62. Channel-Type Molecular Structures

Part 2[1])

Synthesis of Bouquet-Shaped Molecules Based on a β-Cyclodextrin Core

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Dedicated to the memory of Professor *Peter Läuger*

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A new series of channel-type molecules presenting the features of potential transmembrane structures is decribed. They result from the grafting of amphiphilic side chains on a β-cyclodextrin derivative **3** that constitutes the organizing core. They belong to the 'bouquet' family (*B*). Compounds bearing poly(oxyethylene) side chains, B^{O}_{CD} **16** and **17**, and their polymethylene analogues B^{C}_{CD} **18** and **19**, were synthesized. The properties investigated emphasize the suitability of such molecules to be incorporated into lipid bilayer membranes.

Introduction. – We recently reported the design, synthesis, and some properties in homogeneous solution of two molecules B^{O}_{M} and B^{C}_{M} belonging to a new family of species termed 'bouquet' (*B* for 'bouquets', O and C for poly(oxyethylene) and polymethylene side chains, and M for macrocyclic-polyether core), in view of their structural features [1] [2]. They result from the grafting of a bundle of poly(oxyethylene) or polymethylene chains on a central macrocyclic core of the [18]crown-6-type. Under appropriate conditions, the chains may be arranged so as to give to the molecule an overall cylindro-conical shape ressembling that of a bouquet. Such an entity, when incorporated in an organized phase such as a lipid membrane, might form a 'chundle', a transmembrane channel defined by the bundle of chains and the nature of the core.

In order to achieve larger molecular diameters while keeping sufficient rigidity in such 'bouquets', the cyclic oligo-α-D-glucose compounds, the cyclodextrins, appeared particularly well suited to replace the [18]crown-6-type core [3]. They have the shape of a cone with a central cavity having a diameter of *ca.* 4.5, 7.0, and 8.5 Å for α-, β-, and γ-cyclodextrin, respectively, which contain six, seven, and eight α-D-glucose units and bear 18, 21, and 24 OH groups, respectively [2]. The latter may allow the attachment of many side chains, provided their reactivity can be selectively controlled. In the present paper, we describe the design, synthesis, and some properties in homogeneous solution of two new 'bouquets', B^{O}_{CD} and B^{C}_{CD}, based on the grafting of fourteen long chains on a β-cyclodextrin (= CD) core. In a forthcoming paper, we shall describe the incorporation of these molecules into lipid membranes of vesicles and investigations of their potential properties of transmembrane channels.

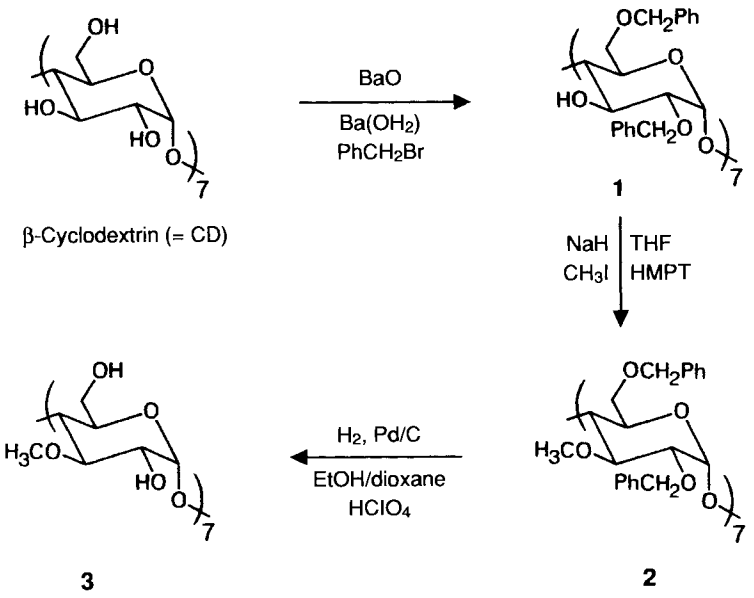
[1]) Part 1: [1b].

Design of the β-Cyclodextrin-Based 'Bouquet' Molecules. – β-Cyclodextrin was selected as core unit. Its internal diameter is large enough to allow the passage of metal ions, hydrated metal ions, as well as of small organic molecules. It possesses seven primary and fourteen secondary OH groups on the smaller and larger rims respectively. In order to obtain a well balanced 'bouquet' structure, an equal number of chains should be attached to each side of the core. This may be achieved by the selective methylation of seven of the fourteen secondary OH functions, *e.g.* those in position 3 of the glucose unit, which are the least reactive ones.

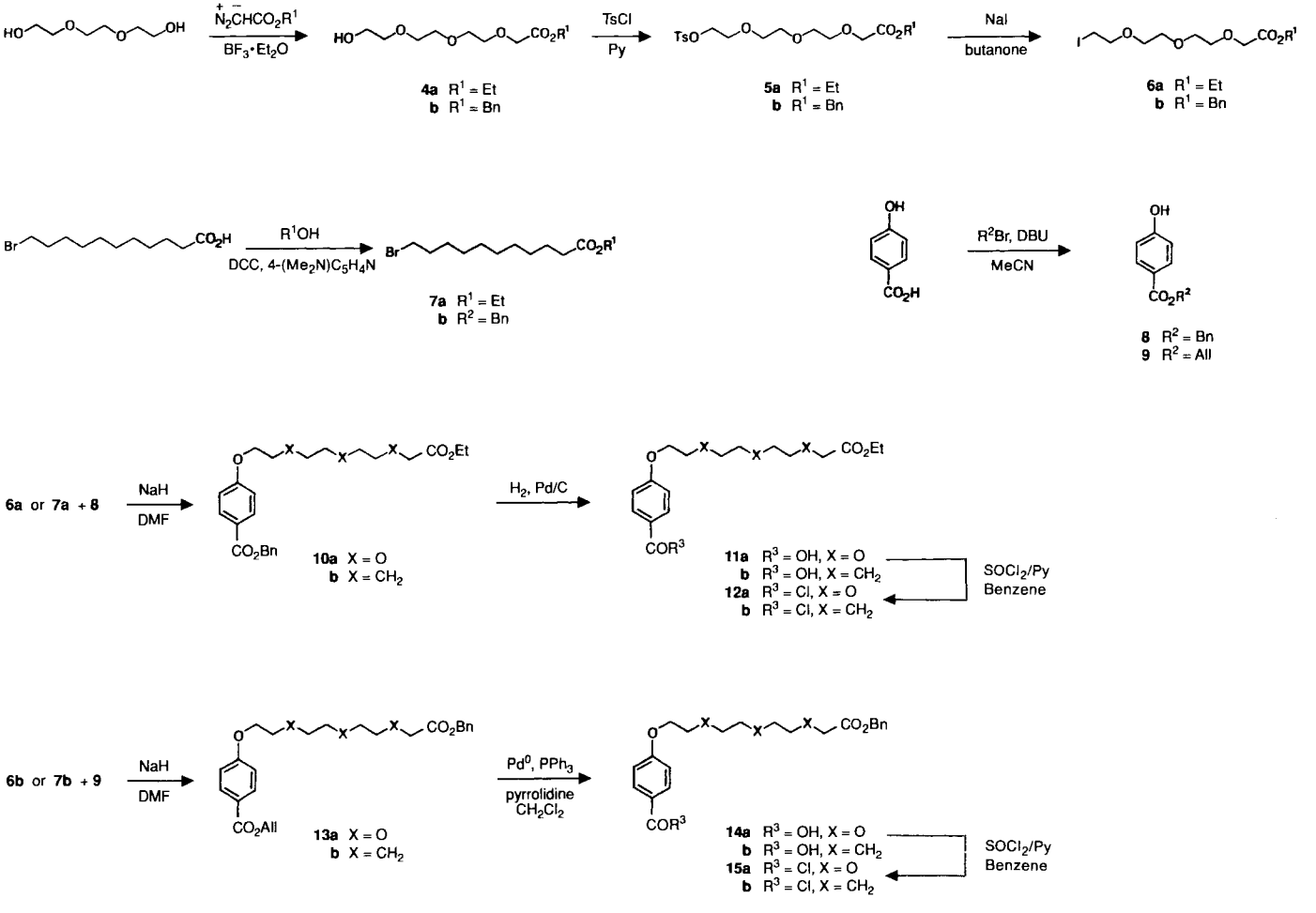
The design of the lateral chains followed the same lines as for the 'bouquets' B_M. They contain *i*) a UV chromophore in order to be able to detect the molecules when incorporated in membranes, *ii*) an oligo(oxyethylene) unit capable of interacting with cations, and *iii*) a terminal hydrophilic group to insure a transverse orientation in lipidic bilayers. Earlier work [3] and preliminary experiments led us to use a 4-substituted benzoic-acid group to attach these chains through esterification on the β-cyclodextrin core. Thus, the linear oligo(oxyethylene) unit was attached as phenol ether to 4-hydroxybenzoic acid, its length being chosen as a function of the thickness of the membrane to be studied. As for the 'bouquets' B_M, the analogous polymethylene molecules B^C_{CD} were also prepared. Thus, we synthesized the 'bouquets' B^O_{CD}COOH (**17**) and B^C_{CD}COOH (**19**; see below, *Scheme 3*) which would be obtained from the corresponding esters B^O_{CD}COOR (**16**) and B^C_{CD}COOR (**18**). Because hydrolysis of the ethyl esters **16a** and **18a** led to the loss of the chains, we synthesized the benzyl esters **16b** and **18b** whose hydrogenolysis easily gave the corresponding acids.

Synthesis of the 'Bouquets' B^O_{CD} and B^C_{CD}. – The synthesis of $3^A,3^B,3^C,3^D,3^E,3^F,3^G$-hepta-*O*-methyl-β-cyclodextrin (**3**) was previously performed [4] as follows: *i*) allylation of the

Scheme 1



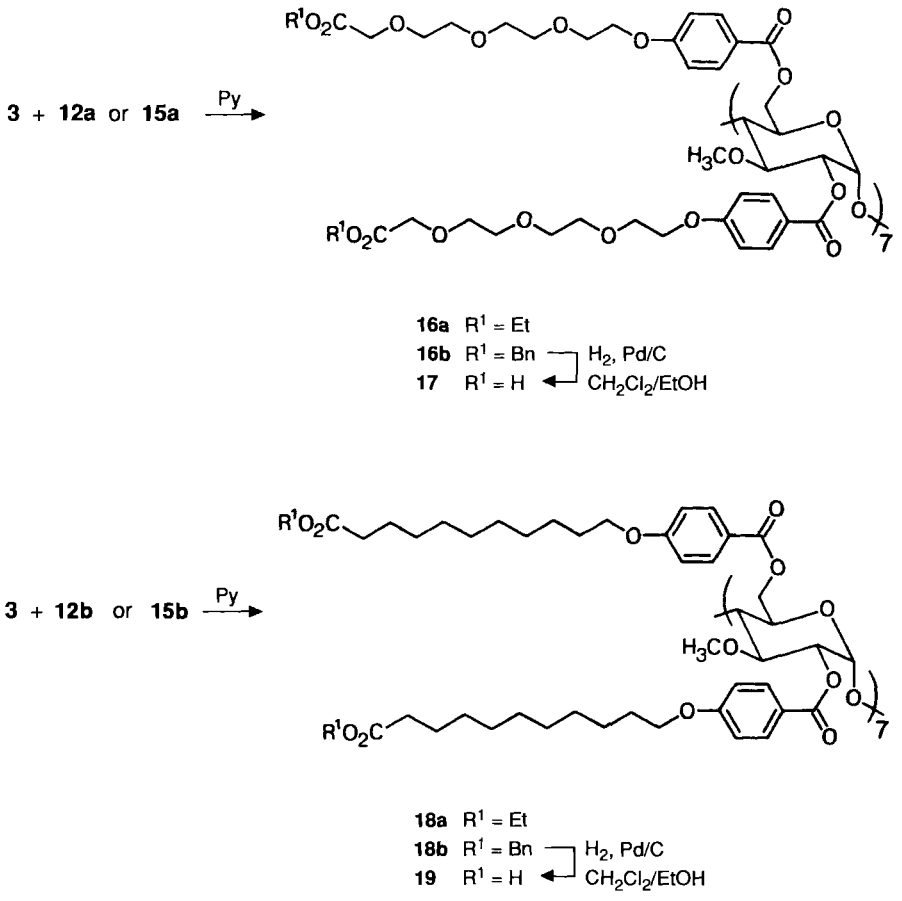
Scheme 2


HO
OH
$\overset{+}{N_2}\overset{-}{C}HCO_2R^1$
$BF_3 \cdot Et_2O$
CO_2R^1
TsCl
Py
TsO
NaI
butanone
I
4a R¹ = Et
b R¹ = Bn
5a R¹ = Et
b R¹ = Bn
6a R¹ = Et
b R¹ = Bn
Br
CO_2H
R^1OH
DCC, 4-$(Me_2N)C_5H_4N$
7a R¹ = Et
b R² = Bn
OH
R^2Br, DBU
MeCN
8 R² = Bn
9 R² = All
6a or 7a + 8
NaH
DMF
CO_2Et
CO_2Bn
10a X = O
b X = CH_2
H_2, Pd/C
COR^3
11a R^3 = OH, X = O
b R^3 = OH, X = CH_2
12a R^3 = Cl, X = O
b R^3 = Cl, X = CH_2
$SOCl_2$/Py
Benzene
6b or 7b + 9
CO_2All
13a X = O
b X = CH_2
Pd^0, PPh_3
pyrrolidine
CH_2Cl_2
14a R^3 = OH, X = O
b R^3 = OH, X = CH_2
15a R^3 = Cl, X = O
b R^3 = Cl, X = CH_2

2- and 6-OH groups of β-cyclodextrin, *ii*) methylation of the remaining 3-OH groups, and *iii*) removal of the allyl groups. In view of difficulties encountered with the final deallylation, we replaced the allyl by a benzyl group (see *Scheme 1*). Thus, **1** was obtained by benzylation (BnBr, $BaO/Ba(OH)_2$, DMSO/DMF, room temp.) of β-cyclodextrin and methylated (NaH, MeI, THF/HMPT, room temp.) according to [4] to afford **2**. Hydrogenolysis of **2** (10% Pd/C, dioxane/EtOH containing $HClO_4$, 50°) gave **3** easily.

