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Fine tuning of sulfoalkylated cyclodextrin structures to improve their mass-transfer properties in an aqueous biphasic hydroformylation reaction

D. Kirschner [a], M. Jaramillo [a], T. Green [a], F. Hapiot [b], L. Leclercq [b], H. Bricout [b], E. Monflier [b,*]

[a] *Department of Chemistry and Biochemistry, Institute of Arctic Biology, University of Alaska, Fairbanks, AK 99775-5940, USA*
[b] *Unité de Catalyse et de Chimie du Solide, UMR CNRS 8181, Université d'Artois, Rue Jean Souvraz SP 18, 62307 Lens cédex, France*

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Abstract

The structure of sulfoalkylated cyclodextrins (CDs) have been varied and optimised to improve their performances as mass-transfer promoters in an aqueous biphasic hydroformylation reaction. Their surface tensions have been measured using the Wilhelmy plate technique and compared. Their behaviour towards two hydrosoluble derivatives of triphenylphosphine has been evaluated by $^{31}P\{^{1}H\}$ and ^{1}H NMR measurements and their catalytic activity has been assessed in a rhodium-catalyzed hydroformylation reaction of 1-decene. The best result was obtained using a β-CD sulfobutylated on the primary face and methylated on the secondary face. Indeed, this CD increased the reaction rate by a factor of 250 without inducing selectivity decrease. The accessibility to the secondary face of the CD appears to be determining in the catalytic process as it governs the approach between the CD-included substrate and the water-soluble catalyst. The impact of the nature of the CD substituents on the chemo- and regioselectivity of the reaction is also discussed.

Keywords: Aqueous organometallic catalysis; Cyclodextrins; Hydroformylation; Molecular recognition; Phase-transfer catalysis

1. Introduction

Among ecological processes in organometallic catalysis, the use of an aqueous–organic two-phase system appeared to be one of the most efficient solution to recover and reuse the catalyst at the end of the chemical reaction [1,2]. The process is based on the coordination of water-soluble phosphane on the catalyst that is thus rendered hydrosoluble. Once the reaction completed, the products and the organometallic catalyst are separated by simple decantation [3–5]. However appropriate for water-soluble substrates, the biphasic processes suffered from a huge loss of attractiveness when hydrophobic substrates were considered because of mass-transfer limitations. As initiated by some of us in the 90s, the use of modified cyclodextrins (CDs) permitted to substantially solve the problem [6,7]. Indeed, chemically modified β-CDs such as the randomly methylated β-CD and the hydroxypropylated β-CD are cheap, non-toxic and bulk commercially available compounds that notably increase the reaction rates, while avoiding the formation of an emulsion and the partition of the catalyst between the organic and aqueous phases [8–12]. These outstanding results were attributed to the complexing and surface-active properties of the chemically modified β-CDs. In fact, molecular dynamics studies [13,14] and surface-tension measurements [15] have recently suggested that chemically modified β-CDs are concentrated at the aqueous–organic interface and promote the reaction of the water-soluble catalyst with highly hydrophobic substrates at the liquid–liquid interface.

In previous studies, we have reported the performances of a variety of sulfopropyl- or sulfobutyl-CDs as mass-transfer promoters in Tsuji-Trost and hydroformylation reactions [16,17]. In particular, the heptakis(2,3-di-*O*-methyl-6-*O*-sulfopropyl)-β-CD was found to be the best mass transfer promoter due its surface-active properties and the absence of interactions with

* Corresponding author. Fax: +33 3 2179 1755.
E-mail address: monflier@univ-artois.fr (E. Monflier).

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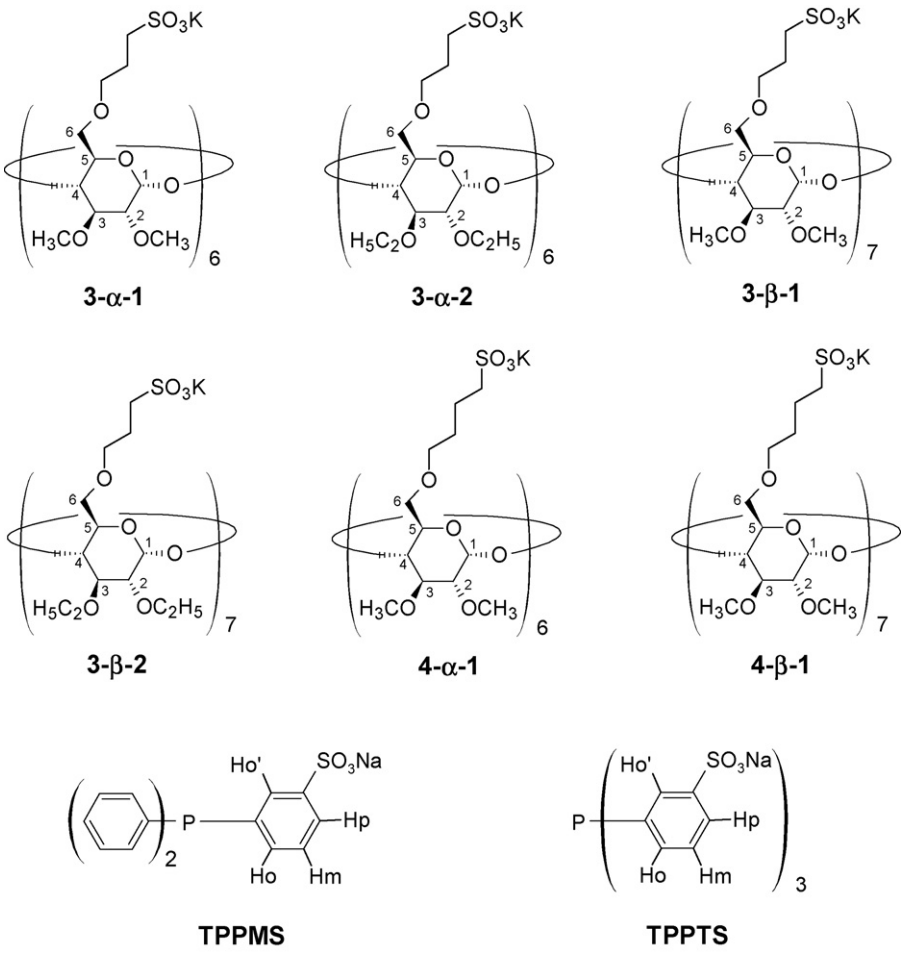


Scheme 1. Structures of β-cyclodextrin derivatives and hydrosoluble ligands used in this work. The sulfoalkylated CDs have been named according to the number of methylene groups (n) on the primary hydroxyle of a glucopyranose unit, the type of CD (α or β) and the number of methylene groups (n') on a secondary hydroxyle of glucopyranose unit. Acronyms of the type n – α (or β) – n' are used in the text.

the catalytically active species and the water-soluble phosphane [17]. This interesting result led us to optimise the structure of this type of CD to improve their catalytic performances.

