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Synthesis and characterization of persilylated cyclodextrins

Valeria Harabagiu[a], Bogdan C. Simionescu[a], Mariana Pinteala[a], C. Merrienne[b], Jacqueline Mahuteau[b], Philippe Guégan[c,*], Hervé Cheradame[c]

[a]'P. Poni' Institute of Macromolecular Chemistry, 6600 Iasi, Romania
[b]RMN BIOCIS, URA 1843, 92296 Chatenay-Malabry Cedex, France
[c]Laboratoire MPI, Université d'Evry Val d'Essonne, 91025 Evry, France

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Abstract

Partially and pertrimethylsilylated α-, β- and γ-cyclodextrins (CDs) were prepared by reacting the native CDs with trimethylsilylimidazole. The selectivity of primary silylation can reach a 9/1 preference for the lower α-CD homologue. This selectivity is lost when α or β CDs are used. The total substitution of hydroxyl groups with bulky trimethylsilyl radicals induces a strong conformational deviation of CD molecules compared to the native precursors. An NMR investigation of persilylated α-CD allowed a complete assignment of all resonance peaks. Persilylated CDs are thermally stable compounds (decomposition temperature around 380 °C), soluble in non-polar solvents (petroleum ether, benzene, toluene) and insoluble in water, dimethylformamide or dimethylsulfoxide. The experimentally determined properties were supported sustained by simulation data.

Keywords: Silylated α, β, γ cyclodextrins; NMR characterization; Modeling

1. Introduction

Cyclodextrins (CDs) have been of continuous interest over the last 50 years. The most frequently, isolated have been α-, β-, γ- and δ-CDs (containing, respectively, 6, 7, 8 and 9 glucopyranose units) though more recently larger oligomers, viz. ε-CD (Ueda, Endo, Nagase, Kobayashi, & Nagai, 1996) have stimulated a large number of investigations. Their peculiar chemical structure, i.e. three different hydroxyl groups in each 1,4-linked glucopyranose structural unit and a spatial arrangement in a toroidal/hollow truncated cone shaped molecule, allows the formation of inclusion complexes. Thus, two aspects of CD-based physico-chemistry are mainly considered: selective chemical modification of hydroxyl groups and complexation of organic molecules (including polymers) by the relatively hydrophobic cavity of CDs.

The selective modification of CDs was performed by a direct procedure, involving a selective activation with bulky triphenylphosphonium salt (Boger, Corcoran, & Lehn, 1978) or protection of primary hydroxyl functions by *t*-butylsilylation (Takeo, Mitoh, & Uemura, 1989) and by an indirect method, based on the protection of all alcohol groups as benzoate esters, followed by selective deprotection of primary hydroxyl groups (Takeo et al., 1989). A particular class of modified CDs is represented by the 'bouquet' molecules having oligomer chains (poly(ethylene oxide) or polyolefin (Canceill, Jullien, Lacombe, & Lehn, 1992; Jullien, Lazrak, Canceill, Lacombe, & Lehn, 1993; Topchieva, Polyakov, Elezkaya, Bystryzky, & Karenzin, 1997), polysiloxane (Bradshaw et al., 1995; Yi et al., 1993), linked to CD molecules. Polyurethanes grafted with CD modified hydroxyethyl methacrylate by γ irradiation and their use as separative membranes were also reported (Sreenivasan, 1996). Since the substitution of hydroxyl groups with less polar organic radicals affects the internal-hydrophobic/external-hydrophilic ratio of CD molecules and their conformation, with a strong influence upon the complexation properties, permethylated CDs were also prepared and their inclusion ability has been demonstrated (Botsi, Yaunakopoulou, Perly, & Hadjoudis, 1995; Casu & Reggiani, 1979). The general idea in the preparation of CD inclusion complexes was the modification of physical (volatility and solubility) or chemical (reactivity) properties

* Corresponding author. Fax: +33-169-477721.
E-mail address: philippe.guegan@chimie.univ-evry.fr (P. Guégan).

