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Sulfobutyl Ether- β -Cyclodextrins: Promising Supramolecular Carriers for Aqueous Organometallic Catalysis

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Abstract: The potentialities of sulfobutyl ether- β -CDs derivatives as supramolecular carrier in a biphasic Tsuji–Trost reaction catalyzed by a water-soluble palladium complex of trisulfonated triphenylphosphine have been investigated. The efficiency of these cyclodextrins (CDs) strongly depends on the average molar substitution degree of cyclodextrin and the highest rate enhancements were obtained with cyclodextrins containing about 7 sulfobutyl ether groups. This result was attributed to the absence of a strong interaction between this cyclodextrin and the trisulfonated triphenylphosphine used to dissolve the catalyst in the aqueous phase and to the presence of an extended hydrophobic cavity allowing a better molecular recognition between the substrate and the cyclodextrin. This constitutes the first example of a non-interacting β -cyclodextrin/phosphine couple with high catalytic activities.

Keywords: aqueous catalysis; cyclodextrins; molecular recognition; palladium; phosphanes

In the field of aqueous phase organometallic catalysis, the cyclodextrins (CDs) are used to increase the mass transfer between organic and aqueous phases.^[1] Indeed, by forming a host/guest complex with the water-insoluble substrate (S) at the liquid/liquid interface, CDs transfer the substrate into the aqueous phase where it reacts with the water-soluble organometallic catalyst. After reaction, the product (P) is released in the organic phase and the transfer cycle can go on (Figure 1).

The efficiency of this process strongly depends on the nature of the CD. So, methylation or hydroxyalkylation of the hydroxy groups of β -CD gives rise to the most efficient CD in terms of rate enhancement.^[2]

In these CD-mediated reactions, it is established that the sodium salt of the trisulfonated triphenylphosphine

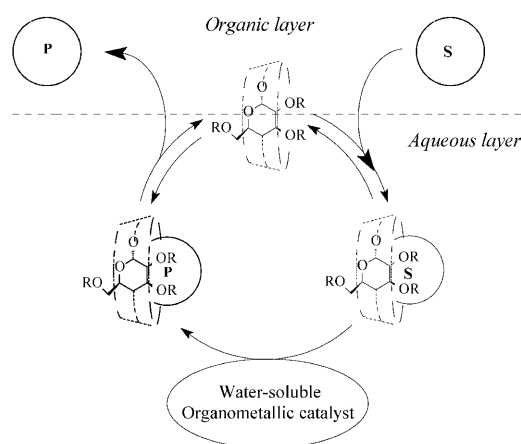


Figure 1. Principle of the aqueous organometallic catalysis mediated by chemically modified cyclodextrins (CDs). CDs are annular molecules comprised of 6, 7 or 8 glycosyl units.

[TPPTS, $P(C_6H_4SO_3Na)_3$] used to dissolve the catalyst in the aqueous phase can be deeply included in the host CDs cavity by the secondary face.^[3] The formation of such inclusion complexes can induce a modification of the catalyst structure and the poisoning of the CD in particular experimental conditions.^[4] To circumvent these drawbacks, the use of chemically modified α -CDs has been recently proposed. Indeed, these CDs possess a cavity that is too small to include the phenyl ring of a sulfonated triphenylphosphine and, consequently, the formation of inclusion complexes was not observed.^[5] However, the use of β -CD derivatives is highly desirable for the development of an economically viable and attractive process. In particular, the cost of native α -CD is notably higher than that of native β -CD because of their lower production yield.^[6]

In this context, we have focused our attention on negatively charged β -CD derivatives. The electronic repulsion between the anionic group of the CD and the sulfonate groups of the water-soluble phosphine is expected to impede the formation of inclusion complexes. Among

the common anionic CD derivatives, namely carboxymethyl- β -CDs, sulfated β -CDs and sulfobutyl ether- β -CDs, the latter are particular promising candidates. Indeed, the randomly sulfobutyl ether- β -CDs (SBE- β -CD) are water-soluble in a broad pH range and studies suggest that these CDs are very effective complexing agents for neutral organic molecule as the charge is spaced away from the CD cavity by neutral spacer groups.^[7] In particular, SBE- β -CD with an average molar substitution degree of 7 for the sulfobutyl ether group has a high intrinsic aqueous solubility (> 50% w/v) and exhibits binding capacities comparable to its β -CD parent.^[8] Moreover, the SBE- β -CDs are commercially available in multi-kilogram quantities and have found industrial applications in drug formulation, cosmetics and as chiral selectors for the separation of enantiomers.^[9]

