NJC
Letter

First evidence of molecular recognition between cyclodextrins and a water-soluble ligand used in aqueous phase organometallic catalysis

Eric Monflier,*[a] Sébastien Tilloy,[a] Catherine Méliet,[b] André Mortreux,[b] Sophie Fourmentin,[c] David Landy[c] and Gheorghe Surpateanu[c]

[a] *Laboratoire de Physico-Chimie des Interfaces et Applications, Faculté des Sciences J. Perrin, Université d'Artois, Rue Jean Souvraz, Sac postal 18, 62307 Lens cédex, France.*
Fax: +33 3 21 79 17 55; e-mail: monflier@univ-artois.fr
[b] *Laboratoire de Catalyse Hétérogène et Homogène, (CNRS URA 402), ENSCL, Bâtiment C7, B.P. 108, 59652 Villeneuve d'Ascq cédex, France*
[c] *Laboratoire de Synthèse Organique et Environnement, Université du Littoral, 145 Route du Pertuis d'Amont, 59140 Dunkerque, France*

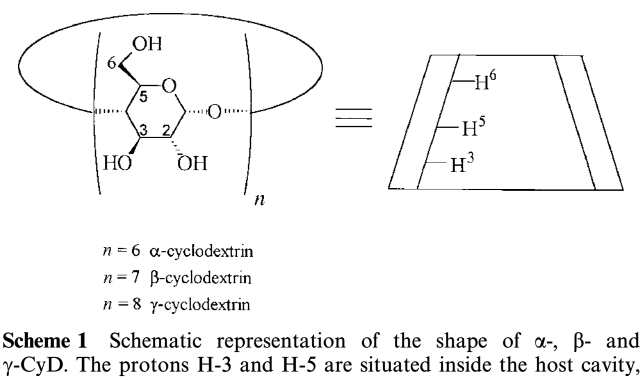
Received (in Montpellier, France) 1st February 1999, Accepted 1st March 1999

The formation of inclusion complexes between the water-soluble phosphane $P(m\text{-}C_6H_4SO_3Na)_3$ and β- and γ-cyclodextrins was proved by UV-vis, circular dichroism and ^1H and ^{31}P NMR spectroscopy.

Premier exemple de complexes d'inclusion entre des cyclodextrines et un ligand hydrosoluble utilisé en catalyse biphasique. Résumé: La formation de complexes d'inclusion entre la triphénylphosphine trisulfonée et les β- et γ-cyclodextrines a été observée par spectroscopie RMN et UV-vis.

Native cyclodextrins are cyclic oligosaccharides composed of six, seven, or eight D-glucopyranose units, which are designated as α-, β-, and γ-cyclodextrin (CyD) (Scheme 1).[1] Due to the hydrophobic character of their internal cavity, these compounds can encapsulate a large variety of compounds.[2] This outstanding property has long been utilized in the food, cosmetic and pharmaceutical industries and even now still finds new potential applications.[3] For instance, the use of CyDs as inverse phase transfer catalysts has been recently reported in aqueous-organic biphasic reactions involving hydrosoluble organometallic catalysts.[4] In such reactions, the immobilization of the metal catalyst in the aqueous layer can be achieved by using the sodium salt of trisulfonated triphenylphosphine [$P(m\text{-}C_6H_4SO_3Na)_3$; TPPTS] as ligand.[5]

We report here that this well-known standard ligand in biphasic catalysis forms inclusion complexes with β- and γ-CyD. Since TPPTS does not possess an evident hydrophobic moiety that can fit into the cavity of CyD, the formation of such complexes is rather unexpected. To the best of our knowledge, this is the first example of supramolecular complexes between a CyD and a water-soluble phosphane used as a ligand for biphasic catalysis.[6]



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

The interaction between β-CyD and TPPTS can be easily detected by UV-vis and circular dichroism spectroscopy. Indeed, hypsochromic and bathochromic effects in the UV-vis absorption band of TPPTS are observed upon addition of β-CyD and an optical activity is induced in the absorption bands of the achiral TPPTS in the presence of β-CyD (Fig. 1).

However, the most relevant information on the interaction between β-CyD and TPPTS has been furnished by NMR spectroscopy. Fig. 2 shows the modifications brought to the ^1H NMR spectra in the presence of increasing amounts of the TPPTS (guest-to-host ratio: 0.25 to 4). Each spectrum denotes chemical shift variations for the guest protons as well as for most of the host protons. The largest differences in the chemical shifts for the β-CyD 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.[7] Indeed, when external interaction phenomena occur between a CyD and a guest molecule, no variation of chemical shifts for these inner protons is observed.

