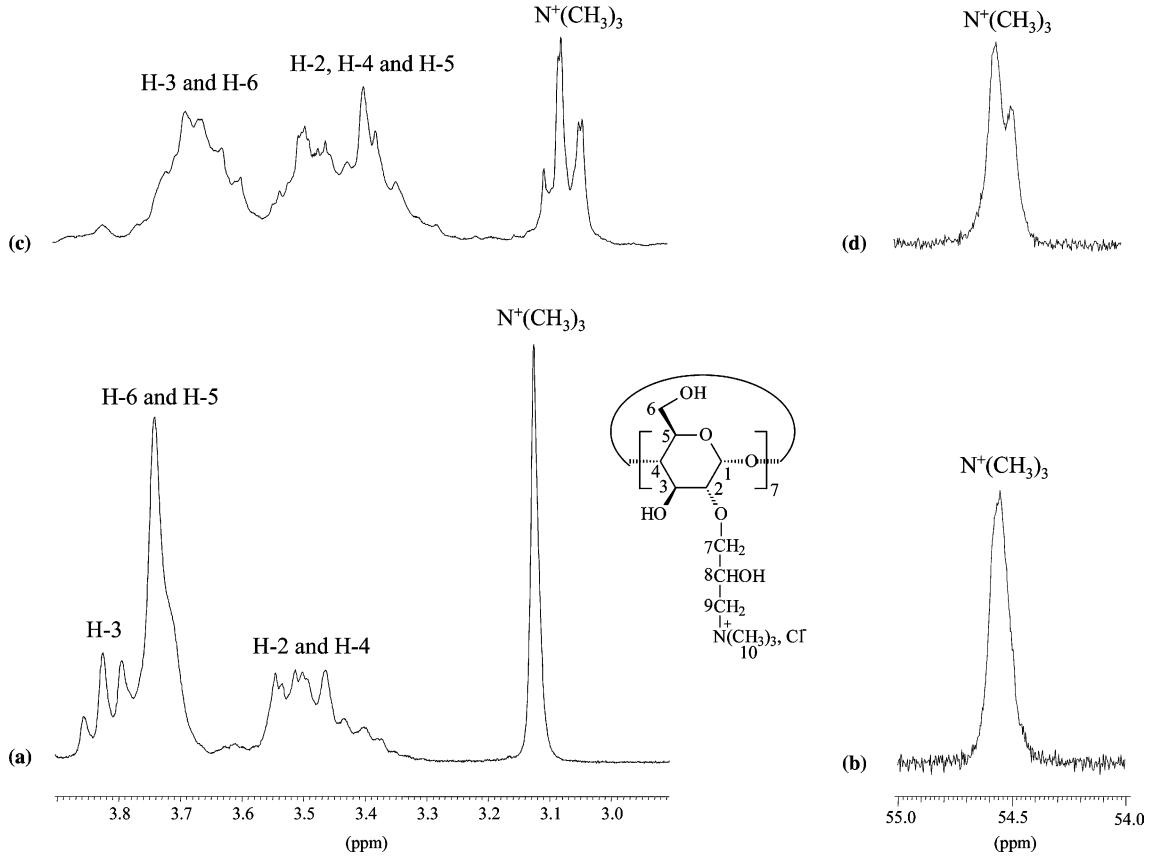


Figure 3. Partial (a) ^{1}H NMR spectrum and (b) ^{13}C NMR spectrum of HTMAP-β-CD alone (10 mM) in D_2O at 298 K; partial (c) ^{1}H NMR spectrum and (d) ^{13}C NMR spectrum of a mixture of HTMAP-β-CD (10 mM) and TPPMS (10 mM) in D_2O at 298 K.

