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Aurélien Cocq, Cyril Rousseau, Hervé Bricout, Estefanía Oliva, Véronique Bonnet, et al.. Oleic Acid Based Cyclodextrins for the Development of New Hydrosoluble Amphiphilic Compounds. *European Journal of Organic Chemistry*, 2019, 2019 (6), pp.1236-1241. 10.1002/ejoc.201801609 . hal-02050385

HAL Id: hal-02050385

<https://hal.science/hal-02050385>

Submitted on 14 Nov 2023

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Oleic Acid Based Cyclodextrins for the Development of New Hydrosoluble Amphiphilic Compounds

Aurélien Cocq,^[a] Cyril Rousseau,^[a] Hervé Bricout,^[a] Estefanía Oliva,^[b] Véronique Bonnet,^[b] Florence Djedaini-Pilard,^[b] Eric Monflier,^[a] and Sébastien Tilloy*^[a]

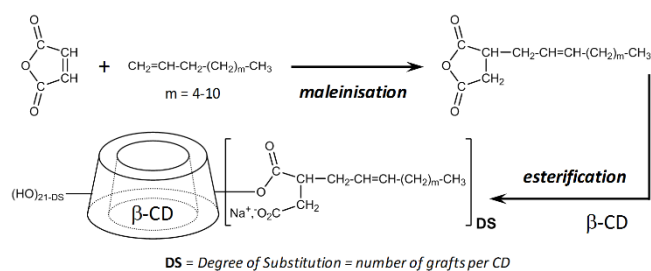
Abstract: A new family of amphiphilic cyclodextrins produced from oleic acid derivatives and maleic anhydride is described. These amphiphilic cyclodextrins are synthesized in two steps. The first step is the alkenylation of maleic anhydride by oleic acid derivatives to produce the oleic succinic anhydrides. The second step is the grafting of the oleic succinic anhydrides on various cyclodextrins. A self-inclusion of the alkyl chain or an inclusion of one alkyl chain in the cavity of another CD is showed by NMR experiments. The twelve amphiphilic cyclodextrins described possess high solubility in water (50-500 g/L at 20°C) and low critical aggregation concentration (16-360 mg/L).

Introduction

Native cyclodextrins (CDs), named α , β and γ -CD, are cyclic oligosaccharides made from enzymatic starch degradation and composed respectively of 6, 7 or 8 glucose units linked via α -1,4 glycosidic bonds. Native CDs are water-soluble compounds and are able to form inclusion complexes with numerous organic molecules.^[1] CDs have been intensively employed in pharmaceutical,^[2] cosmetics,^[3] textile^[4] and food industries.^[5] Chemical modifications of native CDs into more sophisticated molecules can improve their interest for industrial applications. Among all these modified cyclodextrins, amphiphilic cyclodextrins are an interesting family as they can form supramolecular assemblies such as vesicles, micellar systems and nanospheres.^[6] Since thirty years, chemists have developed various amphiphilic cyclodextrins. The first was reported by the group of Kabawata.^[7] Different kinds of CDs can be obtained depending on the functionalization (polysubstitution or monosubstitution) with a direct impact on the physico-chemical properties. The lipophilic grafts are generally alkyl chains linked to the CD structure via ether,^[8] ester,^[9] thioether,^[10] or amide^[11] functions. Inclusion complexes can also be observed between the hydrophobic cavity and the alkyl chain depending on its length. The major drawback of these amphiphilic CDs is their poor water solubility. This solubility generally decreases with the