In this paper, the behaviour of sulfobutyl ether- β -CDs in aqueous organometallic catalysis has been investigated. Firstly, we have studied by NMR, UV-vis spectroscopy and molecular modelling the interactions between the TPPTS and randomly sulfobutyl ether- β -CDs in which the average substitution degree is 1, 4 and 7 for the sulfobutyl ether group (SBE₁- β -CD, SBE₄- β -CD, SBE₇- β -CD, respectively, see Figure 2).

Secondly, the efficiency of SBE- β -CDs as mass transfer promoters has been examined in a Tsuji–Trost reaction catalyzed by a palladium/TPPTS system.^[10]

The interaction between the SBE- β -CDs and the TPPTS ligand was firstly investigated by ¹H NMR spectroscopy (Figure 3).

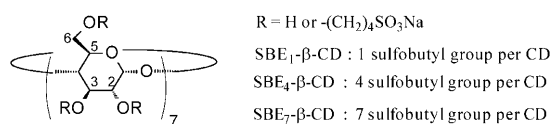


Figure 2. Description of randomly sulfobutyl ether- β -cyclodextrins (SBE- β -CDs).

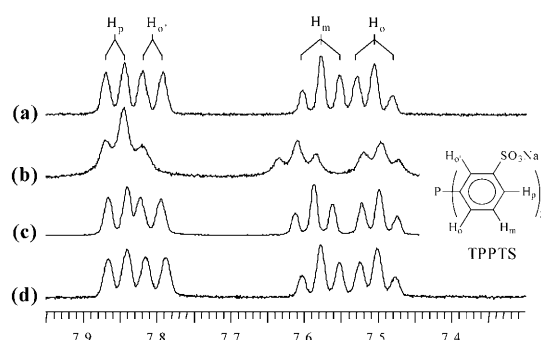


Figure 3. ¹H NMR spectrum of TPPTS (3 mM) in D₂O at 25 °C (a) without cyclodextrin; (b) in the presence of SBE₁- β -CD (3 mM); (c) in the presence of SBE₄- β -CD (3 mM) and (d) in the presence of SBE₇- β -CD (3 mM).

No important chemical shift was detected for TPPTS and SBE₇- β -CD when they were mixed together, contrary to what was observed with SBE₁- β -CD or SBE₄- β -CD. The same behaviour was evidenced by ³¹P{¹H} NMR spectroscopy. Consequently, it appears that the affinity of TPPTS for SBE- β -CDs clearly depends on the substitution degree of the latter. The more they are substituted, the weaker are the interactions between them and TPPTS.

The apparent association constants of these adducts were evaluated by a competition method with methyl orange (MO) from UV-vis spectroscopic data.^[11] An increase of absorption was detected when TPPTS is added to SBE- β -CD/MO solutions, thus illustrating the expulsion of MO from the CD cavity upon inclusion of TPPTS. This enhancement decreases in the order SBE₁- β -CD > SBE₄- β -CD > SBE₇- β -CD, confirming that the TPPTS/CD adduct is more stable with less substituted SBE- β -CD. The apparent association constant values were found to be $790 \pm 70 \text{ M}^{-1}$, $220 \pm 30 \text{ M}^{-1}$ and $21 \pm 7 \text{ M}^{-1}$ for SBE₁- β -CD, SBE₄- β -CD and SBE₇- β -CD, respectively. These values are notably lower than that found for the TPPTS/ β -CD inclusion complex (1200 M^{-1} at 298 K), confirming the detrimental effect of the sulfobutyl arms of the CD.^[3]

In order to determine whether these 1:1 adducts are true inclusion complexes or adducts resulting from external interaction phenomena, two-dimensional T-ROESY experiments have been performed. Indeed, discrimination between inclusion complexes and adducts is possible on the basis of the presence or absence of interaction between the protons located inside the cavity (H-3 and H-5) and the guest. The T-ROESY spectrum of an SBE₁- β -CD/TPPTS mixture (1:1) proves undoubtedly the formation of true inclusion complexes between SBE₁- β -CD and TPPTS (Figure 4).