In this paper, we describe the synthesis of a variety of new sulfoalkylated α- and β-CDs, their surface-active properties and their abilities to bind two water-soluble phosphanes used in aqueous organometallic catalysis (Scheme 1).

We furthermore examine the behaviour of these new compounds in a rhodium-catalyzed biphasic hydroformylation reaction and establish the essential structural features of CDs that control activity. The selectivity in aldehyde and the ratio of linear/branched aldehydes are also discussed.

2. Experimental

2.1. General

2.1.1. NMR analysis

^{1}H, ^{13}C, gCOSY, and gHSQC NMR spectra performed to characterize synthesized cyclodextrins were acquired with a Varian Mercury 300 MHz FT-NMR instrument with D_2O as solvent. Chemical shifts in ^{1}H and ^{13}C NMR are given in ppm relative to internal reference of sodium [D_4]3-(trimethylsilyl)propionate (98% atom D) in D_2O. The ^{1}H and ^{31}P NMR spectra performed to investigate the interactions between cyclodextrins and phosphanes were recorded at 300.13 and 121.49 MHz, respectively, on a Bruker DRX instrument. Chemical shifts in ^{1}H and ^{31}P{^{1}H} NMR are given in ppm relative to external references: sodium [D_4]3-(trimethylsilyl)propionate (98% atom D) in D_2O for ^{1}H NMR and H_3PO_4 in H_2O for ^{31}P{^{1}H} NMR. T-ROESY experiments were carried out as previously reported [18].

2.1.2. Indirect UV detection capillary electrophoresis

Indirect UV detection capillary electrophoresis (CE) electropherograms of each CD were obtained using an Agilent 3D Electrophoresis instrument. Peak area was quantified to estimate the mean degree of substitution (ds) in the sulfoalkylation step. CE conditions are as follows: buffer, 20 mM *p*-toluenesulfonic acid, 40 mM Tris base, pH 8.0; wavelength, 214 nm; applied potential 10 kV; injection, 2 mg/mL, 60 mbar s; capillary dimensions, 32.5 cm × 50 μm i.d. (24 cm to detector).

2.1.3. MALDI/TOF MS analysis

Samples were prepared for mass spectral analysis by spotting the analyte and matrix solutions onto a Ciphergen normal phase NP-20 ProteinChip that has silicon oxide surface chemistry. The matrix solution was prepared by dissolving 5 mg Super DHB (9:1 mixture of 2,5-dihydroxybenzoic acid and 2-hydroxy-5-methoxybenzoic acid) in 200 μL of water/methanol (50:50) containing 30 mM KCl. The analyte (CD) solution was prepared by dissolving 5 mg in 250 μL of water. Consecutive layers were then applied; 1 × 0.5 μL of matrix solution, 3 × 1 μL of analyte solution and then 2 × 0.5 μL of matrix solution (six layers total). Each layer was dried with dry N_2 prior to application of the next layer. Mass spectra were obtained using a Ciphergen PBSIIc mass spectrometer. Mass accuracy is ±1 Da in the 0.5–5 kDa range. The detector voltage was set to 2870 V, laser intensity 220–265, deflector sensitivity 7, with greater than 60 spectra collected for each sample. Data collection was optimised for *m/z* 1000–3000 Da, and the digitizer frequency was 250 MHz.

2.2. Materials

All chemicals were purchased from Strem Chemicals and Aldrich Chemicals in their highest purity. Carbon monoxide/hydrogen mixture (1:1) was used directly from cylinders (>99.9% pure; Air Liquide). Tetrahydrofuran (THF) was freshly distilled over 4 Å sieves. Tris(3-sodium sulfonatophenyl)phosphine (TPPTS – P(*m*-$C_6H_4SO_3Na)_3$) was synthesized as reported by Gärtner et al. [19]. The potassium salt of *meta*-substituted monosulfonated triphenylphosphine (TPPMS – $(C_6H_5)_2$P(*m*-$C_6H_4SO_3Na$)) was prepared by a literature method [20]. Permethylated α-cyclodextrin (Trime-α) was synthesized as reported by Lehn and co-workers [21]. Randomly methylated β-cyclodextrin (Rame-β) and permethylated β-cyclodextrin (Trime-β) were purchased from Aldrich Chemicals. Randomly methylated α-cyclodextrin (Rame-α) was prepared by adapting a procedure reported by Kenichi et al. [22]. Rame-α and Rame-β were native CDs 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%). Heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD was synthesized according to the procedure described by Fugedi [23]. Hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-CD was synthesized according to the procedure of Takeo et al. [24]. Heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-*O*-dialkyl)-β-CD and hexakis(6-*O*-*tert*-butyldimethylsilyl-2,3-*O*-dialkyl)-α-CD were synthesized according to the procedure described by Takeo and Dazuhiko [25]. Heptakis(2,3-*O*-dialkyl)-β-CD and hexakis(2,3-dialkyl)-α-CD were synthesized from their protected analogs according to Takeo and Dazuhiko [25] except that ammonium fluoride was used in place of tetrabutylammonium fluoride. Purification of these last intermediates was accomplished by preparative column chromatography on silica gel using a 4:1 chloroform–MeOH mobile phase.