number of lipophilic groups linked to the CD. To counterbalance the lipophilic character and so to increase the solubility in water of the amphiphilic CDs, some other substituents such as polyethylene oxide grafts^[12] or ionic^[13] functions can be linked. For example, surface active alkenyl succinyl-CDs were synthesized by the same methodology described for starch succinylation and other natural polymers.^[14] More precisely, the group of de Rossi has showed that it was possible to synthesize amphiphilic β -CD esters of alkenyl succinic acids.^[15] These alkenyl succinyl- β -CDs were synthesized in two steps (Scheme 1). This first step was the reaction of a terminal alkene (from 1-octene to 1-tetradecene) with maleic anhydride to give an alkenyl succinic anhydride (maleinisation reaction). In the second step, this latter reacted with native β -CD to produce the various alkenyl succinyl- β -CDs with a number of grafts per CD (Degree of Substitution: DS) generally low ($DS \leq 1$). The hydrophobicity of the alkyl chain is counterbalanced, in this case, by the presence of a free carboxylate group obtained after the grafting of the alkenyl succinic anhydride onto β -CD. Physicochemical studies of these amphiphilic CDs were performed. Interesting properties such as aggregation, self-organized properties between the alkyl chain and the CD cavity, emulsifying properties and supramolecular organization in water were described.^[16] Recently, Lu showed that octadecenyl succinyl- β -CD with low DS (0.02-0.13) can be used to stabilize pickering emulsions^[17] and the group of Luo found that octenyl succinyl- β -CD with DS of 0.016 to 0.045 can be used as emulsion stabilizer.^[18] It is important to underline that all synthesized CDs were obtained as a mixture.

In order to improve the eco-compatibility of this kind of CD derivatives, the coupling between a CD and oleic succinic anhydride was envisaged. Indeed, oleic acid derivatives are industrially produced from renewable resources. We described here the synthesis of several amphiphilic oleic succinyl-CDs formed by coupling various CDs (native, methylated or hydroxypropyl-CDs) with oleic succinic anhydrides. The physico-chemical properties of these new CDs were also described.



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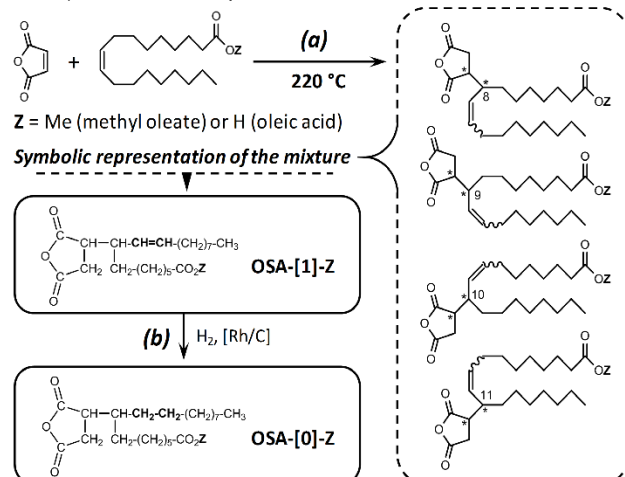
Scheme 1: Schematic representation of the formation reaction of alkenyl succinyl-CDs (for simplification, only one kind of graft is represented, among the two possible, knowing that each hydroxyl groups of the β -CD can react with one or the other carbonyl group of the succinic anhydride used).