For the synthesis of the side chains, ethyl and benzyl diazoacetates [5] were reacted with triethyleneglycol [1] to give the ethyl and benzyl hydroxyesters **4a** and **4b**, respectively, which were then transformed *via* the corresponding (tosyloxy)esters **5** into iodoesters **6a** and **6b**, respectively (see *Scheme 2*). The ethyl and benzyl bromoesters **7a** and **7b**, respectively, were obtained by esterification of 11-bromoundecanoic acid. The halogenoesters **6a** and **7a** and **6b** and **7b** were then condensed with the 4-hydroxybenzoates **8** and **9** (from 4-hydroxybenzoic acid, benzyl or allyl bromide, and DBU in MeCN at 70°, according to [6]), respectively, using NaH in DMF at 70° (*Scheme 2*), and the

Scheme 3

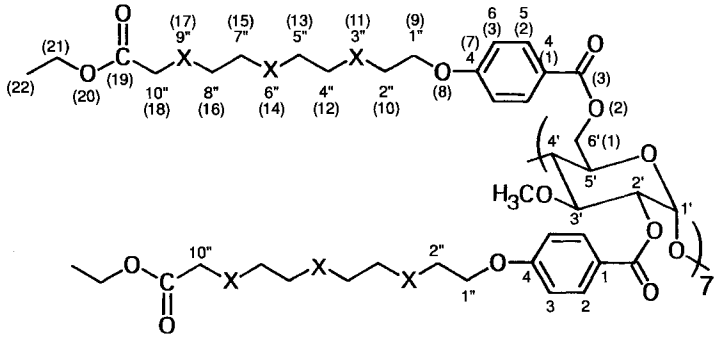


desired acids **11** and **14** were obtained by hydrogenolysis (10% Pd/C, EtOH or EtOH/CH_2Cl_2, room temp.) of the diesters **10** or by metal-catalysed isomerisation of the diesters **13** followed by hydrolysis [7] (Pd^0, PPh_3, pyrrolidine, CH_2Cl_2, room temp.)

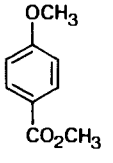
The peresterification of hepta-*O*-methyl-β-cyclodextrin **3** was achieved by repeated reaction (2 or 3 times) with the acyl chlorides **12** or **15** (4-(dimethylamino)pyridine, pyridine, 7 days, 60°) to yield **16** and **18** [3] (*Scheme 3*). Saponification of the tetradecaethyl esters **16a** and **18a** led to cleavage of the chains from the cyclodextrin core. The target tetradecaacids **17** and **19** were obtained by hydrogenolysis (CH_2Cl_2/EtOH, 10% Pd/C, room temp.), respectively, in quantitative yield.

The structure of the esters **16** and **18** was confirmed by their microanalytical and spectral (NMR, mass) properties. Besides TLC analysis, NMR spectroscopy, especially ^{13}C-NMR (see *Fig. 2a* and *b*), was crucial for ascertaining the purity of these fully esterified compounds: due to the high symmetry of the structures, the absence of partially esterified materials was easily checked. Furthermore, the compound **16a** appears to be at least 99% pure, since the electrospray mass spectrum contained no other ions (< 1%) than the three ions corresponding to **16a** with 3, 4, and 5 [NH_4^+] (see *Exper. Part*).

Spectroscopic Studies. – As in the case of the earlier 'bouquet' structures B_M [1], the properties of the β-cyclodextrin derivatives B_{CD} in homogeneous medium were investigated in particular to obtain reference data for later studies in lipid bilayers. UV and CD spectra in several solvents were collected to study the effects of factors like polarity or structural features of the solvents on the spectra, in the hope that they might later on give information on the orientation and possibly the conformation in bilayers from spectra observations in membrane medium (unpolar and anisotropic). UV and CD studies were mainly performed on B^o_{CD}COOEt (**16a**) and B^c_{CD}COOEt (**18a**). In view of comparative investigations, the model compound **20**, containing the elementary chromophore, and the



16a X = O[a])
18a X = CH_2[a])



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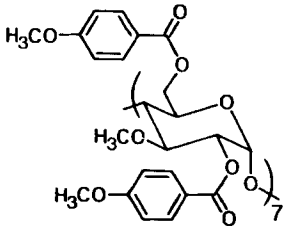

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[a]) For convenience, the side chains of **16a** and **18a** are numbered in the same way. For systematic names, see *Exper. Part*. Numbers in parentheses refer to the distance in bond units to the β-cyclodextrin core (see below, *Fig. 5*).

Table 1. *UV-Spectral Features of* **16a**, **18a**, **17**, *and* **19**–**21** *in Different Solvents*

Solvent	n_D^{25}	Compound	λ_{max} [nm]	ε_{max}
MeOH	1.326	**16a**	256	200000
		20	253	17500
		21	256	
EtOH (95%)	1.359	**16a**	264	210000
		17	258	
		19	258	200000
		20	254	18200
AcOEt	1.370	**16a**	256	280000
Tetrahydrofuran	1.404	**16a**	256	310000
		20	253	18000
Pentanol	1.408	**16a**	270	
		18a[a])	256	290000
		20	254	16800
		21	252	120000
Octanol	1.427	**16a**	270	
		18a	258	250000
		21	256	24000
Decanol	1.437	**20**	254	17300
$CHCl_3$	1.444	**16a**	256	260000
		20	254	16500

[a]) Insoluble in MeOH.

model **21**, devoid of chains, were also examined. All UV spectra display a maximum with a strong molecular extinction coefficient at 250–270 nm (see *Table 1*). The CD spectra display a negative *Cotton* effect that is markedly solvent dependent as well as an intramolecular exciton coupling (see *Table 2* and *Fig. 1*).

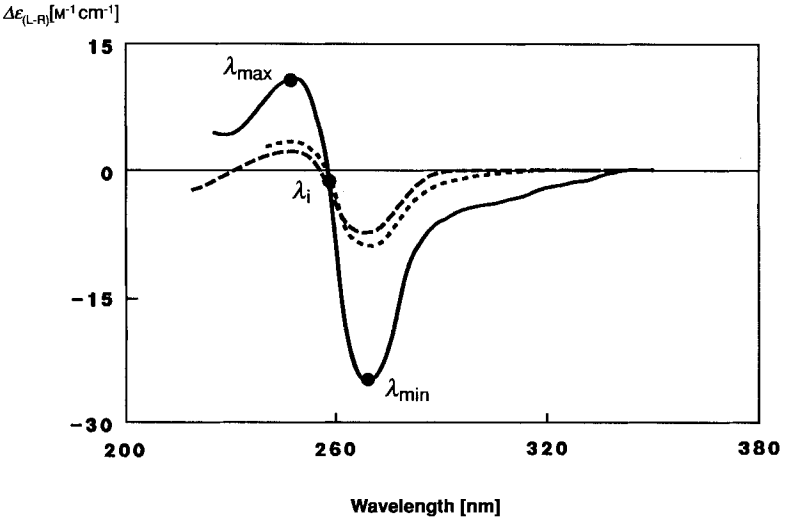

Fig. 1. *CD Spectra of molecule* **21** *in several solvents: MeOH* (—), *pentanol* (· · ·), *and octanol* (---). λ_{max}, λ_i, and λ_{min} indicate the wavelengths mentioned in the text.

Table 2. *CD Data of* **16a**, **18a**, *and* **21** *in Different Solvents.* λ in nm, $\Delta\varepsilon$ in $M^{-1}cm^{-1}$.

Solvent	Compound	λ_{max} ($\Delta\varepsilon$)	λ_i ($\Delta\varepsilon$)	λ_{min} ($\Delta\varepsilon$)
MeOH	**16a**	252 (27)	260 (–6)	272 (–39)
	21	249 (11)	259 (–5)	269 (–22)
Pentanol	**16a**	263 (21)	274 (–16)	283 (–46)
	18a	253 (5)	259 (–30)	274 (–60)
	21	248 (3)	258 (–3)	269 (–9)
Octanol	**18a**	251 (57)	259 (–15)	271 (–97)
	21	247 (2)	257 (–3)	268 (–7)

Because of their high symmetry, the molecules of the B_{CD} type give rather simple NMR spectra (see *Fig. 2a* and *2b*), compared to the B_M species which display complicated

Table 3. *^{13}C-NMR Longitudinal Relaxation Times* T_1 *of* B^{O}_{CD} *COOEt* (**16a**) *in* $CDCl_3$ *at Different Field Strengths and Temperatures*[a])

C-Atom[b])	δ [ppm]	*Exper. A:* 294 K, 4.7 T			*Exper. B:* 313 K, 4.7 T		*Exper. C:* 297 K, 9.4 T	
		T_1 [s]	S.d.[b]) [%]	NOEF[c])	T_1 [s]	S.d.[b]) [%]	T_1 [s]	S.d.[b]) [%]
$COOCH_2CH_3$	170.1			0.17				
COOC(2′)	165.2	1.40	3	0.04	1.00	5	1.30	2
COOC(6′)	165.2	1.55	3		1.00	4	1.50	1
C(4)[d])	162.5	1.25	4	0.21	0.75	2	0.90	1
C(4)[e])	162.3	1.80	1	0.24	1.45	5	1.60	1
C(2)[d])	131.4	0.15	1	0.44	0.15	2	0.25	1
C(2)[e])	131.4						0.30	3
C(1)[d])	121.9	1.10	2	0.05	0.95	7	0.95	2
C(1)[e])	121.7	1.35	3	0.14	1.70	3	1.50	2
C(3)[d])[e])	114.0	0.15	1	0.52	0.15	1	0.30	1
C(1′)	97.7	0.08	3	0.21	0.06	7	0.20	4
C(i)[f])	79.5	0.09	1	0.34			0.35	8
C(i)[f])	78.4	0.09	2	0.16			0.20	6
C(i)[f])	73.4	0.10	2	0.32	0.10	7	0.30	7
C(4″), C(5″), C(7″)[d])[e])	70.6	0.85	4	1.41	0.70	2	0.80	1
	70.5	0.70	1				0.60	1
	70.4	0.85	1	1.76	0.80	3	0.60	1
C(2″)[d])[e])	69.2	0.30	1	1.17	0.25	1	0.40	2
	69.2						0.30	1
C(10″)[d])[e])	68.4	1.60	1	1.79	1.60	1	1.15	1
	68.4						1.05	1
C(1″)[d])[e])	67.4	0.30	3	0.87	0.20	2	0.25	1
	67.3	0.25	1	0.87			0.30	1
C(6′)	62.6	0.05	2	0.38	0.05	11	0.15	4
CH_3CH_2[d])[e])	60.2	3.25	1	1.94	2.30	2	2.55	1
CH_3O–C(3′)	59.9	0.25	3	0.26			0.30	2
CH_3CH_2[d])[e])	13.9	4.15	1	1.74	7.90	3	3.20	1

[a]) Recording conditions: 96 mg of **16a** in 0.5 ml of $CDCl_3$.
[b]) For the atom numbering, see *Formula* **16a**,**18a**; S.d.: standard deviation.
[c]) NOEF: Nuclear *Overhauser* effect factor [9].
[d]) Of the side chain at the secondary C(2′) atom.
[e]) Of the side chain at the primary C(6′) atom.
[f]) C(i) means C(2′), C(3′), C(4′), or C(5′).