2.3. General procedure for the synthesis of sulfoalkylated cyclodextrins

All potassium heptakis(2,3-di-*O*-alkyl-6-*O*-sulfoalkyl)-β-CDs (3-β-1, 3-β-2, 4-β-1) and potassium hexakis(2,3-di-*O*-alkyl-6-*O*-sulfoalkyl)-α-CDs (3-α-1, 3-α-2, 4-α-1) were synthesized according to the procedure of Kirschner and Green [26]. The synthesis of 4-β-1 from heptakis(2,3-di-*O*-methyl)-β-CD (2,3-DM-β-CD) is described here to illustrate a typical synthesis. Intermediate 2,3-DM-β-CD (0.84 g, 0.64 mmol) was dissolved in 150 mL of anhydrous THF under argon in a three-neck RB flask. KH (after removing mineral oil with hexanes, 1.1 g, 27.7 mmol) was slowly added with stirring and allowed to react for 15 min. 18-crown-6 (4.26 g, 16.1 mmol) was added and the mixture was stirred for 30 min. Butane sultone (2.53 g, 18.6 mmol) dissolved in 10 mL anhydrous THF was added dropwise over 15 min and the reaction stirred overnight at room temperature. Excess KH was reacted with methanol to quench reaction, and the mixture was transferred to a round-bottom flask for rotary evaporization of methanol and THF. The solid was dissolved in 30 mL of water. The aqueous solution was then passed through a column of acidic cation exchange resin (Dowex 50W-X8, 25 mm diameter × 350 mm length). After ion exchange, the acid form of the CD in water was extracted three times with methylene chloride, discarding the methylene chloride layer that contains 18-crown-6. The resultant aqueous solution was neutralized with excess $KHCO_3$ (∼10 g). The aqueous solution was rotary evaporated to remove trace amounts of methylene chloride, and then subjected to continuous ultrafiltration with a Amicon Model 8400 Stirred Cell Ultrafiltration Unit (Millipore Corp) using a cellulose acetate 500 MWCO membrane. The purified CD concentrate was rotary evaporated to remove most of the water. The resulting solid was then dried in a vacuum oven (70 °C) to a constant mass to yield 1.60 g of 4-β-1 (0.627 mmol, 98%). In the case of 3-α-1, 4-α-1 and 3-β-1, the purification was performed by using a Regenerated Cellulose 1000 MWCO ultrafiltration membranes. Lower yields obtained for these cyclodextrins (55%, 54% and 61% for 3-α-1, 4-α-1 and 3-β-1, respectively) were typical using these membranes. Samples were analyzed by ^{1}H,^{13}C, gCOSY and gHSQC NMR spectroscopy, elemental analysis, inverse detection capillary electrophoresis and, for some CDs, matrix-assisted laser desorption ionization/time-of-flight mass spectrometry (MALDI/TOF MS). Yields are given for last step in synthesis.

Hexakis(2,3-di-*O*-methyl-6-*O*-sulfopropyl)-α-cyclodextrin (3-α-1): yield, 55.0%; ^{1}H NMR (300 MHz, D_2O): δ 5.10 (H-1), 3.69 (H-4), 3.50 (H-3), 3.19 (H-2), 3.74 (H-5), 3.53 (OCH_2), 3.84, 3.61 (H-6), 3.54 (OCH_3), 3.42 (OCH_3), 2.92 (CH_2S), 1.97 (CH_2CH_2S) ^{13}C NMR (75 MHz, D_2O): δ 101.5 (C-1), 83.4 (C-4), 83.1 (C-3), 82.8 (C-2), 72.9 (C-5), 71.6 (OCH_2), 70.8 (C-6), 62.9 (OCH_3), 59.5 (OCH_3), 50.3 (CH_2S), 26.6 (CH_2CH_2S). Anal. calcd for $K_6C_{66}H_{114}O_{48}S_6{\cdot}6H_2O$: C, 35.86; H, 5.74; S, 8.70. Found C, 35.98; H, 5.63; S, 8.71. Inverse detection CE: mean ds (6.0). MS: calcd for $K_7C_{66}H_{114}O_{48}S_6^+$ 2142, found 2141.

Hexakis(2,3-di-*O*-methyl-6-*O*-sulfobutyl)-α-cyclodextrin (4-α-1): yield, 54.6%; ^{1}H NMR (300 MHz, D_2O): δ 5.12

(H-1), 3.72 (H-4), 3.52 (H-3), 3.22 (H-2), 3.75, (H-5), 3.59, 3.49 (OCH_2), 3.87, 3.61 (H-6), 3.57 (OCH_3), 3.43 (OCH_3), 2.88 (CH_2S), 1.68 (CH_3CH_2O), 1.75 (CH_2CH_2S). ^{13}C NMR (75 MHz, D_2O): δ 101.6 (C-1), 83.5 (C-4), 83.1 (C-3), 82.8 (C-2), 73.0 (C-5), 72.8 (OCH_2), 70.9 (C-6), 62.8 (OCH_3), 59.6 (OCH_3), 52.9 (CH_2S), 29.8 (CH_2CH_2O), 23.3 (CH_2CH_2S). Anal. calcd for $K_6C_{72}H_{126}O_{48}S_6{\cdot}6H_2O$: C, 37.68; H, 6.06; S, 8.38. Found C, 38.18; H, 6.21; S, 8.98. Inverse detection CE: mean ds (5.8).

Hexakis(2,3-di-*O*-ethyl-6-*O*-sulfopropyl)-α-cyclodextrin (3-α-2): yield, 86.5%; ^1H NMR (300 MHz, D_2O): δ 5.03 (H-1), 3.85, 3.68 (OCH_2CH_3), 3.57 (OCH_2CH_3), 3.83, 3.45 (H-6), 3.65 (H-5), 3.42, 3.54 (OCH_2), 3.67 (H-3, H4), 3.24 (H-2), 2.82 (CH_2S), 1.88 (CH_2CH_2S). 1.08 (2 CH_3CH_2O). ^{13}C NMR (75 MHz, D_2O): δ 100.0 (C-1), 82.0 (C-4), 80.5 (C-3), 79.8 (C-2), 73.4 (C-5), 72.0 (OCH_2), 71.5 (C-6), 70.8 (OCH_2CH_3), 69.3 (OCH_2CH_3), 50.5 (CH_2S), 26.9 (CH_2CH_2S), 17.2 (CH_3), 17.1 (CH_3). Anal. calcd for $K_6C_{78}H_{138}O_{48}S_6{\cdot}6H_2O$: C, 39.38; H, 6.36; S, 8.09. Found C, 38.93; H, 6.27; S, 7.88. Inverse detection CE: mean ds (6.0). MS calcd for $K_7C_{78}H_{138}O_{48}S_6^+$ 2310 found 2309.

Heptakis(2,3-di-*O*-methyl-6-*O*-sulfopropyl)-β-cyclodextrin (3-β-1): (reported previously) yield 61%; ^1H NMR (300 MHz, D_2O): δ 5.27 (H-1), 3.85 (H-4), 3.71 (H-3), 3.36 (H-2), 3.85 (H-5), 3.66 (OCH_2), 3.95, 3.73 (H-6), 3.63 (OCH_3), 3.53 (OCH_3), 2.99 (CH_2S), 2.05 (CH_2CH_2S). ^{13}C NMR (75 MHz, D_2O): δ 100.5 (C-1), 80.7 (C-4), 83.6 (C-3), 83.0 (C-2), 73.6 (C-5), 72.4 (OCH_2), 71.6 (C-6), 62.7 (OCH_3), 60.9 (OCH_3), 51.1 (CH_2S), 27.5 (CH_2CH_2S). Anal. calcd for $K_7C_{77}H_{133}O_{56}S_7{\cdot}7H_2O$: C, 35.86; H, 5.74; S, 8.70. Found: C, 36.08; H, 5.45; S, 8.52. Inverse detection CE: mean ds (6.9).