Supporting information for this article is given via a link at the end of

Results and Discussion

These oleic succinyl-CDs were synthesized in two steps. The first step of the synthetic pathway is the alkenylation of maleic anhydride by oleic acid derivatives to produce oleic succinic anhydrides (OSA). This synthesis was inspired by previous works of Candy describing the synthesis of various oleic succinic anhydrides.^[19] Firstly, we tried to reproduce the synthesis with methyl oleate (or oleic acid) and maleic anhydride in an autoclave during 8 h at 220 °C (Scheme 2a). The addition reaction of the maleic anhydride to methyl oleate or oleic acid gave a mixture of regio- and stereoisomers.^[20] This mixture of compounds originated from two coexisting mechanisms (an ene-reaction and a radical reaction).^[21] However, for reasons of simplification, the mixture was represented as a single compound in this work. The nomenclature used to name these compounds is OSA-[1]-Me and OSA-[1]-H for methyl oleate and oleic acid derivatives, respectively (Scheme 2). The term OSA is for Oleic Succinic Anhydride. [1] or [0] is for the number of unsaturation on the aliphatic chain and finally, Z is a methyl or a H group, according to the nature of methyl oleate or oleic acid of the reactant. From methyl oleate and maleic anhydride, OSA-[1]-Me was obtained with the same yield than those reported by Candy (36 %). To improve the efficiency of the reaction, microwave assistance was used to heat the reaction mixture. With microwave activation, the reaction time was significantly reduced from 8 hours to 3 hours with a small improvement in the reaction yield (from 36% to 40%). The same conditions were also applied to the reaction with oleic acid instead of methyl oleate and in this case, the yield in the corresponding product (OSA-[1]-H) was only equal to 27 %. For the both products (OSA-[1]-Me and OSA-[1]-H), the different isomers were not separated and were directly used for the next steps.

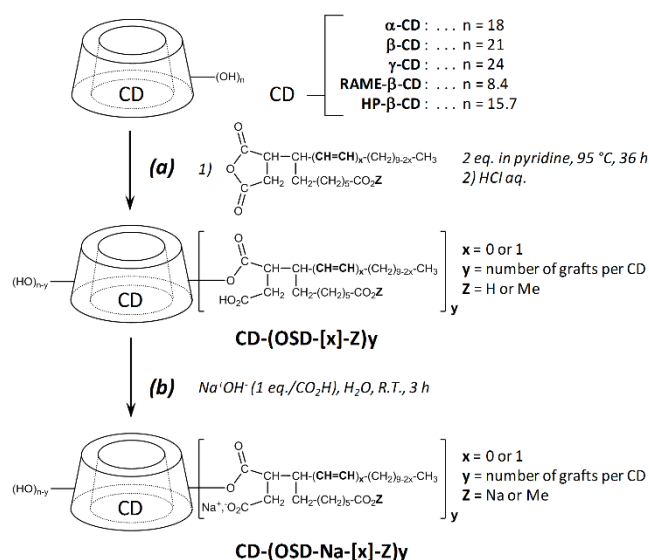
To evaluate if the rigidity of the carbon-carbon double bond of the oleic moiety could influence the physicochemical properties of oleic succinyl-CDs, hydrogenation of this bond was then performed. Various catalysts among the most common for hydrogenation have been envisaged (Pd, Rh or Ru on carbon) (Scheme 2b). No reaction was observed with Pd/C (5 wt. %; 0.04 eq. of Pd per OSA / THF / P(H₂) = 10 bar / 30 °C / 24 h). When the pressure was increased to 40 bar, different products originating from the isomerization of the ethylenic part (C=C double bond migration) and partial reduction were detected. With Ru/C (5 wt. %; 0.04 eq.



Scheme 2: Representation of the different structures of the OSA (Oleic Succinic Anhydrides)

of Ru per OSA / Heptane / P(H₂)=40 bar / 50 °C / 15 h), no reduction of the oleic part but a degradation of the anhydride structure was observed. This kind of behavior was already described in the presence of nickel and platinum catalysts.^[22] The best results for reduction of carbon-carbon double bond were obtained with Rh/C (5 wt. %; 0.01 eq of Rh per OSA / Heptane / P(H₂) = 40 bar / 30 °C / 4h). The hydrogenated compounds were obtained in yield of 90% and 85 % for OSA-[0]-Me and OSA-[0]-H, respectively.