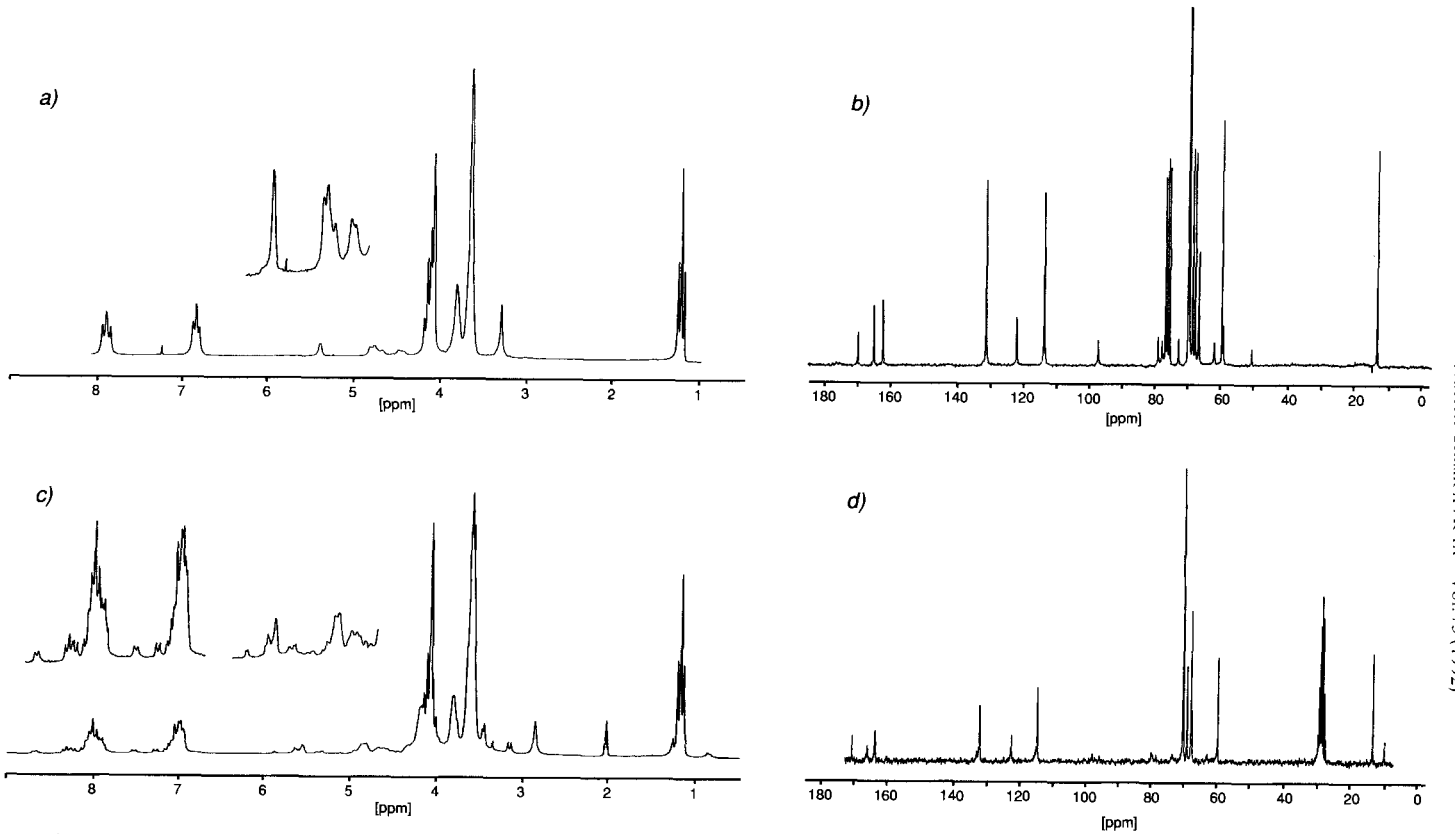

Fig. 2. *^{1}H-NMR* (room temp., 4.7 T) *and ^{13}C-NMR spectra* (room temp., 4.7 T) *of* B^{O}_{CD} *COOEt* (**16a**) a) b) *in $CDCl_3$ and* c) d) *in (D_6)acetone*. The insets show characteristic regions at higher amplification.

Table 4. *^{13}C-NMR Longitudinal Relaxation Time* T_1 *of* B^C_{CD} *COOEt* (**18a**) *in* $CDCl_3$[a])

C-Atom[b])	δ [ppm]	T_1 [s]	S.d.[b]) [%]	NOEF[c])
$COOCH_2CH_3$	173.6			0.34
COOC(2'), COOC(6')	165.4	0.56	2	−0.03
C(4)[d])[e])	163.0	1.20	3	0.12
C(2)[d])[e])	131.6	0.14	3	0.49
C(1)[d])	122.2	0.93	5	0.10
C(1)[e])	121.9	1.33	4	0.21
C(3)[d])[e])	114.0	0.15	2	0.45
C(1')	97.9	0.07	5	0.23
C(i)[f])	79.8	0.05	5	0.24
C(i)[f])	78.4	0.05	4	0.27
C(i)[f])	73.4	0.07	4	0.26
C(i)[f])	70.4	0.05	5	0.23
C(1'')[d])	68.1	0.18	1	0.88
C(1'')[e])	68.0	0.20	2	0.88
C(6')	62.8	0.04	4	0.24
CH_3CH_2[d])[e])	59.9	0.85	4	1.47
C(10'')[d])[e])	34.3	1.92	1	1.81
C(3'' to 8'')[d])[e])	29.3	0.69	1	1.68
	29.1	0.53	1	1.77
C(2'')[d])[e])	25.9	0.53	1	1.64
C(9'')[d])[e])	24.7	1.43	1	1.98
CH_3CH_2[d])[e])	14.1	5.90	3	1.68

[a]) Recording conditions: 90 mg of **18a** in 0.5 ml of $CDCl_3$; 4.7 T, 294 K.
[b–f]) See *Table 3*.

patterns due to the presence of tertiary amide functions [1]. It was thus possible to determine the ^{13}C-NMR longitudinal relaxation times T_1 and to investigate the local motions for both the poly(oxyethylene) and the polymethylene 'bouquets' B^O_{CD}COOEt (**16a**) and B^C_{CD}COOEt (**18a**), respectively. The T_1 values, for **16a** at different magnetic-field strengths and different temperatures, and the nuclear *Overhauser* effect factor (NOEF) [9] are listed in *Tables 3* and *4*.

The solvent affects very strongly the ^{1}H- and ^{13}C-NMR spectra of the B_{CD} compounds. Indeed, whereas in $CDCl_3$ B^O_{CD}COOEt (**16a**) shows the spectra expected for a symmetrical molecule (*Fig. 2a* and *2b*), much more complex patterns are observed in solvents such as acetone (*Fig. 2c* and *2d*), DMSO, pyridine, and, to a lesser extent, DMF and THF. Apparently, the high symmetry is lost and/or several different species may be present. A NOESY spectrum of **16a** in acetone highlights only an interaction between the solvent and the aromatic protons *ortho* to the ester group (*Fig. 3*). The model compound **21**, devoid of chains, exhibits the same behaviour. The spectrum of **21** in (D_5)pyridine, measured at different temperatures, evolves towards the simplified pattern expected as temperature is raised, indicating that an averaging process is taking place through intramolecular conformational motions and/or exchange between different species.

The interaction with H_2O is of special interest considering the possible role of compounds of type B_{CD} as transmembrane channels in contact with two aqueous phases. Due to their insolubility, the NMR spectra of esters **16** and **18** cannot be recorded in H_2O. Moreover, in a membrane, these molecules would be essentially surrounded by lipophilic

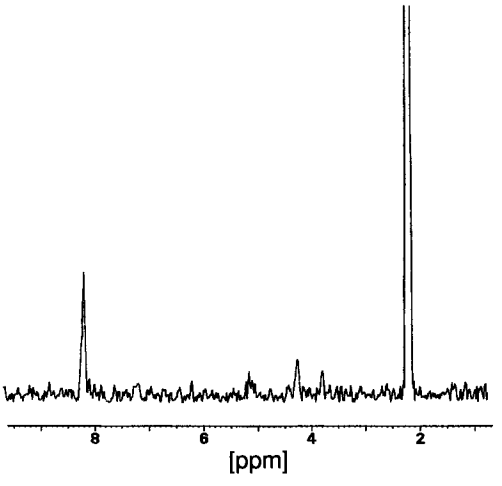

Fig. 3. *Cross section through the 2D NOESY ^{1}H-NMR spectrum of* $B^O_{CD}COOEt$ (**16a**) *in (D$_6$)acetone.* Taken parallel with ν_2 at the shift in ν_1 of the (D$_6$)acetone CHD$_2$ groups. It shows the cross peaks between acetone and the aromatic *H*–C(2).

alkyl chains. We recorded ^{1}H-NMR spectra of **16a** in diluted and in concentrated $CDCl_3$ solutions containing the same amount of H_2O. At the lowest concentration of substrate, the spectrum displayed marked signal broadening. In order to quantify this phenomenon, the proton relaxation times T_1 were measured (*Table 5*). One observes a decrease of T_1 when the concentration of **16a** diminishes. In addition, the relaxation time of the H_2O signal is greatly reduced in presence of **16a**.

Table 5. *^{1}H-NMR Longitudinal Relaxation Time* T_1 *of* $B^O_{CD}COOEt$ (**16a**) *in* $CDCl_3$ *at Different Concentrations*[a])

Proton[b])	*Exper. A* (0.4M)			*Exper. B* (3.2M)			*Exper. C* (6.7M)	
	δ [ppm]	T_1 [s]	S.d.[b]) [%]	δ [ppm]	T_1 [s]	S.d.[b]) [%]	δ [ppm]	T_1[g]) [s]
H–C(2)[d])	7.93	0.04	4	7.86	0.8	3	7.88	1.2
H–C(2)[e])							7.83	2.4
H–C(3)[d])	6.89	0.06	5	6.85	0.3	4	6.82	0.7
H–C(3)[e])							6.78	1.0
H–C(1′)				5.39	0.4	2	5.35	1.3
H–C(i)				4.77	0.3	2	4.71	1.2
CH_3CH_2[d])[e])	4.14	0.1	2				4.06	0.7
CH_2(1″), CH_2(10″),	4.14	0.1	2				4.02	0.7
CH_2(2″), CH_2(4″),							3.76	0.4
CH_2(5″)[d])[e])								
CH_2(7″), CH_2(8″)[d])[e])	3.71	0.1	1	3.66	0.5	1	3.60	0.5
CH_3O–C(3′)				3.30	0.1	4	3.25	0.6
H_2O[h])	1.57	0.4	2					
CH_3CH_2[d])[e])	1.25	0.2	1	1.17	2.0	1	1.13	1.9

[a]) Recording conditions: *Exper. A:* sealed degassed 10-mm tube, containing 5 mg of **16a** in $CDCl_3$ (2 ml); *Exper. B:* sealed degassed 5-mm tube, containing 96 mg of **16a** in $CDCl_3$ (0.5 ml); *Exper. C:* 5-mm tube, containing 200 mg of **16a** in $CDCl_3$ (0.5 ml).

[b–f]) See *Table 3.*

[g]) ± 0.1 s.

[h]) H_2O peak; as a reference, the longitudinal relaxation time T_1 of residual H_2O in the ^{1}H-NMR without degassing in 99% $CDCl_3$ is 5.6 s (S.d. = 1%).

Discussion. – The 'bouquet' molecules B^{O}_{CD} **16** and **17** and B^{C}_{CD} **18** and **19** have unusual structural features. With fully extended chains, their total length between the terminal COOR groups is *ca.* 50 Å. They contain three main structural domains: *i*) a rigid, more or less cylindrical, central core (total length along the molecular axis *ca.* 20 Å) comprising the β-cyclodextrin unit (thickness *ca.* 6–7 Å) and the bundle of seven 4-hydroxybenzoyl residues on each side (length *ca.* 6–7 Å on each side), *ii*) the flexible poly(oxyethylene) and polymethylene chains (length *ca.* 15 Å on each side) and *iii*) the seven terminal COOR functions on each side, whose polarity depends on whether they are in the ester, the acid, or the carboxylate forms. The overall shape of the molecule may be appreciated from the photograph of the molecular model of $B^{O}_{CD}COO^{-}$ (**17**, ionized form) shown in *Fig. 4*, which also presents schematically the structural domains and dimensions. It has features of a molecular bouquet or a sheaf.

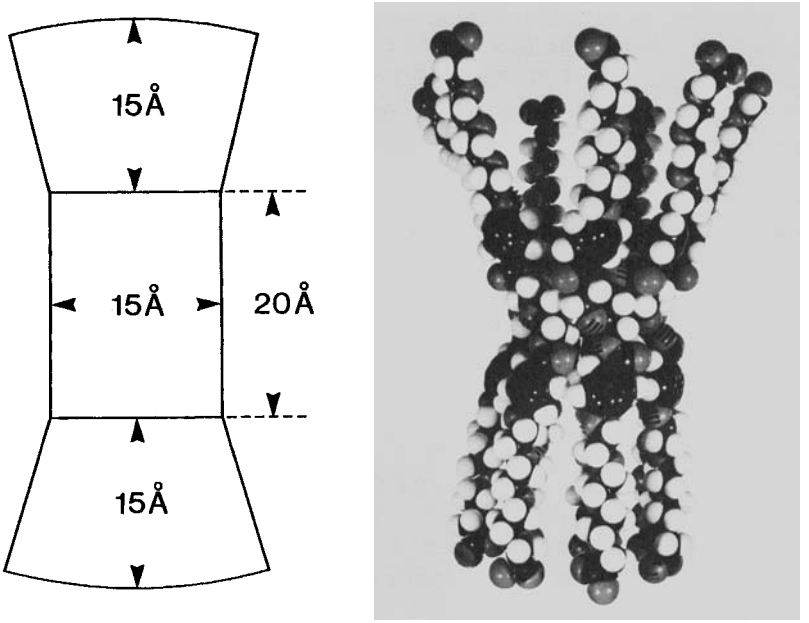

Fig. 4. *Photography of the CPK molecular model of the 'bouquet' molecule* $B^{O}_{CD}COO^{-}$ (**17**, ionized form; right) *and schematic representation of the corresponding structural domains and dimensions* (left)

In more chemical terms, such an entity may also be considered to represent a 'molecular capsule' formed not by self-assembled amphiphilic chains, but by chains covalently bound to a central organizing core. The internal free volume of the rigid core is *ca.* 400 Å^3; in comparison, a small vesicle of 250 Å diameter (internal diameter *ca.* 200 Å) has an internal volume of $4 \cdot 10^6$ Å^3. By the size, the shape (*Fig. 4*), and the molecular weight (5500–6000 range), this unusual type of molecular species may also be expected to display a number of features that combine attributes generally associated with polymolecular vesicles on one hand and macromolecular units on the other hand. Another analogy

brought to mind is between B_{CD} species and polymerized vesicles in which the amphiphilic chains are connected covalently to one another [8].