Heptakis(2,3-di-*O*-methyl-6-*O*-sulfobutyl)-β-cyclodextrin (4-β-1): yield, 98%; ^1H NMR (300 MHz, D_2O): δ 5.19 (H-1), 3.70 (H-4), 3.57 (H-3), 3.26 (H-2), 3.73, (H-5), 3.49 (OCH_2), 3.83, 3.61 (H-6), 3.53 (OCH_3), 3.43 (OCH_3), 2.85 (CH_2S), 1.65 (CH_3CH_2O), 1.72 (CH_2CH_2S). ^{13}C NMR (75 MHz, D_2O): δ 101.8 (C-1), 85.0 (C-4), 84.2 (C-3), 82.3 (C-2), 74.8 (C-5), 74.8 (OCH_2), 73.0 (C-6), 64.1 (OCH_3), 62.1 (OCH_3), 54.9 (CH_2S), 31.9 (CH_2CH_2O), 25.3 (CH_2CH_2S). Anal. calcd for $K_7C_{84}H_{147}O_{56}S_7{\cdot}7H_2O$: C, 37.68; H, 6.06; S, 8.38. Found C, 37.42; H, 6.06; S, 8.86. Inverse detection CE: mean ds (6.8).

Heptakis(2,3-di-*O*-ethyl-6-*O*-sulfopropyl)-β-cyclodextrin (3-β-2): yield, 95.4%; ^1H NMR (300 MHz, D_2O): δ 5.27 (H-1), 3.85, 3.89, 4.04 (OCH_2CH_3), 3.80 (OCH_2CH_3), 4.04, 3.70 (H-6), 3.86 (H-5), 3.64, 3.74 (OCH_2), 3.85 (H-3), 3.78 (H4), 3.44 (H-2), 3.03 (CH_2S), 2.09 (CH_2CH_2S). 1.29 (2 CH_3). ^{13}C NMR (75 MHz, D_2O): δ 100.8 (C-1), 82.5 (C-4), 81.4 (C-3), 80.1 (C-2), 73.9 (C-5), 72.5 (OCH_2), 71.6 (C-6), 71.5 (OCH_2CH_3), 69.8 (OCH_2CH_3), 51.1 (CH_2S), 27.4 (CH_2CH_2S), 17.8, 17.6 (2 CH_3). Anal. calcd for $K_7C_{91}H_{161}O_{56}S_7{\cdot}7H_2O$: C, 39.38; H, 6.36; S, 8.09. Found C, 39.33; H, 6.23; S, 8.28. Inverse detection CE: mean ds (6.8). MS: calcd for $K_8C_{91}H_{161}O_{56}S_7^+$ 2688, found 2688.

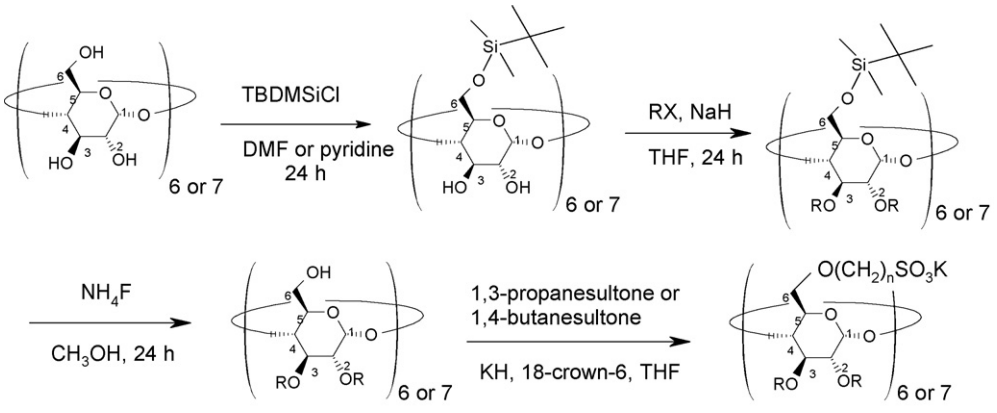
2.4. General procedure for the hydroformylation reaction

All catalytic reactions were performed under nitrogen using standard Schlenk techniques. All solvents and liquid reagents were degassed by bubbling nitrogen for 15 min before each use or by two freeze–pump–thaw cycles before use. $Rh(acac)(CO)_2$ (2.03×10^{-2} mmol), TPPTS (0.105 mmol) and chemically modified cyclodextrin (0.24 mmol) were dissolved in 5.75 mL of water. The resulting aqueous phase and an organic phase composed of olefin (10.17 mmol) and undecane (2 mmol – GC internal standard) were charged under an atmosphere of nitrogen into the 25 mL reactor, which was heated at 80 °C. Mechanical stirring equipped with a multipaddle unit was then started (1500 rpm) and the autoclave was pressurized with 50 atm of CO/H_2 (1/1) from a gas reservoir connected to the reactor through a high pressure regulator valve allowing to keep constant the pressure in the reactor throughout the whole reaction. The reaction medium was sampled during the reaction for GC analyses of the organic phase after decantation. For kinetic measurements the time corresponding to the addition of CO/H_2 was considered as the beginning of the reaction.

3. Results and discussion

Syntheses of the sulfoalkylated CDs were carried out according to Scheme 2.

The first three steps of the syntheses were according to established procedures [23–25]. ^1H and ^{13}C NMR spectra of



Scheme 2. Synthetic scheme for new sulfoalkylated cyclodextrins.

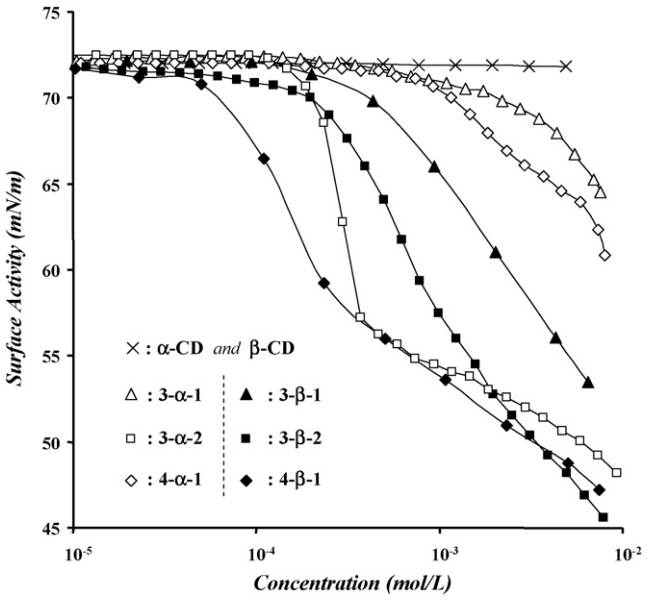


Fig. 1. Surface activity of aqueous solutions containing sulfoalkylated CDs at 25 °C.

all intermediates were consistent with those in the literature. Sulfoalkylation, using either 1,3-propane sultone or 1,4-butane sultone, is traditionally carried out under aqueous basic conditions. However, we found that non-aqueous synthesis in the presence of potassium hydride and 18-crown-6 yields a much higher degree of substitution (ds) of the primary face of the CD compared to the usual aqueous treatment [26]. Indeed, inverse detection (CE) and MALDI/TOF MS reveal nearly complete substitution of the primary hydroxyl groups (see Section 2). For the α-CDs, the ds was ≥5.8 and for the β-CDs, the ds was ≥6.8. The new CDs were also characterized by microanalysis and NMR spectroscopy (^{1}H, ^{13}C, gCOSY, gHSQC), with complete assignments of all carbon resonances for each CD as described in Section 2.