In order to get a better insight into the inclusion process, two-dimensional rotating-frame NOE experiments (ROESY) that provide the most reliable information about the relative interproton distances in CyD complexes have been performed.[7] Fig. 3 displays a partial contour plot of the 2D-ROESY spectrum of a mixture of TPPTS and β-CyD. The strong cross-peaks between the *ortho* and *meta* protons of TPPTS and the H-3 and H-5 protons of CyD indicate that

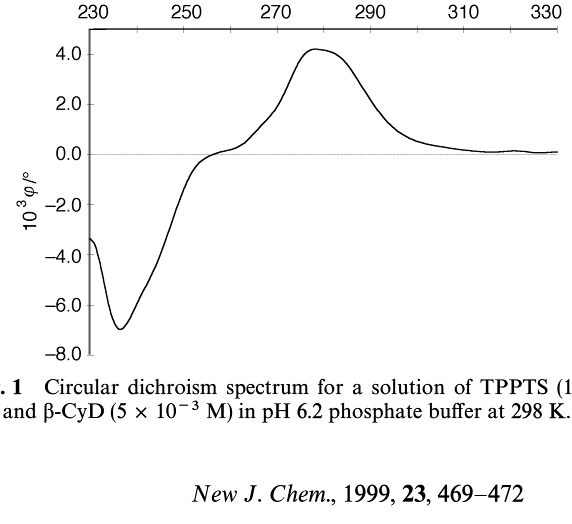


Fig. 1 Circular dichroism spectrum for a solution of TPPTS (10^{-4} M) and β-CyD (5×10^{-3} M) in pH 6.2 phosphate buffer at 298 K.