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of organic compounds or the synthesis of new materials with special characteristics. Derivatized CDs and different inclusion complexes were evaluated as catalysts in organic chemistry (Lewis, Sumpter, & Davis, 1995; Lewis, Sumpter, & Stein, 1996; Reetz & Waldvogel, 1997; de Rossi, Barra, & de Vargas, 1986), water soluble monomers (Glockner, Metz, & Ritter, 2000), enzymatic models (Hattory, 1996),[17] organic sensors (Aoyagi et al., 1997; Corradini et al., 1997; Kuwabara, Matsushita, Nakamura, Ueno, & Toda, 1993; Wang, Ikeda, Ueno, & Toda, 1993) controlled drug release systems containing physically linked active compounds (Kurozumi, Nambu, & Nagai, 1975). Polyrotaxanes based on CD molecules threaded on various polymers such as poly(ethylene oxide) (Harada & Kamachi, 1990a,b) poly (propylene oxide) (Harada & Kamachi, 1990a,b), poly (methylvinyl ether) (Harada, Li, & Kamachi, 1993), polyamides (Wenz, Steinbrunn, & Landfester, 1997), polyesters (Gibson, Liu, Lecavalier, Wu, & Shen, 1995; Kawaguchi, Nishiyama, Okada, Kamachi, & Harada, 2000), cationic polymers (Harada, Adachi, Kawaguchi, Okada, & Kamachi, 1996), polyisobutene (Harada, Li, Suzuki, & Kamachi, 1993), polyazomethines (Simionescu, Grigoras, Farcas, & Stoleru, 1998) or polydimethylsiloxanes (Okamura, Okada, Kawaguchi, & Harada, 2000) were also prepared.

Up to date the silylation of hydroxyl groups in carbohydrate compounds and polymers has been used only as a protecting method (Ogilvie, Beaucage, Schifman, Theriault, & Sadana, 1978; Takeo et al., 1989; Takeo, Uemura, & Mitoh, 1988; Zhang & Robin, 1992). Different types of very efficient silylating agents were required (Lalonde & Chan, 1985; Nouvel et al., 2002; Silylating Agents, 1995). Moreover, the halogenosilanes with bulky organic radicals (*t*-butyltrimehylsilylchlorosilane), in the presence of imidazole as acid acceptor were proved to substitute the primary hydroxyl groups of α-, β- and γ-CDs with a selectivity of 70% (Takeo et al., 1989, 1988).

This paper deals with the synthesis of new, entirely hydrophobic α-, β- and γ-CDs derivatives obtained by persilylation of native CDs with 1-trimethylsilylimidazole. As the substitution of all hydroxyl groups with bulky trimethylsilyl units strongly influenced the conformation of CD molecules, a detailed NMR study and the modeling of molecular geometry were performed in order to establish their stereostructure.

2. Experimental part

α-, β-, γ-CDs (Aldrich) were dried in a vacuum oven at 80 °C for 48 h. *N*-Trimethylsilylimidazole (TMSIm; Aldrich) was used without further purification. The solvents (chloroform, dimethylformamide) were dried by refluxing over CaH_2 and then distilled.

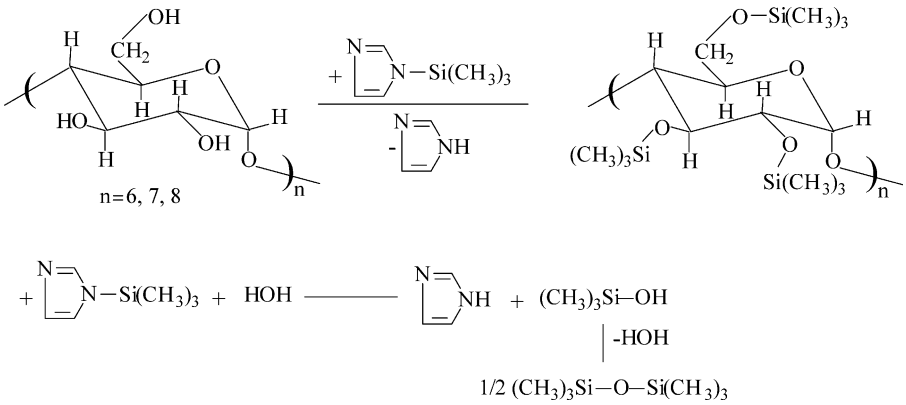
The silylation of CDs was performed in anhydrous conditions, under inert atmosphere. In a round bottomed vessel fitted with reflux condenser and a dropping funnel, a 2 wt% CD solution in DMF was prepared. A calculated excess of TMSIm in chloroform was then dropped over the CD solution, at 20 °C under magnetic stirring. After 3 h, the slurry mixture was diluted with chloroform until it becomes clear. The reaction was monitored by ^{1}H-NMR spectroscopy, following the disappearance of OH protons and stopped with ice. Aqueous phase was then removed and the organic phase was washed with water until neutral pH, and dried over $MgSO_4$. The solvents and hexamethyldisiloxane formed by the hydrolysis of TMSIm excess were removed by vacuum evaporation (60 °C, 24 h). Persilylated CDs were obtained in yields higher than 95% as white powders insoluble in polar solvents and highly soluble in petroleum ether, toluene, chloroform.