The second step of the synthetic pathway is the grafting of the unsaturated or saturated OSA on native CDs (α -CD, β -CD or γ -CD), RANdomlyMETHylated- β -CD (RAME- β -CD) or HydroxyPropylated- β -CD (HP- β -CD). The reaction was done in pyridine with 2 equivalents of OSA with respect to CD and allowed to produce various oleic succinyl-CDs (Scheme 3a). These products were named CD-(OSD-[x]-Z)y with OSD for Oleic Succinic Derivative. [1] or [0] is for the number of unsaturation on the aliphatic chain. Z is H or methyl and y the degree of substitution (DS). Various oleic succinyl-CDs were obtained with DS between 0.9 and 1.8 and with yields from 28% to 92 % (table 1). With native CDs and unsaturated OSA (table 1, entries 1-6), no noticeable difference in the reaction yields (around 80%) and in the substitution degrees (around 1.6) was evidenced except for γ -CD and OSA-[1]-Me since the yield dropped to 30% but with a higher DS (1.8). The reaction with the saturated OSA and β -CD (Table 1, compare entries 3-4 and 7-8) gave the corresponding product in a lower yield and when the OSA with the free carboxylic acid was used (entry 8) the DS dropped from 1.5 to 0.9. With RAME- β -CD (compare entries 3-4 and 9-10), the reaction yield and DS were lower than with native β -CD since the DS dropped to 0.9 and 1. This behavior could be explained by the fact that RAME- β -CD possesses already an average of 12.6 methylated groups per CD and supplementary substitution was more difficult. In the case of HP- β -CD (possessing an average of 5.3 of 2-hydroxypropyl group



Scheme 3: Schematic representation of the formation reaction of the oleic succinyl-CDs (a) and their sodium salts (b) (for simplification, only one kind of graft is represented, among the two possible, knowing that each hydroxyl groups of the CD can react with one or the other carbonyl group of the succinic anhydride used).

Table 1. Degrees of substitution and yields of various OSD-CDs [a]

Entry	OSD-CD	DS [b]	Yield [%] [c]
1	α -CD-(OSD-[1]-Me)1.6	1.6	76
2	α -CD-(OSD-[1]-H)1.6	1.6	83
3	β -CD-(OSD-[1]-Me)1.6	1.6	90
4	β -CD-(OSD-[1]-H)1.6	1.6	86
5	γ -CD-(OSD-[1]-Me)1.8	1.8	30
6	γ -CD-(OSD-[1]-H)1.4	1.4	92
7	β -CD-(OSD-[0]-Me)1.5	1.5	67
8	β -CD-(OSD-[0]-H)0.9	0.9	75
9	RAME- β -CD-(OSD-[1]-Me)0.9	0.9	30
10	RAME- β -CD-(OSD-[1]-H)1.0	1.0	60
11	HP- β -CD-(OSD-[1]-Me)1.7	1.7	28
12	HP- β -CD-(OSD-[1]-H)1.6	1.6	62

[a] The reaction was carried out with 2 equivalents of OSA/CD, in pyridine at 95°C during 36 h. [b] DS were determined by NMR analysis. [c] Yield determined after purification.

per CD), the obtained DS value was similar to that obtained for native β -CD. These results can be explained by the fact that HP- β -CD and native β -CD possess the same amount of hydroxyl groups. Indeed, the hydroxyl group of 2-hydroxypropyl moiety can be also esterified. The synthesized OSD-CDs were insoluble in water. To solubilize these compounds in water, the carboxylic functions were deprotonated to give the corresponding carboxylates by treatment with stoichiometric amount of an aqueous sodium hydroxide solution (Scheme 3b). The corresponding OSD-CD-Na were obtained in a quantitative yield.

Various physical properties such as aqueous solubility, critical aggregation concentration in water (CAC) and surface tension of aqueous solutions were measured for the synthesized OSD-CDs-Na and were gathered in the table 2. The values of aqueous solubility of all OSD-CDs-Na (50 – 500 g/L at 20°C) were high compared to CDs possessing hydrophobic chains. Indeed, one or two carboxylate functions on the succinyl moiety are enough to counterbalance the hydrophobicity of the oleic chain. The aqueous solubilities of OSD-CDs-Na with the terminal methyl ester functions were lower compared with those of OSD-CDs-Na with the terminal carboxylate functions. This increase in water-solubility was due to the number of carboxylate functions per graft (one for the first series (Table 2; entries 1, 3, 5, 7, 9 and 11) against two for the second series (Table 2; entries 2, 4, 6, 8, 10 and 12).