Indeed, the strong interactions observed between the protons of TPPTS and the inner protons H-3 and H-5 of SBE₁- β -CD indicate that one of the sulfonated phenyl groups of TPPTS is included inside the SBE₁- β -CD host cavity. The partial T-ROESY spectrum of a solution containing a 1:1 mixture of SBE₄- β -CD and TPPTS is different from that obtained with SBE₁- β -CD (Figure 5).

Indeed, no intense correlation peaks were observed between the internal protons of the cavity and the TPPTS, indicating that the TPPTS did not penetrate inside the cavity of the CD. Only an interaction between TPPTS and the H-7 protons of the methylene group directly connected to the CD occurred. The absence of contact between the H-8, H-9 and H-10 protons and the TPPTS implies the spacing of the sulfobutyl arms as the petals of an opening flower. Such an association is characteristic of an adduct and cannot be considered as a true inclusion complex.

Finally, T-ROESY experiments on a solution containing a 1:1 mixture of SBE₇- β -CD derivatives and TPPTS

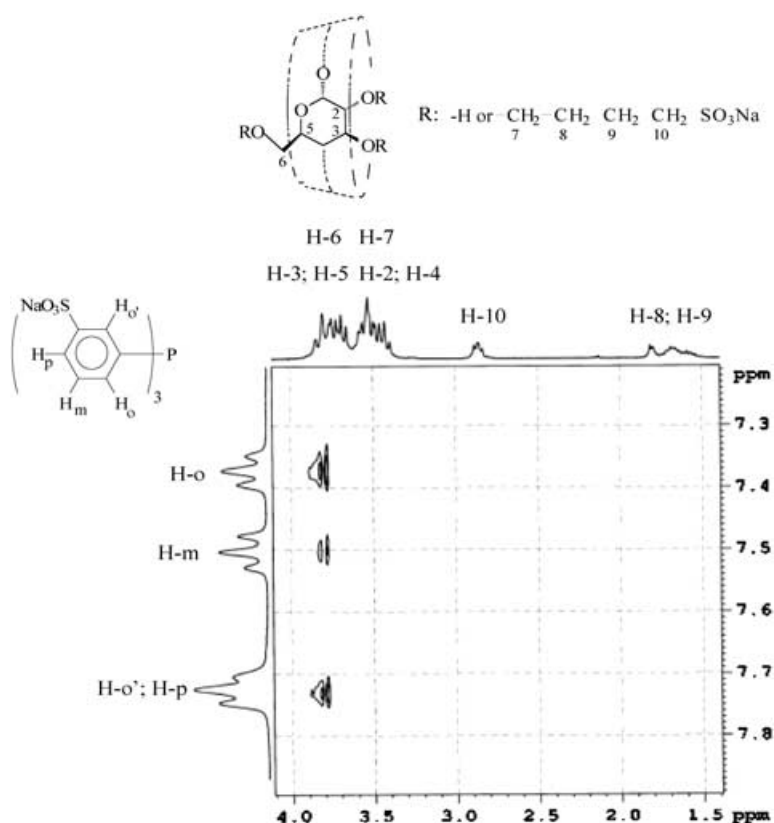


Figure 4. Partial contour plots of the T-ROESY spectrum of equimolar solutions of TPPTS and SBE₁- β -CD (10 mM) in D₂O at 25°C with a 300 ms mixing time.