As in the case of the B_M 'bouquets', the influence of solvents on λ_{max} in the UV spectra of the B_{CD}'s is weak (a few nm). However, the behaviour of B^{O}_{CD}COOEt (**16a**) is noteworthy. In the poorly dissolving solvents pentanol and octanol, a 15-nm red shift is observed which could arise either from an intermolecular aggregation or from an intramolecular collapse of the molecule, causing in both cases a constraint on the chromophores. The CD spectra show strong similarities with some spectra already described for substituted β-cyclodextrins [10]. They do not display qualitative differences between each other, but the $\Delta\varepsilon$ values are not proportional to the molecular masses. Again a bathochromic shift is observed for **16a** in pentanol, in line with the UV data.

The results of *Table 3*, *Exper. A*, for B^{O}_{CD}COOEt (**16a**) show the following: *i*) the longitudinal relaxation times T_1 are generally short (order of magnitude: 0.1 s), suggesting that the dipole-dipole interaction is the major component in the relaxation mechanism [9]; *ii*) the NOEF values are much lower than 1.99, the theoretical value corresponding to extreme-narrowing conditions ($\omega^2\tau_c^2 \ll 1$); this is consistent which slow molecular movements [9]; *iii*) the T_1 and the NOEF values of **16a** increase from the core to the extremities of the molecule; this allows the assignments of all chemical shifts of the chain according to the relaxation times, in agreement with observations on linear molecules [9]; however, in the case of B^{C}_{CD}COOEt (**18a**; *Table 4*), one notes that CH_3CH_2OOC displays a lower value T_1 than C(10″), although it is more distant from the core, an inversion confirmed by the NOEF; *iv*) the relaxation times and the NOEF values are lower for the C-atoms of the chains attached at the secondary C(2′)-atom than for those at the primary C(6′) atom of the glucose moiety. The dipole-dipole contribution T_1^{DD} to the relaxation time T_1 and the correlation time of the molecule τ_c are linked by *Eqn. 1* (in SI units) [11],

$$(T_1^{DD})^{-1} = 1/10\,(\mu_0/4\pi)^2 \sum_{i=1}^{n} (\gamma_C\gamma_H\eta/2\pi)^2\,(\rho_{CH_i})^{-6}\,[J_0(\omega_H - \omega_C) + 3J_1(\omega_C) + 6J_2(\omega_H + \omega_C)] \quad (1)$$

with γ_C, γ_H = gyromagnetic ratios of ^{13}C and ^{1}H nuclei, ρ_{CH_i} = through-space ^{13}C–$^{1}H_i$ distance; ω_H, ω_C = *Larmor* pulsations of ^{1}H and ^{13}C nuclei, and J_0, J_1, and J_2 = spectral density functions describing the frequency distribution of the internuclear vector ρ_i movement. Assuming isotropic molecular reorientation, the correlation time τ_c is expressed by *Eqn. 2* [11].

$$J_0(\omega) = J_1(\omega) = J_2(\omega) = \tau_c/(1 + \omega^2\tau_c^2) \quad (2)$$

The short T_1 values suggest that dipole-dipole relaxation is the main relaxation mechanism for C-atoms carrying at least one proton. Furthermore, the simplifying assumption of isotropic molecular reorientation allows the calculation of the correlation times for the C-atoms investigated. The results are given in *Table 6*. In order to visualize more easily the numerical values, the inverse of the correlation times (the reorientation rates v_c) are presented in the histogram of *Fig. 5* as a function of the 'distance' to the center of the cyclodextrin core, given in number of chemical bonds. One can see the following: *i*) there is a large increase in mobility from the core to the extremities of these 'bouquets' by a factor of 100; the mobility begins to increase only for C-atoms further from the core than the methylene group at position 9 ($CH_2(1'')$); *ii*) the chains display a similar behaviour in

Table 6. *Correlation Times for the C-Atoms Carrying at Least One H-Atom in* B^{O}_{CD} *COOEt* (**16a**) *and* B^{C}_{CD} *COOEt* (**18a**)[a])

C-Atom[b])	B^{O}_{CD} COOEt (**16a**)		B^{C}_{CD} COOEt (**18a**)	
	δ [ppm]	τ_c [ps][c])	δ [ppm]	τ_c [ps]
C(2)[d])	131.4	320 ± 60	131.6	420
C(2)[e])	131.4	285 ± 100	131.6	420
C(3)[d])[e])	114.0	285 ± 100	114.0	380
C(1′)	97.7	1200 ± 800	97.9	2500
C(i)[f])	79.5	650 ± 500	79.8	2500
C(i)[f])	78.4	775 ± 375	78.4	2500
C(i)[f])	73.4	510 ± 320	73.4	2500
C(i)			70.4	2500
C(4″), C(5″), or C(7″)[d])[e])	70.6	29 ± 1	68.1	132
	70.5	36 ± 4	68.0	120
	70.4	34 ± 6	34.3	12
C(2″)[d])[e])	69.2	75 ± 5	29.3[g])	33
C(10″)[d])[e])	68.4	18 ± 3	29.1[g])	45
C(1″)[d])[e])	67.4	88 ± 10	25.9	45
	67.3	88 ± 7	24.9	13
C(6′)	62.6	510 ± 320	62.8	2000
CH_3CH_2	60.2	8 ± 1	59.9	28

[a]) Calculated from the ^{13}C-NMR relaxation time (*Tables 3* and *4*). The τ_c values were calculated using *Eqns. 1* and *2* with the assumption of isotropic rotational reorientation. Parameters used: $n_H = 1$, $r_{CH} = 0.109$ nm, $\omega_H(4.7T)/2\pi = 200.000$ MHz, $\omega_H(9.4T)/2\pi = 400.000$ MHz, $\omega_C(4.7T)/2\pi = 50.288$ MHz, $\omega_C(9.4T)/2\pi = 100.577$ MHz; $h/2\pi = 1.0546 \cdot 10^{-34}$ $m^2 \cdot kg \cdot s^{-1}$; $\gamma_H = 2.675 \cdot 10^8$ $rad \cdot s^{-1} \cdot T^{-1}$; $\gamma_H = 3.977$ γ_C, $\mu_0 = 4\pi \cdot 10^{-7}$ $m \cdot kg \cdot s^{-2} \cdot A^{-2}$.

[b,d–f]) See *Table 3*.

[c]) The error margins correspond to the exploitation of the data for two values of magnetic field.

[g]) Several peaks.

B^{O}_{CD}COOEt (**16a**) and in B^{C}_{CD}COOEt (**18a**), whereas the 'bouquet' core carrying polymethylene chains seems less mobile than that of the poly(oxymethylene) analog; on the basis of intrinsic chain-conformational features, one would have expected the poly(oxyethylene) chains to display a greater mobility than the polymethylene chains; the fact that both behave similarly could indicate that they are significantly entangled, which would decrease the flexibility difference between them; *iii*) in the case of **18a**, mobility evolution along the lateral chains does not conform to the expected behaviour, *i.e.* an increase from the core towards the chain extremities; the external methylene group at position 21 (CH_3CH_2OOC) displays a reduced mobility compared with the more internal one at position 18 (CH_2(10″)); this unusual behaviour could indicate interactions between the terminal groups; since they describe a greater volume, these extremities would be more sensitive to steric hindrance; such phenomena were already observed in the arborol series [12].

Consequently, in $CDCl_3$, the 'bouquet' molecules B_{CD} may be described as a rigid cylindrical core carrying on each of its discoidal faces a bundle of moving, more or less entangled chains. Such a geometry would seem to be quite appropriate to promote a transmembrane incorporation into lipid bilayers. However, chain entangling may be detrimental to channel opening. Recent computational studies on lipid membranes led to the conclusion that lipid alkyl chains are significantly entangled [13].

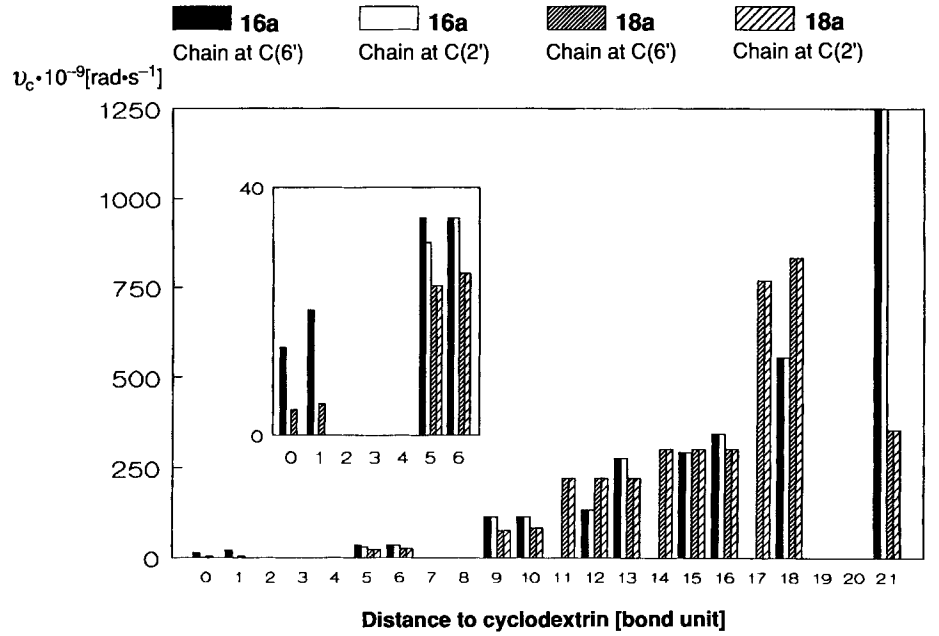

Fig. 5. *Plot of the reorientation rate* ν_c (inverse of the correlation time τ_c) *as a function of the distance from the β-cyclodextrin core.* The distance is expressed in bond units as defined in *Formula* **16a** and **18a**.

Moreover, it is possible to draw the curve of the experimental NOEF *vs.* the observed correlation time τ_c and to compare the experimental data with the theoretical curve given by *Eqn. 3* [11] for isotropic molecular reorientation conditions (*Eqn. 2*):

$$\text{NOEF} = (\gamma_H/\gamma_C)\,[(6J_2(\omega_H + \omega_C) - J_0(\omega_H - \omega_C))/(J_0(\omega_H - \omega_C) + 3J_1\omega_C + 6J_2(\omega_H + \omega_C))] \quad (3)$$

The results are shown in *Fig. 6*. Assuming dipole-dipole relaxation to be the major relaxation mechanism, the marked departure of the experimental values from the theoretical curve could be due to deviation from isotropic molecular reorientation and to local anisotropic motions. One may expect a more pronounced deviation at the level of the less mobile positions which would display more strongly the motional anisotropy, as is indeed observed. Such a deviation from isotropy would be in line with the fact that the C_7 symmetry axis represents probably the major inertia axis and, therefore, the preferential reorientation axis of these molecules.