For each compound, the critical aggregation concentration (CAC) and the surface tension (ST) value obtained at this concentration were determined by the Wilhelmy method. For the CAC, two trends are emerging: one for OSD-CDs-Na possessing the methyl ester group (one carboxylate function - table 2, entries 1, 3, 5 and 7), and another for those possessing the carboxylic acid groups (two carboxylate functions - table 2, entries 2, 4, 6 and 8). The dicarboxylate derivatives have a higher CAC than their ester counterparts. For RAME- β -CD and HP- β -CD derivatives (Table 2, entries 9-12), the variation of CAC are less marked. All OSD-CDs-Na have a value of surface tension from 28 to 52 mN/m at the CAC at 20°C. These values indicated that they possessed a good surface activity compared to the native CDs which are not surface active.^[23]

A self-inclusion of the alkyl chain and also inclusion of one alkyl chain in the cavity of other CDs were already described with

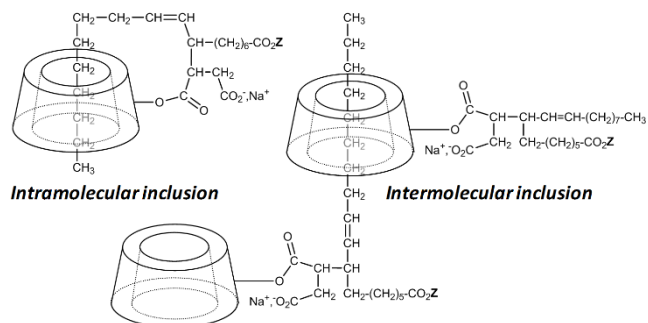
Table 2. Physico-chemical properties of the OSD-CDs-Na

Entry	OSD-CD-Na	Solubility at 20°C (g/L) - (mM)		CAC at 20°C (mg/L) - (μ M)		Surface Tension (mN/m) ^[a]
1	α -CD-(OSD-Na-[1]-Me)1.6	85	52	25	15	33
2	α -CD-(OSD-Na-[1]-Na)1.6	200	121	340	206	36
3	β -CD-(OSD-Na-[1]-Me)1.6	50	28	20	11	39
4	β -CD-(OSD-Na-[1]-Na)1.6	286	158	170	94	38
5	γ -CD-(OSD-Na-[1]-Me)1.8	87	43	16	8	30
6	γ -CD-(OSD-Na-[1]-Na)1.4	333	176	360	190	39
7	β -CD-(OSD-Na-[0]-Me)1.5	50	28	47	27	28
8	β -CD-(OSD-Na-[0]-Na)0.9	280	184	170	112	38
9	RAME- β -CD-(OSD-Na-[1]-Me)0.9	416	247	41	24	32
10	RAME- β -CD-(OSD-Na-[1]-Na)1.0	500	288	32	18	35
11	HP- β -CD-(OSD-Na-[1]-Me)1.7	312	146	98	46	36
12	HP- β -CD-(OSD-Na-[1]-Na)1.6	400	178	122	54	52

[a] Surface tension value at the CAC concentration and at 20°C.