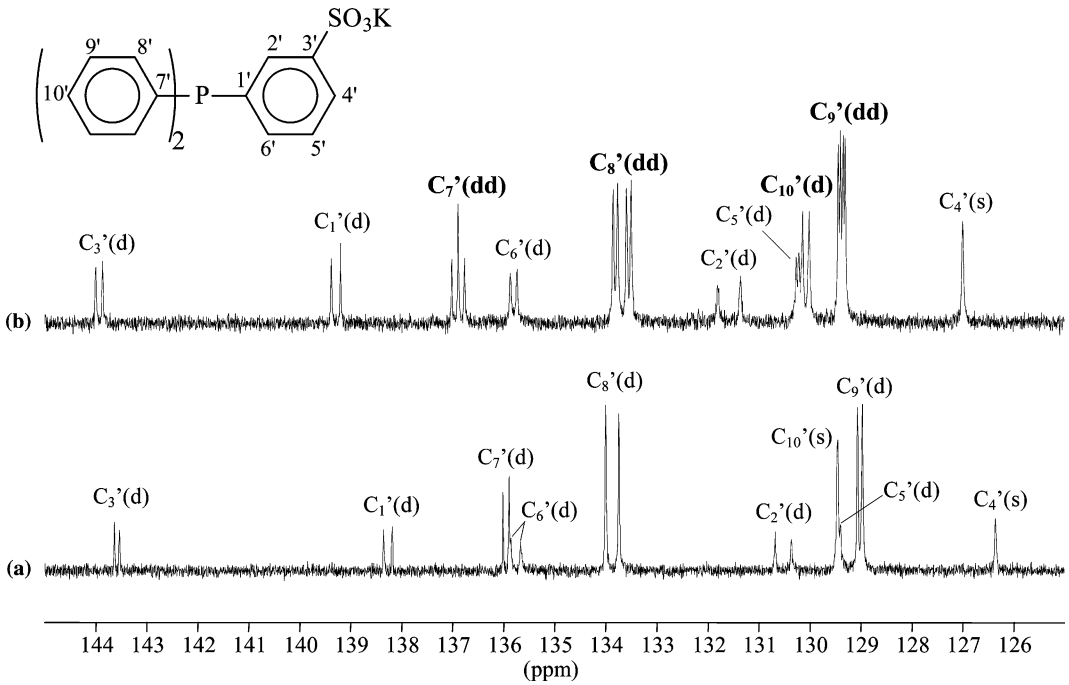


Figure 4. $^{13}C\{^{1}H\}$ NMR spectrum of TPPMS (15 mM) in D_2O at 298 K (a) without HTMAP-β-CD and (b) in the presence of HTMAP-β-CD (15 mM).

plots. The ΔH^0 and ΔS^0 values were found to be -51 ± 4.2 kJ mol^{-1} and -74.8 ± 1.1 J mol^{-1} K^{-1}, respectively. These values are different of those found for the TPPMS/β-CD inclusion complex (-39.2 ± 3.1 kJ mol^{-1} and -57.0 ± 4.6 J mol^{-1} K^{-1} for the ΔH^0 and ΔS^0, respectively [20]). The more