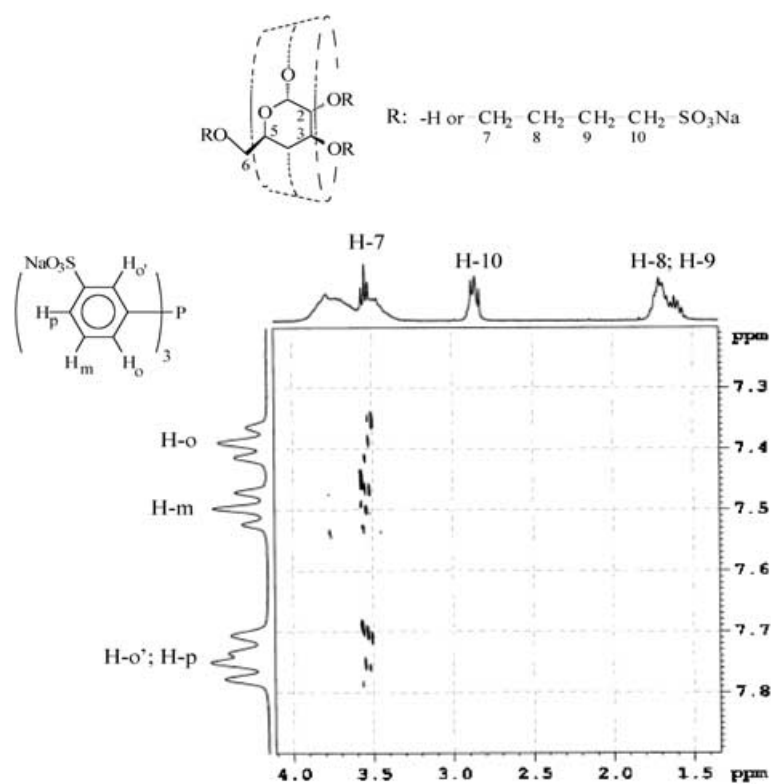


Figure 5. Partial contour plots of the T-ROESY spectrum of equimolar solutions of TPPTS and SBE₄- β -CD (10 mM) in D₂O at 25°C with a 300 ms mixing time.

were also performed. No cross-peaks could be observed suggesting that no inclusion compound or adduct was formed with this CD. This result was fully supported by a molecular modelling study conducted with an SBE₇- β -CD isomer where three sulfobutyl arms are grafted on the primary side of β -CD and four on the secondary side. Indeed, when the TPPTS is docked into this SBE₇- β -CD isomer from its secondary face, the total energy increases continuously so that no true inclusion compound may be formed (Figure 6).

The differences in the MM3 energetic components between the free species and the most included conformation (before overlap between the van der Waals spheres of host and guest) showed that the sulfobutyl arms prevent the TPPTS inclusion by electrostatic repulsion (difference of 366.1 kcal/mol in favour of the free species). In contrast, the van der Waals term is favourable (difference of 21.5 kcal/mol in favour of the inclusion compound). A more accurate representation of the inclusion in aqueous medium was given by the AM1 Hamiltonian coupled with the COSMO simulation of water. As expected, the complex is not stabilized since the energetic difference corresponds to 49.8 kcal/mol in favour of the free species. Thus, the destabilizing effect of seven sulfobutyl arms is sufficient to dissociate the CD/TPPTS complex.

In this second part of this study, the efficiency of SBE- β -CDs as mass transfer promoters has been examined in a Tsuji–Trost reaction catalyzed by a palladium/TPPTS system with the water-insoluble allyl undecyl carbonate as substrate and diethylamine as allyl scavenger.^[12] Figure 7 displays the influence of the SBE- β -CDs on the relative reaction rate for different CD/TPPTS ratios. The relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of CD and the initial catalytic activity without CD.