cyclodextrins mono-substituted with alkenylsuccinyl chains possessing 8 to 12 carbons for the aliphatic moiety.^[24] Thus, the possibility of a such behavior was checked for β -CD-(OSD-Na-[1]-Me)1.6. Two different kinds of complexes could be formed either by an intra- or an inter-molecular inclusion (Scheme 4). We performed T-ROESY NMR experiments to demonstrate the interactions between the protons situated inside the CD cavity (H3 and H5) and those of the aliphatic chain (Figure 1). The experiment highlighted correlation spots between the internal CD protons (3-4 ppm) and the protons of the aliphatic chain (0.5-1.5 ppm) indicating that these protons are spatially close (Figure 1a). To obtain a better insight into the inclusion phenomenon, the same T-ROESY NMR experiment was performed in [D6]DMSO instead of D₂O. Indeed, DMSO was known as a dissociate solvent for inclusion complex with CD.^[25] The spectrum showed also correlation spots between the internal CD protons and the protons of the aliphatic chain (see supporting information). Another T-ROESY NMR experiment was realized with a mixture of β -CD and sodium oleate in DMSO (see supporting information). In this case, no correlation peak was observed. These two experiments confirmed the stability of the intra-molecular complexes. To estimate the stability of these inclusion complexes, NMR experiments were performed in the presence of selected guests possessing high affinity for the β -CD cavity. The selected compounds were tris(3-sulfonatophenyl) phosphane sodium salt (TPPTS – Figure 1b), adamantane carboxylate sodium salt (SAC – Figure 1c) and tris[4-(4-sulfonatophenyl)phenyl] phosphane sodium salt (P(Biph)₃TS – Figure 1d). These molecules form inclusion complexes with β -CD with a binding constant of $1.2 \times 10^3 \text{ mol}^{-1} \cdot \text{L}$,^[26] $40 \times 10^3 \text{ mol}^{-1} \cdot \text{L}$,^[27] and $100 \times 10^3 \text{ mol}^{-1} \cdot \text{L}$,^[28] respectively. The T-ROESY spectra of the different mixtures show that only P(Biph)₃TS displaces totally the alkyl chain from the inside of the CD cavity. With TPPTS and the adamantane carboxylate sodium salt, a mixture was observed since alkyl chains and selected guests are inside the CD cavity. These

experiments show that the inclusion complexes formed between alkyl chains and the CDs cavities are very stable.



Scheme 4: Representation of the two different kinds of inclusion complexes

Conclusions

We have described the synthesis of new amphiphilic oleic succinyl-CDs obtained by esterification of various CDs by oleic succinic anhydride derivatives made from oleic acid or its methyl ester. Although the work-up led to a mixture of modified CDs, the syntheses were reproducible and did not necessitate tedious and time-consuming purifications. In addition, the physicochemical properties of these compounds were significant. Indeed, the oleic succinyl-CDs possess a high solubility in water (50-500 g/L), a low surface tension and a low critical aggregation concentration. These properties confer to these compounds a great ability to be used for emulsion stabilizer or as surfactant.