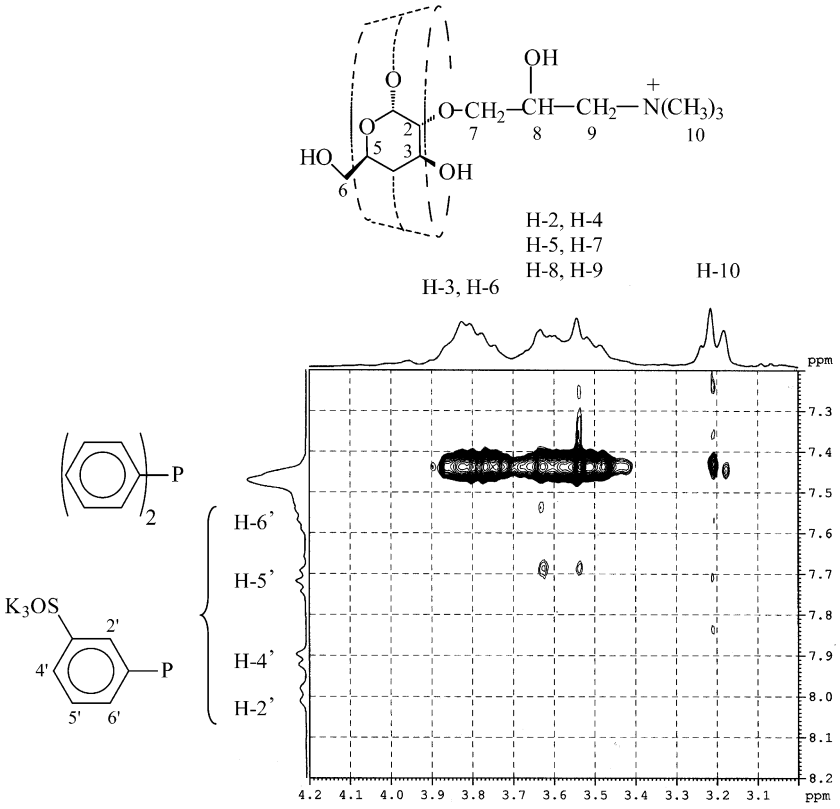


Figure 5. Partial contour plot of the T-ROESY spectrum of a solution containing HTMAP-β-CD (5 mM) and TPPMS (5 mM) in D_2O at 298 K with a 300 ms mixing time.

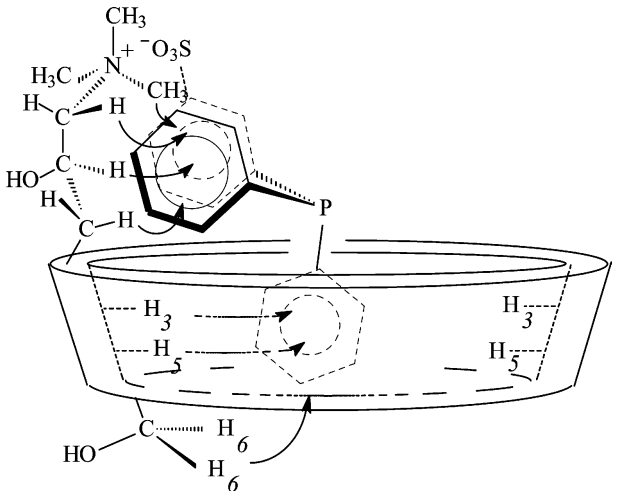


Figure 6. Schematic representation for the TPPMS/HTMAP-β-CD inclusion complex. The interactions observed in the T-ROESY spectrum are also indicated.

favorable ΔH^0 is indicative of stronger hydrophobic and van der Walls interactions and, consequently, of a deeper penetration [31]. The more unfavorable ΔS^0 is undoubtedly in relation with this deeper penetration as a loss of flexibility of the guest is expected when the guest penetrates deeply in the cavity. Moreover, the ionic bound between the sulfonate and the ammonium contributes also to reduce notably the mobility of the guest in the cavity.

In conclusion, we have demonstrated that TPPMS forms 1:1 inclusion complexes with the RAME-β-CD, the HP-β-CD and the HTMAP-β-CD. Although the association constants cannot be determinated with a high accuracy in all cases, it appears that the these modified CDs present a better affinity for the TPPMS ligand than native β-CD, confirming that poisoning of the CD by the TPPMS occurs with the modified CDs. The case of the HTMAP-β-CD is particularly illustrative. Indeed, the lack of activity of this CD in aqueous organometallic catalysis is likely due to the formation of this highly stable complex.

References

1. G. Wenz: *Angew. Chem., Int. Ed.* **33**, 803 (1994).
2. H. Zahalka and H. Alper: *Organometallics* **5**, 1909 (1986).
3. J.T. Lee and H. Alper: *J. Org. Chem.* **55**, 1854, (1990).
4. C.A. Sumpter and J. Stein: *J. Inorg. Organomet. Polymers* **6**, 123, (1996).
5. E. Karakhanov, A. Maximov, and A. Kirillov: *J. Mol. Catal. A: Chem.* **25**, 157 (2000).
6. M. Dessoudeix, M. Urrutigoïty, and P. Kalck: *Eur. J. Inorg. Chem.* **7**, 1797, (2001).
7. A. Harada, Y. Hu, and S. Takahashi: *Chem. Lett.* 2083 (1986).
8. E.A. Karakhanov, T.Y. Filippova, S.A. Martynova, A.L. Maximov, V.V. Predeina and I.N. Topchieva: *Cat. Today* **44**, 189 (1998).