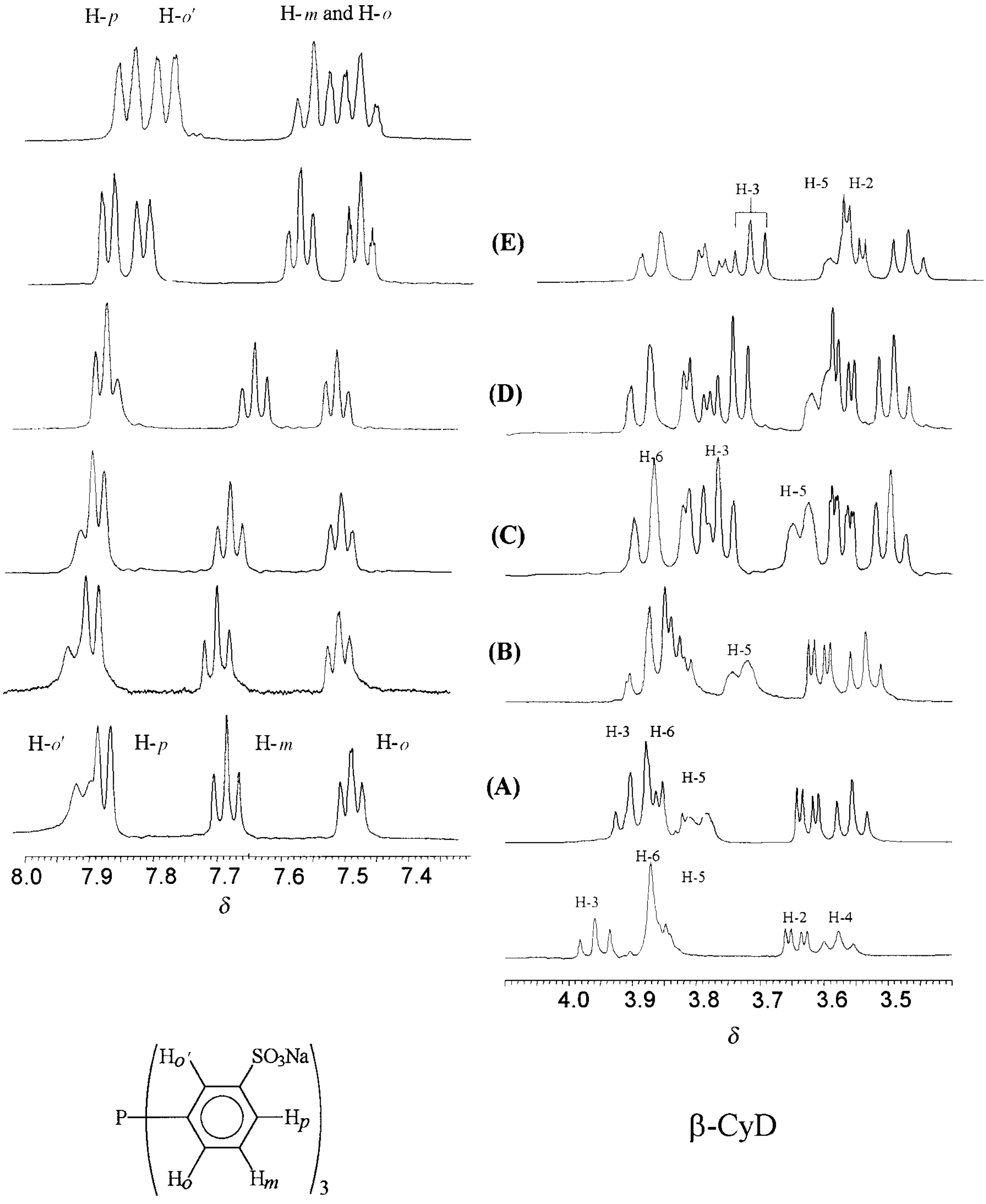


Fig. 2 Partial ^1H NMR spectra (400 MHz) of solutions of TPPTS + β-CyD complexes in D_2O at 298 K. [β-CyD]: 1×10^{-2} M. [TPPTS]/[β-CyD] ratio: (*A*) 0.25, (*B*) 0.5, (*C*) 1.0, (*D*) 2.0, (*E*) 4.0. Unlabelled curves are of the pure compounds.

the phenyl groups of TPPTS are included, at least partially, in the hydrophobic cavity. Moreover, as no cross-peak between the protons of TPPTS and the H-6 proton of β-CyD is observed, the inclusion occurs through the upper rim of β-CyD.

The ^{31}P NMR spectra of TPPTS and of its oxide $[O{=}P(C_6H_4SO_3Na)_3]$ in the presence of β-CyD supply further information on this inclusion. Indeed, whereas the ^{31}P chemical shifts of TPPTS shift progressively to lower frequencies in the presence of increasing amounts of β-CyD (Fig. 4), no variation of the ^{31}P NMR chemical shift of the phosphane oxide is observed in the presence of β-CyD. These ^{31}P NMR studies show the crucial role played by the phosphorus atom in the inclusion process. In fact, the phosphorus atom of TPPTS is likely included deeply into the hydrophobic cavity and constitutes the hydrophobic part of TPPTS. With the phosphane oxide, this hydrophobic site is suppressed due to hydrogen bonding between water and the P=O group, so that inclusion does not occur.

Quantitative analysis of the ^{31}P and ^1H NMR data establishes the existence of different kinds of complexes in solution. Indeed, a formation constant for a 1 : 1, 1 : 2 or 2 : 1 complex cannot be calculated by computer fitting of the chemical shift variations of the TPPTS protons and the inner protons (H-3, H-5) of β-CyD.[8] Attempts to determinate the host-guest stoichiometry by Job's method have also failed.[8] However, an apparent formation constant for a 1 : 1 complex can be evaluated as 1200 M^{-1} ±10% from UV-vis spectroscopic data.[9] The excellent definition of the isosbestic point indicates that the UV-vis spectra are not biased by experimental error and lead to an accurate value for this apparent formation constant (Fig. 5).[10]

The above results strongly suggest that the inclusion of TPPTS into the cavity of β-CyD is a complex process that leads to the formation of various complexes in equilibrium. Further investigations are currently under way to determine the number of inclusion complexes, their stoichiometry, their association constants and their geometry.

The formation of inclusion complexes between TPPTS and γ-CyD or α-CyD has also been investigated by NMR spectroscopy. The ^{1}H NMR spectrum of a 1 : 1 mixture of γ-CyD and TPPTS reveals shifts to lower frequencies for the signal associated with H-3 and H-5, indicating that adduct formation is occurring in a manner analogous to that demonstrated above for β-CyD. No chemical shift changes were observed in the spectrum of α-CyD in the presence of TPPTS, indicating the absence of inclusion complexes. The shape and size of α-CyD are likely to be less suitable for the TPPTS ligand than those of β- and γ-CyD.