For CD/TPPTS ratios inferior to 1, no significant improvement was detected with the SBE₁- β -CD and the SBE₄- β -CD derivatives. In contrast, a slight increase in the reaction rate could be measured under the same catalytic conditions for the SBE₇- β -CD derivative. These

results can be easily rationalized by considering a poisoning of the SBE₁- β -CD and SBE₄- β -CD cavities by the TPPTS and the absence of an interaction between SBE₇- β -CD and TPPTS. Indeed, as the TPPTS is in excess towards CD, the cavity of SBE₁- β -CD and SBE₄- β -CD derivatives is partially occupied by the TPPTS and unavailable to transfer the substrate into the aqueous phase. In the case of the SBE₇- β -CD, the cavity is free and can transfer more efficiently the substrate. However, the rate increase remained very modest owing to the low concentration of mass transfer promoter. For CD/TPPTS ratios superior to 1, all SBE- β -CD derivatives allowed an increase of the reaction rates. Indeed, uncomplexed SBE- β -CDs were always available in the medium to transfer the substrate as the SBE- β -CD derivatives are in excess towards TPPTS. However, the rate increase was much more marked with SBE₄- β -CD and SBE₇- β -CD than with SBE₁- β -CD (38 and 54 for SBE₄- β -CD and SBE₇- β -CD, respectively, vs. 6 for the SBE₁- β -CD at CD/TPPTS ratio of 2). Moreover, it must be pointed out that the SBE₄- β -CD and SBE₇- β -CD derivatives enhance similarly the reaction rates for CD/TPPTS ratios superior to 1 and this increase is much more important than in the case of the SBE₁- β -CD. Consequently, it seems that the presence of several sulfoalkyl ether arms on the CD improves the ability of the CD to transfer the substrate into the aqueous phase. In so far as the SBE- β -CDs derivatives have no surface active properties, the higher efficiency of SBE₄- β -CD and SBE₇- β -CD derivatives could be attributed to their capacity to accommodate more easily the substrate in the cavity. This higher binding ability towards allyl undecyl carbonate is likely in connection with the presence of an extended hydrophobic cavity in these host compounds.^[7,8] Unfortunately, we have not been able to verify this assumption as all attempts to determine the association constants of SBE- β -CD derivatives with the allyl undecyl carbonate have failed. However, this assumption is fully supported by data reported in the literature.^[8]

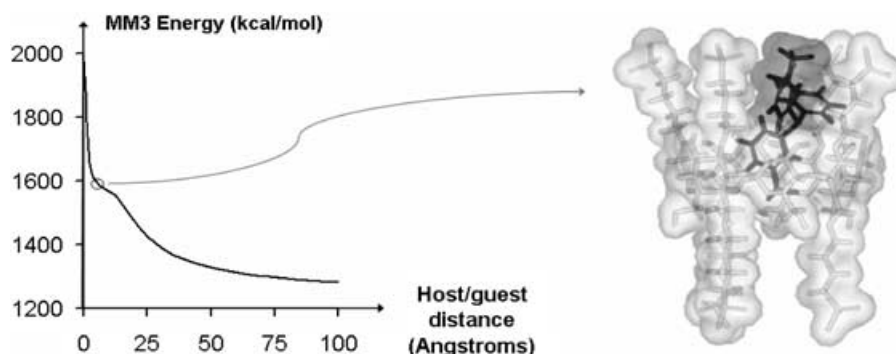


Figure 6. Docking results for the SBE₇- β -CD/TPPTS system (MM3 total energy as a function of the host/guest distance). The most included conformation (before overlap between the van der Waals spheres of host and guest) is illustrated by stick models and van der Waals surfaces.