9. H. Arzoumanian, and D. Nuel: *C. R. Acad. Sci. Paris, Série IIc*, 289 (1999).
10. C. Pinel, N. Gendreau-Diaz, A. Bréhéret, and M. Lemaire: *J. Mol. Catal. A.: Chem.* **112**, L157 (1996).
11. S. Tilloy, F. Bertoux, A. Mortreux, and E. Monflier: *Catal. Today* **48**, 245 (1999).
12. T. Lacroix, H. Bricout, S. Tilloy, and E. Monflier: *Eur. J. Org. Chem.* 3127 (1999) .
13. S. Tilloy, H. Bricout, and E. Monflier: *Green Chem.* **4**, 188 (2002).
14. E. Monflier, S. Tilloy, E. Blouet, Y. Barbaux, and A. Mortreux: *J.Mol. Catal. A: Chem.* **109**, 27 (1996).
15. E. Monflier, S. Tilloy, F. Bertoux, Y. Castanet, and A. Mortreux: *New J. Chem.* **21**, 857 (1997).
16. E. Monflier, G. Fremy, Y. Castanet, and A. Mortreux: *Angew. Chem. Int. Ed. Engl.* **34**, 2269 (1995).
17. T. Mathivet, C. Méliet, Y. Castanet, A. Mortreux, L. Caron, S.Tilloy, and E. Monflier: *J. Mol. Catal. A.: Chem.* **176**, 105 (2001).
18. L. Caron, M. Canipelle, S. Tilloy, H. Bricout, and E. Monflier: *Eur. J. Inorg. Chem.* 595 (2003).
19. C. Binkowski, J. Cabou, H. Bricout, F. Hapiot, and E. Monflier: *J.Mol. Catal. A.: Chem.* **215**, 23 (2004).
20. M. Canipelle, L. Caron, C. Christine, S. Tilloy, and E. Monflier: *Carbohyd. Res.* **337**, 281 (2002)..
21. A. Deratani, G. Lelièvre, T. Maraldo, and B. Sébille: *Carbohyd. Res.* **192**, 215 (1989).
22. D. Landy, S. Fourmentin, M. Salome, and G. Surpateanu: *J. Incl. Phenom.* **38**, 187 (2000).
23. H.J. Schneider, F. Hacket, and V. Rüdiger: *Chem. Rev.* **98**, 1755 (1998).
24. T. Irie, K. Fukunaga, J. Pitha, K. Uekama, H.M. Fales, and E.A. Sokolowski: *Carbohydr. Res.* **192**, 167 (1989).
25. J. Pitha, T. Rao, B. Lindberg, and P. Seffers: *Carbohydr. Res.* **200**, 429 (1990).
26. V.M.S. Gil, and N.C. Oliveira: *J. Chem. Educ.* **67**, 473 (1990).
27. K. Connors: *Binding Constants. The Measurement of Molecular Complex Stability*, Wiley, New York (1987).
28. L. Fielding: *Tetrahedron* **56**, 6151 (2000).
29. N. Tanaka, A. Yamaguchi, Y. Araki, and M. Araki: *Chem. Lett.* 715 (1987).
30. K.B. Lipkowitz: *Chem. Rev.* **98**, 1829 (1998).
31. M.V. Rekharsky, and Y. Inoue: *Chem. Rev.* **98**, 1875 (1998).
32. S. Tavornvipas, F. Hirayama, H. Arima, K. Uekama, T. Ishiguro, M. Oka, K. Hamayasu, and H. Hashimoto: *Int. J. Pharm.* **249**, 199 (2002).
33. K. Kano, T. Kitae, Y. Shimofuri, N. Tanaka, and Y. Mineta: *Chem. Eur. J.* **6**, 2705 (2000).