Pergamon

Tetrahedron Vol. 51, No. 37, pp. 10131-10148, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00608-7

The Intramolecular Inclusion of Aromatic Esters within β-Cyclodextrin as a Function of Chain Length - A Detailed NMR Study

Stephen Hanessian*, Aziza Benalil and Minh Tan Phan Viet

Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Centre-ville, Montréal, P.Q., H3C 3J7 (Canada).

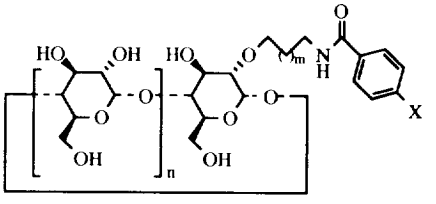
Abstract: p-Substituted aromatic esters were attached to the C2 hydroxyl groups of β-cyclodextrin (β-CD) through amide linkages with ω-aminoalkyl ethers. The inclusion of the aromatic moiety in the β-CD cavity was studied by ^{1}H and ^{13}C NMR techniques. A chain length of five carbon atoms allow complete intramolecular inclusion of the aromatic ring. This derivative was found to be the least susceptible to hydrolysis at pH 9.8 at two different concentrations due to the shielding effect of the inclusion process on the ester function. Other derivatives were also studied as controls.

The cyclodextrins (CDs) have distinguished themselves as a unique class of macrocyclic carbohydrate oligomers that exhibit a number of fascinating physico-chemical and chemical properties.[1,2] In view of their torus shaped structures with hydrophobic interiours, they are able to act as hosts to a variety of organic molecules, thus forming so-called inclusion compounds.[1-3] Applications of CDs in catalysis,[1-3] as enzyme models,[4] in separation technology,[5] in chiral discrimination,[6] in asymmetric reactions,[7] and in medicinal or industrial chemistry[8] are impressive.

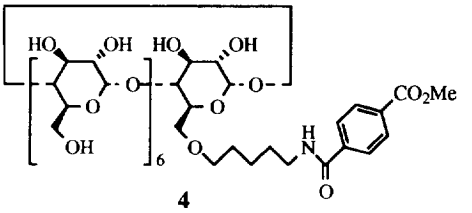
The chemical literature is abound with reports on the inclusion of organic molecules in the cavity of CDs, a phenomenon which is admirably suited for study by NMR techniques.[9] There are however, comparatively much fewer examples of *intramolecular* inclusion of organic functional groups through attachment to the primary or secondary face of CDs. Recent reports have described the attachment of aromatic D- and L- amino acids to 6-amino-6-deoxy-β-CD *via* an amide bond, and the study of chiral discrimination by ^{1}H NMR spectroscopy.[10] Related studies have involved other appendages.[11]

In an effort to study the effect of varying the distance between an aromatic ester capable of being intramolecularly included in β-CD, and its qualitative rate of hydrolysis[12], we synthesized a series of C2-O-substituted alkyl ethers of β-CD, in which the ω position carried a methyl terephthalamide group (Fig. 1). Thus, treatment of β-CD with ω-azido-1-iodoalkanes in the presence of sodium hydride in DMSO led to the corresponding 2-O-(3-azidopropyl), -(4-azidobutyl), and -(5-azidopentyl) ethers as chromatographically and

constitutionally homogeneous solids.[13] Reduction of the azido group and condensation with terephthalic acid monomethyl ester and with p-bromobenzoic acid, gave the corresponding amide derivatives **1-3** and **5** (Fig. 1). The 6-O-substituted isomer **4** was also prepared and characterized. The 5-aminopentyl derivatives **6** and **7** substituted at the C2 hydroxy group of α-CD were also prepared for comparison.



Compound	n	m	X
1	6	3	CO_2Me
2	6	2	CO_2Me
3	6	1	CO_2Me
5	6	3	Br
6	5	3	CO_2Me
7	5	3	Br



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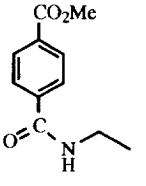

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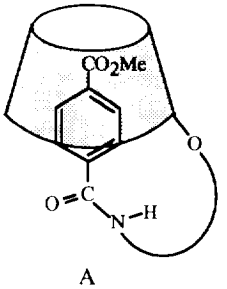
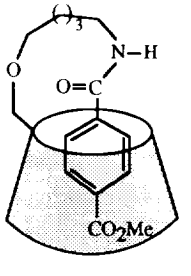


A



B

Fig. 1. Structure of the compounds.

RESULTS AND DISCUSSION

While the NMR spectra of symmetrically substituted CDs are simple and easily assigned[14], there are seven chemically non-equivalent glucopyranose units in monofunctionalized CDs each of which has a distinct spin system owing to the asymmetry of the compound.[15] Fig. 2 shows expanded regions of the 600 MHz ^1H NMR spectra of compounds **1-4**. The aromatic and anomeric protons which can be easily assigned, resonate between 7.95 and 8.08 ppm and between 4.94 and 5.14 ppm respectively. However, assignment of the 3-4 ppm region of the spectra was non-trivial due to the overlapping of the signals, and required experimentation as discussed below.

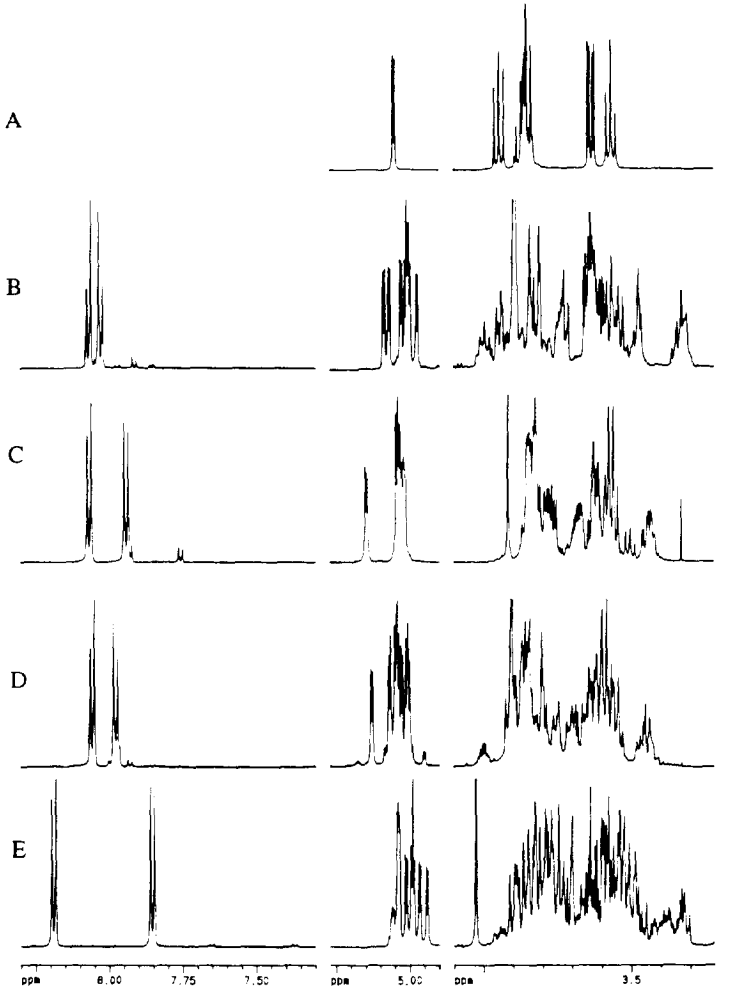


Fig. 2. Comparison of ^1H NMR spectra of β-CD (A) and compounds **1** (B), **2** (C), **3** (D) and **4** (E) (10 mM solution in D_2O, 303°K).

Regular 2D proton-proton correlation spectra do not have adequate resolution to allow detailed analysis. Therefore, high resolution selective 2D spectra, typically with FID digital resolution of ~ 1 Hz in f1 and of ≤ 0.35 Hz in f2, were recorded. A series of selective 2D TOCSY (total correlated spectroscopy)[16] spectra with a spectrum width of about 120 Hz in f1 centered around the anomeric protons region were acquired. The mixing time was progressively increased until complete transfer of magnetisation from H1 to the most distant protons H6 (from 30 to 250 msec). In favorable cases where the signals of the anomeric protons are sufficiently dispersed, the spin system of each pyranose unit could be separated and assigned. The ^{13}C signals of each unit were assigned from the 2D ^{1}H-^{13}C HMQC (heteronuclear multiple quantum coherence)[17] spectra.

The identification of the substituted pyranose unit was made possible from the large chemical shift change of some carbon and proton atoms induced by the substitution. The HMBC (heteronuclear multiple bond correlation)[18] spectra showed the correlation between each C4 carbon and the H1 proton of the adjacent unit due to the long-range coupling between these two atoms. This, allowed the determination of the sequence of the seven pyranose units. This sequence was confirmed by a high resolution selective 2D ROESY (rotating frame Overhauser enhancement)[19] experiment correlating the H1 proton of a given glucopyranose unit to the H4 proton of the adjacent one since the distance between these two atoms is close enough to give a nOe. The orientation of the phenyl residue with respect to the macrocycle ring was determined by a high resolution selective 2D ROESY experiment correlating the aromatic protons to the rest of the spectrum. However, the orientation of the aliphatic chain relative to the macrocycle ring could not be determined from a 2D ROESY experiment correlating the protons of the aliphatic chain to the rest of the spectrum.

For compounds **1-4**, the seven glucopyranose units are numbered from *a* to *g* with *a* being assigned to the unit which has the highest chemical shift for the anomeric proton H1 and *g* to the unit which has the lowest chemical shift for H1.

Compound 1

The spin system of each pyranose unit obtained from the 2D selective TOCSY, starting from the anomeric proton H1, is shown in Fig. 3B, and compared to the same region of the ^{1}H NMR spectrum of β-CD (Fig. 3A). As shown in Table 1, the comparison of the chemical shifts of the observed peaks to those of β-CD indicates that the H3 and H5 protons of the *c*, *e*, and *f* units and the H4 and H6 protons of unit *f* exhibit remarkably large upfield shifts ranging from 150-330 Hz. Moderate upfield shifts ranging from 36-126 Hz are observed for the H3 protons of the *a* and *d* units and for the H5 protons of the *d* and *g* units.

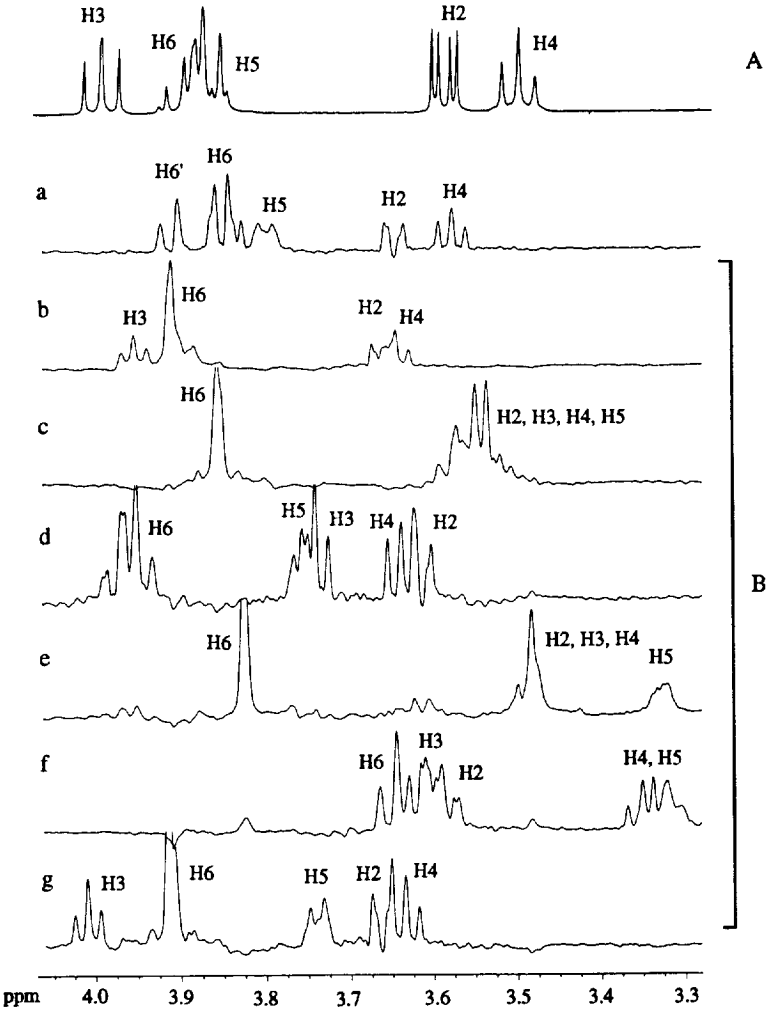


Fig. 3. Rows from the 2D selective TOCSY spectra of the seven pyranose units (*a-g*) of **1** starting from the anomeric protons H1 (B), comparing to a partial ^{1}H NMR spectrum of an equimolar solution of β-CD (A) (10 mM solution in D_2O at 600 MHz and 303°K, mixing time : 250 msec).

Table 1. ^{1}H NMR chemical shift data (in ppm) of **1** and β-CD (600 MHz, 10 mM in D_2O, 303°K), and their corresponding variation (in Hz). The positive and negative values in parentheses indicate downfield and upfield shifts respectively of **1** relative to β-CD.

Compd.	Glucose Unit	Proton H1	H2	H3	H4	H5	H6
1	*a*	5.11	3.67	3.86 (-60)	3.61	3.81 (-36)	3.87 3.92
	b	5.09	3.67	3.97 (+6)	3.66	3.91 (+24)	3.92
	c	5.04	3.59	3.56 (-240)	3.52	3.52-3.62[a] (-210 to -150)	3.87
	d	5.03	3.62	3.75 (-126)	3.65	3.77 (-60)	3.95 3.99
	e	5.02	3.50	3.49 (-282)	3.50	3.32 (-330)	3.83
	f	5.01	3.59	3.62 (-204)	3.36 (-132)	3.32 (-330)	3.62 (-144) 3.67 (-138)
	g	4.99	3.67	4.02 (+36)	3.65	3.75 (-72)	3.92
β-CD		5.06	3.64	3.96	3.58	3.87	3.86 3.90

[a]Exact values were not obtained due to overlap of the signals.

The two dimensional ^{1}H-^{13}C HMQC spectra showed that all C2's resonate in the range 72.5-73.0 ppm, except for C2*e* which resonates downfield at 79.4 ppm. This carbon atom is correlated to H2*e* which has an upfield resonance comparing to the other H2's. This behavior, which has been observed in the literature[20], is expected when a monosubstitution on CD occurs on C2 position and is ascribed to an electronic effect. Thus, in compound **1** the substituent is on C2*e*. The HMBC spectrum (Fig. 4) showed the correlation between each C4 and the H1 of the adjacent unit in compound **1**. The sequence of the seven pyranose units (Fig. 5A) was thus determined and furthermore confirmed by the ROESY experiment correlating the H1 proton of each glucopyranose unit to the H4 proton of the adjacent one.

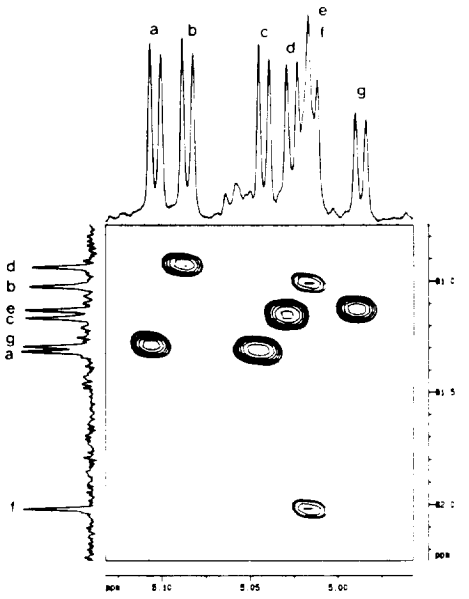


Fig. 4. A portion of the HMBC spectrum of **1** showing the correlation between each C4 and the H1 of the adjacent unit.

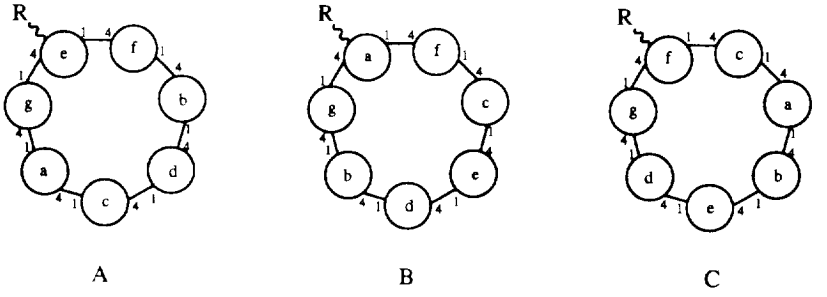


Fig. 5. Notation of the pyranose units from the HMBC and ROESY spectra. A : compound **1**, R = -$(CH_2)_5NHCOPhCO_2Me$, B : compound **2**, R = -$(CH_2)_3NHCOPhCO_2Me$ and C : compound **4**, R = -$(CH_2)_5NHCOPhCO_2Me$.

In view of the known affinity of an aromatic moiety towards the hydrophobic cavity of the CD[1,2], it was anticipated that a change in the resonance of the H3 and H5 protons located inside the cavity[9d,21] would result. A 2D ROESY experiment correlating the aromatic protons to the 3-4 ppm region of the ^1H NMR spectra of **1** (Fig. 6) indicates a nOe effect between the aromatic protons and the H3 and H5 protons even in a dilute solution (0.6 mM). The phenyl residue is thus definitively included inside the cavity forming an intramolecular inclusion complex (Fig. 1A). During this ROESY experiment, the two pairs of ortho hydrogens exhibit different ROEs *vis-a-vis* H3 and H5 protons (spectrum not shown). However, due to the lack of complete resolution in the rest of the spectrum, it was not possible to determine the exact position of the phenyl residue inside the cavity.

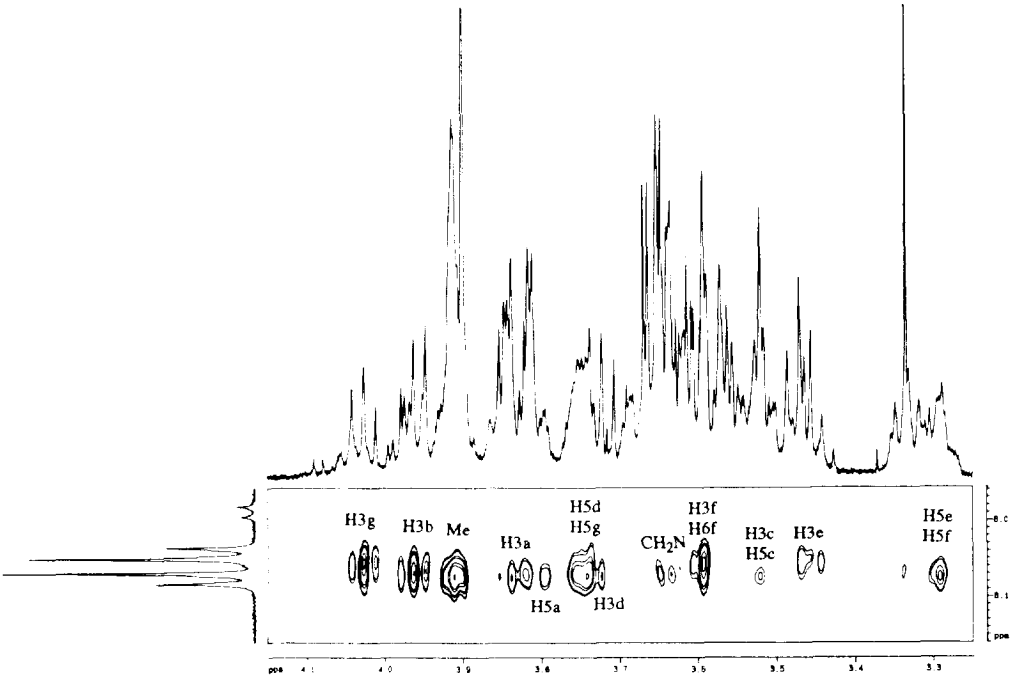


Fig. 6. Part of 2D ROESY spectra of **1** covering the aromatic protons (0.6 mM solution in D_2O, mixing time of 300 ms at 303°K).

The upfield shifts observed for H3 and H5 of the *e*, *f*, *c*, and *d* units, H5*g*, H3*a* and H6*f* attributed to the anisotropic ring current effect of the phenyl residue, indicate that these protons face the phenyl ring, while H3*b*, H5*b*, H5*a* and H3*g* are in the plane of the phenyl ring. The observed upfield or downfield shifts of H3 and H5 favor an intramolecular inclusion. There was no evidence for an intermolecular inclusion from this change in the resonance of H3 and H5 on the TOCSY spectra recorded at 0.6, 2.5, 10 and 20 mM. Another consequence of the intramolecular inclusion complex formation is the abnormal upfield shift of H4 of the unit *f* which is adjacent to the unit containing the substituent. This, may be attributed to a distorsion of the macrocycle in order to accommodate the phenyl moiety in the cavity.

When the same 2D ROESY spectrum was recorded in DMSO as solvent instead of D_2O, there was no nOe effect between the phenyl residue and the H3 and H5 protons. The formation of an inclusion complex is thus inhibited in DMSO solution presumably due to strong hydrogen bonding.

Compound 2

As shown in Fig. 2, the anomeric protons H1 in **2** are overlapped except H1*a* and H1*g*. For this reason, only the spin system of the *a* and *g* units were assigned. H3*a* and H3*g* resonate upfield at 3.58 and 3.65 ppm respectively compared to the other overlapped H3 signals which are found in the range of 3.80-3.88 ppm. H5*a* and H5g have the same upfield resonance at 3.58 ppm, while the other overlapped H5 protons resonate between 3.67-3.80 ppm.

The glucose unit *a* which bears the substituent was identified by virtue of the upfield chemical shifts of the H2 proton resonance and the downfield chemical shift of the C2 carbon resonance. A ROESY experiment correlating the H1 to the H4 signal of the adjacent unit indicates that the *g* unit, which exhibits an upfield shift for its H4 signal comparing to the other H4 signals, is adjacent to the unit *a* bearing the substituent.

These results indicate that an intramolecular inclusion complex is prevalent in **2** also (Fig. 1A). However, comparison of the chemical shifts of the H5 protons of the unit bearing the substituent and of its adjacent unit in **1** and **2**, coupled to the lack of any upfield change in the resonance of the H6 protons in **2**, we conclude that the phenyl residue is somewhat less included in the cavity in the case of **2** compared to **1**.

Compound 3

The results of assignment of the ^{1}H NMR spectra by TOCSY experiments, summarized in Table 2, and the sequence of the seven pyranose units shown in Fig. 5B, indicate the formation of an intramolecular inclusion complex in compound **3** as well (Fig. 1A). Upfield shifts of H4 and H6 of the unit *f* which is adjacent to the unit *a* bearing the substituent were observed. However, comparing the chemical shifts of the H5 and H6 protons of the unit containing the substituent and of its adjacent one in compounds **1**-**3**, we conclude that the phenyl residue in **3** is less included inside the cavity as compared to **1** but more included than in the case of **2**.

Table 2. ^{1}H NMR chemical shift data (in ppm) of **3** and β-CD (600 MHz, 10 mM in D_2O, 303°K), and their corresponding variation (in Hz). The positive and negative values in parentheses indicate downfield and upfield shifts respectively of **3** relative to β-CD.

Compd.	Glucose Unit	Proton H1	H2	H3	H4	H5	H6
3	*a*	5.14	3.46	3.55 (-246)	3.60	3.48 (-234)	3.82
	b	5.09	3.65	3.88 (-48)	3.58	3.82 (-30)	3.86 3.91
	c	5.07	3.65	3.92 (-24)	3.61	3.77 (-60)	3.85 3.87
	d	5.06	3.62	3.70 (-156)	3.56	3.67 (-120)	3.87 3.90
	e	5.04	3.63	3.82 (-84)	3.62	3.77 (-60)	3.93
	f	5.02	3.63	3.71 (-150)	3.47 (-66)	3.45 (-252)	3.66 (-120) 3.72 (-108)
	g	5.01	3.66	3.93 (-18)	3.61	3.73 (-84)	3.85 3.98
β-CD		5.06	3.64	3.96	3.58	3.87	3.86 3.90

Compound 4

TOCSY experiments effected on **4** are shown in Fig. 7B and are compared to the same areas in the spectrum of β-CD (Fig. 7A). The chemical shifts calculated from these experiments and summarized in Table 3 indicate once again a change in the resonance of H3, H5 and of H6 protons. This is due to the anisotropic effect of the phenyl residue which is included in the cavity (Fig. 1B).

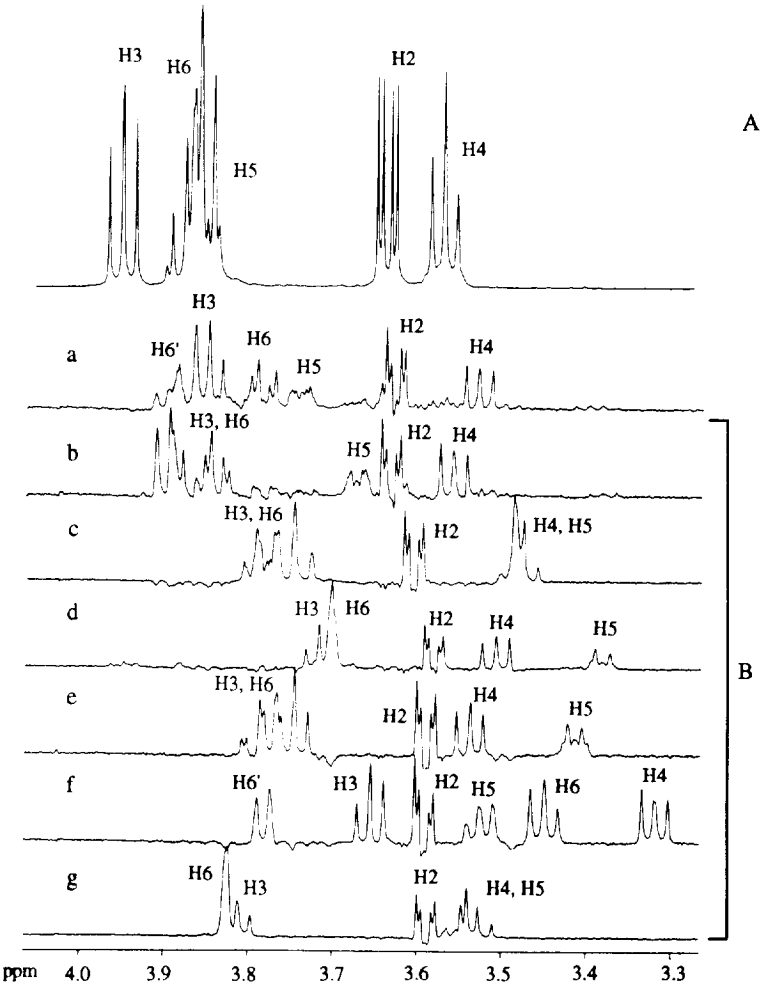


Fig. 7. Rows of the selective 2D TOCSY spectra of the seven pyranose units (*a-g*) of **4** starting from the anomeric protons H1 (B), comparing to a partial ^{1}H NMR spectrum of an equimolar solution of β-CD (A) (10 mM solution in D_2O at 600 MHz and 303°K, mixing time : 250 msec).

For this compound, remarkable upfield shifts are observed for H4*f* and H6*f* resonances (Table 3). Furthermore, an upfield shift was observed for C5*f* in the HMQC spectra. This behavior is expected when a

monosubstitution occurs on the C6 position which is the case in compound **4** in which the substituent is on C6*f*. The sequence of the seven pyranose units (Fig. 5C) determined from a ROESY experiment correlating each H1 to the H4 of the adjacent unit indicates also that the unit *a* containing the substituent is adjacent to the unit which exhibits an upfield shift for its H4 (unit *c*).

Table 3. ^{1}H NMR chemical shift data (in ppm) of **4** and β-CD (600 MHz, 10 mM in D_2O, 303°K), and their corresponding variation (in Hz). The positive and negative values in parentheses indicate downfield and upfield shifts respectively of **4** relative to β-CD.

Compd.	Glucose Unit	Proton H1	H2	H3	H4	H5	H6
4	*a*	5.09	3.63	3.85 (-66)	3.54	3.76 (-66)	3.79 3.90
	b	5.08	3.63	3.90 (-36)	3.57	3.68 (-114)	3.84 3.90
	c	5.01	3.61	3.76 (-120)	3.46 (-72)	3.46 (-246)	3.78
	d	4.99	3.59	3.72 (-144)	3.51	3.39 (-288)	3.70
	e	4.98	3.60	3.76 (-120)	3.53	3.42 (-270)	3.78
	f	4.96	3.60	3.66 (-180)	3.32 (-156)	3.52 (-210)	3.45 (-246) 3.78 (-72)
	g	4.94	3.60	3.81 (-90)	3.52	3.53 (-204)	3.82
β-CD		5.06	3.64	3.96	3.58	3.87	3.86 3.90

In an effort to obtain crystalline derivatives that were suitable for single crystal X-ray structural analysis of an intramolecular inclusion complex, we prepared the p-bromoamides **5** and **7**. Unfortunately, these were amorphous solids that could not be induced to crystallize. Their ^{1}H and ^{13}C NMR spectra at 400 MHz and 100.6 MHz respectively were in agreement for the formation of inclusion compounds also. The analogous observations were also made with the α-CD derivative **6**.

Hydrolysis studies

In order to gain further insight into the effects of inclusion of compounds **1-4** in β-CD, we undertook a qualitative study of the relative rates of hydrolysis of the ester function in dilute (0.05 mM), and concentrated (10 mM) buffer solution at pH 9.8. As shown on Fig. 8A, 50 % of hydrolysis was observed after 30 h for **1**, 5h for **2**, 7.5 h for **3** and 12 h for **4** in a 0.05 mM solution. While in a solution 20 times more concentrated, 50 % of hydrolysis was seen after 55 h for **1**, 9 h for **2**, 20 h for **3** and 26 h for **4** (Fig. 8B). These results strongly suggest that the phenyl residue in compounds **1-4** is included in the cavity, and that it is "protected" from hydrolysis to varying degrees.[22] Compound **1** appears to be the least affected and **2** the most. This trend is more apparent in a concentrated solution.

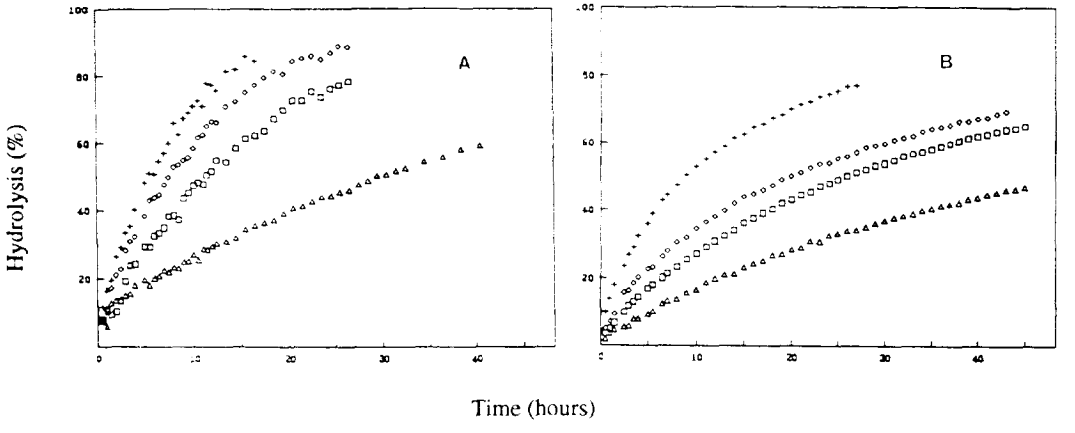


Fig. 8. Hydrolysis rate of the methyl ester group of **1** (△), **2** (+), **3** (◇) and **4** (□) in a 0.05 mM (A) and 10 mM buffer solution (B) (pH 9.8, carbonate buffer, 303°K).

As a control experiment, we prepared compound **8**[23] which would be expected to form an inclusion complex, thus simulating any effect resulting from an intermolecular association between two molecules of the tethered esters. Its capacity to form inclusion complex with CD was ascertained by ^{1}H NMR studies of a mixture of **8** (5 mM) and 2 equivalents of β-CD in D_2O. The expected upfield shifts of H5 (-114 Hz) and of H3 (-66 Hz) were observed as shown in Figure 9. The hydrolysis of a 5 mM solution of **8** in the presence and absence of 2 equivalents of β-CD was effected in a pH 9.8 buffer. A level of 50 % of hydrolysis was reached after 5 h and 12 h in the absence and presence of β-CD respectively. These results are in accord with the literature where an inhibition of the hydrolysis of the alkyl esters by CDs has been reported[22].

The differences in hydrolysis rate at 50 % completion of compounds **1-4** are also a reflection of their rates of inclusion within the cavity, which in turn, may depend on a number of factors related to their stabilities. Further studies are in progress and will be reported in due course.

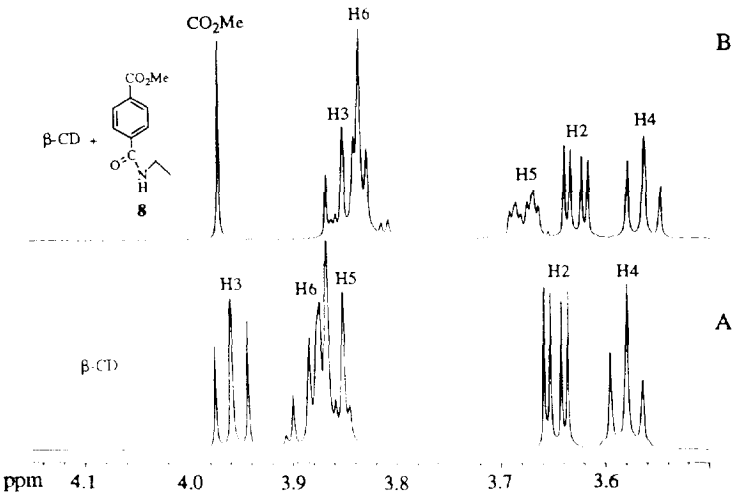


Fig. 9. Partial ^1H NMR of a 10 mM solution of β-CD (A) and of a mixture solution of β-CD and compound **8** (10 mM for β-CD and 5 mM for **8**) in D_2O at 303°K (B).

EXPERIMENTAL

General. The cyclodextrins and all reagents were purchased from Aldrich and used without further purification. α- and β- CD were dried under vaccum at 90°C for 20 hours before use. DMF was distilled from CaH_2. Medium pressure chromatography was performed using a fluid Metering pump and medium pressure column (15x200 mm). The column was packed manually with Lickroprep RP18 (40-63 μm, Merck). Thin layer chromatography (TLC) was performed on glass plates coated with a 0.02-mm layer of silica gel 60 F-254 purshased from Merck. The eluent solvent for TLC was CH_3CN-H_2O, 4 : 1. Spot detection was carried out by the molybdate reagent. Optical rotations were measured at 25°C at the sodium line on a Perkin-Elmer 241 spectropolarimeter. The IR spectra were recorded on a Perkin-Elmer 721 spectrophotometer using KBr pellets. Fast atom bombardement (FAB) mass spectra (carrier gas, Xenon) were recorded on a Kratos MS 50 instrument. The ^1H NMR spectra were measured on a Brucker AMX 600 spectrometer, operating at 600.14 MHz for ^1H and 150.90 MHz for ^{13}C or on a Brucker ARX 400 spectrometer operating at 400.10 MHz for ^1H and 100.13 for ^{13}C, using D_2O as solvent and DSS as reference. All chemical shifts are quoted in ppm on the δ scale, J values are expressed in Hz.

2-O-[5-(*mono*-Methylterephthaloyl)-aminopentyl]-β-cyclodextrin (1).

2-O-(5-Aminopentyl)-β-cyclodextrin[13] dried under vacuo at 70°C overnight (60 mg, 0.05 mmol) was dissolved in DMF (10 mL) then treated with 1 equivalent of dicyclohexylcarbodiimide, 1-hydroxybenzotriazole hydrate, and terephthalic acid mono methyl ester. The mixture was stirred overnight at room temperature. After removal

of DMF in vacuo, the residue was suspended in water (20 mL) then washed with dichloromethane (2x10 mL). The aqueous phase was concentrated in vacuo to give a residue which was applied on a reversed phase column (Lichroprep C18, 2x20 cm). Stepwise elution with water (500 mL), 10 % methanol (200 mL), then 30 % methanol (300 mL) gave the product as a colorless solid (50 mg, 76 %); mp 235°C (dec); $[\alpha]_D^{25}$ +100.0° (c 0.22, MeOH); IR (KBr) 1700, 1620 (CO); ^{1}H NMR (D_2O, 600 MHz, the carbon atoms in the aliphatic chain are numbered from α to ε) : δ 1.48-1.56 (m, 1H, Hδ); 1.48-1.60 (m, 2H, Hγ); 1.60-1.69 (m, 2H, Hβ); 1.80-1.89 (m, 1H, H'δ); 3.32 (m, 2H, H5*e*, H5*f*); 3.35 (m, 1H, Hε); 3.36 (m, 1H, H4*f*); 3.50 (m, 3H, H2*e*, H3*e*, H4*e*); 3.52-3.62 (m, 4H, H2*c*, H3*c*, H4*c*, H5*c*); 3.59 (dd, 1H, H2*f*); 3.61 (t, 1H, H4*a*); 3.62 (m, 2H, H2*d*, H6*f*); 3.65 (m, 2H, H4*d*, H'ε); 3.66 (t, 1H, H4*b*); 3.67 (m, 4H, H2*a*, H2*b*, H2*g*, H6'*f*); 3.75 (m, 2H, H3*d*, H5*g*); 3.76 (m, 1H, Hα); 3.77 (m, 1H, H5*d*); 3.81 (m, 1H, H5*a*); 3.83 (m, 1H, H6*e*); 3.86 (m, 1H, H3*a*); 3.87 (m, 2H, H6*a*, H6*c*); 3.91 (s, 3H, CH_3); 3.92 (m, 3H, H6'*a*, H6*b*, H6*g*); 3.95 (m, 1H, H6*d*); 3.97 (t, 1H, H3*b*); 3.99 (m, 1H, H6'*d*); 4.02 (m, 2H, H3*g*, H'α); 4.99 (d, 1H, J = 3.6, H1*g*); 5.01-5.02 (m, 2H , H1*e*, H1*f*); 5.03 (d, 1H, J = 3.6, H1*d*); 5.04 (d, 1H, J = 3.6, H1*c*); 5.09 (d, 1H, J = 3.6, H1*b*); 5.11 (d, 1H, J = 3.6, H1*a*); 8.04 (d, 2H, J = 8.5, ph); 8.08 (d, 2H, J = 8.6, ph); ^{13}C NMR (D_2O, 150.9 MHz) : δ 22.1, 27.4, 28.7 (Cβ, Cγ, Cδ); 40.4 (Cε); 53.7 (CH_3); 60.6, 60.7, 60.8 (C6); 70.6 (Cα); 72.20, 72.29 (C5*e*, C5*f*, C5*c*); 72.5, 72.6, 72.72, 72.75 (C2, C5*g*, C5*d*, C5*a*); 72.8 (C5*b*); 72.90, 72.96 (C2); 73.8 (C3*c*); 73.9 (C3*d*); 74.00 (C3*g*); 74.09 (C3*a*, C3*b*); 74.5 (C3*f*); 74.8 (C3*e*); 79.4 (C2*e*); 81.3 (C4*d*); 81.4 (C4*b*); 81.50 (C4*e*); 81.53 (C4*c*); 81.63 (C4*g*); 81.65 (C4*a*); 82.38 (C4*f*); 101.7 (C1*e*); 102.1 (C1*g*); 102.3 (C1*f*); 102.5 (C1*b*); 102.6 (C1*a*); 102.7 (C1*c*, C1*d*); 128.2, 129.9, 132.5, 139.6 (ph); 168.0, 169.1 (CO); FAB MS calcd for $C_{56}H_{87}O_{38}N$ 1404.4803 (M+Na), found 1404.4760.

2-O-[4-(*mono*-Methylterephthaloyl)-aminobutyl]-β-cyclodextrin (2).

Essentially the same procedure was used to give **2** as a colorless solid, yield 75 %; mp 230°C (dec); $[\alpha]_D^{25}$ +114.2° (c 0.40, H_2O); IR (KBr) 1700, 1620 (CO); ^{1}H NMR (D_2O, 600 MHz, the carbon atoms in the aliphatic chain are numbered from α to δ) : δ 1.75-1.82 (m, 4H, Hβ, Hγ); 3.54 (m, 2H, Hδ); 3.56-3.98 (m, H2, H3, H4, H5, H6, Hα); 4.02 (s, 3H, CH_3); 5.03-5.07 (m, 6H, H1); 5.16 (d, 1H, J = 3.6, H1*a*); 7.95 (d, 2H, J = 8.5, ph); 8.08 (d, 2H, J = 8.5, ph); ^{13}C NMR (D_2O, 150.9 MHz) : δ 26.0, 27.4 (Cβ, Cγ); 40.6 (Cδ); 53.7 (CH_3); 60.7, 60.8, 60.9 (C6); 72.50, 72.55, 72.6, 72.72, 72.78, 72.8 (C2, C5, Cα); 73.2, 73.9, 74.0, 74.1 (C3); 81.0 (C2); 81.5, 81.6, 81.70, 81.73, 81.77, 81.9, 82.1 (C4); 101.0, 102.3, 102.53, 102.58, 102.70, 102.75 (C1); 128.1, 129.7, 130.0, 132.7, 139.5 (ph); 168.2, 169.3 (CO); FAB MS calcd for $C_{55}H_{85}O_{38}N$ 1390.4647 (M+Na), found 1390.4775.

2-O-[3-(*mono*-Methylterephthaloyl)-aminopropyl]-β-cyclodextrin (3).

Essentially the same procedure was used to give **3** as a colorless solid, yield 70 %; mp 225°C (dec); $[\alpha]_D^{25}$ +143.0° (c 0.5, H_2O); IR (KBr) 1700, 1620 (CO); ^{1}H NMR (D_2O, 600 MHz, the carbon atoms on the aliphatic chain are numbered from α to γ) : δ 1.86-1.98 (m, 2H, Hβ); 3.45 (m, 1H, H5*f*); 3.46 (dd, 1H, H2*a*); 3.47 (m, 1H, H4*f*); 3.48 (m, 1H, H5*a*); 3.55 (t, 1H, H3*a*); 3.56 (t, 1H, H4*d*); 3.58 (t, 1H, H4*b*); 3.60 (m, 2H, H4*a*, Hγ); 3.61 (t, 2H, H4*g*); 3.62 (m, 2H, H2*d*, H4*e*); 3.63 (m, 2H, H2*f*, H2*e*); 3.65 (m, 3H, H2*f*, H2*c*, H'γ); 3.66 (m, 2H, H2*g*, H6*f*); 3.67 (m, 1H, H5*d*); 3.70 (t, 1H, H3*d*); 3.71 (m, 2H, H3*f*, H6'*f*); 3.73 (m, 1H, H5*g*); 3.77 (m, 2H, H5*c*, H5*e*), 3.82 (m, 3H, H3*e*, H5*b*, H6*a*), 3.85 (m, 2H, H6*c*, H6*g*); 3.86 (m, 1H, H6*b*); 3.87 (m, 2H, H6'*c*, H6*d*); 3.88 (t, 1H, H3*b*); 3.90 (m, 1H, H6'*d*); 3.91 (m, 1H, H6'*b*); 3.92 (m, 4H, H3*c*, CH_3);

3.93 (m, 2H, H3*g*, H6*e*); 3.95 (m, 1H, Hα); 3.98 (m, 1H, H6'*g*); 4.05 (m, 1H, H'α); 5.01 (d, 1H, J = 3.6, H1*g*); 5.02 (d, 1H, J = 3.6, H1*f*); 5.04 (d, 1H, J = 3.6, H1*e*); 5.06 (d, 1H, J = 3.6, H1*d*); 5.07 (d, 1H, J = 3.6, H1*c*); 5.09 (d, 1H, J = 3.6, H1*b*); 5.14 (d, 1H, J = 3.6, H1*a*); 7.99 (d, 2H, J = 8.5, ph); 8.08 (d, 2H, J = 8.5, ph); ^{13}C NMR (D_2O, 150.9 MHz) : δ 28.9 (Cβ); 39.4 (Cγ); 53.3 (CH_3); 60.2, 60.4, 60.5 (C6); 71.9, 72.0, 72.1, 72.2, 72.3, 72.4, 72.5, 72.6 (C2, C5, Cα); 73.2 (C3*a*); 73.50 (C3*d*); 73.51 (C3*e*); 73.6 (C3*b*); 73.7 (C3*c*, C3*g*); 74.0 (C3*f*); 80.0 (C2*a*); 80.2 (C4*a*); 81.0 (C4*e*); 81.1 (C4*f*); 81.30 (C4*c*); 81.33 (C4*d*); 81.38 (C4*g*); 81.5 (C4*b*); 100.3 (C1*a*); 101.4 (C1*g*); 102.0 (C1*f*); 102.1 (C1*c*); 102.2 (C1*b*); 102.3 (C1*e*); 102.4 (C1*d*); 127.7, 129.7, 132.4, 139.0 (ph); 167.7, 169.0 (CO); FAB MS calcd for $C_{54}H_{83}O_{38}N$ 1354.4671 (M+H), found 1354.4724.

6-O-[5-(*mono*-Methylterephthaloyl)-aminopentyl]-β-cyclodextrin (4).

6-O-(5-Azidopentyl)-2,3-dodecabenzyl-β-cyclodextrin described previously[13] (200 mg, 0.1 mmol) was reduced with Ph_3P/NH_4OH method[24] to give a solid which was applied on a short silica gel column eluted first with CH_2Cl_2-MeOH, 9:1, to remove triphenylphosphine oxide and excess triphenylphosphine, then with CH_2Cl_2-MeOH-H_2O, 80:19:1 to 30:10:1 to get the amine as a solid, (200 mg, 100 %), Rf 0.20 (CH_2Cl_2-MeOH-H_2O, 80:19:1). The coupling conditions of the amine and methylterephthalate are the same than described above. The crude product was applied on a short silica gel column which was eluted with CH_2Cl_2-MeOH, 10:1 to CH_2Cl_2-MeOH-H_2O, 80:19:1to get the protected compound as a solid, (150 mg, 70 %), Rf 0.60 (CH_2Cl_2-MeOH, 7:1). The benzyl groups were removed by hydrogenolysis of the compound with palladium hydroxide on charcoal (Pearlman's catalyst) in MeOH at 120 psi for 2 days to give a solid which was further purified on a reverse phase column (Lichroprep C18, 2x 20 cm). The elution conditions applied are the same than in **1** to give the compound as a colorless solid (60 mg, 73 %). mp 235°C (dec); $[\alpha]_D^{25}$ +100.0° (c 0.22, MeOH); IR (KBr) 1700, 1620 (CO); ^{1}H NMR (D_2O, 600 MHz, the carbon atoms in the aliphatic chain are numbered from α to ε) : δ 1.37-1.50 (m, 2H, Hγ); 1.52-1.67 (m, 4H, Hβ, Hδ);); 3.32 (m, 2H, H4f, Hε); 3.35 (m, 1H, Hα); 3.39 (m, 1H, H5*d*); 3.42 (m, 1H, H5*e*); 3.45 (m, 1H, H6*f*); 3.46 (m, 2H, H4*c*, H5*c*); 3.51 (m, 2H, H4*d*; H'ε); 3.52 (m, 2H, H4*g*, H5*f*); 3.53 (m, 2H, H5*g*, H4*e*); 3.54 (m, 1H, H4*a*); 3.56 (m, 1H, Hα'); 3.57 (m, 1H, H4*b*); 3.59 (m, 1H, H2*d*); 3.60 (m, 3H, H2*e*, H2*g*, H2*f*); 3.61 (m, 1H, H2*c*); 3.63 (m, 2H, H2*a*, H2*b*); 3.66 (m, 1H, H3*f*); 3.68 (m, 1H, H5*b*); 3.70 (m, 2H, H6*d*); 3.72 (m, 1H, H3*d*); 3.76 (m, 3H, H3*e*, H3*c*, H5*a*); 3.78 (m, 5H, H6*e*, H6*c*, H6'*f*); 3.79 (m, 1H, H6*a*); 3.81 (m, 1H, H3*g*); 3.82 (m, 2H, H6*g*); 3.84 (m, 2H, H6*b*); 3.85 (m, 1H, H3*a*); 3.90 (m, 3H, H3*b*, H6'*a*, H6'*b*); 4.02 (s, 3H, Me); 4.94 (d, 1H, H1*g*); 4.96 (d, 1H, H1*f*); 4.98 (d, 1H, H1*e*); 4.99 (d, 1H, H1*d*); 5.01 (d, 1H, H1*c*); 5.08 (d, 1H, H1*b*); 5.09 (d, 1H, H1*a*); 7.95 (d, 2H, ph); 8.08 (d, 2H, ph); ^{13}C NMR (D_2O, 150.9 MHz) : δ 22.9, 27.8, 28.5, 40.3 (pentyl); 54.0 (Me); 60.4 (C6*d*); 60.6, 60.7 (C6*e*, C6*c*); 61.03, 61.07 (C6*a*, C6*b*, C6*g*); 70.4 (CH_2O, C6*f*); 71.8 (C5*f*); 72.6, 72.7, 72.8, 72.9, 73.0 (C2, C5); 73.8 (C3*f*), 73.9 (C3*b*); 74.0 (C3*e*, C3*d*, C3*a*); 74.1 (C3*g*); 74.3 (C3*c*); 81.5 (C4*d*); 81.74 (C4*g*); 81.78 (C4*b*); 81.8 (C4*e*); 81.9 (C4*a*); 82.0 (C4*c*); 83.0 (C4*f*); 102.4 (C1*c*, C1*f*); 102.5 (C1*d*); 102.7 (C1*a*, C1*e*); 102.8 (C1*g*, C1*b*); 127.5, 130.3, 133.3, 139.4 (ph); 168.3 (CO); FB MS calcd for $C_{56}H_{87}O_{38}N$ 1382.4984 (M+H), found 1382.4919.

2-O-[5-(p-Bromobenzoyl)-aminopentyl]-β-cyclodextrin (5).

Essentially the same procedure was used as above, using p-bromobenzoic acid as acid, to give **4** as a colorless solid, yield 80 %; mp 245°C (dec); $[\alpha]_D^{25}$ +142.7° (c 0.32, H_2O); IR (KBr) 1630 (CO); ^{1}H NMR (D_2O, 400

MHz, the carbon atoms in the aliphatic chain are numbred from α to ε) : δ 1.40-1.98 (m, 6H, Hβ, Hγ, Hδ); 3.40 (m, 2H, Hε); 3.52-4.13 (m, H2, H3, H4, H5, H6, Hα); 5.08-5.10 (m, 7H, H1);7.69 (d, 2H, J = 8.5, ph); 7.91 (d, 2H, J = 8.5, ph); ^{13}C NMR (D_2O, 100.6 MHz) : δ 22.2, 27.4, 28.6, (Cβ, Cγ, Cδ); 40.3 (Cε); 60.6, 60.7, 60.8 (C6); 70.8 (Cα); 72.1, 72.4, 72.5, 72.6, 72.8 (C2, C5); 73.8, 73.9, 74.0, 74.3, 74.6 (C3); 79.5 (C2); 81.6, 81.70, 81.73, 81.78, 82.4 (C4); 101.6, 102.2, 102.3, 102.5, 102.6 (C1); 126.1, 129.7, 131.7, 134.0 (ph); 169.1 (CO); FAB MS calcd for $C_{54}H_{84}O_{36}NBr$ 1402.4034 (M+H), found 1402.4076.

2-O-[5-(*mono*-Methylterephthaloyl)-aminopentyl]-α-cyclodextrin (6).

Essentially the same procedure was used to give the compound **6** as a colorless solid, yield 86 %; mp 212°C (dec); $[\alpha]_D^{25}$ +109.6° (c 0.25, H_2O); IR (KBr) 1620, 1710 (CO); ^{1}H NMR (D_2O, 400 MHz, the carbon atoms in the aliphatic chain are numbered from α to ε) : δ 1.30-178 (m, 6H, Hβ, Hγ, Hδ); 2.80 (m, 1H, Hε); 3.05 (m, 1H, H'ε); 3.42-4.10 (m, H2, H3, H4, H5, H6, Hα); 3.96 (s, 3H, CH_3); 4.94-5.05 (m, 7H, H1); 8.17 (d, 2H, J = 7.8, ph); 8.59 (d, 2H, J = 7.8, ph); ^{13}C NMR (D_2O, 100.6 MHz) : δ 23.5, 28.7, 29.7 (Cβ, Cγ, Cδ); 41.1 (Cε); 53.9 (CH_3); 60.6, 60.9 (C6); 72.5, 72.6, 72.8 (C2, C5, Cα); 73.3, 73.7, 74.0, 74.5, 74.7, 74.8 (C3); 80.3 (C2); 81.4, 81.9, 82.0, 82.4 (C4); 102.7, 102.8, 102.9, 103.0 (C1); 127.7, 131.9, 132.0, 139.9 (ph); 167.8, 168.6 (CO); FAB MS calcd for $C_{50}H_{77}O_{33}N$ 1220.4456 (M+H), found 1220.4419.

2-O-[5-(p-Bromobenzoyl)-aminopentyl]-α-cyclodextrin (7).

Essentially the same procedure was used to give the compound **7** as a colorless solid, yield 71 %; mp 235°C (dec); $[\alpha]_D^{25}$ +99.6° (c 0.25, MeOH); IR (KBr) 1620 (CO); ^{1}H NMR (D_2O, 400 MHz, the carbon atoms in the aliphatic chain are numbered from α to ε) : δ 1.35-1.75 (m, 6H, Hβ, Hγ, Hδ); 3.10 (m, 2H, Hε); 3.50-4.30 (m, H2, H3, H4, H5, H6, Hα); 5.00-5.10 (m, H1); 5.20-5.26 (m, H1); 8.01 (d, 2H, J = 8.3, ph); 8.10 (d, 2H, J = 8.4, ph); ^{13}C NMR (D_2O, 100.6 MHz) : δ 23.3, 28.7, 29.5, (Cβ, Cγ, Cδ); 40.9 (Cε); 60.9, 61.0 (C6); 72.3, 72.4, 72.8, 72.9, 73.3 (C2, C5, Cα); 74.0, 74.6, 74.7, 74.8, 75.0 (C3); 80.4 (C2); 81.6, 81.9, 82.2 , 82.40, 82.46, 82.63 (C4); 102.1, 102.4, 102.5, 102.8, 102.9 (C1); 126.3, 129.6, 133.0, 134.5 (phenyl); 169.1 (CO); FAB MS calcd for $C_{48}H_{74}O_{31}NBr$ 1240.3506 (M+H), found 1240.3441.

Acknowledgements. We acknowledge generous financial support from the National Science and engineering Council of Canada.

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(*Received in USA* 12 *May* 1995; *accepted* 19 *July* 1995)