IR spectra were registered on a Bruker IFS 28. Preliminary and detailed NMR characterization was performed on a Bruker AC 200, and a Bruker ARX 400. Measurements were carried out on about 50 mg of persilylated-α-CD dissolved into 1 cm^3 of CD_2Cl_2 (except for the 200 MHz experiments that were carried out in $CDCl_3$). Spectra are referenced to TMS as internal standard. The probe temperature has been stabilized at 300 K. SEC curves were obtained by separation of silylated CD solutions in chloroform on Gel 500, 10^3, 10^4 Å Polymer Laboratories columns (flow, 1 ml/min; polystyrene standards). MALDI-TOF MS analysis was performed using a Perseptive Biosystems Voyager-DE Pro STR time of flight mass spectrometer. This instrument was equipped with a nitrogen laser ($\lambda = 337$ nm). External calibration using PEO was performed with the same matrix as in the experiments (2-nitrophenyloctyl ether 10^{-1} M in THF). The concentration of CD solutions was 10^{-3} M (analyte concentration). For all analyses, typically 20 μl of the analyte solution were added to a 20 μl solution of matrix and thoroughly mixed then centrifuged. About 0.5 μl of the resulting mixture was spotted onto the sample plate and allowed to air dry at room temperature. TGA results were obtained on a Derivatograph MOM Budapest. The molecular geometry modeling was performed with Hyperchem program and the MM + method was used for the modeling of molecular mechanics.

3. Results and discussion

3.1. Synthesis of partially and persilylated CDs

The silylation of CD molecules was performed with a relatively new silylating agent, *N*-trimethylsilylimidazole $(TMSIm)^{(Silylating\ agent)}$ (Scheme 1) that was proved to be much more efficient than any other systems. Poor silylation was observed by use of a mixture of trimethylchlorosilane and pyridine and only partially and unselectively silylated β-oligomers were obtained with a large excess of trimethylchlorosilane/imidazole (OH/SiCl/Im = 1/20/20 M ratio) system within 72 h.



Scheme 1.

Persilylation of CDs with TMSIm in homogeneous conditions was achieved by using a mixture of DMF (solvent of native CDs) and chloroform (solvent of silylated CDs). The hydrophilicity of CD molecules decreases as the degree of silylation increases and the solubility in DMF is thus reduced. A colloidal dispersion of partially modified CDs is obtained after several hours of reaction in DMF. The homogenization of the reaction mixture through addition of chloroform yielded the expected decrease of reaction duration and of the required excess of reagents to reach high degrees of substitution.

The aim of this work is the persilylation of CD molecules. However, as one can see from Table 1, interesting partially substituted α- and β-CDs were obtained in DMF solution using various TMSIm/OH molar ratios. The persilylation of the α-isomer with a 5-fold excess of TMSIm was not achieved in heterogeneous conditions, despite a quite long reaction time. Homogenizing the mixture by adding chloroform allowed the total substitution of OH groups of this isomer in the presence of a lower excess of silylating agent. The β- and γ-oligomers showed a greater facility toward the silylation reaction; a higher degree of substitution was obtained for β-CD as compared to α-CD in DMF after 72 h. Also, the γ-oligomers can be persilylated in heterogeneous reaction mixtures in a reasonable time although its total transformation requires higher reaction times and/or higher [TMSIm]/[OH] molar ratios than in homogeneous conditions. These results have to be compared with the one observed for the reaction between CDs, chlorotrimethylsilane and imidazole, that did not allow complete substitution of the hydroxy groups. Such an improvement of the silylation reaction can be explained only by a complexation between CDs and TMSIm that facilitates the reaction. The vicinity of the two reagents in the complexed form increases the conversion of the hydroxy groups into silyl ether functions.