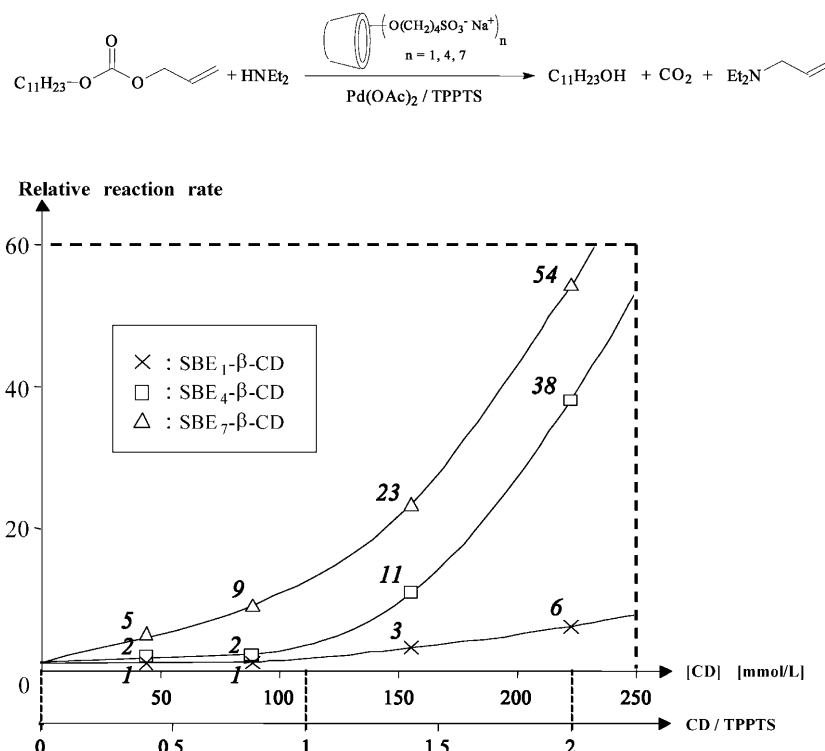


Figure 7. Relative reaction rate vs. [CD]/[TPPTS] ratio. Pd(OAc)_2 (0.044 mmol), TPPTS (0.401 mmol), required amount of SBE- β -CD, water (2 g), allyl undecyl carbonate (1.12 mmol) and diethylamine (2.24 mmol), T 20 °C. The relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of cyclodextrin and the initial catalytic activity without cyclodextrin. The initial catalytic activity without cyclodextrin is 1.4 $\mu\text{mol/h}$ (reference).

In conclusion, this work has demonstrated that attachment of several sulfobutyl arms on the β -CD reduces the affinity of the cyclodextrin for the TPPTS ligand and increases its carriers properties. The highest rate enhancements were obtained with cyclodextrins containing about 7 sulfobutyl ether groups. This constitutes the first example of a non-interacting β -cyclodextrin/phosphine couple with high catalytic activities. Experiments are currently under way to study the behaviour of this promising CD in other biphasic transition metal-catalyzed reactions.

Experimental Section

General Methods

The ^1H and ^{31}P NMR spectra were recorded at 300.13 and 121.49 MHz on a Bruker Avance DRX, respectively. ^1H and $^{31}\text{P}\{^1\text{H}\}$ chemical shifts are given in ppm relative to external references: sodium 3-(trimethylsilyl)propionate- d_4 (98% atom D) in D_2O for ^1H NMR and H_3PO_4 in H_2O for $^{31}\text{P}\{^1\text{H}\}$ NMR. The 2D T-ROESY experiments were run using the software supplied by Bruker. Mixing times for T-ROESY experiments were set at 300 ms. 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 dimensions, respectively. They were transformed in the non-phase-sensitive mode after QSINE window processing. Gas chromatographic analyses were carried out on a Shimadzu GC-17A gas chromatograph equipped with a methyl silicone capillary column (25 m \times 0.25 mm) and a flame ionization detector (GC:FID). UV-Visible spectrometry was performed with a UV-Visible Perkin Elmer Lambda 2S spectrometer. The temperature of the 10 mm cell was kept constant at 298 K by means of a thermostatted bath.

Materials

D_2O (99.95% isotopic purity) was obtained from Merck. Palladium acetate was purchased from Aldrich. Tris(3-sodium sulfonatophenyl)phosphine [TPPTS, $\text{P}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_3$] was synthesized as reported by Gärtner et al.^[13] The purity of the TPPTS was carefully controlled. In particular, $^{31}\text{P}\{^1\text{H}\}$ NMR indicated that the product was a mixture of the phosphine (ca. 98%) and its oxide (ca. 2%). The SBE- β -CD derivatives were prepared according to the general procedure of Stella and Rajewski.^[14]

Association Constant

The apparent association constants were evaluated by a competition method with methyl orange (MO) from UV-Vis spec-

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