The surface-active properties of these new CDs have been investigated by surface-tension measurements using a Wilhelmy plate (Fig. 1).

Through the analysis of the different curves, three main conclusions can be drawn. First, except 3-α-2, no critical aggregation concentration was observed suggesting that the CDs under study should be considered as hydrotropic molecules and not as surfactants. Second, the surface tensions are lower for methylated β-CDs than for methylated α-CDs for a given sulfoalkyl chain (compare 3-α-1 with 3-β-1 or compare 4-α-1 with 4-β-1). These results are all the more surprising since the hydrophilic/hydrophobic balance is rather constant. Third, the number and position of the methylene groups, either on the primary or secondary face of the CDs, appeared to have a non-negligible influence on the behaviour of the CDs in water. Thus, the reinforcement of the hydrophobicity tends to give the CDs a more marked surface-active character since for a given series (α- or β-CDs), increasing the number of methylene groups leads to a decrease in the surface tension.

The behaviour of the above sulfoalkylated CDs towards hydrosoluble phosphanes such as the sodium salt of the *meta*-substituted trisulfonated triphenylphosphane (TPPTS) and the sodium salt of the *meta*-substituted monosulfonated triphenylphosphane (TPPMS), two phosphanes widely used in aqueous organometallic catalysis [5], was investigated by NMR spectroscopy. The ^{31}P{^{1}H} and ^{1}H NMR spectra of 1:1 mixtures of sulfoalkylated CDs and TPPTS are very similar to that obtained for free TPPTS, indicating that no interaction between both constituents takes place (see Fig. 2 and supporting information).

The absence of interaction between sulfoalkylated α-CDs and TPPTS is logical since the latter is too large to enter into the cavity of α-cyclodextrin [27]. On the contrary, the absence of interaction between TPPTS and sulfoalkylated β-CDs should be attributed to the presence of methyl groups on the secondary face rather than the presence of sulfoalkyl groups on the primary face. Indeed, the absence of interactions between the TPPTS and Trime-β suggests that the steric hindrance generated by the methyl groups on the second face is sufficient to impede TPPTS penetration into the cavity.

By contrast, with TPPMS as a guest, the complexation power of the sulfoalkylated CDs can be put forward on ^{31}P{^{1}H} spectra (Fig. 3).

These ^{31}P{^{1}H} spectra are especially interesting because upfield or downfield shifts are observed depending on the CD cavity size. Actually, the ^{31}P{^{1}H} signal of the TPPMS is well defined and upfield shifted in the presence of sulfoalkylated β-CDs whereas it experiences spectral broadening and downfield shift in the presence of sulfoalkylated α-CDs. These differences clearly indicate that the inclusion process of TPPMS into CD cavity is affected by the CD size. In fact, the degree of freedom of TPPMS into cavity and the exposure of the phosphorus atom to water are reduced in the case of α-CD due to the narrowing of the CD cavity [28]. Unexpectedly, smaller chemical shifts were observed for 3-α-2 and 3-β-2 suggesting a weaker interaction of TPPMS with these sterically demanding ethylated CDs. Finally, it is worth mentioning that the permethylation of the secondary face of the α-CD appears as a crucial parameter for the inclusion of TPPMS into the α-CD cavity. Indeed, it should be noticed that TPPMS does not interact (or very weakly) with the native α-CD or Rame-α.

The interaction of TPPMS with the various sulfoalkylated CDs was also supported by ^{1}H NMR spectra. Indeed, chemical shift changes in the aromatic protons of TPPMS in the CD/TPPMS mixtures compared to pure TPPMS were observed (Fig. 4).

A comparison with permethylated CDs (Trime-β and Trime-α) give additional insight in the recognition process since the chemical shift variations are similar for TPPMS included in Trime-β, 3-β-1 and 4-β-1 or in Trime-α, 3-α-1 and 4-α-1. Hence, the inclusion of TPPMS is believed to occur by the common moiety of the hosts namely the secondary face of the CDs as already observed previously with various modified β-cyclodextrins [18,29,30]. However, penetration of TPPMS by the secondary face was unambiguously established by 2D NMR experiments. For instance, the T-ROESY spectrum of an equimolar 4-α-1/TPPMS mixture exhibited only intense cross-peaks between the TPPMS protons and the inner protons (H-3

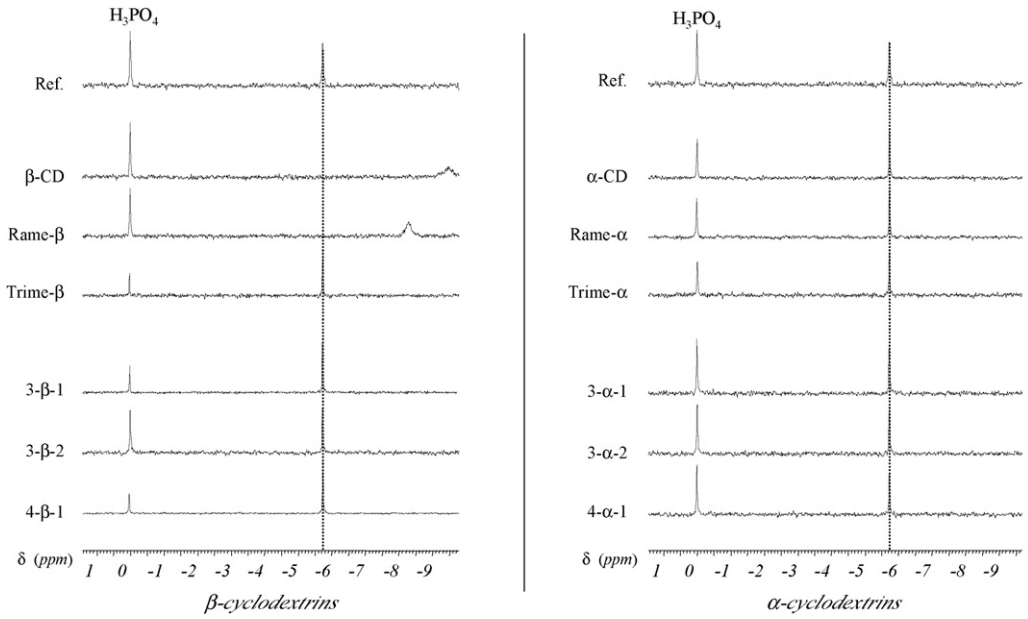


Fig. 2. $^{31}P\{^{1}H\}$ NMR spectra of TPPTS (3 mM) in D_2O at 25 °C in the presence of various cyclodextrins (3 mM). For comparison, the $^{31}P\{^{1}H\}$ spectra obtained with native CDs, partially methylated CDs (Rame-α or Rame-β) and permethylated CDs (Trime-α or Trime-β) are displayed.

and H-5) or the methyl groups of the CD. Furthermore, absence of cross-peaks between TPPMS and the H-6 protons or sulfobutyl chain of 4-α-1 confirms an inclusion process by the secondary face (Fig. 5).