The dimension of CD molecule influences not only the reactivity of OH groups towards TMSIm, but also their selectivity. Fig. 1 presents the ^{1}H-NMR spectra of hexakis(random-mono-*O*-trimethylsilyl)-α-CD (α-CD-$Si_{1\times6}$) and of heptakis(random-mono-*O*-trimethylsilyl)-β-CD (β-CD-$Si_{1\times7}$) (samples 1 and 5 in Table 1). Native β-CD is presented as a reference. α-CD-$Si_{1\times6}$ gives two singlet peaks for (Si)−CH_3 protons around 0 ppm with an integral ratio of about 9/1, showing one major population of (Si)−CH_3. The same integral ratio is calculated between the

Table 1
Silylation of α-, β- and γ-CD with TMSIm in various reaction conditions

Crt. No.	Sample code CD-$Si_{m\times n}$[a]	TMSIm/OH^{2+3+6} (M)	CD/DMF/chloroform (w/v/v)	Time (h)	Substitution degree[b]	
					Total (%)	Substituted OH^6/OH^{2+3} (molar ratio)
1	α-CD-$Si_{1\times6}$	2/3	4/100/0	24	33.3	9/1
2	α-CD-$Si_{2.3\times6}$	5/1	4/100/0	72	76.6	n.d.
3	α-CD-$Si_{3\times6}$	5/1	4/100/65	24	100	1/2
4	α-CD-$Si_{3\times6}$	3/1	4/100/65	40	100	1/2
5	β-CD-$Si_{1\times7}$	2/3	2/100/0	24	33.3	1/1
6	β-CD-$Si_{2.6\times7}$	3/1	2/100/0	72	86.7	n.d.
7	β-CD-$Si_{3\times7}$	5/1	2/100/0	24	100	1/2
8	β-CD-$Si_{3\times7}$	3/1	2/100/65	24	100	1/2
9	γ-CD-$Si_{3\times8}$	5/1	6/100/0	14	100	1/2
10	γ-CD-$Si_{3\times8}$	2/1	6/100/85	10	100	1/2

n.d., not determined.
[a] Number of silyl ether functions (*m*) per structural unit × the number of glucopyranose units (*n*) in CD molecule.
[b] As calculated from ^{1}H-NMR spectra.

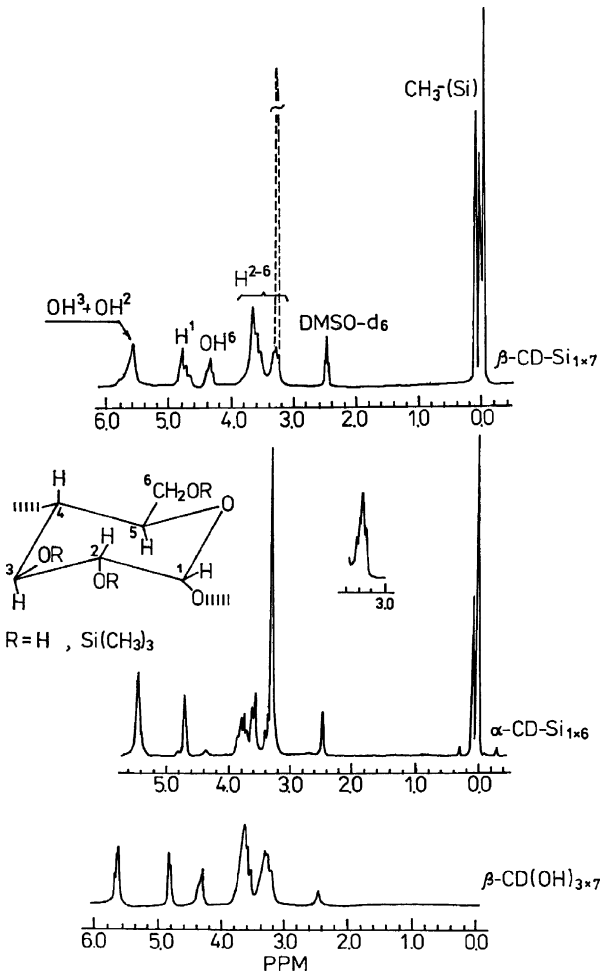


Fig. 1. ^{1}H-NMR spectra (200 MHz) of native β-cyclodextrin (DMSO-d_6) (bottom) and of hexakis(random-mono-*O*-trimethylsilyl)-α-CD (α-CD-$Si_{1\times6}$), (middle) and heptakis(random-mono-*O*-trimethylsilyl)-β-CD (β-CD-$Si_{1\times7}$) (top) ($CDCl_3$/DMSO-d_6, 1/3 v/v).