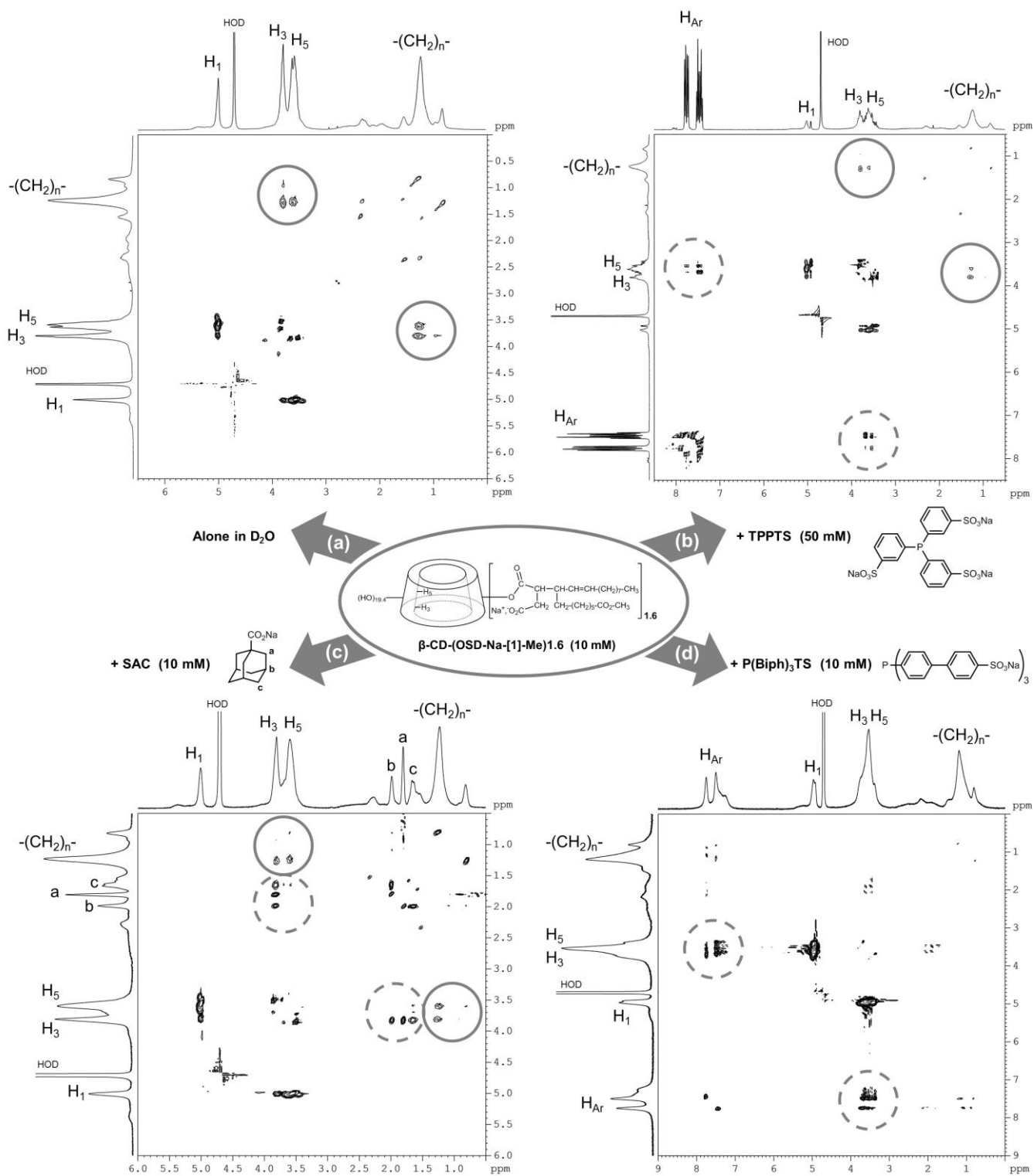


Figure 1: T-ROESY NMR Spectrum of the β -CD-(OSD-Na-[1]-Me)_{1.6} with different guests (10 mM CD, 1 eq. guest or 5 eq for the TPPTS, D₂O, 20°C)

Experimental Section

All chemicals were purchased from Fisher Scientific and Aldrich Chemicals in their highest purity. All solvents were used as supplied without further purification. Distilled water was used in all experiments. Analytical thin-layer chromatography (TLC) was performed on E. Merck aluminium-backed silica gel (Silica Gel F254). Compounds were identified by using UV fluorescence and/or staining with a solution of phosphomolybdic acid in aqueous sulfuric acid and ethanol. NMR spectra were recorded with a Bruker DRX300 spectrometer operating at 300 MHz for ^1H nuclei and at 75 MHz for ^{13}C nuclei. CDCl_3 (99.50% isotopic purity), $[\text{D}_6]\text{DMSO}$ (99.80% isotopic purity) and D_2O (99.92% isotopic purity) were purchased from Euriso-Top.

General procedure for the synthesis

The detailed syntheses and characterizations of the products are gathered in supporting information.