The inclusion of TPPMS by the secondary face of the CD was also confirmed with α-CD bearing ethyl groups on the secondary face by performing the T-ROESY experiment on an equimolar 3-α-2/TPPMS mixture (Fig. 6).

Intense cross-peaks were detected between the H_p proton of TPPMS and the methyl groups of the 3-α-2 ethoxyls. Concurrently, small contacts detected between H_p and methylenes of the ethoxyls indicate that H_p is more directed towards water than into the CD cavity. Inclusion of the phosphine by secondary face was also evidenced by absence of cross-peaks between the TPPMS protons and the protons of the sulfopropyl chains.

In the light of the above results, the mass-transfer properties of the above sulfoalkylated CDs have been evaluated in the rhodium-catalyzed hydroformylation reaction of 1-decene in an organic–aqueous biphasic system using $Rh(acac)(CO)_2$ (acac: acetylacetonate) as a catalyst and TPPTS as a hydrosoluble ligand (Table 1). TPPTS has been preferred to TPPMS since it does not interact with the mass-transfer promoter whatever its nature.

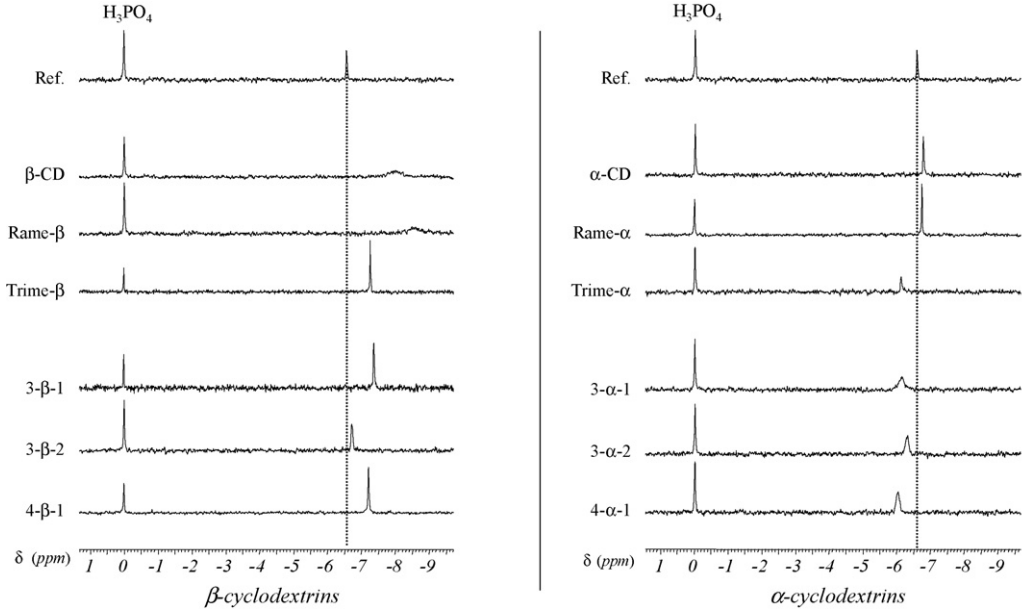


Fig. 3. $^{31}P\{^{1}H\}$ NMR spectra of TPPMS (3 mM) in D_2O at 25 °C in the presence of various cyclodextrins (3 mM). For comparison, the $^{31}P\{^{1}H\}$ spectra obtained with native CDs, partially methylated CDs (Rame-α or Rame-β) and permethylated CDs (Trime-α or Trime-β) are displayed.

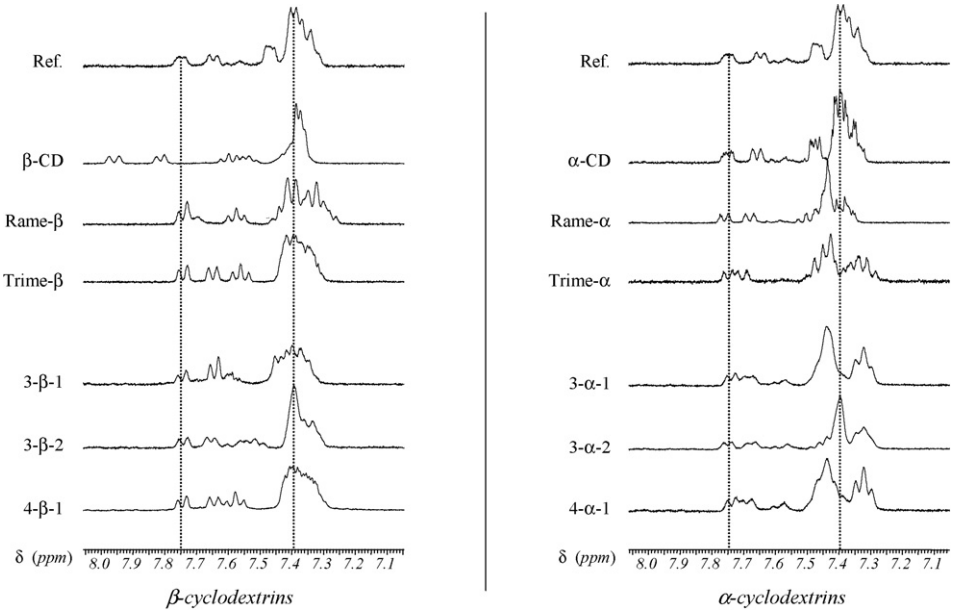


Fig. 4. ^{1}H NMR spectra of TPPMS (3 mM) in D_2O at 25 °C in the presence of various cyclodextrins (3 mM). For comparison, the ^{1}H spectra obtained with native CD, partially methylated CDs (Rame-α or Rame-β) and permethylated CDs (Trime-α or Trime-β) are displayed.