peaks of unsubstituted OH^{2+3} (at 5.8 ppm) and OH^6 (at 4.3 ppm) groups for α-CD-$Si_{1\times6}$, denoting a high selectivity of primary hydroxyl groups toward TMSIm. The analysis of ^{1}H-NMR spectrum of β-CD-$Si_{1\times7}$ homologue proves a rather non-selective substitution. The peak integral ratio between unsubstituted OH^{2+3} and OH^6 is about 2/1 and the three singlet peaks corresponding to (Si)–CH_3 protons are of similar importance (three trimethylsilylether groups linked in different environments). The selectivity difference between α- and β-CD homologues suggests a preferential orientation of the strong α-CD/TMSIm complex, with silyl functions close to the OH^6, and a weak complexation of TMSIm in β-CD cavity, without any specific orientation. This assumption is in tune with the values of the association constants between CDs and imidazole (1.08–1.23 for α-CD and 0.28–0.41 for β-CD in water solution, depending on buffer nature) (Rekharsky & Inoue, 1998) knowing that the solvent is different and that the imidazole molecule has in our case a quite bulky substituent.

3.2. Structural characterization of persilylated CDs

IR spectra of persilylated CDs are presented in Fig. 2. The study of Casu, Reggiani, Gallo, and Vigevani (1968) on the conformation of *O*-methylated amylose and CDs was used for the interpretation. Characteristic absorptions of different bonds or groups of bonds are located in the 750–1500 and 2800–3000 cm^{-1} regions (the last is the one shown in dots). All persilylated CDs present a characteristic bending band at 843 cm^{-1}, attributed to C^1 atom and another one split into two stretching bands at 1142–1160 cm^{-1} (C^1–O). C–O–C and Si–O–C groups give superposed bands at 1000–1100 cm^{-1}, while Si–CH_3 bond presents absorption at 1251 cm^{-1}. IR spectra of persilylated α- and β-CD did not show a band around 3500 cm^{-1}, characteristic to OH units or to included H_2O molecules. In contrast, γ-CD-Si_3 presents in this region a short absorption (as compared to the dimension of other bands of the spectrum) that could be attributed to a small amount of complexed water not removed during drying or to incomplete silylation.

A preliminary investigation of NMR spectra of persilylated CDs (Figs. 3–5) shows quite unusual behavior. Following total substitution, the characteristic signals of OH protons have entirely disappeared and a multitude of singlet peaks corresponding to trimethylsilyl units appeared around 0 ppm. The H^1 anomeric proton observed as a doublet peak at 4.8 ppm, corresponding to 6, 7 or 8-fold symmetries for native CDs shows a much more complicated structure in persilylated derivatives. For α-CD-$Si_{3\times6}$ (Fig. 3), the modification of the molecule symmetry was assigned