Temperature and concentration changes yield unexpected effects on relaxation times. Indeed, an increase in temperature from 294 to 313 K (*Table 3*, *Exper. A* and *B*) mostly decreases the ^{13}C relaxation times in the rigid core of B^{o}_{CD}COOEt (**16a**) and leaves those of the chains more or less unchanged. A large increase in concentration (from 0.4 to 67 mM, *Exper. A–C* in *Table 5*) of **16a** in $CDCl_3$ leads to an increase in the proton T_1 values. In both cases, the effect observed is contrary to expectations: a raise in temperature should shorten the motional correlation times and lengthen the relaxation times; a concentration increase should increase the viscosity, lengthen correlation times, and shorten the relax-

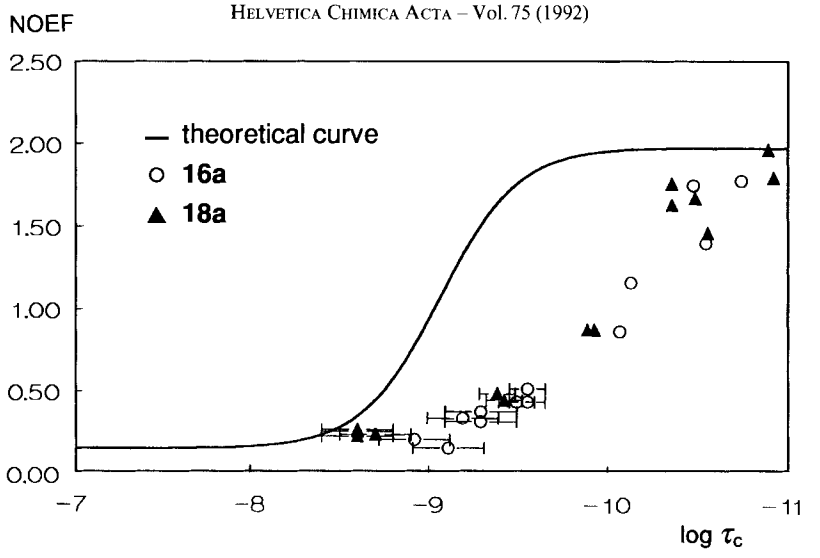

Fig. 6. *Plot of the experimental points and the theoretical curve giving the NOEFs as a function of the correlation time* τ_c *for* $B^{Q}_{CD}COOEt$ (**16a**) *and* $B^{Q}_{CD}COOEt$ (**18a**). The experimental points and theoretical curve were obtained as indicated in *Table 6*.

ation times. In both experiments, the ^{13}C and ^{1}H relaxation times of **16a** increase as the motional correlation times also increase. The theoretical relation between relaxation time and correlation time indicates that as τ_c increases, T_1 first decreases, goes through a minimum, and then increases; for short τ_c, the extreme-narrowing conditions $\omega^2\tau_c^2 \ll 1$ are fulfilled. The results obtained for **16a** would, therefore, correspond to the upward branch of $T_1 = f(\tau_c)$, meaning that the NMR behaviour of this molecule lies outside the extreme-narrowing domain. This would be in line with its large size and with the fact that the relatively flexible chains behave more 'normally' than the rigid core. An estimate of τ_c may be made from *Eqn. 4*:

$$\tau_c = 4\pi\eta a^3/3kT \tag{4}$$

where η and a are the viscosity of the medium and the molecular radius, respectively. Making the gross approximation of a spherical molecule of radius 35 Å, one obtains $\tau_c = 3$ ns. Such a value, despite its highly approximate character, would, nevertheless, be in line with the NMR results.

The complex NMR spectra observed in a number of solvents (see above, *Fig. 2c* and *d*) may indicate *i*) the presence of impurities which in $CDCl_3$ solution would give accidentally overlapping signals, *ii*) a mixture of species of 7-fold symmetry induced by differential solvation effects, or *iii*) the loss of the C_7 symmetry due to a conformational distorsion. Since compound **21** devoid of chains also shows the same phenomenon, the perturbation must take place at the level of the rigid core comprising the aromatic groups and the β-cyclodextrin ring. In cases *ii*) and *iii*), the observations also imply that exchange between different species or conformations must be slow on the NMR time scale. Indeed, the high-temperature NMR measurements show that the signals due to the protons of a given type coalesce, so that spectra corresponding to average 7-fold symmetry are obtained (*e.g.* in (D_5)pyridine, signals of protons at the glucose residue of **21**, separated by

ca. 50 Hz, coalesce at *ca.* 80°). This first eliminates case *i*) since the signals of a mixture of different compounds would not be expected to coalesce, confirming the purity of the materials, already ascertained in other ways (see above). The explanation *ii*) appears very unlikely. Indeed, one could hardly imagine several C_7 symmetrical forms involving the solvent and exchanging slowly on the NMR time scale. Finally, the most reasonable explanation of the solvent effects is probably a conformational distorsion leading to a loss of C_7 symmetry[2]). That is either revealed only in certain solvents or induced by them. The spectrum in $CDCl_3$ is then either due to the absence of distorsion or to a lower barrier to conformational exchange or to accidental overlap of the signals in this solvent. These considerations also raise the question of to what extent the internal space of the structures is conserved or collapsed.

There clearly exists a strong interaction between H_2O and B^O_{CD}COOEt (**16a**) in $CDCl_3$ solution. Since the decrease of the ^{1}H-NMR longitudinal relaxation time T_1 is relatively homogeneous on all observed positions on dilution with $CDCl_3$, the interaction does not seem to take place in a particular site. The presence of a single H_2O signal and the strong reduction of its relaxation time T_1 show that there is probably a rapid exchange between the interacting and free molecules of H_2O. These observations constitute an argument in favour of a hydrated internal volume in membrane medium.

Conclusion. – The synthesis of new molecules of the 'bouquet' type, B^O_{CD} **16** and **17** and B^C_{CD} **18** and **19**, based on a β-cyclodextrin core, was achieved. The spectral data indicate that the poly(oxyethylene) and polymethylene analogs display a similar geometry allowing the use of the polymethylene species as a convenient conformational reference for later studies in bilayer membranes. In both B^C_{CD} and B^O_{CD}, a central, 20-Å long cylindrical rigid core carries a moving bundle of chains at each extremity. Such a structure should be well suited for incorporation in lipid bilayer membranes. The poly(oxyethylene) analog **16a** exhibits a strong interaction with H_2O. Furthermore, the 'bouquets' B_{CD} display an unusual behaviour in several organic solvents, indicating a dissymmetric distorsion of the central rigid core. The present B_{CD} molecules also represent an unusual class of molecular objects, of 'molecular capsule' type, whose behaviour is in itself worth of more detailed investigation. The B_{CD}'s as well as the B_M's based on an [18]crown-6 macrocyclic core [1] may be incorporated into lipid membranes, where they could potentially act as artificial channels of 'chundle'-type structure. Such studies will be reported later.

Experimental Part

General. Anh. solvents (*SDS*), kept on molecular sieves (3–4 Å), were used as obtained. All catalytic hydrogenations were performed at a 1-bar pressure. Solvents for absorption spectra were of spectroscopic grade; pentanol and octanol were distilled twice over activated charcoal before use. Solns. for absorption spectra were prepared from a stock soln. in CH_2Cl_2 or $CHCl_3$: aliquots of the mother soln. were put into volumetric flasks, and after complete evaporation, the flasks were filled with the appropriate solvent. Column chromatography (CC): silica gel *60* (0.040–0.063 mm) *Merck*. Anal. and prep. TLC: silica gel plates (anal. or prep.) *Merck* or *Macherey-Nagel* or type-*E* alumina *Merck*; detection by UV (254 nm), I_2, or 5% H_2SO_4 soln. M.p.: *Kofler* hot-stage. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter. UV Spectra: *Perkin-Elmer-554* spectrometer. CD Spectra: *Mark-V-Jobin-Yvon* spectrometer; corrected for solvent residual absorption; in all cases, the absorbance was less than 1.4. ^{1}H-NMR

[2]) In a very recent paper (*J. Incl. Phenom. Recogn.* **1992**, *12*, 121), *Stoddart* and coworkers reported similar observations for several per-2,3-*O*-benzoyl-α-cyclodextrin derivatives.

Spectra: *AM-200-SY-Bruker* (4.7 T) *AM-400-Bruker* (9.4 T), and *AM-500-Bruker* (11.75 T); *Aspect-3000* calculator; spectrometer, chemical shifts in ppm rel. to protonated solvent as internal reference (^{1}H: $CHCl_3$ in $CDCl_3$, 7.26 ppm; CHD_2OD in CD_3OD, 3.30 ppm; CHD_2COCD_3 in D_6(acetone), 2.04 ppm; ^{13}C: $^{13}CDCl_3$ in $CDCl_3$, 76.9 ppm; $^{13}CD_3OD$ in CD_3OD, 49.0 ppm; $^{13}CD_3COCD_3$ in (D_6)acetone, 29.8 ppm); coupling constants J in Hz; unless otherwise specified, at r.t. (22 ± 2°); the tubes were carefully degassed by two thaw-freeze cycles under 10^{-6} Torr before sealing; longitudinal relaxation times T_1 were measured with the *Bruker* inversion recovery program; ^{13}C relaxation experiments were done in two series: the first one devoted to the measurement of short relaxation times, the second to long ones (8–10 regularly spaced points); NOEF measurements were also done in two series, and the error was estimated to be 20%. MS: FAB-MS (pos. mode) were performed by the Service de Spectrométrie de Masse du CNRS, Vernaison, and electrospray (ES) MS in Dr. *Van Dorsselaer*'s laboratory, Université Louis Pasteur, Strasbourg. Microanalyses were performed by the Service Central d'Analyses du CNRS, Vernaison, or by the Service de Microanalyses de l'Université P. et M. Curie, Paris.

Ethyl {2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy}acetate (**4a**) *and Ethyl {2-{2-[2-(Tosyloxy)ethoxy]ethoxy}-ethoxy}acetate* (**5a**) were already described [1].

2^A,2^B,2^C,2^D,2^E,2^F,2^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-Tetradeca-O-benzyl-β-cyclodextrin (**1**). Anh. BaO (30 g), $Ba(OH)_2 \cdot 8\,H_2O$ (30 g), and benzyl bromide (60 ml) were successively added to a soln. of β-cyclodextrin (6 g, 5.25 mmol; *Fluka*, desolvated) in DMF/DMSO 1:1 (300 ml) under N_2. After stirring at r.t. for 5 days under N_2, 28% NH_3 soln. (65 ml) was added. The mixture was additionally stirred for 30 min and then extracted with AcOEt (3 × 300 ml). The org. phase was washed several times with sat. NaCl soln., dried (Na_2SO_4), and evaporated under vacuum (20, then 2–3 Torr). The resulting oil (27 g) was submitted to CC (SiO_2 (500 g), CH_2Cl_2, then CH_2Cl_2/Et_2O 9:1). Recrystallisation from EtOH/acetone 65:35 gave **1** (3.68 g, 29%). Fine white needles. TLC (SiO_2, CH_2Cl_2/Et_2O 9:1): R_f 0.5 (UV, H_2SO_4). M.p. 215°. ^{1}H-NMR ($CDCl_3$): 7.4 (*m*, 5 arom. H); 7.24 (*s*, 5 arom. H); 5.22 (br. *s*, OH); 5.15–4.87 (*AB*, J = 12, PhCH_2); 4.86 (*s*, H–C(1)); 4.57–4.32 (*AB*, J = 12, PhCH_2); 4.14 (*m*, H–C(3)); 3.81 (*m*, 1 H–C(6)); 3.55 (*m*, H–C(2), H–C(4), H–C(5), 1 H–C(6)). ^{13}C-NMR ($CDCl_3$): 138.0, 137.4, 128.6, 128.2, 128.0, 127.8, 127.35, 127.2 (arom.); 101.8 (C(1)); 83.3 (C(4)); 78.3 (C(2)); 73.8 (PhCH_2); 73.6 (C(3)); 73.0 (PhCH_2); 70.3 (C(5)); 68.5 (C(6)). Anal. calc. for $(C_{20}H_{22}O_5)_7$ (2396.66): C 70.16, H 6.48; found: C 70.16, H 6.52.

2^A,2^B,2^C,2^D,2^E,2^F,2^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-Tetradeca-O-benzyl-3^A,3^B,3^C,3^D,3^E,3^F,3^G-hepta-O-methyl-β-cyclodextrin (**2**). Under N_2, **1** (478 mg, 0.2 mmol) was added to a suspension of NaH (140 mg of 50% oil dispersion, washed twice with dry pentane; 2.8 mmol, 2 equiv.) in THF (freshly distilled over CaH_2; 10 ml) and dry HPMT (1 ml). After stirring at r.t. for 1 h, MeI (0.5 ml, large excess) was added and stirring under N_2 continued at r.t. for 48 h. Again, NaH (50% dispersion; 140 mg), followed by MeI (0.5 ml) were added, and the mixture was stirred for further 3 days. After dilution with H_2O, the mixture was extracted with AcOEt, the org. phase successively washed with $NaHSO_3$ and H_2O, dried (Na_2SO_4), and evaporated, and the residue chromatographed on a small column or on plates (SiO_2, CH_2Cl_2/Et_2O 95:5): **2** (375 mg, 75%). Colourless oil. TLC: (SiO_2, CH_2Cl_2/Et_2O 9:1): R_f 0.5 (UV, H_2SO_4). ^{1}H-NMR ($CDCl_3$): 7.45 (*m*, 5 arom. H); 7.30 (*s*, 5 arom. H); 5.20 (*d*, J = 3, H–C(1)); 4.87–4.78 (*AB*, J = 12, PhCH_2); 4.52–4.45 (*AB*, J = 12, PhCH_2); 3.95 (*m*, 2 H–C(6)); 3.8 (*m*, H–C(3), H–C(4), H–C(5)); 3.66 (*s*, CH_3O); 3.52 (*m*, H–C(2)). ^{13}C-NMR ($CDCl_3$): 138.7, 138.2, 128.1, 128.0, 127.5, 127.4, 127.2 (arom.); 99.2 (C(1)); 81.95 (C(4)); 79.9 (C(3)); 79.5 (C(2)); 73.1, 72.4 (PhCH_2); 71.2 (C(5)); 69.1 (C(6)); 61.3 (CH_3O). FAB-MS: 2518 ([M + Na]$^+$, calc. 2518).

3^A,3^B,3^C,3^D,3^E,3^F,3^G-Hepta-O-methyl-β-cyclodextrin (**3**) [4]. A mixture of **2** (375 mg), 10% Pd/C (150 mg), dioxane (5 ml), EtOH (5 ml), and $HClO_4$ (2 drops) was hydrogenated at 50° for 4 h. After cooling to r.t., the suspension was neutralized with solid K_2CO_3 (100 mg) for a few min and filtered, and the resulting filtrate was evaporated under vacuum to yield **3** (185 mg, 100%). White powder. TLC (SiO_2, $CHCl_3$/MeOH/H_2O 65:25:4): R_f 0.1 (H_2SO_4). M.p. *ca.* 210°. ^{1}H-NMR (CD_3OD): 4.96 (*d*, J = 2, H–C(1)); 3.8 (*m*, 2 H–C(6)); 3.75 (*s*, CH_3O); 3.7–3.6 (*m*, H–C(2), H–C(3), H–C(4), H–C(5)). ^{13}C-NMR (CD_3OD): 103.3 (C(1)); 84.9 (C(4)); 79.9 (C(3)); 75.2 (C(2)); 74.0 (C(5)); 61.8 (C(6)); 60.9 (CH_3O).

Benzyl {2-[2-(2-Hydroxyethoxy)ethoxy]ethoxy}acetate (**4b**). Benzyl diazoacetate [5] (11.4 g, 0.064 mol) in CH_2Cl_2 (10 ml) was added dropwise to a mixture of triethylene glycol (55 ml), $BF_3 \cdot Et_2O$ (one drop), and CH_2Cl_2 (100 ml). After stirring at r.t. for one night, the org. phase was extensively washed with H_2O, dried (Na_2SO_4), and evaporated. The residue (20 g) was submitted to CC (silica gel (200 g), AcOEt): **4b** (13.7 g, 70%). Colourless oil, pure enough for the following steps. TLC (SiO_2, AcOEt): R_f 0.33 (UV). ^{1}H-NMR ($CDCl_3$): 7.31 (*s*, 5 arom. H); 5.14 (*s*, PhCH_2); 4.14 (*s*, OCH_2CO); 3.67–3.55 (*m*, 6 CH_2O); 3.22 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 170.0 (COO); 135.2, 128.3, 128.1 (arom.); 72.3, 70.6, 70.3, 70.2, 70.0 (CH_2O); 68.3 (OCH_2CO); 66.2 (PhCH_2); 61.3 (CH_2OH).

Benzyl {2-{2-[2-(Tosyloxy)ethoxy]ethoxy}ethoxy}acetate (**5b**). A soln. of **4b** (13.5 g, 45 mmol) in pyridine (70 ml) was cooled at −20° and treated with TsCl (13.5 g, 71 mmol). The mixture was stirred at 0° for one night.

After addition of crushed ice, the soln. was extracted with Et_2O and the org. phase washed with 1M HCl, 1M $NaHCO_3$, and H_2O, dried (Na_2SO_4) and evaporated: **5b** (17.6 g, 85%). Yellowish oil. TLC (SiO_2, AcOEt or CH_2Cl_2/Et_2O 95:5): R_f 0.4 (UV). ^{1}H-NMR ($CDCl_3$): 7.80–7.76 (*AA'BB'*, 2 arom. H); 7.34 (*s*, 5 arom. H); 7.34–7.30 (*AA'BB'*, 2 arom. H); 5.17 (*s*, PhCH_2); 4.17–4.12 (*m*, CH_2OTs, OCH_2CO); 3.73–3.56 (*m*, 5 CH_2O); 2.43 (*s*, CH_3).

Ethyl {2-[2-(2-Iodoethoxy)ethoxy]ethoxy}acetate (**6a**). A mixture of **5a** (48 g, 0.12 mol) and NaI (30 g, 0.2 mol) in butanone (200 ml) was refluxed for 7 h. H_2O was added to the partially evaporated soln. and the mixture extracted with Et_2O. The org. phase was washed with $NaHSO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated: **6a** (38.2 g, 88%). Pale yellowish oil, pure enough for the following steps. TLC (SiO_2, CH_2Cl_2/Et_2O 9:1): R_f 0.66 (I_2, H_2SO_4). ^{1}H-NMR ($CDCl_3$): 4.19 (*q*, *J* = 7, CH_3CH_2); 4.13 (*s*, OCH_2CO); 3.77–3.65 (*m*, 5 CH_2O); 3.24 (*t*, *J* = 7, CH_2I); 1.26 (*t*, *J* = 7, CH_3CH$_2$).

Benzyl {2-[2-(2-Iodoethoxy)ethoxy]ethoxy}acetate (**6b**). As described for **6a**, from **5b** (17.5 g, 3.7 mmol), and NaI (11.6 g, 78 mmol) in butanone (75 ml). The residue (15 g) was filtered over a silica-gel column (150 g, CH_2Cl_2/Et_2O 95:5): **6b** (13.4 g, 85%). Pale yellowish oil. TLC (SiO_2, CH_2Cl_2/Et_2O 95:5): R_f 0.54 (UV, H_2SO_4). ^{1}H-NMR ($CDCl_3$): 7.32 (*s*, 5 arom. H); 5.15 (*s*, PhCH_2); 4.19 (*s*, OCH_2CO); 3.70–3.61 (*m*, 5 CH_2O); 3.20 (*t*, *J* = 7, CH_2I). ^{13}C-NMR ($CDCl_3$): 169.8 (COO); 135.2, 128.2–128.0 (arom.); 71.6, 70.6, 70.4, 70.3, 69.9 (CH_2O); 68.4 (OCH_2CO); 66.1 (PhCH_2); 2.64 (CH_2I).

Benzyl 11-Bromoundecanoate (**7b**). Dicyclohexylcarbodiimide (DCC; 5.66 g, 27.5 mmol) was slowly added to a soln. cooled at 0° of 11-bromoundecanoic acid (6.6 g, 25 mmol), benzyl alcohol (2.8 ml, 27.5 mmol), and 4-(dimethylamino)pyridine (150 mg) in CH_2Cl_2 (25 ml). After stirring at 0° for 10 min, then at 20° for 3 h, the suspension was filtered. The org. phase was washed with 1M $NaHCO_3$, then 1M HCl, and finally H_2O, dried (Na_2SO_4), and evaporated. The residue was filtered over alumina (150 g, act. II–III, CH_2Cl_2): **7b** (8.85 g, 100%). Colourless oil. TLC (SiO_2, CH_2Cl_2/hexane 1:1): R_f 0.5 (UV). ^{1}H-NMR ($CDCl_3$): 7.36–7.34 (*m*, 5 arom. H); 5.11 (*s*, PhCH_2); 3.40 (*t*, *J* = 6.8, CH_2CO); 2.36 (*t*, *J* = 7.3, CH_2Br); 1.88–1.81 (*m*, CH_2); 1.64–1.57 (*m*, CH_2); 1.45–1.27 (*m*, 6 CH_2).

Benzyl 4-Hydroxybenzoate (**8**). DBU (7.6 ml, 50 mmol) and benzyl bromide (7 ml, 60 mmol) were successively poured into a suspension of 4-hydroxybenzoic acid (6.9 g, 50 mmol) in MeCN (100 ml). After stirring at 70° for 5 h, the soln. was cooled to r.t., diluted with H_2O, and extracted with Et_2O. The org. phase was washed with Na_2CO_3 soln. and H_2O, dried (Na_2SO_4), and evaporated. The oily residue was recrystallised from MeOH/H_2O 2:1: 7.6 g of crystals. The mother liquor was submitted to CC (silica gel (150 g), CH_2Cl_2/Et_2O 9:1): 1.8 g of crystals. Total amount of **8**, 9.4 g (80%). TLC (SiO_2, CH_2Cl_2): R_f 0.5 (UV). M.p. 112–113° ([14b]: 111°). ^{1}H-NMR ($CDCl_3$): 8.02–7.98 (*AA'BB'*, 2 arom. H); 7.44–7.35 (*m*, 5 arom. H); 6.88–6.84 (*AA'BB'*, 2 arom. H); 5.57 (*s*, OH); 5.34 (*s*, PhCH_2).

Allyl 4-Hydroxybenzoate (**9**). As described for **8**. Recrystallisation from hexane/CH_2Cl_2 4:1. Yield 75%. M.p. 100° ([14a]: 105°). ^{1}H-NMR ($CDCl_3$): 8.05–7.95 (*AA'BB'*, 2 arom. H); 6.98–6.91 (*AA'BB'*, 2 arom. H); 6.13–5.93 (*m*, CH); 5.40 (*m*, *J* = 17, 3, CH); 5.30 (*m*, *J* = 17, 3, CH); 4.64–4.60 (*m*, *J* = 5.5, CH_2). ^{13}C-NMR ($CDCl_3$): 166.9 (COO); 160.8, 131.9 (arom.); 131.9 (CH); 121.8 (arom.); 118.1 (CH_2); 115.3 (arom.); 65.5 (CH_2). Anal. calc. for $C_{10}H_{10}O_3$ (178.18): C 67.40, H 5.66; found: C 67.43, H 5.68.

Ethyl {2-{2-{2-[4-(Benzyloxycarbonyl)phenyloxy]ethoxy}ethoxy}ethoxy}acetate (**10a**). A soln. of **8** (5 g, 22 mmol) in dry DMF (50 ml) was added dropwise to NaH (1 g of 50% mineral-oil dispersion, 22 mmol) under N_2 at r.t. After stirring for 30 min, a soln. of **6a** (6.9 g, 20 mmol) in dry DMF (10 ml) was added and the resulting soln. stirred at 70° for 4 h under N_2. After cooling to r.t., the mixture was diluted with H_2O and extracted with AcOEt. The org. phase was washed with 1M NaOH, $NaHSO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated. The residue was submitted to CC (silica gel (500 g), CH_2Cl_2, then CH_2Cl_2/Et_2O 9:1): **10a** (6 g, 73%). Oil. TLC (SiO_2, CH_2Cl_2/Et_2O 9:1): R_f 0.35 (UV). ^{1}H-NMR ($CDCl_3$): 8.04–7.99 (*AA'BB'*, 2 arom. H); 7.43–7.35 (*m*, 5 arom. H); 6.95–6.90 (*AA'BB'*, 2 arom. H); 5.33 (*s*, PhCH_2); 4.22–4.18 (*m*, CH$_2$CH_2OAr); 4.15 (*q*, *J* = 7, CH_3CH_2); 4.14 (*s*, OCH_2CO); 3.90–3.85 (*m*, CH_2CH$_2$OAr); 3.74–3.68 (*m*, 4 CH_2O); 1.27 (*t*, *J* = 7, CH_3CH$_2$). ^{13}C-NMR ($CDCl_3$): 170.2, 166.0 (COO); 162.6, 136.3, 131.6, 128.4, 128.0, 128.0, 122.7, 114.2 (arom.); 70.9 (2), 70.6 (2), 69.5, 68.7, 67.6 (CH_2O); 66.3 (PhCH_2); 60.6 (CH_3CH_2); 14.1 (CH_3CH$_2$).

Ethyl 11-[4-(Benzyloxycarbonyl)phenyloxy]undecanoate (**10b**). As described for **10a**, from **8** (2.5 g, 11 mmol) in DMF (25 ml), 50% NaH dispersion (528 mg, 11 mmol), and **7a** (3 g, 10 mmol) in DMF (5 ml). The residue was recrystallised from hexane: **10b** (3.7 g, 84%). White crystals. TLC (SiO_2, CH_2Cl_2/hexane 4:1): R_f 0.6 (UV). M.p. 52°. ^{1}H-NMR ($CDCl_3$): 8.04–8.00 (*AA'BB'*, 2 arom. H); 7.46–7.35 (*m*, 5 arom. H); 7.91–7.80 (*AA'BB'*, 2 arom. H); 5.34 (*s*, PhCH_2); 4.12 (*q*, *J* = 7, CH_3CH_2); 3.99 (*t*, *J* = 6.5, CH$_2$CH_2OAr); 2.29 (*t*, *J* = 8, CH_2CO); 1.83–1.76 (*m*, CH_2CH$_2$OAr); 1.62–1.58 (*m*, CH_2CH$_2$CO); 1.44–1.30 (*m*, 6 CH_2); 1.25 (*t*, *J* = 7, CH_3CH$_2$). ^{13}C-NMR ($CDCl_3$): 173.6, 166.1 (COO); 163.0, 136.4, 131.6 128.4, 128.0, 122.4, 114.1 (arom.); 68.2 (CH_2OAr); 66.2 (PhCH_2); 60.0

(CH_3CH_2); 34.3 (CH_2CO); 29.4–29.0, 25.9, 24.9 (CH_2); 14.2 (CH_3CH_2). Anal. calc. for $C_{27}H_{36}O_5$ (440.56): C 73.60, H 8.24; found: C 73.64, H 8.13.

Benzyl {2-{2-[2-(4-(Allyloxycarbonyl)phenyloxy]ethoxy}ethoxy}ethoxy}acetate (**13a**). As described for **10a**, from **9** (6.23 g, 35 mmol), DMF (60 ml), 50% NaH dispersion (1.7 g, 35 mmol), and **6b** (13.5 g, 33 mmol). CC (silica gel, CH_2Cl_2/Et_2O 9:1) gave **13a** (12 g, 80%). Colourless oil. TLC (SiO_2, CH_2Cl_2/Et_2O 9:1): R_f 0.4 (UV, H_2SO_4). ^{1}H-NMR ($CDCl_3$): 8.02–7.94 (*AA'BB'*, 2 arom. H); 7.28 (*s*, 5 arom. H); 6.95–6.87 (*AA'BB'*, 2 arom. H); 6.09–5.92 (*m*, J = 16, 10.5, 5.5, CH); 5.43–5.33 (*m*, J = 1.5, CH); 5.33–5.27 (*m*, CH); 5.16 (*s*, PhCH_2); 4.80–4.75 (*m*, CH_2O); 4.18 (*s*, OCH_2CO); 4.18–4.13 (*m*, CH_2OAr); 3.85–3.82 (*m*, CH_2CH_2OAr); 3.76–3.64 (*m*, CH_2O). ^{13}C-NMR ($CDCl_3$): 169.9, 165.5 (COO); 162.3, 135.2 (arom.); 132.2 (CH); 131.2, 128.2, 128.0, 122.4 (arom.); 117.5 (CH_2); 113.9 (arom.); 70.6 (2), 70.5 (2), 70.3 (2), 69.2 (CH_2O); 68.3 (OCH_2CO); 67.3 (CH_2OAr); 66.1 (PhCH_2); 64.85 (CH_2O).

Benzyl 11-[4-(Allyloxycarbonyl)phenyloxy]undecanoate (**13b**). As described for **10a**, from **9** (3.9 g, 22 mmol), DMF (50 ml), 50% NaH dispersion (1.1 g, 22 mmol) and **7b** (7.1 g, 20 mmol). The residue was recrystallised from hexane: **13b** (7.48, 83%). Crystals. TLC (SiO_2, CH_2Cl_2): R_f 0.4 (UV). M.p. 45°. ^{1}H-NMR ($CDCl_3$): 8.03–8.00 (*AA'BB'*, 2 arom. H); 7.35 (*s*, 5 arom. H); 6.92–6.89 (*AA'BB'*, 2 arom. H); 6.13–5.94 (*m*, J = 17, 10, 5.5, CH); 5.45–5.34 (*m*, J = 1.5, CH); 5.30–5.24 (*m*, CH); 5.12 (*s*, PhCH_2); 4.82–4.77 (*m*, CH_2O); 3.99 (*t*, J = 6.5, CH_2CH_2OAr); 2.36 (*t*, J = 7, CH_2CO); 1.86–1.72 (*m*, CH_2CH_2CO); 1.69–1.62 (*m*, CH_2CH_2OAr); 1.44–1.30 (*m*, 6 CH_2). ^{13}C-NMR ($CDCl_3$): 173.0, 165.7 (COO); 162.8, 136.0 (arom.); 132.3 (CH); 131.4, 128.2, 127.9, 122.1 (arom.); 117.6 (CH_2); 113.9 (arom.); 68.0 (CH_2OAr); 65.8 (PhCH_2); 64.9 (CH_2O); 34.1 (CH_2CO); 29.2–28.9 (CH_2); 25.75 (CH_2CH_2OAr); 24.7 (CH_2CH_2CO). Anal. calc. for $C_{28}H_{36}O_5$ (452.57): C 74.30, H 8.02; found: C 74.42, H 8.05.

Ethyl {2-{2-[2-(4-Carboxyphenyloxy)ethoxy]ethoxy}ethoxy}acetate (**11a**). A suspension of **10a** (6 g) and 10% Pd/C (120 mg) in EtOH (60 ml) was hydrogenated at r.t. for 5 h. After filtration, the filtrate was evaporated and the resulting residue recrystallised from hexane/benzene 1:1: **11a** (4.5 g, 85%). Crystals. M.p. 64°. ^{1}H-NMR ($CDCl_3$): 11.4 (*s*, OH); 7.96 (*AA'BB'*, 2 arom. H); 6.89 (*AA'BB'*, 2 arom. H); 4.12 (*q*, J = 7, CH_3CH_2); 4.19–4.12 (*m*, CH_2OAr); 4.09 (*s*, OCH_2CO); 3.85–3.83 (*m*, CH_2CH_2OAr); 3.67 (*m*, 4 CH_2O); 1.21 (*t*, J = 7, CH_3CH_2). ^{13}C-NMR ($CDCl_3$): 170.9, 170.1 (COO); 162.9, 131.9, 121.7, 114.1 (arom.); 70.6 (2), 70.4 (2), 69.3, 68.4, 67.4 (CH_2O); 60.5 (CH_3CH_2); 13.9 (CH_3CH_2). Anal. calc. for $C_{17}H_{24}O_8$ (356.36): C 57.29, H 6.79; found: C 57.58, H 6.85.

Ethyl 11-(4-Carboxyphenyloxy)undecanoate (**11b**). As described for **11a**, from **10b** (3.65 g), 10% Pd/C (70 mg) and EtOH (35 ml): **11b** (2.9 g, 100%). M.p. 91–92°. ^{1}H-NMR ($CDCl_3$): 11.6 (br. *s*, OH); 8.03 (*AA'BB'*, 2 arom. H); 6.89 (*AA'BB'*, 2 arom. H); 4.11 (*q*, J = 7, CH_3CH_2); 3.99 (*t*, J = 6.5, CH_2OAr); 2.28 (*t*, J = 7, CH_2CO); 1.85–1.71 (*m*, CH_2CH_2OAr); 1.63–1.57 (*m*, CH_2CH_2CO); 1.30–1.28 (*m*, 6 CH_2); 1.24 (*t*, J = 7, CH_3CH_2). ^{13}C-NMR ($CDCl_3$): 173.6, 171.6 (COO); 163.5, 132.1, 121.4, 114.1 (arom.); 68.1 (CH_2OAr); 60.0 (CH_3CH_2); 34.2 (CH_2CO); 29.3–29.0, 25.8, 24.8 (CH_2); 14.1 (CH_3CH_2). Anal. calc. for $C_{20}H_{30}O_5$ (350.44): C 68.54, H 8.63; found: C 68.74, H 8.63.

Benzyl {2-{2-[2-(4-Carboxyphenyloxy)ethoxy]ethoxy}ethoxy}acetate (**14a**). Pyrrolidine (1.7 ml, 20 mmol) was added dropwise to a cooled (0°) soln. of **13a** (4.58 g, 10 mmol), tetrakis(triphenylphosphine)palladium(0) (347 mg, 0.3 mmol), and triphenylphosphine (157 mg, 0.6 mmol) in CH_2Cl_2 (50 ml). After stirring at 0° for 30 min, the org. phase was washed with 1M HCl and H_2O, dried (Na_2SO_4), and evaporated. The residue (5 g) was submitted to CC (silica gel (300 g), CH_2Cl_2, then CH_2Cl_2/MeOH 9:1): 3.9 g. Recrystallisation at −20° from MeOH (25 ml) and H_2O (10 ml) gave crystals of **14a** which were immediately dried under vacuum (once dried, they are stable): 3.55 g (85%). TLC (SiO_2, CH_2Cl_2/MeOH 9:1): R_f 0.6 (UV, H_2SO_4). M.p. 69–70°. ^{1}H-NMR ($CDCl_3$): 8.85 (*s*, OH); 8.02–7.97 (*AA'BB'*, 2 arom. H); 7.35 (*s*, 5 arom. H); 6.92–6.88 (*AA'BB'*, 2 arom. H); 5.15 (*s*, PhCH_2); 4.17 (*s*, OCH_2CO); 4.17–4.11 (*m*, CH_2OAr); 3.86–3.81 (*m*, CH_2CH_2OAr); 3.74–3.65 (*m*, 4 CH_2O). ^{13}C-NMR ($CDCl_3$): 170.5, 170.0 (COO); 162.8, 135.2, 131.9, 128.2, 128.0, 121.8, 114.0 (arom.); 70.6, 70.5, 70.3 (2), 69.2 (CH_2O); 68.35 (OCH_2CO); 67.35 (CH_2OAr); 66.2 (OCH_2Ar). Anal. calc. for $C_{22}H_{26}O_8$ (418.43): C 63.15, H 6.26; found: C 63.35, H 6.25.

Benzyl 11-(4-Carboxyphenyloxy)undecanoate (**14b**). As described for **14a**, from pyrrolidine (1.7 ml, 20 mmol), **13b** (4.5 g, 10 mmol), tetrakis(triphenylphosphine)palladium(0) (347 mg, 0.3 mmol), triphenylphosphine (157 mg, 0.6 mmol), and CH_2Cl_2 (75 ml). Recrystallisation from (i-Pr)$_2$O gave **14b** (3.64 g, 88%). TLC (SiO_2, CH_2Cl_2/MeOH 9:1): R_f 0.45 (UV, H_2SO_4). M.p. 87–88°. ^{1}H-NMR ($CDCl_3$): 11.7 (br. *s*, OH); 8.10–8.06 (*AA'BB'*, 2 arom. H); 7.36 (*s*, 5 arom. H); 6.96–6.92 (*AA'BB'*, 2 arom. H); 5.14 (*s*, PhCH_2); 4.02 (*t*, J = 6.5, CH_2OAr); 2.38 (*t*, J = 7, CH_2CO); 1.90–1.75 (*m*, CH_2CH_2OAr); 1.75–1.60 (*m*, CH_2CH_2CO); 1.60–1.31 (*m*, 6 CH_2). ^{13}C-NMR ($CDCl_3$): 173.4, 171.6 (COO); 163.5, 136.05, 132.1, 128.3, 127.9, 121.4, 114.1 (arom.); 68.15 (CH_2OAr); 65.9 (PhCH_2); 34.17 (CH_2CO); 29.3–24.8 (CH_2). Anal. calc. for $C_{25}H_{32}O_5$ (412.51): C 72.79, H 7.82; found: C 72.63, H 7.74.

General Procedure for the Preparation of **16** *and* **18**. A mixture of acid **11** or **14** (2.1 mmol, 3 equiv.), anh. benzene (2.5 ml), dry pyridine (0.25 ml), and $SOCl_2$ (2.5 ml) was refluxed at 80° for 10 min. The mixture was evaporated, the residue taken up in anh. benzene (10 ml), refluxed for 1 min, and the soln. again evaporated. Anh. benzene (10 ml) was added and the mixture refluxed for 2–3 min. After filtration and benzene washing of the pyridinium chloride, the filtrate was evaporated. The formed acyl chloride **12** or **15**, resp. was immediately dissolved in a soln. of 4-(dimethylamino)pyridine (50 mg) in pyridine (5 ml). The resulting mixture was poured on **3** (60 mg, 0.05 mmol). After stirring at 60° for 3 days under inert atmosphere, a second batch of acyl chloride **12** or **15** (1.4 mmol, 2 equiv.) in pyridine (3 ml) was added, and stirring was maintained for 3 days. After cooling at r.t., the mixture was diluted with H_2O and extracted with AcOEt. The org. phase was washed with 1M HCl and H_2O, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography. If the crude product was not completely esterified, it was treated again under the same conditions.

3^A,3^B,3^C,3^D,3^E,3^F,3^G-Hepta-O-methyl-β-cyclodextrin 2^A,2^B,2^C,2^D,2^E,2^F,2^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-Tetradecakis{4-{2-{2-{2-[(ethoxycarbonyl)methoxy]ethoxy}ethoxy}ethoxy}benzoate} (**16a**). According to the *General Procedure*, from **3** (93 mg, 0.075 mmol) and **11a** (1.12 g, 3.15 mmol, 3 equiv.; then 750 mg, 2.1 mmol, 2 equiv.): 1.25 g of crude residue. CC (silica gel (150 g), CH_2Cl_2/MeOH 95:5) gave **16a** (285 mg, 60%). Resin. TLC (SiO_2, CH_2Cl_2/MeOH 95:5): R_f 0.3 (UV, H_2SO_4). $[\alpha]_{589}^{25} = +58$, $[\alpha]_{578}^{25} = +61$; $[\alpha]_{546}^{25} = +69$; $[\alpha]_{436}^{25} = +115$, ($c = 3$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$)[3]: 7.97–7.87 (*AA'BB'*, 4 arom. H); 6.90–6.83 (*AA'BB'*, 4 arom. H); 5.41 (br. *s*, H–C(1')); 4.82–4.44 (*m*, H–C(2'), H–C(4'), H–C(6')); 4.20–4.09 (*m*, H–C(3'), 2 CH_2OAr, 2 OCH_2CO, 2 CH_3CH_2); 3.83–3.67 (*m*, H–C(5'), H–C(6'), 10 CH_2O); 3.30 (br. *s*, CH_3O); 1.22 (*t*, $J = 7$, 2 CH_3CH_2). ^{13}C-NMR ($CDCl_3$): 170.1, 170.1, 165.3, 165.3 (COO); 162.6, 162.4, 131.5, 122.2, 122.0, 114.0 (arom.); 97.8 (C(1')); 79.5 (C(4')); 78.5 (C(3')); 73.5 (C(2')); 70.6, 70.5, 70.4, 69.2 (C(5'), CH_2O); 68.5 (OCH_2CO); 67.3 (CH_2OAr); 62.6 (C(6)); 60.5 (CH_3CH_2); 60.1 (CH_3O); 14.0 (CH_3CH_2). FAB-MS: 5970 ($[M + H]^+$, calc. 5971). Anal. calc. for $C_{287}H_{392}O_{133}$: C 57.74, H 6.62; found: C 57.94, H 6.62.