In conclusion, our work demonstrates for the first time that β- and γ-cyclodextrins form inclusion complexes with TPPTS. During the complexation process, the phosphorus atom of TPPTS is likely to be included in the hydrophobic cavity. This result has important implications in aqueous biphasic reactions: CyDs must not be considered just as inverse phase transfer catalysts but also as compounds that can modify the equilibrium between the different catalytic species by trapping the ligand.[5] Under particular conditions, the generation of new and more active species may also occur. Finally, some fruitful developments in host-guest chemistry or in separation technology could also be envisaged in the near future.

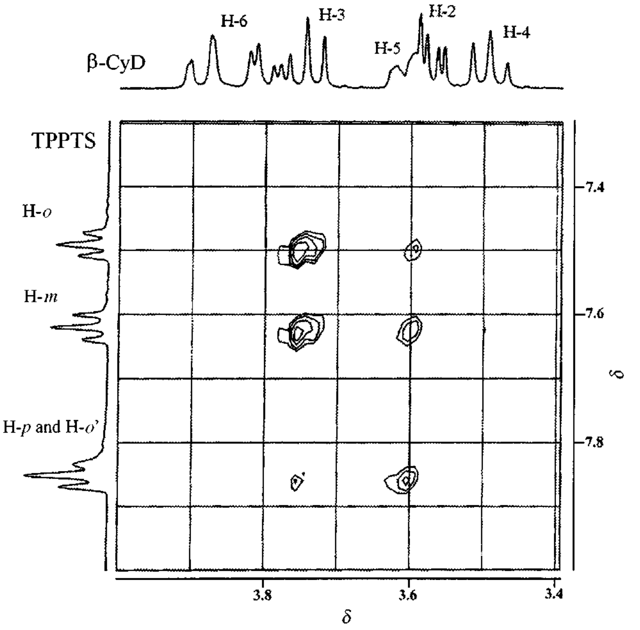


Fig. 3 Partial contour plot of the ROESY spectrum of a solution containing β-CyD (10^{-2} M) and TPPTS (2×10^{-2} M) in D_2O at 298 K (400 MHz). The ROESY experiments were obtained using the program provided by the Bruker library with a 500 ms spin-lock time. These bidimensional experiments were acquired using 1K data points and 512 time increments. The treatment of the 2D map was realized with a QSINE sequence.

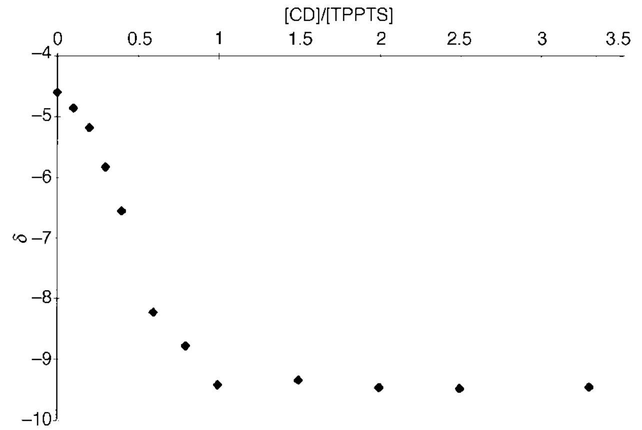


Fig. 4 ^{31}P NMR chemical shift variations as a function of [β-CyD]/[TPPTS] ratio. [TPPTS]: 3×10^{-3} M. ^{31}P{H} NMR spectra (121 MHz) were recorded in H_2O at 298 K.

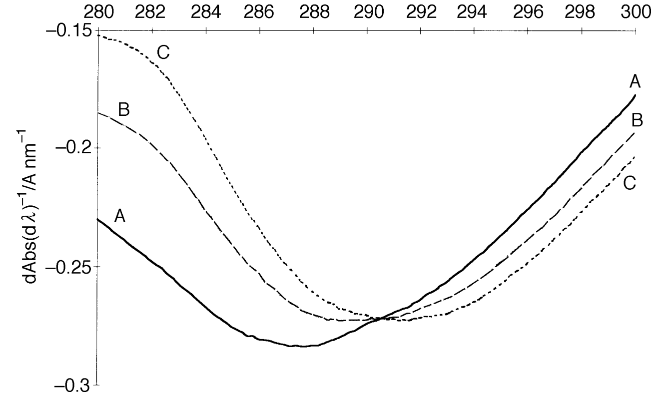


Fig. 5 Derivative of the absorption spectra of TPPTS at varying β-CyD concentrations in pH 6.2 phosphate buffer at 298 K. [TPPTS]: 10^{-4} M. [β-CyD]: (*A*) 0, (*B*) 0.88×10^{-3}, (*C*) 5×10^{-3} M.