OSA-[1]-Me: Maleinised methyl oleate

28 g of methyl oleate (74 % of purity) (20.72 g, 69.88 mmol) and 8.22 g of maleic anhydride (83.8 mmol, 1.2 eq.) were mixed and heated under microwaves at 220 °C during 3 h. The brown oil obtained was purified by distillation with a Kugelrohr apparatus under reduced pressure. At P = 2.5 mbar, OSA-[1]-Me was isolated at 275 °C. OSA-[1]-Me was purified by chromatography on silica gel with hexane/dichloromethane. A yellow oil was obtained with a yield of 40 %.

OSA-[1]-H: Maleinised oleic acid

27 g of oleic acid (87 % of purity) (23.49 g, 83.20 mmol) and 9.79 g of maleic anhydride (99.84 mmol, 1.2 eq.) were mixed and heated under microwaves at 220 °C during 3 h. The brown oil obtained was purified by distillation with a Kugelrohr apparatus under reduced pressure. At P = 2.5 mbar, OSA-[1]-H was isolated at 300 °C. OSA-[1]-H was purified by chromatography on silica gel with hexane/acetone. A yellow oil was obtained with a yield of 27 %.

OSA-[0]-Me: Hydrogenated maleinised methyl oleate

1 g of OSA-[1]-Me (2.52 mmol) in 10 mL of THF was mixed with 106 mg of Rhodium on carbon 5% (50.6 μmol , 0.02 eq.) at 50 °C under 40 bar of dihydrogen during 24 h. The crude product was filtered on celite and the THF was evaporated. A yellow oil was obtained with a yield of 90 %.

OSA-[0]-H: Hydrogenated maleinised methyl oleate

1g of OSA-[1]-H (2.63 mmol) in 10 mL of THF was mixed with 108 mg of Rhodium on carbon 5% (52.5 μmol , 0.02 eq.) at 50 °C under 40 bar of dihydrogen during 24 h. The crude product was filtered on celite and THF was evaporated. A yellow oil was obtained with a yield of 85 %.

OSD-CDs: Oleic succinyl-CDs

Native or modified cyclodextrins were firstly dried by heating 2 h at 80 °C, 2 h at 100 °C, and 2 h at 120 °C under reduced pressure. Then, 2.50 g of dried cyclodextrin were dissolved in 75 mL of anhydrous pyridine under nitrogen and 2 eq. of maleinised oleic derivative were added. The mixture was stirred 36 h at 95 °C under nitrogen. At the end of the reaction, 15 mL of water were added and solvents were evaporated under reduced pressure. The lightly brown solid obtained was acidified with aqueous HCl until pH = 2 (approximately 2 mL of a solution at 35 %), filtered, washed with water until pH = 5-6 and dried. The diacid resulting of the hydrolysis

of the maleinised oleic derivative which has not reacted was eliminated by washing with diethyl ether, except for the RAME- β -CD. In this case, the crude product was purified by chromatography on silica gel with acetonitrile/water (from 100/0 to 70/30, Rf: 0.70 in 70/30 acetonitrile/water). A white solid was obtained in all cases.

OSD-CDs-Na: Sodium salts of oleic succinyl-CDs

1 g of esterified cyclodextrin was dispersed in 20 mL of water. Then, 1 equivalent of Na^+OH^- per CO_2H group was added and the mixture was then stirred during 3 h at 20 °C up to a total solubilization. Water was then evaporated under reduced pressure. A white solid was obtained with a quantitative yield.

Acknowledgments

This work was performed, in partnership with the SAS PIVERT, within the frame of the French Institute for the Energy Transition (Institut pour la Transition Énergétique (ITE) P.I.V.E.R.T.) (<http://www.institut-pivert.com>) selected as an Investment for the Future (Investissements d'Avenir). This work was supported, as part of the Investments for the Future, by the French Government under the reference ANR-001-01. Jérémy Ternel, Nicolas Kania, and Dominique Prévost are acknowledged for NMR analysis and technical assistance. PIVERT is acknowledged for the financial support of AC thesis.

Keywords: Cyclodextrin • Maleic anhydride • Maleinisation • Oleic acid • Succinic anhydride

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Layout 2: