Analysis of the Conformational Behaviour of Perfunctionalized β-Cyclodextrins. Part 1. Evidence for Insertion of one of the Rim Substituents into the Cyclodextrin Cavity in Organic Solvents

Ludovic Jullien, Josette Canceill, Liliane Lacombe and Jean-Marie Lehn
Laboratoire de Chimie des Interactions Moléculaires, Collège de France, 11 Place Marcelin Berthelot, F-75005 Paris, France

Several functionalized β-cyclodextrins have been shown to exhibit conformational isomerism. The analysis of the conformational behaviour of several derivatives strongly suggests that a slow exchange occurs between C_7 and C_1 conformers, the C_1 probably involving insertion of one of the primary rim substituents in the cyclodextrin cavity. The significance of the structural features of cyclodextrin substituents for the occurrence of conformational isomerism is examined. The relevance of the use of cyclodextrins for the design of molecular devices is discussed.

Cyclodextrins (CDs) are cyclic oligomers of α-(1-4) linked D-glucose monomers. These molecules and their derivatives have received considerable attention because of their ability to form inclusion complexes.[1] Recent developments have led to increased interest in numerous areas of chemistry.[2] Our laboratory is currently involved in the design and synthesis of cyclodextrin-based compounds that may act as artificial ionic channels[3] or photophysical models.[4] During the design of the target molecules, it was considered *a priori* that the expected conformation of the core of functionalized cyclodextrins would conform to that obtained from X-ray structures of native cyclodextrins.[5] In fact, this 'reasonable' assumption was based on a limited number of examples[6] and some results from our laboratory[3a,7] and others[8] could have led us to be suspicious, especially in the case of sterically hindered molecules. As conservation of fundamental features of cyclodextrins, such as the existence of an internal cavity or high symmetry, motivated at least in part the choice of these molecules for our purposes, we have examined in more detail the conformations of a number of derivatized β-cyclodextrins.* The purpose of this paper is to analyse the conformational behaviour of some of these molecules.

The commonly available native CDs have six (α-CD),† seven (β-CD)* and eight (γ-CD)‡ D-glucopyranose units.[1] The structures of these molecules are well documented.[9] The glucopyranose units are in the $^4C_1$ chair conformation and the overall shape of the molecules is that of a truncated cone with a symmetrical axis of order 6 (α-CD), 7 (β-CD) or 8 (γ-CD). The 'top' perimeter of the torus is lined with the primary hydroxy groups (at C-6 of the sugar units) whereas the wider 'bottom' is ringed by the secondary hydroxy groups (at C-2 and C-3 of the sugar units). The height of the CDs is in the range 9–10 Å, whereas a recent statistical analysis of solid-state structures of cyclodextrins gave 4.88, 5.68 and 6.49 Å as mean values for the distance from the CD macrocycle centroid to the glucose centroid.[5]

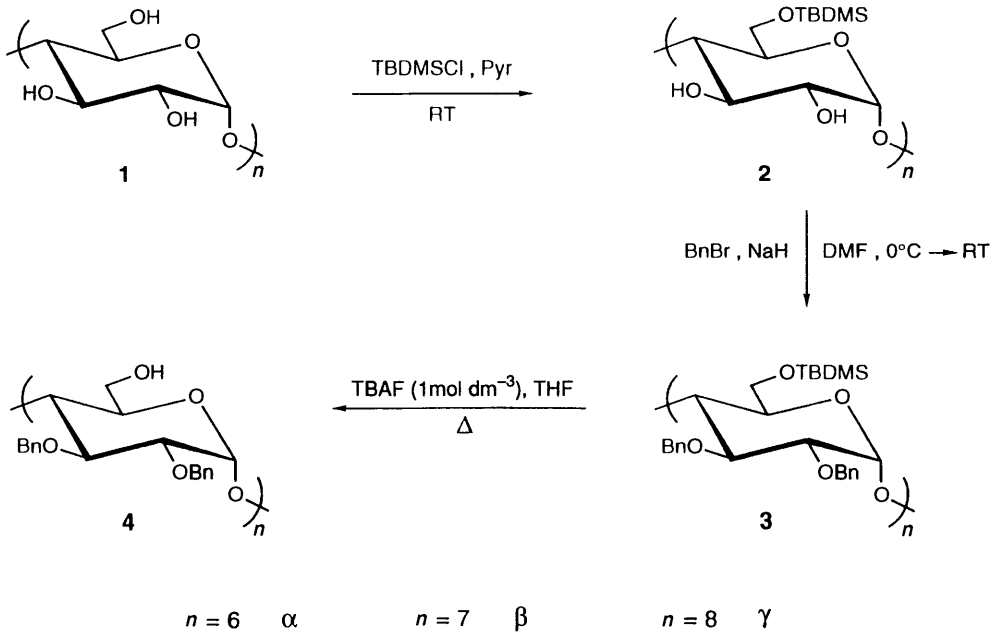
At the time we started to synthesize perfunctionalized β-cyclodextrins (1988), only one publication had mentioned the unexpected loss of symmetry occurring on the NMR timescale in some α-CD derivatives.[7] However, it was 14 years after this first report that a detailed investigation of the abnormal conformational behaviour of the previously examined compound was published.[8] Unfortunately, a satisfactory, complete picture explaining the observations could not be drawn and these authors concluded that 'Indeed, in the fullness of time, it might transpire that the parent CDs and simple CD derivatives with their rigid, well-defined cavities will be the exceptional compounds.' Our group reported in 1992 evidence for a conformational equilibrium occurring in β-CD series.[3a] Exploring a totally different family of β-CD derivatives, we unexpectedly encountered once again the above mentioned conformational behaviour. Both these observations led us to examine the nature of this conformational isomerism.

Results

Evidence for a Conformational Equilibrium.—When any CD perfunctionalization takes place satisfactorily, CD symmetry is normally preserved and NMR characterization is generally easy; otherwise, loss of symmetry gives very complicated NMR spectra the interpretation of which presents many difficulties. During the preparation of water-soluble cyclodextrins carrying naphthoyl units regularly disposed either on the primary or on the secondary CD rims, we synthesized several compounds by reaction of 2-substituted 6-naphthoic acids with the per-2,3-di-*O*-benzyl-β-CD **4β** and then on the corresponding α- and γ-CD **4α** and **4γ**. The per-2,3-di-*O*-benzyl-β- and γ-CDs **4β** and **4γ** were synthesized according to the procedure described for the α derivative **4α** (Scheme 1).[10] It involves (*i*) the protection of the CD 6-positions by silylation with *tert*-butyl(dimethyl)silyl chloride (TBDMSCl) in β- and γ-CDs **1β** and **1γ** to give **2β**[11,12] and **2γ**;[11] (*ii*) the benzylation of all the 2- and 3-hydroxy groups to yield **3β** and **3γ**; (*iii*) the removal of the protecting silyl groups finally to afford **4β** and **4γ**. Acylation of the per-2,3-di-*O*-benzyl-CDs was done by reaction with the appropriate acid under classical conditions. From our previous observations, it was expected that the acylation would take place easily, whatever the condensation conditions, either acyl chloride–pyridine or acid–DCC–DMAP§ combinations. Reaction between 2-methoxy-6-naphthoic acid[13] and per-2,3-di-*O*-benzyl-β-CD **4β** was investigated first. After classical DCC–DMAP treatment, the first eluted cyclodextrin fraction during purification by preparative TLC gave the ^{1}H NMR spectrum in $CDCl_3$ presented in Fig. 1(*a*). The rather complicated pattern suggested, at first glance, that perfunctionalization had not been achieved and this fraction was consequently treated once

* Cyclomaltoheptaose.
† Cyclomaltohexaose.
‡ Cyclomaltooctaose.

§ Dicyclohexylcarbodiimide–dimethylaminopyridine.



Scheme 1

more using the same conditions. After purification, the 'compound' isolated exhibited exactly the same R_f value by TLC and the same NMR spectra as above. This acylation was done independently using different conditions (treatment with 2-methoxy-6-napthoyl chloride in pyridine at 70 °C overnight). Once more, the same 'compound' was isolated. Careful examination of the complicated ^{1}H NMR spectra indicated that several signals [marked with an asterisk in Fig. 1(*a*)] could have arisen from the expected symmetrically substituted β-cyclodextrin. The ^{13}C NMR spectrum of the 'compound' in $CDCl_3$ [Fig. 1(*b*)] confirmed this assumption. Indeed, the number of the largest peaks in each chemical shift region corresponded to that expected for a symmetrically substituted β-cyclodextrin. Closer examination of the ^{13}C NMR spectrum in the region of the cyclodextrin carbon C-1 was very instructive [see the spectrum expansion in Fig. 1(*b*)]. A distinct series of seven small peaks of equal intensity was seen around the largest signal expected to be C-1 of the symmetrical form. As there are seven glucose units in the β-cyclodextrin torus, this pattern of peaks strongly indicated that the isolated fraction was indeed a mixture of *at least** two β-cyclodextrins: (*i*) the symmetrical perfunctionalized form and (*ii*) an asymmetric form. The mixture was analysed by elemental analysis and electrospray mass spectrometry. The results were in agreement with the expected molecular formula $(C_{32}H_{30}O_7)_7$ at least 95% pure. Consequently, as reaction conditions used to synthesize this mixture were far from drastic, it seemed reasonable to suppose that no CD backbone rearrangement had occurred during the acylation reaction and that both mixture components were isomers. The nature of this isomerism was clarified by a series of experiments.

(*a*) Hydrogenolysis of the mixture was performed to cleave the 14 protecting benzyl groups on the CD secondary face. The crude product of this reaction gave a well-defined spot on TLC and its ^{1}H and ^{13}C NMR spectra exhibited the typical pattern expected for the symmetrical per-6-(2-methoxy-6-naphthoate) β-cyclodextrin derivative. Thus, both isomers gave the same product after hydrogenolysis.

(*b*) It was possible to find a convenient eluting system to resolve the mixture by TLC and observe directly two distinct spots on the analytical plates (silica; benzene–EtOAc 9:1). Nevertheless, it was impossible to achieve the separation or any enrichment on a preparative scale. This suggested the existence of a slow equilibrium between both isomers. This was checked by 2D-TLC. After elution in two perpendicular directions, a spot put in a corner of a small square plate evolved four clear spots when enough time (4 h under a saturated atmosphere of benzene) had elapsed between both elutions. Existence of an equilibrium between both isomers was therefore clearly demonstrated.

(*c*) The ^{1}H NMR spectrum of the mixture of isomers in $C_2D_2Cl_4$ recorded under ambient conditions gave a pattern similar to that obtained in $CDCl_3$. Warming the solution to 413 K led to a broadening and a simplification of the spectrum consistent with the beginning of a coalescence phenomenon. Cooling the mixture to room temperature afforded a spectrum identical with that recorded before the high-temperature spectrum.

It was concluded from these observations that the components of the mixture were actually two conformers of per-2,3-di-*O*-benzyl-per-6-*O*-(2-methoxy-6-naphthoyl)-β-cyclodextrin **28**β in slow equilibrium at room temperature (Scheme 5, see later). Relative areas of ^{1}H NMR signals arising from both conformers were measured to determine the equilibrium constant. The 1-H and the methoxy group of the naphthoyl units were the most suitable signals because they can easily be identified for both symmetrical and unsymmetrical forms. In $CDCl_3$ at room temperature, the equilibrium constant K_T ($CDCl_3$) for eqn. (1) was estimated to be 0.86 ± 0.04 corresponding to a standard Gibbs free energy difference ΔG°_{295} ($CDCl_3$) equal to 0.4 ± 0.1 kJ mol^{-1}.

symmetrical conformer s $\rightleftharpoons$ unsymmetrical conformer u

$$K_T(CDCl_3) = [u]/[s] \quad (1)$$

This series of experiments showed that **28**β exhibits conformational behaviour consistent with a large degree of flexibility in the β-CD ring in $CDCl_3$ at room temperature and exists as a mixture of at least two conformers in identical amounts. Nevertheless, the energy barrier between these

* Indeed, any supplementary unsymmetrical form which should be present as a minor (less than 5%) component of the mixture would be extremely difficult to detect and it is therefore impossible to assert that there are no other species present. In the following text, only two species will be considered.

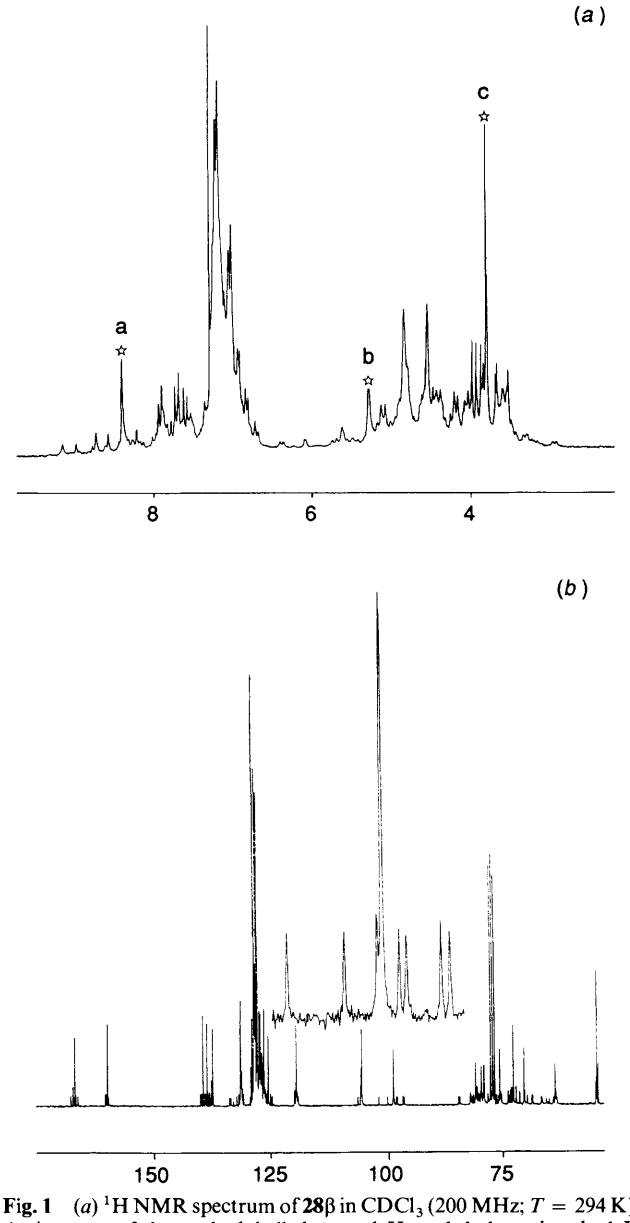


Fig. 1 (*a*) ^{1}H NMR spectrum of **28**β in $CDCl_3$ (200 MHz; T = 294 K). Assignment of the peaks labelled ☆: a, 1-H naphthalene ring; b, 1-H glucose ring; c, MeO naphthalene ring; (*b*) ^{13}C NMR spectrum of **28**β in $CDCl_3$ (75 MHz; T = 294 K) with an expansion of the 100 ppm region.

conformers is high. Such conformational behaviour has already been observed in the B_{CD} *bouquet* series based on **29**.[3a] Thus, NMR experiments showed that the complicated patterns obtained for **29** in [$^2H_5$]pyridine at room temperature were simplified by coalescence around 363 K. Furthermore, our observations were consistent with those reported for the per-2,3-benzoyl-α-CD.[8] According to these authors, this α-CD exists in solution either as a symmetrical C_6 form, a less symmetrical C_3 form or as a mixture of both. The value observed for the interconversion barrier was also found to be high (81 kJ mol^{-1}).[8]

Solvents exert a strong influence on the observed conformational equilibrium which is revealed dramatically by the ^{1}H NMR spectra. The effect of a solvent change on the equilibrium constant K_{295} was investigated for the per-2,3-di-*O*-benzyl-per-6-*O*-(2-methoxy-6-napthoyl)-β-CD **28**β. Solvents of very different polarity were examined (Table 1). Although the displacement of conformational equilibria gives spectacular changes in the ^{1}H NMR spectra, the corresponding standard

Table 1 Equilibrium constants K_{295} and Gibbs free-energy differences $\Delta G°_{295}$ for the interconversion: sym ⇌ unsym between symmetrical and unsymmetrical conformers of **28**β in several solvents at 295 K as estimated by ^{1}H NMR spectroscopy (see the Experimental section)

Solvent	K_{295}	$\Delta G°_{295}$/kJ mol^{-1}
CD_2Cl_2	0.53 ± 0.02	1.6 ± 0.1
[$^2H_8$]THF	0.73 ± 0.02	0.8 ± 0.1
$C_2D_2Cl_4$	0.83 ± 0.03	0.5 ± 0.1
$CDCl_3$	0.86 ± 0.04	0.4 ± 0.1
C_6D_6	0.89 ± 0.04	0.3 ± 0.1
CCl_4	1.28 ± 0.02	−0.6 ± 0.1
CS_2	2.50 ± 0.20	−2.2 ± 0.2
[$^2H_6$]DMSO	2.50 ± 0.20	−2.2 ± 0.2
$CDCl_3$–$CF_2ClCFCl_2$ 1:3	3.60 ± 0.30	−3.1 ± 0.3
CD_3COCD_3	5.1 ± 0.5	−4.0 ± 0.3

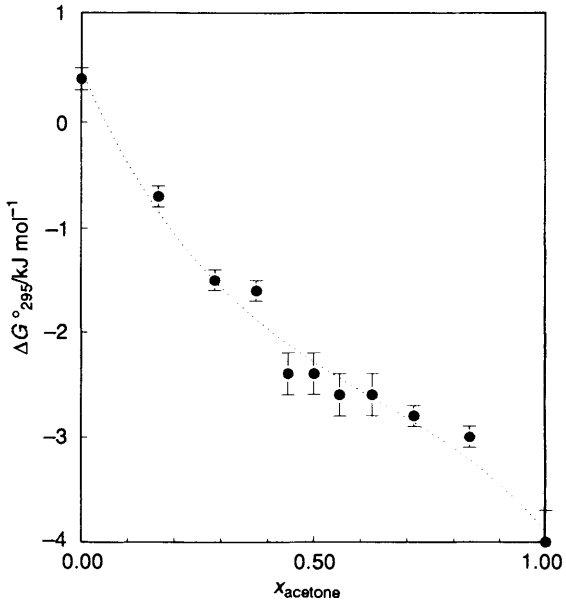


Fig. 2 Variation of $\Delta G°_{294}$ as a function of the mole fraction of acetone in mixtures of $CDCl_3$ and CD_3COCD_3

Gibbs free-energy differences $\Delta G°_{295}$ remain to within a few kJ mol^{-1}. This means that (*i*) the free enthalpies of both conformers are rather similar whatever the external conditions and (*ii*) the conformational equilibrium is not very sensitive to the nature of the solvent. The evolution of $\Delta G°_{295}$ in mixtures of $CDCl_3$ and [$^2H_6$]acetone was found to be non-ideal (Fig. 2) and did not follow the $E_T(30)$ evolution.[14,16]

Experiments were carried out to examine whether solvents also exert a strong influence on the height of the energy barrier between the two conformers. As coalescence between ^{1}H NMR signals occurred at too high a temperature in **28**β, we synthesized some other β-CDs to permit this study in several solvents. The per-2,3-di-*O*-benzyl-6-*O*-benzoyl-β-CD **30** obtained from reaction between benzoic acid and **4**β was thus a convenient substrate (Scheme 5, see later). At room temperature, its ^{1}H NMR spectra exhibits broadened signals [Fig. 3(*a*) and 3(*b*)]. To verify that the broadening of NMR signals arose from a coalescence phenomenon, an investigation at low and high temperature was done. Fig. 3(*a*) presents the evolution of the ^{1}H NMR spectrum of **30** in CD_2Cl_2 at decreasing temperatures. It is consistent with an exchange taking place, the rate of which gradually decreased as the temperature decreased. The spectrum recorded at 203 K is analogous to that of the naphthoyl derivative **28**β in [$^2H_6$]acetone at room temperature [*cf.* Fig. 1(*a*) and Fig. 3(*a*)] and it seems reasonable to suppose that the nature of exchange is the same in both cases, *i.e.*, interconversion between two conformers. A solution of **30** in

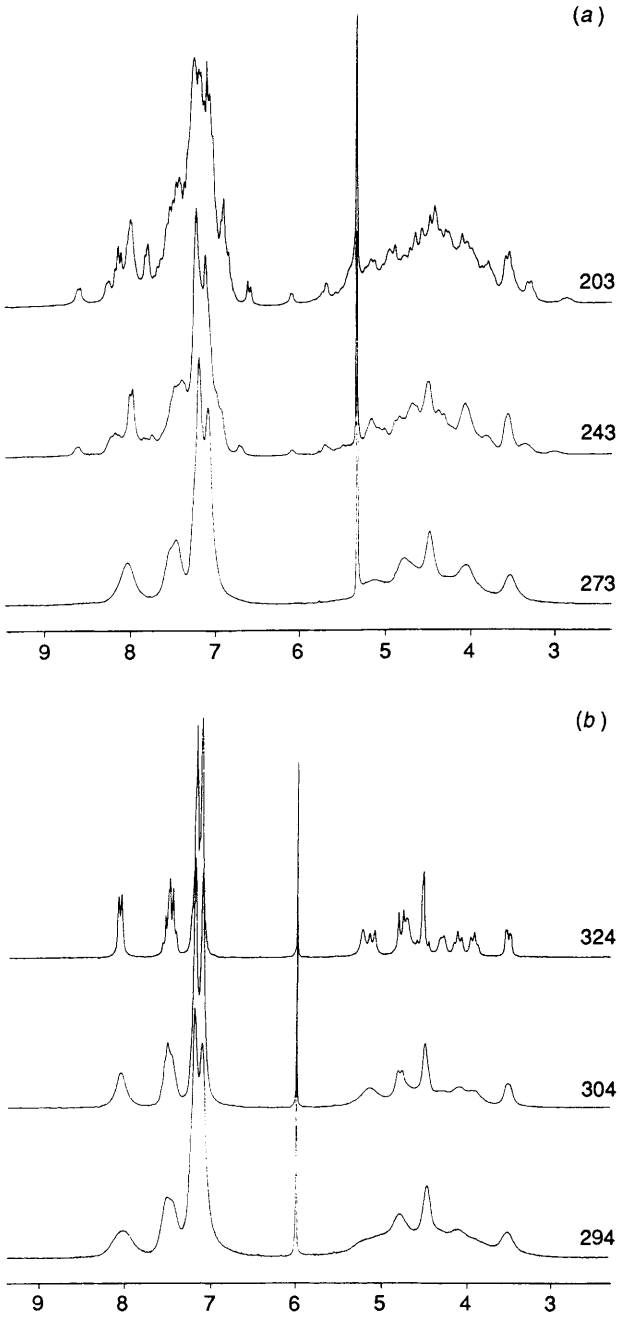


Fig. 3 ^{1}H NMR spectra of the per-2,3-di-*O*-benzyl-6-*O*-benzoyl-β-CD **30** recorded at several temperatures in CD_2Cl_2 (*a*) and in $C_2D_2Cl_4$ (*b*)

$C_2D_2Cl_4$ was then warmed. At 304 K, the broadened peaks seen at 294 K became narrower and at 324 K, the ^{1}H NMR spectrum conformed to a symmetrical perfunctionalized β-CD. The same experiment was done in [$^2H_6$]acetone and displayed patterns conforming both qualitatively and quantitatively to those observed in CD_2Cl_2 and in $C_2D_2Cl_4$.

Investigation of the Conformational Isomerism of β-CD Derivatives.—Such similarity of conformational behaviour in totally different CD series and in different solvents was intriguing and we decided to analyse the factors inducing this phenomenon through both spectroscopic and synthetic studies. Two complementary approaches were followed to determine the nature of the conformational isomerism occurring in our β-CD derivatives. Spectroscopic investigations (NMR, circular dichroism) were carried out in order to analyse the nature of the isomerism present in **28**β and will be published elsewhere. At the same time, synthetic studies were performed in two directions. The first (*a*) analysed the consequences of changes in the CD macrocycle size, all other things remaining equal, after synthesis of α-, β-, γ-CD homologues. The second approach (*b*) examined the significance of the perturbations on the conformational behaviour induced by changes of structural elements in the β-CD derivatives. Furthermore, we hoped to determine from the synthetic studies which persubstituted CD series would exhibit such a conformational equilibrium.

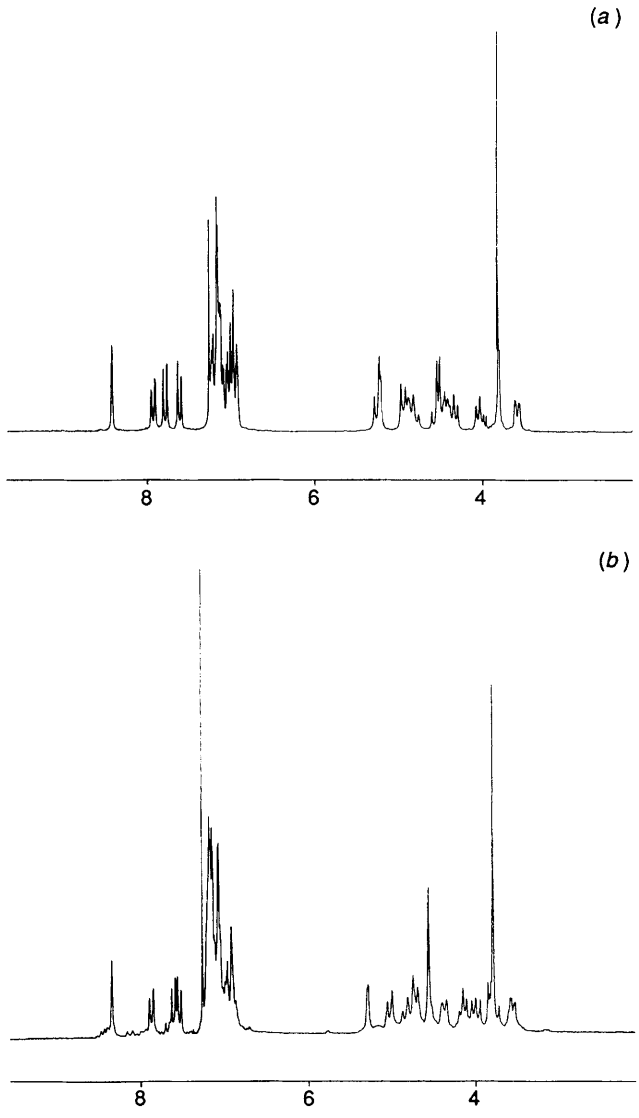


Fig. 4 ^{1}H NMR spectrum of **28**α (*a*) and **28**γ (*b*) in $CDCl_3$ (200 MHz; T = 294 K)

(*a*) The series of compounds resulting from condensations of 2-methoxy-6-naphthoic acid with the per-2,3-di-*O*-benzyl-CDs was chosen to evaluate the significance of the CD diameter. The synthesis of the α and γ derivatives was achieved and the resulting reaction products **28**α and **28**γ (Scheme 5) were characterized by TLC, NMR, elemental microanalysis and electrospray mass spectrometry to be > 95% pure. **28**α, **28**β and **28**γ gave a complete series of molecules with which to check the significance of internal CD volume on conformational properties (Table 2). Unlike the β-CD derivative, none of the new compounds **28**α and **28**γ displayed two spots on TLC. Fig. 4(*a*) and 4(*b*) show the ^{1}H NMR spectra of the α- and γ-CD derivatives in $CDCl_3$ at room temperature. As far as NMR can be used to detect any unsymmetrical form, the α-CD **28**α exists only in symmetrical form at room temperature in $CDCl_3$. Like the β-CD analogue, the γ-CD **28**γ does give a mixture of

Table 2 Proportions of symmetrical and unsymmetrical forms of **28α**, **28β** and **28γ** at room temperature in $CDCl_3$ as analysed by ^1H NMR spectroscopy

Compound	Symmetrical form (%)	Unsymmetrical form (%)	$\Delta G^{\circ}_{295}(CDCl_3)$/ kJ mol^{-1}
28α	>95	<5	>7.2
28β	55	45	0.4 ± 0.1
28γ	55	45	0.4 ± 0.1

conformers, the symmetrical form being the most abundant component. Closer examination of the ^1H NMR spectrum of **28γ** did not show any clear indication that conformational equilibrium in this derivative would involve any form of lower order of symmetry (either 4 or 2) besides the C_8 conformer. Moreover, the strong similarity that exists between the NMR spectra of the homologues **28β** and **28γ** suggests that the unsymmetrical conformer is of C_1 symmetry. Table 2 analyses the results. It is notable that the β-CD and the γ-CD exhibit the same proportion of unsymmetrical form. The temperature coalescence in $C_2D_2Cl_4$ of the signals for the γ-CD derivative **28γ** was estimated to be much lower than for the β-CD homologue (363 K instead of 413 K).

(*b*) The significance of structural elements in the β-CD series was then investigated. We examined first the results of modifications made at the sugar 6-position, the glucose 2- and 3-positions remaining benzylated. Secondly, we examined the significance of steric hindrance on the secondary face upon removal of the benzyl protecting groups.

Keeping secondary β-CD face constant (2,3-di-*O*-benzyl), we changed either the nature of the function or the nature of the acid which was used to obtain esters borne on all the 6-positions of the molecules. During the synthesis performed in the course of this work, several differently per-6-functionalized per-2,3-di-*O*-benzyl derivatives were obtained and their ^1H NMR in $CDCl_3$ at room or at low temperature were recorded. The per-6-deoxy-per-6-azido-per-2,3-di-*O*-benzyl-β CD **34** was obtained by benzylation of the per-6-azido-β-CD.[18] The per-6-acetyl-per-2,3-di-*O*-benzyl-β-CD **31** was synthesized according to the procedure described for the α-derivative[19] and kindly provided by the reference authors. The per-2,3,6-tri-*O*-benzyl-β-cyclodextrin **35** was prepared as described.[20] Table 3(*a*) sums up the results. None of these derivatives gave any trace of an unsymmetrical form at room temperature in $CDCl_3$. This is especially amazing in the case of **4α**, **4β** and **4γ**. In contrast with what was observed in the per-2,3-dibenzoyl-α-CD series,[8] none of the per-2,3-dibenzyl-6-hydroxy-CDs gave a conformational equilibrium at room temperature. Furthermore, this absence in the case of the per-6-*O*-acetyl or per-6-*O*-benzoyl derivatives **31** and **30** shows that introduction of an ester in the sugar 6-position is not a sufficient constraint for a conformational equilibrium to be observed. On the other hand, at 183 K, the per-6-*O*-benzoyl derivative exhibits a slow conformational equilibrium in [$^2H_6$]acetone. Interestingly, the spectrum of the corresponding per-6-*O*-benzyl derivative **35** is in agreement either with a rapid exchange or with the presence of only one conformer under the same conditions. The difference in structure between both compounds being rather small, this shows how sensitive the conformational behaviour is to structural features.

As the results in the series of homologues **28α**, **28β** and **28γ** strongly support the involvement of the available internal free volume in the observation of the conformational equilibrium, the significance of steric hindrance on the CD primary face was examined in the per-6-*O*-acyl-per-2,3-di-*O*-benzyl-β-CD series. Reactions of **4β** with acids of increasing bulk and/or rigidity were performed. The per-6-*O*-acetyl derivative **31** is the smallest of the acylated CDs. The per-6-dodecyl-β-CD **32** was considered as an example of molecule with a flexible substituent of moderate bulk. Benzoyl-6-substituted 2-naphthoyl and 4′-(benzyloxycarbonyl)biphenyl-4-carbonyl groups were then chosen as rigid units in the range of the internal volume size. Among the naphthoyl series, the effect of the introduction of bulky groups at variable distances from the naphthalene unit was examined. A trityl group was introduced at a large distance from the naphthalene core. The linking unit bearing the trityl group **7** was readily obtained from the reaction of the 2-(2-chloroethoxy)ethanol **5** with trityl chloride to give **6**, followed by halogen exchange. **17** was obtained by *O*-alkylation with the iodide **7**, under classical conditions, of the allyl ester **15** which in turn was obtained by allylation[21] of the corresponding carboxy naphthol **14**[13] (Scheme 2). Removal of the allyl group was eventually achieved to afford **21**.[22] Two analogues **22** and **23** bearing the less hindered methyl and benzyl groups at the end of a triethyleneglycol spacer were synthesized according to a similar procedure. 6-TBDMS-2-naphthoic acid **20** was synthesized by reaction of TBDMSCl on the naphthoate **15** followed by allyl deprotection (Scheme 3). 4′-(Benzyloxycarbonyl)biphenyl-4-carboxylic acid **25** was synthesized by monoesterification of the commercially available 4,4′-biphenyldicarboxylic acid **24**.[23] Finally, we designed a substituent, **27**, bearing a tetraphenyl unit at a short distance from the carboxy anchoring unit to be the bulkiest of the series. It was synthesized from the reaction of 4-tritylphenol **26** on sodium chloroacetate

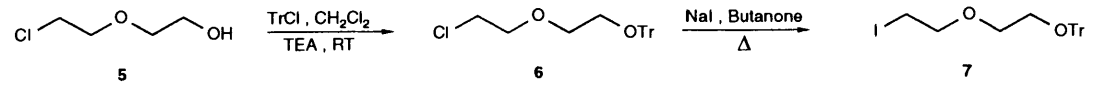
Table 3 (*a*) Proportions of symmetrical and unsymmetrical forms of several per-6-substituted β-CDs as analysed by ^1H NMR spectroscopy

X	Solvent	*T*/°C	Unsymmetrical form (%)	Symmetrical form (%)
3β	$CDCl_3$	23	<5[a]	>95
4β	$CDCl_3$	23	<5[a]	>95
30	$CDCl_3$	23	<5[a]	>95
30	CD_2Cl_2	−70	70	30
30	CD_3COCD_3	23	<5[a]	>95
30	CD_3COCD_3	−70	90	10
31	$CDCl_3$	23	<5[a]	>95
34	$CDCl_3$	23	<5[a]	>95
35	$CDCl_3$	23	<5[a]	>95
35	CD_3COCD_3	23	<5[a]	>95
35	CD_3COCD_3	−70	<5[a,b]	>95[b]

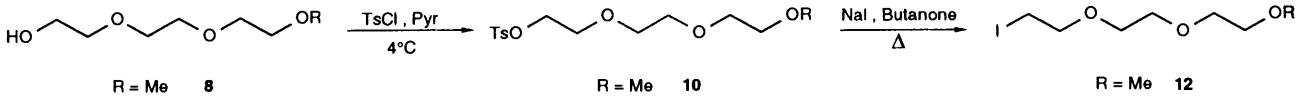
(*b*) Proportions of symmetrical and unsymmetrical forms of several per-6-acylated β-CDs at room temperature in $CDCl_3$ as analysed by ^1H NMR spectroscopy

X	Unsymmetrical form (%)	Symmetrical form (%)
28β	45	55
30	<5[a]	>95
31	<5[a]	>95
32	<5[a]	>95
33	40	60
37	40	60
38	40	60
39	<5[a]	>95

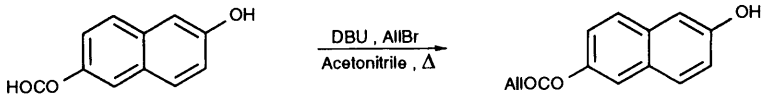
[a] Under the limit of detection. [b] Weak broadening of the signals.



5 6 7



R = Me 8
R = Bn 9
R = Me 10
R = Bn 11
R = Me 12
R = Bn 13



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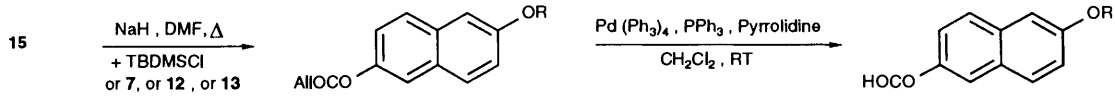
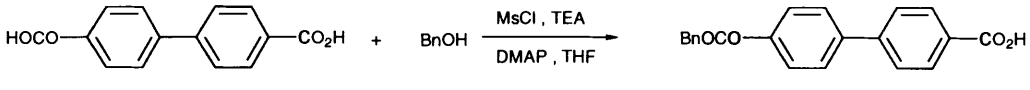
Scheme 2

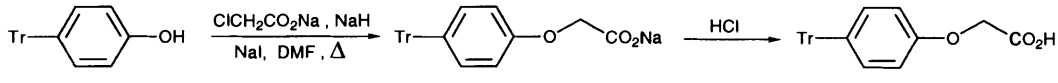


R = TBDMS 16 , 20
R = OTr 7 , 17 , 21
R = OMe 12 , 18 , 22
R = OBn 13 , 19 , 23

Scheme 3



24 25



26 27

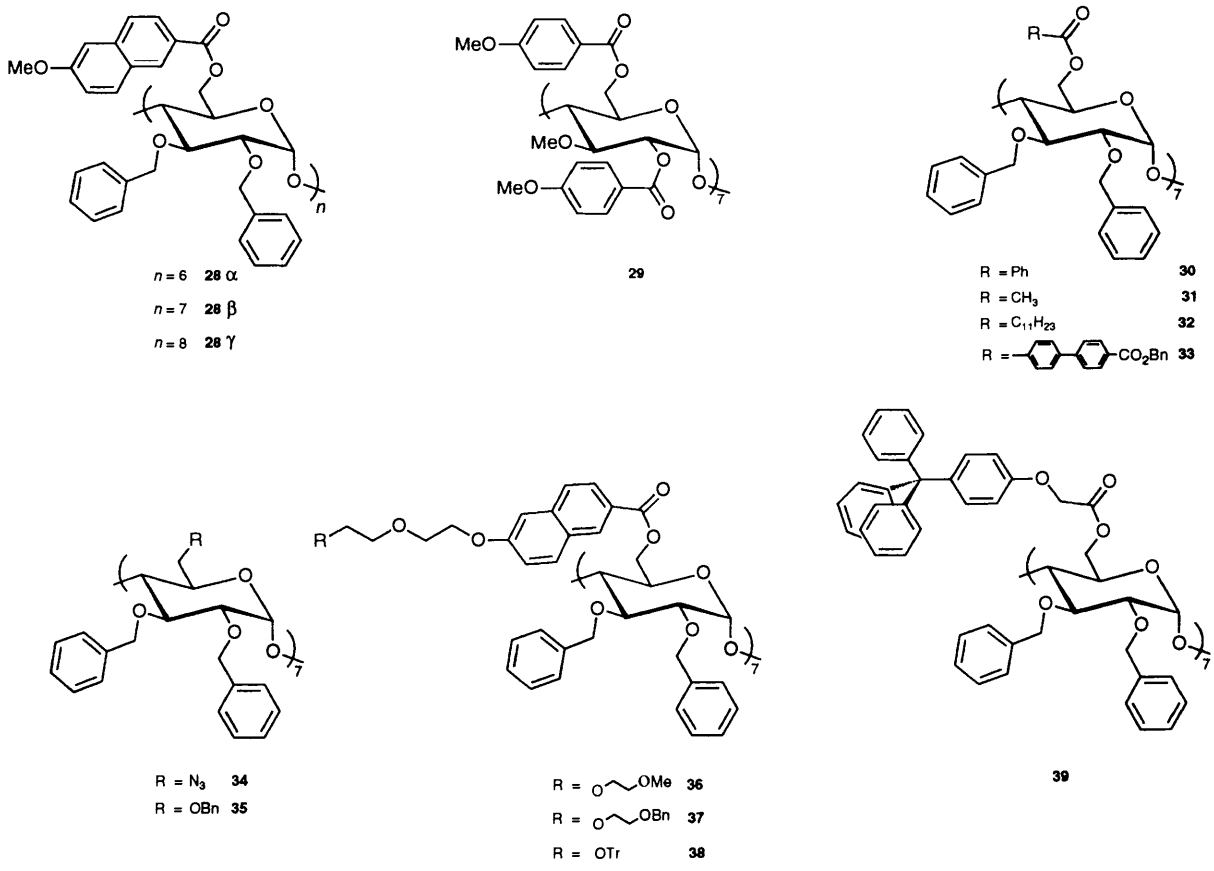
Scheme 4

followed by a neutralization (Scheme 4). Condensations of all these acids on the per-2,3-di-*O*-benzyl-β-CD yielded the corresponding substituted CDs, the ^1H NMR spectra of which were recorded in $CDCl_3$ at room temperature [Table 2(*b*)]. Several notable observations were made.

Among all the derivatives at position 6 which were investigated, only the naphthoate **28**α, **28**β, **28**γ, **36**, **37**, **38** and the biphenyl **33** esters exhibited 'abnormal' conformational behaviour. Interestingly, none of the derivatives bearing either small and mobile (acetyl **31**, dodecyl **32**) or bulky (**39**) groups on position 6 displayed unsymmetrical forms. Such bell-shaped behaviour is, once more, in agreement with the involvement of the free internal CD volume in the conformational equilibrium. Only those CDs carrying substituents whose size is related to the CD cavity volume display a conformational equilibrium at room temperature.

Comparison between benzoyl **30** and biphenyl carbonyl **33** molecules is quite interesting. Both substituents have the same local steric hindrance near the anchoring acyl group but only **33** exhibits conformational isomerism, suggesting that this isomerism is sensitive to steric hindrance at large distance if the substituent is rigid. This result is surprising if we compare it with the entries **36**, **37**, **38** of Table 3(*b*) which suggest that the position of the conformational equilibrium does not depend on steric hindrance at the linker extremity if the linker is flexible.

The inability to obtain the perester by reaction of 6-

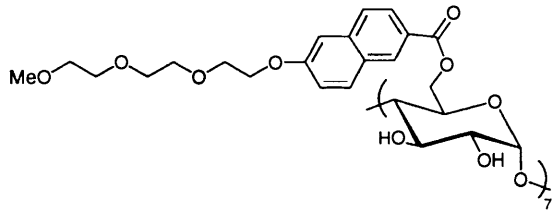


Scheme 5

TBDMS-2-naphthoic acid **20** and 4β was unexpected. We cannot exclude the possibility that its sensitivity precluded its isolation. Nevertheless, it is also possible that this compound cannot be obtained using the synthetic conditions employed: behaviour that would be quite singular.

We finally determined whether the presence of a belt of benzyl groups on the secondary face was necessary to observe the conformational equilibrium so as to ascertain the significance of steric hindrance on the secondary CD face. Removal of the benzyl protecting groups in **36** by catalytic hydrogenation afforded **40** which displayed, in $CDCl_3$ or in [$^2H_6$]acetone at room temperature, the expected ^1H NMR spectrum for a symmetrically substituted β-CD. The signals were broadened and the broadening takes place to a greater extent in [$^2H_6$]-acetone than in $CDCl_3$. Clearly, the removal of the benzyl groups strongly affects the conformational equilibrium. In order to examine whether this change was due to an increase in the exchange rate between the conformers or to a large prevalence of one conformer over the other, low temperature ^1H NMR experiments were carried out. Even at 203 K, when **40** begins to precipitate in [$^2H_6$]acetone, the signals are in agreement with a symmetrically substituted form, albeit being broadened due to the precipitation. It therefore seems reasonable to suppose that the free energy of the symmetrical conformer is much lower than that of the unsymmetrical one when the benzyl belt on the secondary face is absent.

Finally, as all synthetic studies strongly implicated the involvement of the molecular internal volume in the CD conformational behaviour, we tried to investigate how solutes might influence the ratio of CD conformers in **28**β with the hope that internal conformers should be displaced upon addition of convenient solutes (competition experiments). Adamantane and 2-methylnaphthalene were chosen because of the ability of adamantane and 2-substituted naphthalene derivatives to give



40

host–guest compounds with the native β-CD.[24] Even in presence of a hundredfold molar excess in [$^2H_6$]acetone at room temperature, no change in conformational behaviour was observed. This result is actually not really surprising as modification of the nature of solvent has already been shown not strongly to affect the CD conformational behaviour. Moreover, the enthalpic contribution to solute complexation is expected to be small in such organic solvents and in the same range as that of the intramolecular competing naphthoate when the entropic term probably favours 'autosolvation' or 'autocomplexation'.

Discussion

It is quite usual to consider cyclodextrins as possessing a rigid macrocyclic backbone. This has yielded the classical picture of truncated cones of high symmetry. In fact, this view does not take into account numerous experimental observations[3a,7,8] and theoretical calculations[9,25] which have been made over the last few years, especially on functionalized CD derivatives. Nevertheless, direct observation of conformational isomerism

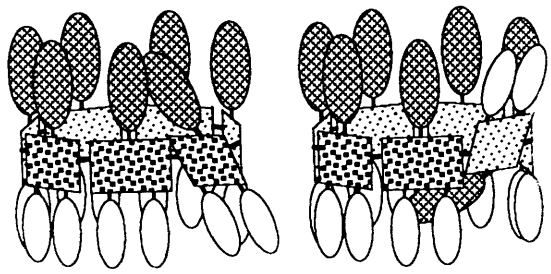


Fig. 5 β-CD conformational isomers resulting from alteration of the relative orientation of the D-glucopyranoside rings. One of the CD primary rim substituents points either upwards (*a*) or down (*b*) into the molecule interior.

in CD series remains quite marginal and unclear. Previous studies and our present results indicate that this behaviour is in fact probably less unusual than was previously thought taking into account the conditions of experiments. Two questions need to be addressed. What is the nature of the conformers in equilibrium? Is it possible to foresee whether an unknown CD derivative will exhibit any conformational isomerism? This question is especially important as far as characterization of new CDs is concerned.

Flexibility of the CD macrocycle increases the number of conformational isomerisms that should, *a priori*, exist in such a molecule. Three different possibilities of isomerism can be considered: (*i*) conformers can exist at the level of the glucose unit through $^4C_1 \rightleftharpoons {}^1C_4$ interconversion; (*ii*) conformational isomerism can result from alteration of the relative orientation of the D-glucopyranose rings; (*iii*) conformational isomerism may affect the CD torus itself (collapse of internal CD cavity or chiral twist of CD torus for instance). In case (*ii*), two possibilities can be envisaged according to the naphthoyl orientations in the unsymmetrical form. In the first one, alteration of the glucose orientation yields a compact cluster of naphthoyl groups [Fig. 5(*a*)]. In the second, one napthoyl group points downwards and the others upwards giving a sort of 'self-satisfied' form [Fig. 5(*b*)].

The strong similarity in free energy of both conformers speaks strongly against the $^4C_1 \rightleftharpoons {}^1C_4$ hypothesis to explain the conformational isomerism. Firstly, molecular dynamics calculations suggest that the energy cost of such an interconversion would be high. Secondly, the small structural difference between the benzoate and the 2-methoxynapthoate groups would not account for the dramatic change in the energy barrier according to such a mechanism. Similarly, a deformation of the CD torus would not readily account for the dramatic changes associated with slight structural variations of the substituents. These considerations led us to examine an explanation based on an alteration of relative orientations of the D-glucopyranoside rings, as has already been done in previous papers.[7,8] The final issue is thus to determine how the glucopyranoside rings are oriented, the organization of the substituents on the primary rim and the driving force for this abnormal conformational isomerism.

The 'Self-satisfaction' Model.—Figs. 5(*a*) and 5(*b*) show two possible organizations of the substituents on the primary rim. They differ in the orientation of one of the substituents on the primary CD rim, which points either into or outfrom the CD cavity. Experimental observations strongly suggest that Fig. 5(*b*) constitutes the most realistic picture of the unsymmetrical conformer of persubstituted CDs in our series. (*i*) The height of energy barrier between conformers could not be easily explained on the basis of Fig. 5(*a*) as only minor structural changes would be required to interconvert conformers; neither the loss of favourable Van der Waals interactions between substituents in unsymmetrical forms nor the small CD backbone rearrangements would cost more than 40 kJ mol.$^{-1}$. (*ii*) It seems that a 'scale' relating the CD and the 6-substituent is associated with the phenomenon of conformational isomerism; only substituents of appropriate size lead to isomerism and this size satisfactorily correlates with the CD cavity size (phenyl, naphthoyl groups in the β-CD derivatives). This observation is easily accounted for on the basis of the picture presented in Fig. 5(*b*). If the 6-CD substituent is small* enough, it will easily move into the large surrounding free volume a process that would be fast as it is smaller. As the bulk of the 6-CD substituent is progressively increased, the available internal space is reduced and the exchange rate between forms with a primary substituent located inside or outside the molecular cavity will decrease because of the higher energy barrier for interconverting internal and external forms. As the substituent size is further increased, it finally cannot be accommodated within the CD interior and thus moves only into the external space. (*iii*) The significance of linker flexibility in the naphthoyl series also indicates the role of the cavity in the conformational isomerism; the decrease in the exchange rate between conformers when the 6-substituent is elongated at constant substituent rigidity (phenyl to biphenyl for instance) is especially satisfying and would not be explainable on the basis of Fig. 5(*a*). (*iv*) Eventually, even if the flexibility of the CD torus does increase with the cavity size, structural parameters such as torsion angles or relative orientation of the glucose units along the CD torus remain comparable in all CDs. It therefore seems reasonable to suppose that it is the absence of a sufficiently large internal molecular free volume resulting from the existence of the CD cavity which forbids the existence of an unsymmetrical conformer in the α-CD derivative **28**α. In both other cases (β- and γ-CD derivatives: **28**β and **28**γ), the largest CD internal volume would accommodate at least one rim substituent and the compounds could therefore display unsymmetrical conformers. The difference in coalescence temperature for **28**β and **28**γ would also be in agreement with such an explanation. Indeed, even if it is difficult quantitatively to compare the energies of activation of the interconversion process because estimation of the width of signal splitting is impossible, one may suppose that the lower coalescence temperature in the γ-derivative suggests a lower energy. This would be in line with the lower steric hindrance expected to occur in this larger homologue.

Therefore, it seems highly probable that the nature of conformational isomerism occurring in our β-CD series is conveniently described by an equilibrium between a mean symmetrical form where all 6-substituents are disposed on the outer side of the primary CD rim and a form where one of the 6-substituents is located inside the CD cavity as pictured in Fig. 5(*b*).† Such conformational behaviour has also been investigated in the calixarene series.[29] Further investigations based on NMR spectroscopy and circular dichroism are underway in order to confirm this assumption.

* The words small and large are defined in comparison to the CD diameter which gives the scale.

† Recently, the X-ray structure of an inclusion complex of heptakis(2,6-di-*O*-methyl)-β-cyclodextrin was elucidated.[26] It is fully consistent with our scheme, especially as far as the naphthoyl orientation is concerned. Moreover, in a recently published X-ray structure, it was shown that a terephthaloyl unit included in a β-CD exhibited a tilt.[27] Such observations are consistent with the CNDO/2 semiempirical calculations on several CDs which foresee that complexed guests are tilted within the CD cavity.[28]

The Release of Steric Hindrance on the Secondary CD Face can Trigger the Loss of CD Symmetry.—Previous investigations have emphasized the significance of the hydroxy belt on the primary CD face to account for symmetry reduction in several solvents.[7,8] This feature may play a role in the balance of the conformational equilibrium, but represents just one of the numerous subtle parameters that influence CD conformations. Indeed, we have seen in the course of our work that even with no hydroxy groups present in CD derivatives, loss of symmetry may occur. Furthermore, the observations that very similar compounds (for instance perbenzyl **35** and perbenzoyl **30** CD derivatives) did not exhibit the same conformational behaviour suggests that the effective driving force of conformational changes probably results more from additions and cancellations of weak effects. The purpose of this discussion is to examine the significance of some structural parameters and to analyse the likely origins of conformational equilbria in such CD derivatives.

Cyclodextrins functionalized on one face, either primary or secondary, by convenient hydrophobic residues constitute series of amphiphiles the behaviour of which can be analysed by monolayer experiments.[30] On the assumption that the CD axis lies perpendicular to the water subphase in such systems and that the packing at high surface pressure is hexagonal, it is possible to measure the surface of the projection of the amphiphile into the water surface plane. Experiments performed on the per-2,3-di-*O*-benzyl-α-, -β- and -γ-CDs, **28**α, **28**β and **28**γ and on the per-6-*O*-2-naphthoyl-β-CD synthesized in the course of a previous work[4a] have shown that the surface corresponding to the secondary face bearing the benzyl groups exceeds by far that corresponding to the cyclodextrin torus or that corresponding to the persubstituted primary face.[31] That means that in **28**α, **28**β and **28**γ, at high surface pressure, there remain benzyl groups external to the CD core even when the internal CD void is closed by compressed benzyl residues. Moreover, the number of substituents on the secondary face is twice that on the primary face in all per-2,3-di-*O*-benzyl, per-6-*O*-acylated CDs but the area corresponding to the secondary rim is only about 1.2–1.5 times larger than that on the primary rim (based on measurements on CPK models). This suggests that in most if not all of the per-2,3-di-*O*-benzyl-CDs synthesized in the course of this work, the secondary face displays a larger steric hindrance than the primary one. Consequently, a release of steric congestion lowering the energy of the per-2,3-di-*O*-benzyl per-6-*O*-functionalized CDs would result from an increase of the mean distance between the benzyl groups, *i.e.*, an increase of the CD cone angle. It could therefore happen in some cases that the system reacts by loss of symmetry, several primary positions pointing inwards to a greater extent than in the symmetrical form [Figs. 5(*a*) and 5(*b*)]. In the case of the largest CDs, the release of steric hindrance on the secondary face would equilibrate the loss of energy associated with the torsions of the CD backbone and with the increase of steric hindrance on the primary face. Such a model would be in line with our observations. Without benzyl groups on the secondary face, we observed no conformational equilibrium at all, thus pointing to the significance of steric hindrance on the secondary face to the conformational isomerism. Furthermore, in the series of homologues **28**α, **28**β and **28**γ, only the α derivative **28**α exists as a pure symmetrical conformer. This would agree with the absence of a large enough cavity in the α-CD derivative **28**α to release the steric hindrance occurring on the secondary rim.

Significance of CD Functionalization to Abnormal Conformational Behaviour.—As a pure CD derivative exhibiting such conformational isomerism could easily be mistaken for an impure CD (and thus be discarded), it is important to try to give guidelines for deciding whether a given derivatized CD would *a priori* display conformational isomerism. Dramatic changes which were observed either by us or by others upon changing environmental parameters such as the solvent strongly suggest that these changes involve interactions with the medium and are not based solely on the intrinsic structure of the modified CDs. Nevertheless, from our synthetic studies, it appears that the major structural feature for observing, at room temperature, rather long-lived unsymmetrical conformers is the presence of a crown of *aromatic units of suitable size* linked to a *sterically hindered CD* through a functional group of restricted flexibility such as an *ester group*.

The significance of the aromatic units is related to two things not directly involving conformational properties: (*i*) the ability of CD to give inclusion complexes with aromatics[1,32] and (*ii*) the effects on complexation behaviour of several cyclophanes with solvent changes.[33] Cyclodextrin complexation with 2-naphthalene derivatives in water has been extensively investigated and is known to give 1:1 complexes.[24] Among the three classes of CD, β-CD is the best host, its cavity size probably being best fitted to the naphthalene structure. The free-energy changes associated with this complexation in water are to within a few kJ mol^{-1} at 293 K. Even if the solvents used during our investigations did not provide a driving force for complexation as large as that in water, one cannot exclude that such a sort of 'autocomplexation' is a contributing factor with the naphthalene substituents. Compared with intermolecular associations, such autocomplexation would not involve too large an entropic change arising from a decrease in translational and rotational terms and should thus occur more easily. Indeed, the use of fluorophore mono- or bi-functionalized CDs as sensors is based on equilibria between autocomplexed forms and guest complexation.[34] Solvent effects on the complexation of aromatic molecules by cyclophane-type molecules is well documented.[33] An increase in complex stability is generally expected to be observed when the 'polarity' of the solvent is increased. The free energy of complexation was shown in some cases to correlate well with empirical scales of solvent polarity such as the $E_T(30)$ scale.[14,33] Such an observation is explained in terms of solvophobic effects whose origin is linked to energy terms such as poor free energy of solvation of the empty host or cancellation of unfavourable solvation terms of the substrate. This influence of solvents on complexation ability led us to consider our persubstituted CDs not only as acylated CDs but also as *cyclophane-type structures borne on the CD rims*, the CD possibly playing a second role. In the case of these CDs, the solvophobic effect would result from the poor ability of solvent molecules to solvate the interior of the cylinder formed by the aromatic substituent organization or the CD core. The CDs would react by 'autosolvation' with their own mobile substituents, aromatic planes exhibiting a convenient affinity for both sites, thus leading to unsymmetrical conformers. Such a process is relevant to polymer behaviour in poor solvents.[35] None of the empirical polarity scales [*Z*, $E_T(30)$,[14] *etc.*] which were examined was able satisfactorily to account for the observed CD conformational behaviour. It is thus astonishing to see that non-polar solvents such as CS_2 or CCl_4 and polar solvents such as $(CD_3)_2SO$ or $(CD_3)_2CO$ cause similar conformational changes. Examination of the results on the basis of solvent cohesive pressures which should give insights into differences of molecular volume between conformers seems inappropriate.[15] Finally, no simple explanation related to molecular size of the solvent was found. In fact, owing to the complexity of the analysis of the factors which should contribute to the solvent effect on such a conformational equilibrium and to the small Gibbs free energy differences, which lie in the energy range for rotation around a single bond, one would hardly expect to arrive at a simple and definitive scheme for explaining the solvent effects. The evolution of

ΔG°_{295} in mixtures of $CDCl_3$ and [$^2H_6$]acetone was found to be non-ideal (Fig. 2) and did not follow the expected $E_T(30)$ evolution,[16] confirming the inadequacy of this parameter to describe this conformational equilibrium. This may result from preferential solvation of the solute which is strongly solute dependent.[17] Therefore, the specificity of the solvent effects remains to be clarified. Even these probably result from a combination of multiple properties such as shape or dipole moments since no solvent-scale parameter was able to account for the experimental observations. Such behaviour is also probably related to the complexation of neutral molecules by hollow rigid hosts which efficiently trap the guests in organic solvents whose molecular size and shape forbid suitable cavity solvation.[36,37] Complexation and/or structural adjustments would conform to the 'Nature abhors a vacuum' principle.

The role of steric hindrance has already been emphasized in the preceding paragraphs. It seems evident that it provides at least part of the driving force for the conformational isomerism.

A remarkable observation is the significance of the ester function. **30** and **35** differ only by the nature of the bridge linking the phenyl group to the CD 6-position. Nevertheless they exhibit very different conformational behaviour. Similarly, **4α** differs from the previously investigated per-2,3-di-*O*-benzoyl-α-CD[7,8] only by the nature of the link between the phenyl groups and the CD core (CH_2 instead of CO) but their conformational behaviour is very different. Whereas on the ^1H NMR timescale the carbonyl-containing molecules present a slow exchange between two conformers at low temperature, the methylene-containing ones exist either as unique species or as mean forms resulting from a rapid exchange between conformers. One could envisage the nature of the substituents exerting a direct influence on the glucopyranose ring conformation to explain the striking difference in behaviour.[38] However, since position 6 is not contained in the pyranose ring, such an explanation does not seem appropriate. Considered as static groups, benzoyl esters and benzyl ethers give rise to a similar degree of steric hindrance, the replacement of CH_2 by CO leading to almost no change in size. However, the dynamics of both groups are expected to be different. In the ester case, COO conjugation with the aromatic ring would tend to reduce the number of allowed motions and cause the movement of the aromatic plane to conform to that of the glucopyranoside ring to which it is linked to a greater extent than in the ether case.* The benzyl group contains the CH_2 unit which increases the mobility compared with the ester. This leads to a decoupling between both the motions and the orientations of the glucopyranoside ring and the aromatic plane and could account for the weaker ability of benzyl derivatives to undergo conformational isomerism.

Up to now, most of our molecular devices based on β-CD components display features which would effectively favour conformational isomerism.[3,4] This may explain some of our previous observations. Some photophysical measurements would be in line with existence of minor conformers in slow equilibrium with symmetrical β-CDs. Intramolecular 'complexation' of CD substituents would also partially explain the behaviour of CD-based bouquets which effectively transport cations, but at a slow rate.[3b]

Conclusions

We have demonstrated that an equilibrium between rather long-lived conformational isomers exists in several series of β-cyclodextrin derivatives, thus confirming the previous observation on α-cyclodextrin derivatives. Our synthetic studies strongly suggest that the existence of such an isomerism results from a combination of several effects. The rule that seems to emerge from this investigation is that sterically hindered CDs bearing aromatic units of size compatible with the CD cavity and linked to the CD core by ester (or probably some analogous) groups may exhibit conformational isomerism. The true nature of unsymmetrical CD conformers, although to be confirmed by further spectroscopic investigations, appears to be a sort of 'autocomplexed' form with one of the CD substituents on the primary rim being included in the molecule core.

Our results also have marked bearing on three important features of CD research: (1) the effect of the substituents on the complexation ability of CD derivatives, since substrate binding may be strongly influenced by deformation or by 'self-satisfaction'; (2) the use of CD derivatives for constructing organized polymolecular arrays, since 'inverted' structures such as that in Fig. 5(*b*) may disrupt the regularity of the supramolecular architecture; (3) the use of CD derivatives as building blocks for molecular devices. This investigation emphasizes the necessary care to be taken when designing new molecular arrays and devices exhibiting sufficient motional freedom. Indeed, if the introduction of some flexibility favours adaptability and increases the probability of achieving any required behaviour, it simultaneously increases the risk of interference by the device itself. Consequently, conservation of the attractive CD features such as high symmetry or large internal cavity, in complicated devices requires not only a careful consideration of the functions to be introduced, but also an analysis of the substituents in terms of the features which could interfere with the desired properties by formation of unfavourable conformers.

Experimental

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). Melting points were recorded on a Kofler Heizbank. ^1H NMR and ^{13}C NMR spectra were recorded on an AM 200 SY Bruker spectrometer at room temperature unless stated otherwise. Chemical shifts are given in ppm with the protonated or ^{13}C-labelled solvent as an internal reference (^1H NMR: $CHCl_3$ in $CDCl_3$ 7.26 ppm, CHD_2OD in CD_3OD 3.30 ppm, CHD_2COCD_3 in CD_3COCD_3 2.04 ppm; ^{13}C NMR $^{13}CDCl_3$ in $CDCl_3$ 76.9 ppm, $^{13}CD_3OD$ in CD_3OD 49.0 ppm, $^{13}CD_3COCD_3$ in CD_3COCD_3 29.8 ppm); coupling constants *J* are given in Hz. Mass spectra (FAB positive) were performed by the *Service de Spectrométrie de Masse du CNRS* (Vernaison) or (electrospray ES) in Dr. Van Dorsselaer's laboratory, University Louis Pasteur (Strasbourg). Column chromatography was performed on Merck Silica gel 60 (0.040–0.063 mm). Fluorescent silica plates (analytical or preparative), Merck or Macherey-Nagel, or Merck type E alumina were used for thin layer chromatography (TLC). The analytical plates were visualized by UV (254 nm), iodine (I_2) or sulfuric acid solution (5%). Anhydrous solvents (SDS), kept over molecular sieves (3–4 Å) were used as obtained. All catalytic hydrogenations were performed at $p = 1$ bar ($= 10^5$ Pa). Abbreviations: THF, tetrahydrofuran; TBDMS, *tert*-butyldimethylsilyl; DMSO, dimethyl sulfoxide; TEA, triethylamine; TsCl, toluene-*p*-sulfonyl chloride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF, dimethylformamide; DCC, dicyclohexylcarbodiimide.

$6^A,6^B,6^C,6^D,6^E,6^F$-Hexa-*O*-(*tert*-butyldimethylsiloxy)-α-cyclodextrin **2α**; $6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Hepta-*O*-(*tert*-butyldimethylsiloxy)-β-cyclodextrin **2β** and $6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-Octa-*O*-(*tert*-butyldimethylsiloxy)-γ-cyclodextrin **2γ** were synthesized

* PC model simulations showed that rotations of the phenyl group around the carbonyl–phenyl bond in the benzoyl group occurred within the range 8–10 kJ mol^{-1}. This value is in the same range as ΔG°_{295} (Table 1).

according to the procedure of reference 12 (respective yields: 50, 84, 62%). Their properties are in agreement with the literature.[10,12] $2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F$-Dodeca-*O*-benzyl-$6^A,6^B,6^C,6^D,6^E,6^F$-hexa-*O*-(*tert*-butyldimethylsiloxy)-α-cyclodextrin **3α** and $2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F$-Dodeca-*O*-benzyl-α-cyclodextrin **4α** were synthesized according to the procedure of Takeo *et al.*[10] 10-iodo-2,5,8-trioxadecane **12** was obtained from the 10-tosyl-2,5,8-trioxadecane **11** by halogen exchange (NaI–butanone, heat). Triethyleneglycol monobenzyl ether **9** was obtained by monoalkylation of triethylene glycol as the solvent with benzyl bromide–KOH. 6-Methoxy-2-naphthoic acid and 6-hydroxy-2-naphthoic acid **14** were synthesized as described in reference 13. The synthesis of **29** has already been described.[3a] $2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-tetradeca-*O*-benzyl-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-hepta-*O*-acetyl-β-cyclodextrin **31** was generously provided by the authors of reference 19. $2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^A,6^B,6^C,6^D,6^E,6^F,6^G$-henicosa-*O*-benzyl-β-cyclodextrin **35** was prepared as described by Ohno (BnBr–NaH–DMF).[20]

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-(tert-*butyldimethylsiloxy*)-*β-cyclodextrin* **3β**.—Sodium hydride (662 mg, 22 mmol; 80% mineral oil) was added at 0 °C to a solution of **2β** (889 mg; 0.46 mmol) in anhydrous DMF (14 cm^3) and the mixture was stirred for 1 h at 0 °C. Benzyl bromide (2.6 cm^3; 22 mmol) was added dropwise. After being stirred for 1 h at 0 °C, the mixture was allowed to attain room temperature and stirred for a further 2 h at this temperature. After cooling to 0 °C, the excess of hydride was decomposed with methanol. The resulting solution was extracted with pentane. The organic phase was extensively washed with water, dried over Na_2SO_4 and then concentrated. Purification of the residue by column chromatography (silica gel; gradient elution with CH_2Cl_2 in pentane) gave **3β** as a white solid (1.003 g, 68%). **3β** was finally recrystallized by slow evaporation of a solution in pentane–MeOH. δ_H(200 MHz; $CDCl_3$) 7.44–7.12 (m, 10 H), 5.41 (d, J = 3, 1 H), 5.17 and 4.81 (AB, J_{AB} = 11, 2 H), 4.52 (AB, J_{AB} = 15, 2 H), 4.36 (br d, J = 11, 1 H), 4.12 (m, 2 H), 3.82 (m, 2 H), 3.48 (m, 1 H), 0.97 (s, 9 H), 0.12 (s, 3 H) and 0.11 (s, 3 H); δ_C(50.3 MHz; $CDCl_3$) 139.3, 138.2, 128.2, 127.9, 127.7, 127.6, 127.4, 127.1, 97.9, 80.8, 79.3, 77.7, 75.3, 72.6(2), 62.4, 25.9, 18.3, −4.8 and −5.2 [Found: C, 68.5; H, 7.95. Calc. for $(C_{26}H_{36}O_5Si)_7$: C, 68.39; H, 7.95%]; TLC (SiO_2; CH_2Cl_2–pentane 2:3): R_f = 0.47.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,2^H,3^A,3^B,3^C,3^D,3^E,3^F,3^G,3^H$-*hexadeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-*octa*-O-(tert-*butyldimethylsiloxy*)-*γ-cyclodextrin* **3γ**.—Procedure as for **3β**: NaH 80% (331 mg, 11.5 mmol); **2γ** (504 mg, 0.23 mmol), DMF (12 cm^3), BnBr (1.3 cm^3; 11 mmol). **3γ** was obtained as a white solid (575 mg, 69%) which was recrystallized by slow evaporation of a solution in a mixture of pentane–MeOH. δ_H(200 MHz; $CDCl_3$) 7.31–7.13 (m, 10 H), 5.43 (d, J = 3, 1 H), 5.25 and 4.83 (AB, J_{AB} = 11, 2 H), 4.67 and 4.55 (AB, J_{AB} = 12, 2 H), 4.36 (br d, J = 11, 1 H), 4.09 (m, 2 H), 3.79 (m, 2 H), 3.47 (m, 1 H), 0.96 (s, 9 H), 0.10 (s, 3 H) and 0.09 (s, 3 H); δ_C(50.3 MHz; $CDCl_3$) 139.3, 138.2, 127.9, 127.8, 127.7, 127.4, 127.2, 126.6, 97.9, 80.7, 79.6, 77.6, 75.4, 72.7, 72.6, 62.4, 25.9, 18.2, −4.8 and −5.2 [Found: C, 68.35; H, 7.95. Calc. for $(C_{26}H_{36}O_5Si)_8$: C, 68.39; H, 7.95%]; TLC (SiO_2; CH_2Cl_2–hexane 2:3): R_f = 0.68.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-*β-cyclodextrin* **4β**.—A solution of **3β** (670 mg, 0.21 mmol) in dry THF (5 cm^3) was refluxed for 1 h with 1 mol dm^{-3} tetrabutylammonium fluoride in THF (0.25 cm^3) and then concentrated. The residue was dissolved in chloroform. The organic phase was washed with a saturated aqueous NaCl solution, dried on Na_2SO_4 and concentrated. Preparative TLC (silica gel; CH_2Cl_2–MeOH 9:1) followed by a filtration on a short column (silica gel 50 g; CH_2Cl_2–MeOH 9:1) afforded **4β** as a white solid (450 mg, 94%): m.p. 163–164 °C; δ_H(200 MHz; $CDCl_3$) 7.4–7.1 (m, 10 H), 5.13 (d, J = 3, 1 H), 5.10 (br s, 1 H), 4.98 and 4.89 (AB, J_{AB} = 11, 2 H), 4.64 and 4.56 (AB, J_{AB} = 12, 2 H), 4.1–3.8 (m, 4 H), 3.74 (m, 1 H) and 3.59 (m, 1 H); δ_C(50.3 MHz; $CDCl_3$) 139.0, 138.3, 128.0, 127.9, 127.7, 127.3, 127.2, 126.9, 98.1, 80.5, 78.8, 78.6, 74.9, 73.0, 72.8 and 61.7 [Found: C, 69.75; H, 6.55. Calc. for $(C_{20}H_{22}O_5)_7$: C, 70.16; H, 6.48%].

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,2^H,3^A,3^B,3^C,3^D,3^E,3^F,3^G,3^H$-*hexadeca*-O-*benzyl*-*γ-cyclodextrin* **4γ**.—Procedure as for **4β**. **3γ** (1.593 g, 0.44 mmol), THF (50 cm^3), TBAF 1 mol dm^{-3} (5 cm^3; 5 mmol). Final purification: column chromatography (silica gel; gradient elution with MeOH in chloroform). **4γ** as a white powder (872 mg, 73%). δ_H(200 MHz; $CDCl_3$) 7.3–7.1 (m, 10 H), 5.87 (br s, 1 H), 5.04 (br s, 1 H), 4.89 and 4.65 (AB, J_{AB} = 11, 2 H), 4.57 and 4.48 (AB, J_{AB} = 12, 2 H), 4.1–3.7 (m, 5 H) and 3.56 (m, 1 H); δ_C(50.3 MHz; $CDCl_3$) 139.0, 138.3, 128.0, 127.9, 127.6, 127.4, 127.1, 126.8, 98.6, 80.9, 78.6, 78.1, 74.5, 73.1 (2) and 60.8 [Found: C, 69.45; H, 6.55. Calc. for $(C_{20}H_{22}O_5)_8$: C, 70.16; H, 6.48%]; TLC (SiO_2; $CHCl_3$–MeOH 9:1): R_f = 0.48.

1-*Chloro*-5-*trityloxy*-3-*oxapentane* **6**.—A mixture of **5** (2.50 g; 20 mmol), trityl chloride (6.13 g, 22 mol), triethylamine (5 cm^3), DMAP (98 mg, 0.8 mmol) and dry CH_2Cl_2 (30 cm^3) was stirred overnight at room temperature. The organic phase was washed with 1 mol dm^{-3} HCl and then saturated aq. NaCl, dried (Na_2SO_4) and evaporated. The residue was recrystallized in EtOH 95% to yield **6** as pale pink crystals (5.96 g, 81%), m.p. 120 °C; δ_H(200 MHz; $CDCl_3$) 7.53–7.48 and 7.37–7.25 (m, 15 H), 3.82 (t, J = 5, 2 H), 3.72 (t, J = 5, 2 H), 3.67 (t, J = 5, 2 H) and 3.28 (t, J = 5, 2 H); δ_C(50.3 MHz; $CDCl_3$) 144.0, 128.6, 127.6, 126.8, 86.6, 71.3, 70.7, 63.3 and 42.7 (Found: C, 75.35; H, 6.35. Calc. for $C_{23}H_{23}ClO_2$: C, 75.29; H, 6.32%); TLC (SiO_2; CH_2Cl_2–hexane 1:1): R_f = 0.41.

1-*Iodo*-5-*trityloxy*-3-*oxapentane* **7**.—A mixture of **6** (4.25 g; 12 mmol), NaI (21.50 g, 143 mmol) and butanone (50 cm^3) was refluxed for 2 days. H_2O was added to the partially evaporated solution and the mixture extracted with Et_2O. The organic phase was washed with $NaHSO_3$ solution and water, dried (Na_2SO_4) and evaporated. The residue was recrystallized in EtOH 95% to give **7** as pale pink crystals (3.59 g, 68%), m.p. 107 °C; δ_H(200 MHz; $CDCl_3$) 7.53–7.48 and 7.37–7.25 (m, 15 H), 3.82 (t, J = 7, 2 H), 3.70 (t, J = 5, 2 H), 3.31 (t, J = 7, 2 H) and 3.27 (t, J = 5 Hz, 2 H); δ_C(50.3 MHz; $CDCl_3$) 144.0, 128.6, 127.6, 126.8, 86.6, 71.9, 70.3, 63.4 and 2.9 (Found: C, 60.4; H, 5.05. Calc. for $C_{23}H_{23}IO_2$: C, 60.27, H, 5.06%); TLC (SiO_2; CH_2Cl_2–hexane 1:1): R_f = 0.40.

8-O-*Benzyl*-1-*iodo*-3,6-*dioxaoctane* **13**.—TsCl (20.95 g; 0.11 mol) was added in portions into a solution of **9** (24.0 g, 0.1 mmol) and anhydrous pyridine (100 cm^3) cooled to 0 °C. After one night at 0 °C, the mixture was poured onto crushed ice and extracted with Et_2O. The organic phase was washed with 1 mol dm^{-3} HCl and water, dried (Na_2SO_4) and evaporated to yield **11** as a pale yellow liquid (31.7 g) used without purification for the next step. A mixture of **11** (15.8 g; 0.04 mol), NaI (12.0 g; 0.08 mol) and butanone (75 cm^3) was refluxed for 2 h. H_2O was added to the partially evaporated solution and the mixture extracted with Et_2O. The organic phase was washed with $NaHSO_3$ solution and water, dried (Na_2SO_4) and evaporated to give **13** as a pale yellow liquid used without purification for the next step (14.45 g; quantitative yield). δ_H(200 MHz; $CDCl_3$) 7.35 (m, 5 H), 4.60 (s, 2 H), 3.80 (t, J = 7, 2 H), 3.7 (m, 8 H) and 3.25 (t, J = 7, 2 H); δ_C(50.3 MHz; $CDCl_3$) 138.0, 128.0, 127.3, 127.2, 72.9, 71.7, 70.45, 70.4, 70.0, 69.25 and 2.7; TLC (SiO_2; CH_2Cl_2–AcOEt 99:1): R_f = 0.49.

Allyl 6-Hydroxy-2-naphthoate **15**.—DBU (1.7 cm^3; 11 mmol) and allyl bromide (1.5 cm^3; 17 mmol) were successively poured into a suspension of **14** (2.03 g; 12 mmol) in dry acetonitrile (20 cm^3) and dry DMF (4 cm^3). After being stirred at 70 °C for 6 h, the solution was cooled to room temperature, diluted with H_2O and extracted with Et_2O. The organic phase was washed with saturated $NaHCO_3$ solution and H_2O, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2; gradient elution with Et_2O in CH_2Cl_2) to yield **15** as a pale brown solid (1.95 g, 73%): m.p. 80 °C; δ_H(200 MHz; $CDCl_3$) 10.20 (br s, 1 H), 8.50 (s, 1 H), 7.98 (d, J = 9, 1 H), 7.92 and 7.72 (AB, J_{AB} = 9, 2 H), 7.18 (s, 1 H), 7.16 (d, J = 9, 1 H), 6.05 (ddt, J = 5, 10 and 17, 1 H), 5.42 (d, J = 17, 1 H), 5.28 (d, J = 10, 1 H) and 4.82 (d, J = 5 Hz, 2 H); δ_C(50.3 MHz; $CDCl_3$) 165.5, 157.6, 137.0, 132.4, 130.7, 130.4, 126.5, 126.0, 124.9, 123.6, 119.4, 117.5, 108.6 and 64.7 (Found: C, 73.65; H, 5.35. Calc. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30%); TLC (SiO_2; CH_2Cl_2): R_f = 0.50.

Allyl 6-(tert-*Butyldimethylsiloxy*)-2-*naphthoate* **16**.—A mixture of **15** (399 mg, 1.6 mmol), TBDMSCl (590 mg, 3.9 mmol, 2.5 equiv.), imidazole (57 mg, 0.8 mmol) and dry pyridine (3 cm^3) was stirred for 24 h at room temperature. The solution was mixed with Et_2O, washed with 1.2 mol dm^{-3} HCl and saturated NaCl, then dried over Na_2SO_4. After purification by column chromatography (SiO_2; gradient elution with CH_2Cl_2 in hexane), **16** was isolated as a viscous colourless liquid (456 mg, 85%). δ_H(200 MHz; $CDCl_3$) 8.58 (s, 1 H), 8.05 (dd, J = 2 and 9, 1 H), 7.84 (d, J = 9, 1 H), 7.73 (d, J = 9, 1 H), 7.22 (d, J = 2, 1 H), 7.14 (d, J = 2 and 9, 1 H), 6.10 (ddt, J = 5, 10 and 17, 1 H), 5.46 (d, J = 17, 1 H), 5.32 (d, J = 10, 1 H), 4.89 (d, J = 5, 2 H), 1.05 (s, 9 H) and 0.29 (s, 6 H); δ_C(50.3 MHz; $CDCl_3$) 166.2, 155.6, 137.0, 132.4, 130.8, 128.0, 126.6, 125.5, 125.3, 122.7, 117.9, 114.6, 65.3, 25.5, 18.1 and −4.4 (Found: C, 70.1; H, 7.75. Calc. for $C_{20}H_{26}O_3Si$: C, 70.13; H, 7.65%); TLC (SiO_2; CH_2Cl_2–hexane 1:1): R_f = 0.50.

Allyl 6-(5-*trityloxy*-3-*oxapentyl*)-2-*naphthoate* **17**.—A solution of **15** (0.971 g, 4.6 mmol) and **7** (2.52 g, 5.5 mmol) in dry DMF (10 cm^3) was added dropwise to a suspension of sodium hydride (165 mg of 80% mineral-oil dispersion; 5.5 mmol) in dry DMF (10 cm^3). After being stirred at room temperature for 15 min, the mixture was stirred at 70 °C overnight. After being cooled to room temperature, the mixture was diluted with water and extracted with Et_2O. The organic phase was washed with water and saturated NaCl, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2; gradient elution with CH_2Cl_2 in pentane) to yield **17** as a colourless solid which was recrystallized in 95% EtOH (1.517 g, 59%), m.p. 77 °C; δ_H(200 MHz; $CDCl_3$) 8.57 (s, 1 H), 8.06 (dd, J = 9 and 2, 1 H), 7.84 (d, J = 9, 1 H), 7.74 (d, J = 9, 1 H), 7.60–7.45 and 7.40–7.15 (m, 16 H), 6.11 (ddt, J = 17, 10 and 4, 1 H), 5.47 (dd, J = 17 and 1, 1 H), 5.34 (dd, J = 10 and 1, 1 H), 4.90 (dd, J = 4 and 1, 2 H), 4.31 (t, J = 5, 2 H), 3.99 (t, J = 5, 2 H), 3.80 (t, J = 5, 2 H) and 3.31 (t, J = 5, 2 H); δ_C(50.3 MHz; $CDCl_3$) 166.3, 158.7, 144.0, 137.1, 132.4, 130.8, 128.6, 127.9, 127.6, 126.8, 125.8, 125.3, 119.8, 118.0, 106.8, 86.6, 70.9, 69.6, 67.7, 65.4 and 63.4 (Found: C, 79.5; H, 6.15. Calc. for $C_{37}H_{34}O_5$: C, 79.54; H, 6.13%); TLC (SiO_2; CH_2Cl_2): R_f = 0.58.

Allyl 6-O-(8-*Benzyloxy*-3,6-*dioxaoctyl*)-2-*naphthoate* **19**.—Procedure as for **17**. **15** (170 mg, 0.78 mmol), **13** (300 mg, 0.85 mmol), NaH 80% (25 mg, 0.85 mmol). Purification on preparative TLC (SiO_2; CH_2Cl_2–Et_2O 9:1) to yield **19** as a colourless viscous liquid (225 mg, 65%). δ_H(200 MHz; $CDCl_3$) 8.54 (s, 1 H), 8.04 (dd, J = 9 and 2, 1 H), 7.82 (d, J = 9, 1 H), 7.73 (s, J = 9, 1 H), 7.35–7.10 (m, 7 H), 6.09 (ddt, J = 17, 10 and 5, 1 H), 5.46 (dd, J = 17 and 1, 1 H), 5.32 (dd, J = 10 and 1, 1 H), 4.88 (dd, J = 5 and 1, 2 H), 4.56 (s, 2 H), 4.25 (m, 2 H), 3.93 (m, 2 H) and 3.80–3.60 (m, 8 H); δ_C(50.3 MHz; $CDCl_3$) 166.2, 158.6, 138.1, 136.9, 132.3, 130.8, 128.1, 127.8, 127.4, 126.6, 125.7, 125.1, 119.6, 117.9, 106.6, 73.1, 70.8, 70.6, 69.5, 69.4, 67.5 and 65.3 (Found: C, 71.85; H, 6.7. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71%); TLC (SiO_2; CH_2Cl_2–Et_2O 9:1): R_f = 0.63.

6-(tert-*Butyldimethylsilyloxy*)-2-*naphthoic Acid* **20**.—Pyrrolidine (333 μl; 4 mmol) was added dropwise to a cooled (0° C) solution of **16** (650 mg, 2 mmol), tetrakis(triphenylphosphine)palladium(0) (80 mg, 0.07 mmol) and triphenylphosphine (36 mg, 0.14 mmol) in dry CH_2Cl_2 (10 cm^3). The reaction was stirred for 1 h at room temperature after which the organic phase was washed with 1 mol dm^{-3} HCl and H_2O, dried (Na_2SO_4) and evaporated. The residue was recrystallized from aqueous EtOH to give **20** as white crystals (190 mg, 31.5%); m.p. 200 °C; δ_H(200 MHz; $CDCl_3$) 8.66 (s, 1 H), 8.08 (dd, J = 2 and 9, 1 H), 7.88 (d, J = 9, 1 H), 7.75 (d, J = 9, 1 H), 7.24 (m, 1 H), 7.16 (dd, J = 2 and 9, 1 H), 1.04 (s, 9 H) and 0.29 (s, 6 H); δ_C(50.3 MHz; $CDCl_3$) 172.2, 156.0, 137.5, 131.8, 131.1, 128.0, 126.8, 125.7, 124.5, 122.9, 114.7, 25.6, 18.2 and −4.3; TLC (SiO_2; CH_2Cl_2–MeOH 9:1): R_f = 0.4.

6-(5-*Trityloxy*-3-*oxapentyl*)-2-*naphthoic Acid* **21**.—Procedure as for **20**. Pyrrolidine (200 μl, 3.3 mmol), **17** (917 mg, 1.64 mmol), tetrakis(triphenylphosphine)palladium(0) (66 mg, 0.057 mmol), triphenylphosphine (30 mg, 0.115 mmol, CH_2Cl_2 (10 cm^3). The residue was washed with CH_2Cl_2 and recrystallized from $CHCl_3$ to give **21** as white crystals (818 mg, 95%); m.p. 160 °C; δ_H(200 MHz; $CDCl_3$) 8.56 (s, 1 H), 8.03–7.83 (m, 3 H), 7.51–7.21 (m, 17 H), 4.38–4.33 (m, 2 H), 4.99–3.94 (m, 2 H), 3.79–3.74 (m, 2 H), 3.24–3.19 (m, 2 H) and 2.9 (br s, 1 H) (Found: C, 78.68; H, 5.83. Calc. for $C_{34}H_{30}O_5$: C, 78.74; H, 5.83%).

6-(8-*Benzyloxy*-3,6-*dioxaoctyl*)-2-*naphthoic Acid* **23**.—Procedure as for **20**. The allyl ester **19** (1.10 g, 2.4 mmol), $Pd(PPh_3)_4$ (83 mg, 0.072 mmol), PPh_3 (38 mg, 0.144 mg), pyrrolidine (400 μl, 4.8 mmol), CH_2Cl_2 (15 cm^3). Purification by column chromatography (silica gel; CH_2Cl_2–MeOH 9:1) to give **23** as white crystals after recrystallization in AcOEt (700 mg, 70%); m.p. 106 °C; δ_H(200 MHz; $CDCl_3$) 8.56 (s, 1 H), 8.08–8.07 (m, 1 H), 7.82–7.68 (m, 2 H), 7.35–7.12 (m, 7 H), 4.58 (s, 2 H), 4.27–4.23 (m, 2 H), 3.97–3.92 (m, 2 H) and 3.78–3.64 (m, 8 H); δ_C(50.3 MHz; $CDCl_3$) 171.5, 158.8, 137.5, 137.3, 131.5, 130.8, 128.2, 127.75, 127.5, 127.4, 126.7, 125.9, 124.4, 119.7, 106.7, 73.1, 70.8, 70.6, 69.5, 69.4 and 67.5 (Found: C, 70.0; H, 6.35. Calc. for $C_{24}H_{26}O_6$: C, 70.23; H, 6.39%); TLC (SiO_2; CH_2Cl_2–MeOH 9:1): R_f = 0.40.

4′-*Benzyloxycarbonylbiphenyl*-4-*carboxylic Acid* **25**.—TEA (5.6 cm^3; 40 mmol) and methanesulfonyl chloride (1.55 cm^3; 20 mmol) were poured successively into a solution of biphenyl-4,4′-dicarboxylic acid (2.40 g, 10 mmol) in THF (50 cm^3) cooled to −10 °C. The reaction was stirred for 1 h −10 °C after which benzyl alcohol (2.3 cm^3; 22 mmol) and DMAP (488 mg, 4 mmol) were added and the mixture was stirred overnight at room temperature. After addition of water, the aqueous phase was extracted with EtOAc. The organic phase was washed with 1 mol dm^{-3} NaOH. The resulting aqueous phase was acidified with concentrated HCl and extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4) and evaporated to give 680 mg of a crude white powder which was recrystallized from 95% EtOH (70 cm^3) to afford **25** as white crystals (500 mg, 15%); m.p. 243–244 °C; δ_H(200 MHz; [$^2H_6$]DMSO) 13.1 (br s, 1 H), 8.07–8.03 (m, 4 H), 7.81–7.77 (m, 4 H), 7.47–7.35 (m, 5 H) and 5.35 (s, 2 H); δ_C(50.3 MHz; [$^2H_6$]DMSO) 166.9, 165.2, 143.6, 143.3, 142.8, 136.05, 130.5, 129.95, 129.9, 129.2, 129.1, 128.4, 128.0, 127.8, 127.2, 127.0 and 66.2 (Found: C, 75.75; H, 4.8. Calc. for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85%); TLC (SiO_2; CH_2Cl_2–MeOH 95:5): R_f = 0.25.

4-Tritylphenoxyacetic Acid **27**.—4-Tritylphenol (3.30 g, 10 mmol) was added dropwise to a suspension of NaH (360 mg, 15 mmol) in dry DMF (35 cm^3). After addition of sodium chloroacetate (845 mg, 10 mmol) and NaI (1.50 g, 10 mmol), the mixture was stirred at 80 °C for 24 h. The resulting solution was poured onto crushed ice, acidified with 1 mol dm^{-3} HCl and extracted with AcOEt. The organic phase was washed with H_2O, dried (Na_2SO_4) and evaporated. The crude residue was recrystallized from MeOH to yield **27** as colourless crystals (2.00 g, 51%); m.p. 232 °C; δ_H(200 MHz; [$^2H_6$]DMSO) 7.30–7.10 (m, 15 H), 7.03–6.83 (AB, J_{AB} = 9, 4 H) and 4.63 (s, 2 H); δ_C(50.3 MHz; [$^2H_6$]DMSO) 170.0, 155.7, 146.5, 138.9, 131.5, 130.4, 127.6, 125.9, 113.5, 64.5 and 63.8 (Found: C, 82.1; H, 5.65. Calc. for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62%); TLC (SiO_2; CH_2Cl_2–MeOH 9:1): R_f = 0.27.

$2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F$-*Dodeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F$-*hexa*-O-(6-*methoxy*-2-*naphthoyl*)-α-*cyclodextrin* **28**α.—Dicyclohexylcarbodiimide (DCC; 80 mg, 0.375 mmol) was added slowly to a solution cooled to 0 °C of **4**α (51 mg, 0.025 mmol), 6-methoxy-2-napthoic acid (80 mg, 0.375 mmol, 2.5 equiv.), DMAP (45 mg, 0.375 mmol) in dry CH_2Cl_2 (2.5 cm^3). After being stirred at 0 °C for 10 min, then at room temperature overnight, the suspension was diluted with ethyl ether and filtered. The organic phase was washed with 1 mol dm^{-3} HCl and saturated NaCl, dried (Na_2SO_4) and evaporated. The residue was purified by preparative TLC (silica gel; CH_2Cl_2–Et_2O 98:2) to give **28**α as white crystals from MeOH (65 mg; 83%). δ_H(200 MHz; $CDCl_3$) 8.46 (s, 1 H), 7.97 (dd, J = 9 and 1, 1 H), 7.82 (d, J = 9, 1 H), 7.65 (d, J = 9, 1 H), 7.30–6.90 (m, 12 H), 5.26 (s, 1 H), 5.29 and 4.98 (AB, J_{AB} = 11, 2 H) 5.00–4.75 (m, 2 H), 4.70–4.30 (m, 4 H), 4.08 (t, J = 9, 1 H), 3.82 (s, 3 H) and 3.62 (dd, J = 10 and 3, 1 H); δ_C(50.3 MHz; $CDCl_3$) 165.8, 159.1, 139.0, 138.1, 136.9, 130.9, 128.2, 128.0, 127.9, 127.5, 127.2, 126.9, 126.6, 126.1, 125.9, 125.1, 119.0, 105.5, 98.6, 80.2, 79.5, 79.0, 75.4, 72.8, 70.6, 64.0 and 55.0 [Found: C, 72.95; H, 5.8. Calc. for $(C_{32}H_{30}O_7)_7$: C, 72.99; H, 5.74%]; TLC (SiO_2; CH_2Cl_2–Et_2O 97:3): R_f = 0.50.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-(6-*methoxy*-2-*naphthoyl*)-β-*cyclodextrin* **28**β.—Procedure as for **28**α. 6-Methoxy-2-naphthoic acid (90 mg, 0.44 mmol, 2.5 equiv.), DMAP (55 mg, 0.44 mmol), **4**β (60 mg, 0.025 mmol), dry CH_2Cl_2 (2.5 cm^3), DCC (90 mg; 0.44 mmol). Purification by preparative TLC (SiO_2; CH_2Cl_2–Et_2O 97:3) to give **28**β as a white powder after being washed with MeOH (70 mg, 75%). δ_C(50.3 MHz; $CDCl_3$) (C_7 conformer) 165.8, 159.1, 139.0, 138.1, 136.9, 130.9, 128.2, 128.0, 127.9, 127.5, 127.2, 126.9, 126.6, 126.1, 125.9, 125.1, 119.0, 105.5, 98.6, 80.2, 79.5, 79.0, 75.4, 72.8, 70.6, 64.0 and 55.0 [Found: C, 72.95; H, 5.82. Calc. for $(C_{32}H_{30}O_7)_7$: C, 72.99; H, 5.74%]; TLC (SiO_2; CH_2Cl_2–Et_2O 97:3): R_f = 0.50; ESMS, 3684 (calc. 3686).

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,2^H,3^A,3^B,3^C,3^D,3^E,3^F,3^G,3^H$-*Hexadeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-*octa*-O-(6-*methoxy*-2-*naphthoyl*)-γ-*cyclodextrin* **28**γ.—Procedure as for **28**α. 6-Methoxy-2-naphthoic acid (103 mg, 0.50 mmol; 2 equiv), DMAP (62 mg, 0.50 mmol), **4**γ (68 mg, 0.025 mmol), dry CH_2Cl_2 (2.5 cm^3), DCC (103 mg, 0.50 mmol). Purification by preparative TLC (SiO_2; benzene–AcOEt 9:1) and column chromatography (SiO_2; $CHCl_3$–Et_2O 95:5) to give **28**γ as a white powder after lyophilization in benzene (34 mg, 32%). δ_C(50.3 MHz; $CDCl_3$) (C_8 conformer) 165.7, 159.0, 138.9, 138.1, 136.8, 130.8, 128.0, 127.9, 127.6, 127.3, 127.1, 126.8, 126.6, 125.8, 125.1, 118.9, 105.4, 98.5, 80.4, 78.9 (2), 75.0, 72.8, 70.6, 63.7 and 55.0 [Found: C, 72.95; H, 5.75. Calc. for $(C_{32}H_{30}O_7)_8$: C, 72.99; H, 5.74%]; TLC (SiO_2; benzene–AcOEt 9:1): R_f = 0.35.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-*benzoyl*-β-*cyclodextrin* **30**.—Procedure as for **28**α. **4**β (60 mg, 0.025 mmol), benzoic acid (43 mg, 0.35 mmol), DMAP (43 mg, 0.35 mmol), CH_2Cl_2 (5 cm^3), DCC (72 mg, 0.35 mmol). Purified by preparative TLC (CH_2Cl_2–Et_2O 97:3). **30** crystallized from MeOH as white crystals. δ_H(200 MHz; $CDCl_3$) see Fig. 3 [Found: C, 72.87; H, 5.90. Calc. for $(C_{27}H_{26}O_6)_7$: C, 72.63; H, 5.87%]; TLC (SiO_2; CH_2Cl_2–Et_2O): R_f = 0.50.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-*dodecanoyl*-β-*cyclodextrin* **32**.—Procedure as for **28**α. Dodecanoic acid (158 mg, 0.8 mmol), DMAP (20 mg, 0.2 mmol), **4**β (108 mg, 0.045 mmol), DCC (164 mg, 0.8 mmol). Purification by preparative TLC (SiO_2; AcOEt–Hexane 15:85) to give **32** as a colourless resinous solid (64 mg, 38%). δ_H(200 MHz; $CDCl_3$) 7.30–7.10 (m, 10 H), 5.04 (d, J = 3, 1 H), 5.02 and 4.76 (AB, J_{AB} = 11, 2 H), 4.56 and 4.46 (AB, J_{AB} = 12, 2 H), 4.10–3.99 (m, 2 H), 3.77 (t, J = 9, 1 H), 3.48 (dd, J = 9 and 3, 1 H), 2.31 (t, J = 7, 2 H), 1.60 (m, 2 H), 1.27 (m, 16 H) and 0.90 (t, J = 7, 3 H); δ_C(50.3 MHz; $CDCl_3$) 172.7, 139.0, 138.2, 128.1, 127.9, 127.7, 127.4, 127.1, 126.9, 98.6, 80.5, 79.4, 78.7, 75.2, 72.9, 70.0, 63.0, 34.0, 31.9, 29.6, 29.4, 29.2, 24.9, 22.6 and 14.0 [Found: C, 73.2; H, 8.5. Calc. for $(C_{32}H_{44}O_7)_7$: C, 73.25; H, 8.45%]; TLC (SiO_2; AcOEt–hexane 15:85): R_f = 0.33.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-(4′-*benzyloxycarbonylbiphenyl*-4-*carbonyl*)-β-*cyclodextrin* **33**.—Procedure as for **28**α. Benzyl hydrogen biphenyl-4,4′-dicarboxylate **25** (93 mg, 0.28 mmol, 2 equiv.), DMAP (34 mg, 0.28 mmol), **4**β (50 mg, 0.02 mmol), dry CH_2Cl_2 (2.5 cm^3), DCC (60 mg, 0.28 mmol). Purification by preparative TLC (SiO_2; CH_2Cl_2–acetone 98:2) to give 75 mg of **33** which yielded a white powder after crystallization from MeOH (70 mg, 76%). C_7 conformer δ_C(50.3 MHz; $CDCl_3$) 165.9, 165.3, 144.2, 143.9, 138.9, 138.1, 136.0, 130.2, 130.1, 129.8, 129.5, 128.5, 128.3, 128.1, 128.0, 127.8, 127.5, 127.4, 127.2, 127.0, 126.6, 126.1, 98.8, 80.4, 79.6, 78.7, 75.3, 72.9, 70.5, 66.6 and 64.0 [Found C, 74.85; H, 5.45. Calc. for $(C_{41}H_{36}O_8)_7$: C, 74.98; H, 5.53%]; TLC (SiO_2; CH_2Cl_2–acetone 98:2): R_f = 0.43 (2 spots).

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-[6-(8-*benzyloxy*-3,6-*dioxaoctyloxy*)-2-*naphthoyl*]-β-*cyclodextrin* **37**.—Procedure as for **28**α. 6-(8-Benzyloxy-3,6-dioxaoctyloxy)-2-naphthoic acid **23** (160 mg, 0.385 mmol, 2.5 equiv.), DMAP (10 mg; 0.077 mmol), **4**β (60 mg, 0.025 mmol), dry CH_2Cl_2 (5 cm^3), DCC (80 mg, 0.385 mmol). Purification by preparative TLC (SiO_2; CH_2Cl_2–MeOH 97:3) to give **37** as a resinous solid (100 mg, 77%). δ_C(50.3 MHz; $CDCl_3$) (C_7 conformer) 165.8, 158.3, 139.0, 138.3, 138.1, 136.8, 130.9, 130.8, 128.2, 128.0, 127.8, 127.5, 127.4, 127.2, 127.0, 126.7, 126.0, 125.9, 125.2, 119.2, 106.8, 106.5, 98.5, 80.6, 79.4, 79.0, 75.4, 73.1, 72.7, 70.8, 70.6, 69.5, 67.6, 67.4 and 63.9 [Found: C, 71.75; H, 6.4. Calc. for $(C_{44}H_{46}O_{10})_7$: C, 71.92; H, 6.31%]; TLC (SiO_2; CH_2Cl_2–MeOH 97:3). R_f = 0.30; ESMS, 5144 (calc. 5144).

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-[6-(5-*trityloxy*-3-*oxapentyloxy*)-2-*naphthoyl*]-β-*cyclodextrin* **38**.—Procedure as for **28**α. 6-(5-Trityloxy-3-oxapentyloxy)-2-naphthoic acid **21** (172 mg, 0.33 mmol, 2.5 equiv.), DMAP (40 mg, 0.33 mmol), **4**β (45 mg, 0.019 mmol), dry CH_2Cl_2 (5 cm^3), DCC (70 mg, 0.33 mmol). Purification by column chromatography (10 g SiO_2; CH_2Cl_2–acetone 98:2) to give **38** as a white powder after trituration in MeOH (95 mg, 85%). δ_C(50.3 MHz; $CDCl_3$) (C_7 conformer) 165.8, 158.3, 144.1, 139.1, 138.1, 136.9, 131.0, 130.9, 128.6, 128.3, 128.0, 127.8, 127.6, 127.2, 126.8, 126.3, 126.1, 125.9, 125.2, 119.3,

106.5, 98.5, 86.6, 80.7, 79.4, 79.0, 75.4, 73.1, 72.8, 72.3, 70.8, 70.6, 69.6, 67.5, 63.9 and 63.4 [Found: C, 76.82; H, 6.18. Calc. for $(C_{54}H_{50}O_9)_7$: C, 76.94; H, 5.98%]; TLC (SiO_2; CH_2Cl_2–acetone 98:2): R_f = 0.50; ESMS, 5898 (calc. 5900).

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-*Tetradeca*-O-*benzyl*-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*hepta*-O-(4-*tritylphenoxyacetyl*)-β-*cyclodextrin* **39**.—Procedure as for **28α**. 4-tritylphenoxyacetic acid **28** (169 mg, 0.44 mmol, 2.5 equiv.), DMAP (61 mg, 0.44 mmol), **4β** (60 mg, 0.025 mmol), dry CH_2Cl_2 (5 cm^3), DCC (91 mg; 0.44 mmol). Purification by preparative TLC (SiO_2; $CHCl_3$–Et_2O 97.5:2.5) to give **39** as a white powder after trituration in MeOH (95 mg, 75%). δ_H(200 MHz; $CDCl_3$) 7.30–6.95 (m, 25 H), 7.02 and 6.64 (AB, J_{AB} = 9, 4 H), 5.04 (s, 1 H), 5.02 and 4.76 (AB, J_{AB} = 11, 2 H), 4.80–4.35 (m, 4 H), 4.44 (s, 2 H), 4.12 (m, 1 H), 4.05 (t, J = 8, 1 H), 3.74 (t, J = 8, 1 H) and 3.48 (dd, J = 9 and 3, 1 H); δ_C(50.3 MHz; $CDCl_3$) 168.2, 155.8, 146.9, 139.8, 138.9, 138.0, 132.1, 131.0, 128.1, 127.9, 127.7, 127.3, 127.1, 126.9, 125.7, 113.7, 98.7, 80.2, 79.4, 78.8, 75.2, 72.9, 70.1, 65.3, 64.3 and 63.9 [Found: C, 77.9; H, 5.8. Calc. for $(C_{47}H_{42}O_7)_7$: C, 78.43; H, 5.89%]; TLC (SiO_2; $CHCl_3$–Et_2O 97.5:2.5): R_f = 0.66.

$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-*Hepta*-O-[6-(8-*methoxy*-3,6-*dioxaoctyloxy*)-2-*naphthoyl*]-β-*cyclodextrin* **40**.—A mixture of **36** (100 mg), 10% Pd–C (100 mg) and one drop of $HClO_4$ in dioxane (3 cm^3) and ethanol (3 cm^3) was stirred under hydrogen for 9 h at 50 °C. After neutralization (solid K_2CO_3), filtration and extensive washing of the solids (CH_2Cl_2–EtOH), the solution was evaporated and the residue was purified by column chromatography (5 g SiO_2; CH_2Cl_2–MeOH 85:15) to give **40** as a slight yellow powder which rapidly turned brownish on exposure to air (35 mg, 90%). δ_H(200 MHz; $CDCl_3$) 8.25 (s, 1 H), 7.75 (d, J = 9, 1 H), 7.60 (d, J = 9, 1 H), 7.46 (d, J = 9, 1 H), 7.05 (d, J = 9, 1 H), 6.88 (s, 1 H), 6.78 (br s, 1 H), 5.27 (s, 1 H), 4.99 (s, 1 H), 4.81 (d, J = 10, 1 H), 4.5–4.0 (m, 5 H), 4.0–3.4 (m, 12 H) and 3.35 (s, 3 H); δ_C(50.3 MHz; $CDCl_3$) 165.8, 158.4, 136.9, 130.7, 127.7, 126.6, 125.5, 124.7, 119.4, 106.6, 102.1, 83.4, 73.6, 73.3, 71.9, 70.8, 70.6, 70.5, 70.2, 69.5, 67.4, 62.9 and 58.8. TLC (SiO_2; CH_2Cl_2–MeOH 85:15): R_f = 0.5; ESMS, 3251 (calc. 3251).

Spectroscopic Measurements.—Equilibrium constants were estimated by integration of ^{1}H NMR signals arising from both symmetrical and unsymmetrical conformers. This estimation was made by measuring the heights of the corresponding most deshielded signals (proton 1 of the naphthalene rings, protons 2 for the phenyl rings). Integration of each signal was obtained upon multiplying the height of the signal by its width at half-height. The precision of this measurement is evaluated to be 5–10%.

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