Notes and references

1 (*a*) J. Szejtli, *Chem. Rev.*, 1998, **98**, 1743; (*b*) G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 803.

2 E. Fenyvesi, L. Szente, N. R. Russell and M. McNamara, in *Comprehensive Supramolecular Chemistry*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, Pergamon, Oxford, 1996, vol. 3, pp. 305–356.

3 A. R. Hedges, *Chem. Rev.*, 1998, **98**, 2035.

4 T. Okano, in *Aqueous-Phase Organometallic Catalysis*, ed. B. Cornils and W. A. Hermann, Wiley-VCH, Weinheim, Germany, 1998, pp. 221–233.

5 (*a*) E. Monflier, S. Tilloy, Y. Castanet and A. Mortreux, *Tetrahedron Lett.*, 1998, **39**, 2959; (*b*) E. Monflier, S. Tilloy, F. Bertoux, Y. Castanet and A. Mortreux, *New J. Chem.*, 1997, **21**, 857; (*c*) E. Monflier, S. Tilloy, G. Fremy, Y. Castanet and A. Mortreux, *Tetrahedron Lett.*, 1995, **36**, 9481; (*d*) E. Monflier, G. Fremy, Y. Castanet and A. Mortreux, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2269.

6 Second-sphere coordination adducts of *trans*-$[Pt(PMe_3)Cl_2(NH_3)]$ and *trans*-$[Pt(PEt_3)Cl_2(NH_3)]$ complexes with cyclodextrins have been reported: D. R. Alston, A. M. Z. Slawin, J. F. Stoddart, D. J. Williams and R. Zarzycki, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1184.

7 (*a*) H. J. Schneider, F. Hacket and V. Rüdiger, *Chem. Rev.*, 1998, **98**, 1755; (*b*) A. Bax and D. G. Davis, *J. Magn. Reson.*, 1985, **63**, 207; (*c*) A. A. Bothner-By, R. L. Stephens, J. Lee, C. D. Warren and R. W. Jeanloz, *J. Am. Chem. Soc.*, 1984, **106**, 811; (*d*) Y. Inoue, *Ann. Rep. N.M.R. Spectrosc.*, 1993, **27**, 59.

8 K. Connors, *Binding Constants. The Measurement of Molecular Complex Stability*, Wiley, New York, 1987.

9 UV-vis data collected with a 10 mm cell at a TPPTS concentration of 10^{-4} M fit surprisingly well with a 1 : 1 equilibrium. The algorithmic treatment was applied to the derivative of the UV spectra so that no effect from the refractive index relative to the cyclodextrin was observed. Assuming a 1 : 1 inclusion mechanism, the observed UV-vis absorption of TPPTS (A_{OBS}) and complex concentration [COMP] are described as follows:

$$A_{OBS} = \varepsilon_{TPPTS} \cdot [TPPTS] + \varepsilon_{COMP} \cdot [COMP] \qquad (1)$$

$$[\mathrm{COMP}] = -\frac{1}{2}\left\{\left(\frac{1}{K_\mathrm{f}} + [\mathrm{CD}]_\mathrm{T} + [\mathrm{TPPPTS}]_\mathrm{T}\right)^2 - 4[\mathrm{CD}]_\mathrm{T} \cdot [\mathrm{TPPTS}]_\mathrm{T}\right\}^{1/2} + \frac{1}{2}\left(\frac{1}{K_\mathrm{f}} + [\mathrm{CD}]_\mathrm{T} + [\mathrm{TPPTS}]_\mathrm{T}\right) \qquad (2)$$

where K_f and T stand for formation constant and total, respectively. For a given value of K_f, [COMP] is known and $\varepsilon_\mathrm{COMP}$ may be calculated from eqn. (1) for each value of $[\mathrm{CD}]_\mathrm{T}$. The standard deviation over $\varepsilon_\mathrm{COMP}$ then has to be minimized relative to K_f.

10 The value of the apparent formation constant was also confirmed by carrying out UV-vis measurements with a 1 mm cell at a TPPTS concentration of 10^{-3} M and by a spectral displacement method with methyl orange, with the TPPTS concentration was fixed at 10^{-3} M.

Letter 9/00898E