Several conclusions can be drawn when analysing the results of Table 1. First, changing a methyl to an ethyl group on the secondary face of β-CD (3-β-1 vs. 3-β-2) substantially decreases the relative reaction rate, which is defined as the ratio between the initial catalytic activity in the presence of a CD and the initial catalytic activity without CD (compare entries 1 and 2). Conversely, a lengthening of the sulfoalkyl chain from propyl to butyl on the primary face has a positive impact on the relative reaction rate. Thus, with a relative reaction rate of 250, 4-β-1 appears to be the best cyclodextrin ever used as mass-

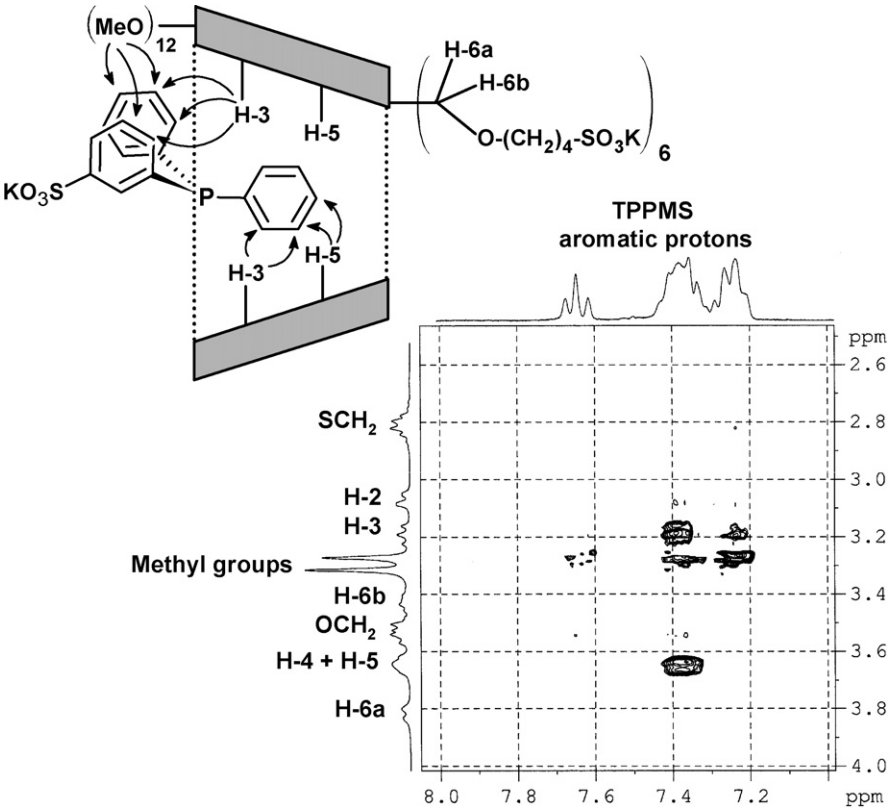


Fig. 5. 2D T-ROESY spectrum (300 MHz) of a 1:1 mixture of 4-α-1 (10 mM) and TPPMS (10 mM) in D_2O at 25 °C. The deduced structure of the inclusion complex was also indicated.

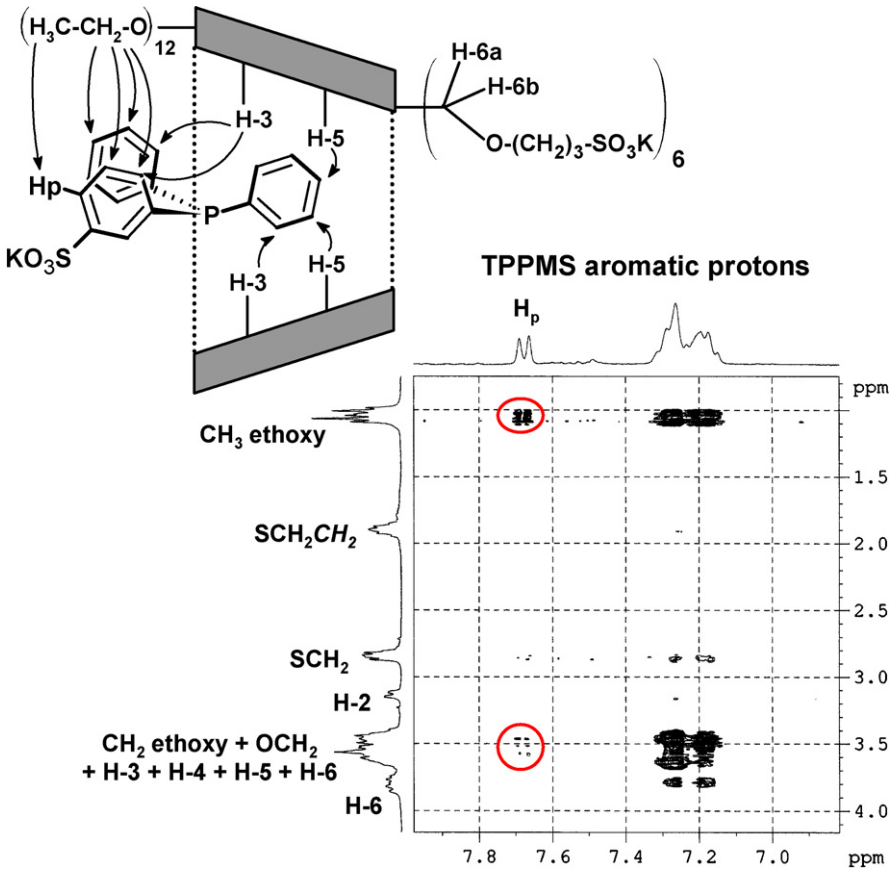
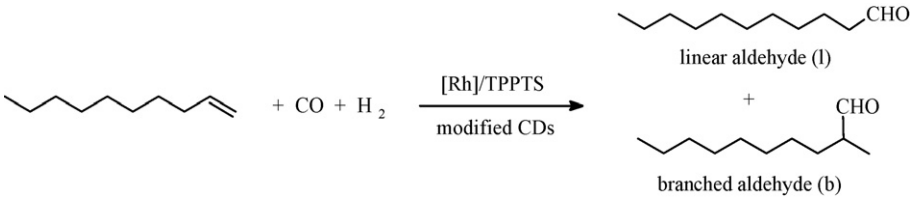
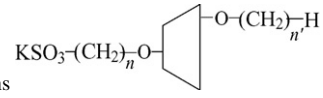


Fig. 6. 2D T-ROESY spectrum (300 MHz) of a 3-α-2/TPPMS mixture (10 mM/10 mM) in D_2O at 25 °C and the deduced host–guest structure. Cross-peaks between H_p and the methyl and methylene groups of 3-α-2 are circled.