3^A,3^B,3^C,3^D,3^E,3^F,3^G-Hepta-O-methyl-β-cyclodextrin 2^A,2^B,2^C,2^D,2^E,2^F,2^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-Tetradecakis{4-[10-(ethoxycarbonyl)decyloxy]benzoate} (**18a**). According to the *General Procedure*, from **3** (60 mg, 0.05 mmol) and **11b** (735 mg, 2.1 mmol, 3 equiv.; then 490 mg, 1.4 mmol, 2 equiv.): 1.5 g of crude residue. Two CC's (silica gel (150 g), CH_2Cl_2/acetone 97:3, then silica gel (25 g)) gave **18a** (100 mg, 35%). Resin. TLC (SiO_2, CH_2Cl_2/acetone 97:3): R_f 0.33 (UV, H_2SO_4). $[\alpha]_{589}^{25} = +65$, $[\alpha]_{578}^{25} = +68$, $[\alpha]_{546}^{25} = +77$, $[\alpha]_{436}^{25} = +128$ ($c = 2.65$, $CHCl_3$). ^{1}H-NMR: ($CDCl_3$): 7.97–7.91 (*AA'BB'*, 4 arom. H); 6.86–6.82 (*AA'BB'*, 4 arom H); 5.42 (br. *s*, H–C(1')); 4.90–4.45, 4.25–3.89 (*m*, H–C(2'), H–C(3'), H–C(4'), H–C(5'), 2 H–C(6')); 4.11 (*q*, $J = 7$, 2 CH_3CH_2); 3.92 (*m*, 2 CH_2OAr); 3.32 (br. *s*, CH_3O); 2.28 (*t*, $J = 7$, 2 CH_2CO); 1.76–1.61–1.28 (*m*, 16 CH_2); 1.24 (*t*, $J = 7$, 2 CH_3CH_2). ^{13}C-NMR ($CDCl_3$): 173.6, 173.5, 165.4 (COO); 163.0, 162.9, 131.8, 131.7, 122.3, 122.0, 114.15, 114.0 (arom.); 97.9 (C(1')); 79.8 (C(4')); 78.5 (C(3')); 73.5 (C(2')); 70.4 (C(5')); 68.25, 68.1 (CH_2OAr); 62.8 (C(6')); 60.0 (CH_3CH_2); 59.8 (CH_3O); 34.35, 34.3 (CH_2CO); 29.4–29.1, 25.95, 24.9 (CH_2); 14.2 (CH_3CH_2). FAB-MS: 5910 ($[M + Na]^+$, calc. 5910). Anal. calc. for $C_{329}H_{176}O_{91}$: C 67.12, H 8.15; found: C 67.10, H 8.05.

3^A,3^B,3^C,3^D,3^E,3^F,3^G-Hepta-O-methyl-β-cyclodextrin 2^A,2^B,2^C,2^D,2^E,2^F,2^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G-Tetradecakis{4-{2-{2-{2-[(benzyloxycarbonyl)methoxy]ethoxy}ethoxy}ethoxy}benzoate} (**16b**). According to the *General Procedure*, from **3** (75 mg, 0.06 mmol) and **14a** (1.05 g, 2.5 mmol, 3 equiv.; then 710 mg, 1.7 mmol, 2 equiv.): 1 g of crude mixture. CC (silica gel (100 g), $CHCl_3$/MeOH 9:1) yielded 200 mg of impure product, which was treated a 3rd time with 2 equiv. of acyl chloride **15a** for 3 days. The new residue was purified by CC (silica gel, $CHCl_3$/MeOH 9:1), then by prep. TLC (silica gel, AcOEt/acetone/MeOH 90:7:3): and finally by CC (silica gel (10 g), AcOEt/acetone 7:3): **16b** (62 mg, 15%). Resin. TLC (SiO_2, CH_2Cl_2/MeOH 9:1 or AcOEt/acetone/MeOH 90:7:3): R_f 0.6 and 0.4 (UV, H_2SO_4), resp. $[\alpha]_{589}^{25} = +55$, $[\alpha]_{578}^{25} = +57$, $[\alpha]_{546}^{25} = +65$, $[\alpha]_{436}^{25} = +107$ ($c = 3$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 7.97–7.92 (*AA'BB'*, 4 arom. H); 7.28 (*m*, 10 arom. H); 6.90–6.86 (*AA'BB'*, 4 arom. H); 5.45 (br. *s*, H–C(1')); 5.16–5.15 (2*s*, 2 $PhCH_2$); 4.85–4.73 (*m*, H–C(2'), H–C(4'), H–C(6')); 4.19–4.16 (2*s*, 2 OCH_2CO); 4.10 (*m*, H–C(5'), H–C(6'), H–C(3'), 2 CH_2OAr); 3.82–3.69 (*m*, 10 CH_2O); 3.33 (br. *s*, CH_3O). ^{13}C-NMR ($CDCl_3$):

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[3]) The assignment of the arom. H-atoms was performed with a 96-mg sample in 0.5 ml of $CDCl_3$ (sealed tube) using a ROESY procedure (500 MHz). Cross peaks with the signal of CH_3O–C(3') and of the anomer proton H–C(1') allowed the differentiation of the arom. H-atoms of the moieties at C(2') and C(6'). The following peak correlations were made: 7.87, 6.82 (arom. H) and 5.40 ppm (H–C(1')), from section at 7.87 ppm; 7.92, 6.84 (arom. H), 5.40 (H–C(1')) and 3.3 ppm (CH_3O–C(3')), from section at 7.92 ppm; moreover, the correlation of the H–C(1') signal (5.40 ppm) with the signal at 7.87 ppm was much greater than that at 7.92 ppm. Thus, the protons exhibiting signals at 7.87 and 6.82 ppm belong to the moiety at C(6') of the β-cyclodextrin, whereas the protons exhibiting signals at 7.92 and 6.84 ppm are located on the moiety at C(2').

170.0, 165.3 (COO); 162.6, 162.4, 135.4, 131.6, 128.4, 128.1, 122.5, 122.25, 114.15 (arom.); 97.9 (C(1′)); 79.7 (C(4′)); 78.6 (C(3′)); 73.6 (C(2′)); 70.8, 70.6, 70.5, 69.35 (C(5′), CH_2O); 68.5 (OCH_2CO); 67.4 (CH_2OAr); 66.2 ($PhCH_2$); 62.7 (C(6)); 60.0 (CH_3O). ES-MS[4]): 6835 (calc. 6839). Anal. calc. for $C_{357}H_{420}O_{133}$: C 62.69, H 6.19; found: C 62.40, H 6.19.

$3^A,3^B,3^C,3^D,3^E,3^F,3^G$-Hepta-O-methyl-β-cyclodextrin $2^A,2^B,2^C,2^D,2^E,2^F,2^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Tetradecakis{4-[10-(benzyloxycarbonyl)decyloxy]benzoate} (**18b**). According to the *General Procedure*, from **3** (60 mg, 0.05 mmol) and **14b** (825 mg, 2 mmol, 3 equiv.; then 577 mg, 1.4 mmol, 2 equiv.): *ca.* 1 g of impure residue. This mixture was treated a 3rd time with 2 equiv. of acyl chloride **15b**. The new residue was purified by CC (silica gel (250 g), CH_2Cl_2/acetone 97:3), then by TLC (silica gel, same eluent), and finally by CC (silica gel (25 g)): **18b** (55 mg, 17%). Resin. TLC (SiO_2, CH_2Cl_2/acetone 97:3): R_f 0.6 (UV, H_2SO_4). $[\alpha]_{589}^{25} = +54°$; $[\alpha]_{546}^{25} = +56°$; $[\alpha]_{436}^{25} = +63°$ ($c = 2.5$ $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 7.98–7.92 (*AA′BB′*, 4 arom. H); 7.34 (*s*, 10 arom. H); 6.86–6.83 (*AA′BB′*, 4 arom. H); 5.44 (br. *s*, H–C(1′)); 5.11 (*s*, 2 $PhCH_2$); 4.53–4.49–4.22 (*m*, H–C(2′), H–C(4′), H–C(6′)); 4.0, 3.95, 3.92, 3.85 (*m*, H–C(3′), H–C(5′), H–C(6′), 2 CH_2OAr); 3.34 (*s*, CH_3O); 2.34 (*t*, $J = 7$, 2 CH_2CO); 1.75–1.64–1.28 (*m*, 16 CH_2). ^{13}C-NMR ($CDCl_3$): 173.3, 165.4 (COO); 163.0, 162.9, 136.1, 131.65, 128.4, 127.95, 122.3, 121.95, 114.1, 114.0 (arom.); 97.9 (C(1)); 79.8 (C(4)); 78.5 (C(3)); 73.4 (C(2)); 70.4 (C(5)); 68.1 (CH_2OAr); 65.9 ($PhCH_2$); 62.8 (C(6)); 59.8 (CH_3O); 34.2 (CH_2CO); 29.3–29.1, 25.9–24.9 (CH_2). ES-MS: no M^+ obs.[4]) (calc. 6756). Anal. calc. for $C_{399}H_{504}O_{91}$: C 70.93, H 7.52; found: C 70.56, H 7.42.

Hydrogenolysis of Benzyl Esters **16b** *and* **18b**. A mixture of **16b** or **18b** (50 mg), 10% Pd/C (50 mg), CH_2Cl_2 (5 ml), and 95% EtOH (2.5 ml) was hydrogenated at r.t. for 5 h. After filtration, the catalyst was washed with CH_2Cl_2/95% EtOH 1:1. The filtrate was evaporated to yield 35 mg of acid **17** or **19**, used without further purification. NMR (D_6)DMSO, (D_7)DMF, or (D_5)pyridine: broad signals, difficult to analyze; disappearance of the benzyl groups.

Treatment of **17** with diazomethane gave a sample of the corresponding tetradecamethyl ester. ^{1}H-NMR ($CDCl_3$): 7.99–7.89 (*AA′BB′*, 4 arom. H); 6.93–6.85 (*AA′BB′*, 4 arom. H); 5.43 (br. *s*, H–C(1′)); 4.81–4.51 (*m*, H–C(2′), H–C(4′), H–C(6′)); 4.16–4.14 (*m*, 2 OCH_2CO, 2 CH_2OAr, H–C(3′)); 3.85–3.71 (*m*, H–C(5′), H–C(6′), 10 CH_2O, 2 $COOCH_3$); 3.49 (br. *s*, CH_3O).

$3^A,3^B,3^C,3^D,3^E,3^F,3^G$-Hepta-O-methyl-β-cyclodextrin $2^A,2^B,2^C,2^D,2^E,2^F,2^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Tetradecakis(4-methoxybenzoate) (**21**). According to the *General Procedure* for **16** and **18**, **3** (60 mg, 0.05 mmol) was treated twice with 4-methoxybenzoyl chloride (358 mg, 2.1 mmol, 3 equiv.; then 240 mg, 1.4 mmol, 2 equiv.): 550 mg of crude residue. CC (silica gel (50 g), CH_2Cl_2/MeOH 97.5:2.5) yielded **21** (95 mg, 60%). White powder. TLC (SiO_2, CH_2Cl_2/MeOH 97.5:2.5): R_f 0.33 (UV, H_2SO_4). M.p. *ca.* 175°. ^{1}H-NMR ($CDCl_3$): 8.02–7.91 (*AA′BB′*, 4 arom. H); 6.95–6.83 (*AA′BB′*, 4 arom. H); 5.41 (*d*, $J = 3.3$, H–C(1′)); 4.88 (*m*, H–C(2′)); 4.76–4.49 (*m*, H–C(6′)); 4.25 (*m*, H–C(4′)); 3.90 (*m*, H–C(3′), H–C(5′)); 3.84–3.80 (2*s*, CH_3OAr); 3.32 (*s*, CH_3O–C(3′)). ^{13}C-NMR ($CDCl_3$): 165.4 (COO); 163.4, 163.3, 131.7, 131.6, 122.4, 122.1, 113.5 (arom.); 97.8 (C(1′)); 79.75 (C(4′)); 78.4 (C(3′)); 73.4 (C(2′)); 70.4 (C(5′)); 62.8 (C(6′)); 59.8 (CH_3O); 55.3, 55.2 (CH_3OAr). FAB-MS: 3134 ($[M + Na]^+$, calc. 3134).

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[4]) Using a soln. of $(NH_4)_2CO_3$ in CH_2Cl_2 and MeOH, **16b** was ionized by addition of several NH_4^+ ions corresponding to different states of charge of the molecules, *i.e.* m/z 2295 = [6835 + (3 × 18)]/3, 1726 = [6835 + (4 × 18)]/4, and 1385 = [6835 + (5 × 18)]/5 giving the chemical mass 6835. It was impossible to ionize **18b** by the same technique and consequently to obtain its chemical mass.

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