Table 1
Biphasic rhodium-catalyzed hydroformylation of 1-decene in the presence of sulfoalkylated cyclodextrins[a]





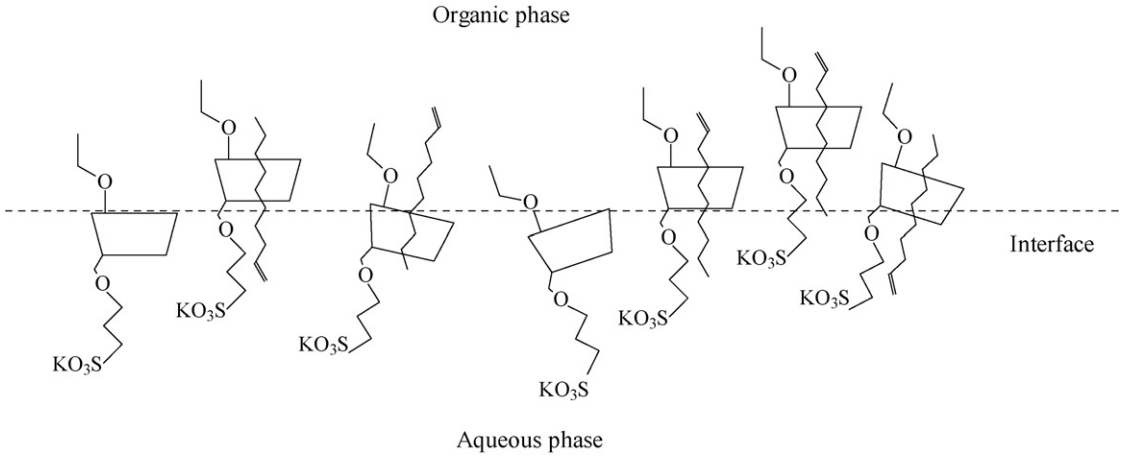
Entry	Modified cyclodextrins			Relative reaction rate[b]	Aldehyde selectivity[c]	l/b Aldehyde ratio[d]
	n	Type	*n′*			
1	3	β	1	210	60	2.6
2	3	β	2	178	71	2.0
3	4	β	1	250	62	2.5
4	3	α	1	117	58	2.5
5	3	α	2	75	69	2.5
6	4	α	1	128	54	2.6

[a] Experimental conditions: $Rh(acac)(CO)_2$ (2.03×10^{-2} mmol), TPPTS (0.105 mmol), H_2O (5.75 mL), 1-decene (10.17 mmol), cyclodextrin (0.24 mmol), undecane (4 mmol, GC internal standard), 1500 rpm, *T*: 80 °C, CO/H_2 (1/1): 50 atm.

[b] 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. The initial catalytic activity without CD is 92 μmol/h. The selectivity and the linear/branched ratio without cyclodextrin are 59% and 2.8, respectively.

[c] (Mol. of aldehydes)/(mol. of converted olefins) × 100.

[d] Ratio of linear-to-branched aldehyde product.



Scheme 3. Schematic representation of sulfopropyl ethyl cyclodextrins adsorption at water/organic interface.

transfer promoter in the hydroformylation reaction. Note also that the formation of an emulsion at the end of reaction was not observed with these CDs and that the separation between the organic and aqueous phases was fast. This behaviour suggests strongly that the reaction occurred at the organic–aqueous interface and repelled the possibility of a transformation of the substrate in CD micelles or aggregates. Second, the initial activities measured with sulfoalkylated α-CD are twice lower than those obtained with sulfoalkylated β-CD whatever the nature of the substituents on the two CD faces. A lengthening of the alkyl chain on the secondary face of α-CDs has detrimental consequences on the catalytic activity (compare entries 4 and 5) when a slight increase in relative reaction rate is observed for longer sulfoalkyl chains on the primary face (compare entries 4 and 6).

These results suggest strongly that efficiency of sulfoalkylated CD does not only depend on its surface activity but also on the accessibility of the CD cavity. Indeed, it should be noticed that the best surface-active CD for a given CD series i.e. 3-α-2 for the α-CD series and 3-β-2 for the β-CD series constitutes the worse CD of the series in terms of reaction rate (entries 2 and 5). This unexpected result could be rationalized by considering that the substrate included in the ethylated CDs cavity cannot easily interact with water-soluble catalytically active species. This reduced access to the substrate could be due to a more marked hydrophobic character of the secondary face of ethylated CDs and to the presence of more sterically demanding substituents on the secondary face of the CDs. Indeed, it is expected that the sulfoalkylated CDs are adsorbed mainly at the liquid/liquid interface with the sulfoalkyl groups in the aqueous phase and the methyl or ethyl groups in the organic phase (Scheme 3).

Unfortunately, this arrangement is not favourable for a reaction between the included olefin and the anionic water-soluble catalytic species due to electrostatic repulsions between the sulfonato groups of the TPPTS ligand and the sulfonato groups of the CD. Consequently, reaction between olefin and catalyst requires likely an unfavourable adsorption type of the CD at the interface where the methyl or ethyl groups point towards the aqueous phase. Due to the more marked hydrophobic character of the ethylated CDs, such an orientation at the interface is less probable in the case of ethylated CD than in the case of methylated CD and, consequently, could explain partially the lower activity observed with ethylated CDs. Furthermore, the steric hindrance generated by the ethyl groups on the secondary face could also contribute to reduce the accessibility of the included olefin. This phenomenon is probably much more pronounced with the ethylated α-CD than with the ethylated β-CD due to the smaller diameter of the α-CD. Consequently, for the catalytic system to be meaningful, the secondary face of the CD should remain wide open and relatively hydrophilic to preserve the approach between the CD-included substrate and the water-soluble catalyst. Finally, note that the CD size cavity has only a slight influence on the aldehyde selectivity, the biggest difference being observed between 3-β-2 and 4-α-1 (entries 2 and 6). Except 3-β-2 that yields a weaker 2.0 linear/branched ratio, the other sulfoalkylated CDs give similar proportions of linear and branched aldehydes (l/b ratio = 2.5 or 2.6) than those obtained in catalytic conditions without CD (l/b ratio = 2.8) [31], indicating that no modification of the catalytic species occurs during the reaction when the sulfoalkylated CDs are used as mass-transfer promoters.

4. Conclusions

To sum up, the optimisation of the structure of sulfoalkylated CDs proved to be necessary to improve the catalytic activity of the hydroformylation of 1-decene. The performances of the studied sulfoalkylated CDs as mass-transfer promoter in this reaction are strongly dependent on their surface-active properties and the accessibility to their cavity. The most efficient CD appeared to be a β-CD sulfobutylated on its primary face and methylated on its secondary face. The whole structure greatly diminishes the surface tension between the organic and aqueous phases without being micellar and favours the catalytic process to take place. Work is currently underway to exploit these cyclodextrins in other biphasic transition-metal-catalyzed reactions.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2008.01.038.

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