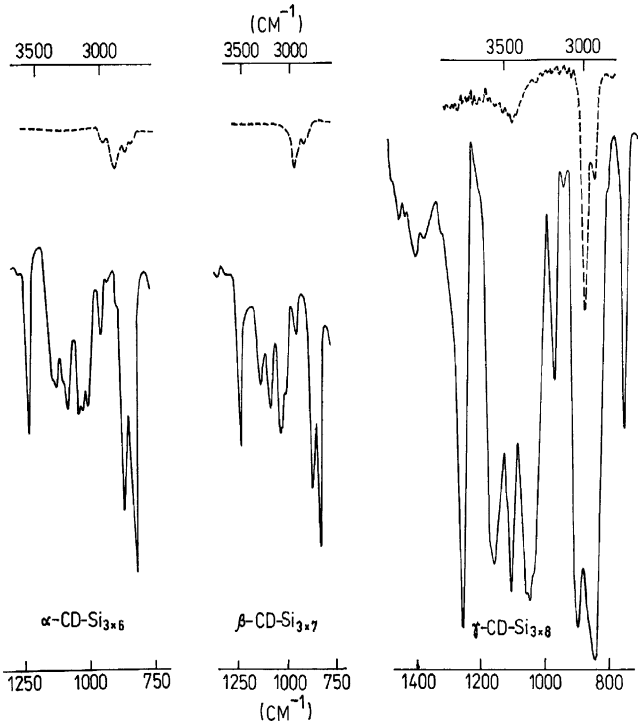


Fig. 2. FT-IR spectra of persilylated CDs ($CHCl_3$ solution).

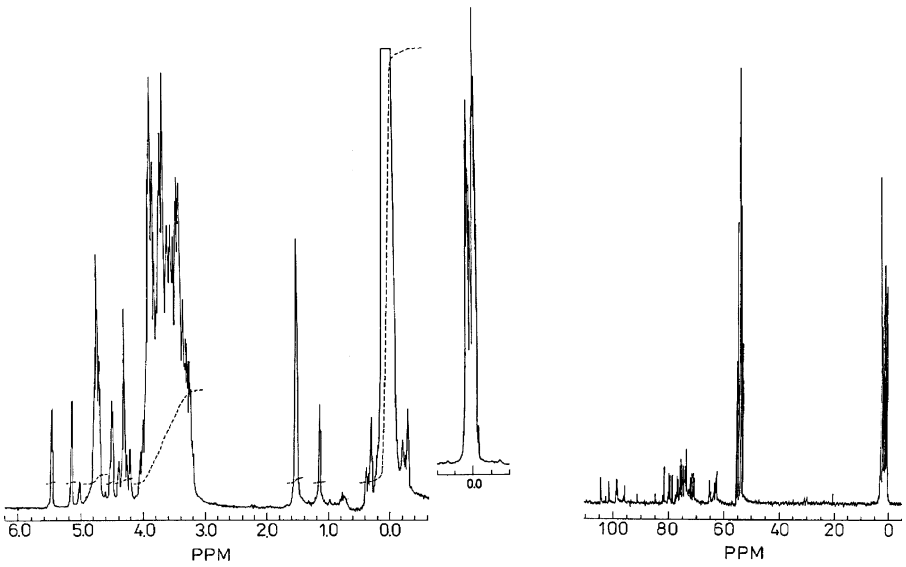


Fig. 3 ^{1}H- and ^{13}C-NMR spectra of α-CD-$Si_{3\times6}$ ($CDCl_3$ and CD_2Cl_2, respectively; 200 MHz).

since the signal of anomeric protons is splitted into at least five different significant subsignals, spreaded between 4.6 and 5.6 ppm. As for the C^1 anomeric carbon atoms, these present in ^{13}C-NMR spectrum show six distinct signals located between 95.1 and 103.6 ppm. One can suppose that the persilylated α-CD is characterized by a strong deviation of the conformations of each of its six structural units from the chair conformation of the glucopyranose units in the native precursor and that these conformations are stable at least on the NMR time scale.

The same conformational modification was observed after the persilylation of the β- and γ-homologues (Figs. 4 and 5), but the anomeric protons are spread on a lower chemical shift range, 4.4–5.05 and 4.5–4.9 ppm, respectively. Both β- and γ-persilylated oligomers do not show clear peaks in the region of anomeric protons (Figs. 4a and 5). A rather large resonance signal with three maxima at 4.5, 4.9 and 5.05 ppm (a smaller difference as compared to the lower oligomers) was observed in the ^{1}H-NMR spectrum of γ-CD-$Si_{3\times8}$. Moreover, for this higher homologue, the accumulation for 48 h was not sufficient to obtain a reliable ^{13}C-NMR spectrum. The occurring of conformational transitions could originate such a behavior and a higher flexibility of this molecule can be envisaged, *in compare to α and β-CD*. Thus, a possible explanation for the observed NMR characteristics of the three-persilylated CDs oligomers seems to be consistent with different conformations of each structural unit and with an increased flexibility as the dimension of the molecule is increasing. For persilylated α-CD, the very different conformations of structural units are stabilized by the steric hindrance induced by the presence of 18 bulky trimethylsilyl groups in a small molecular volume.

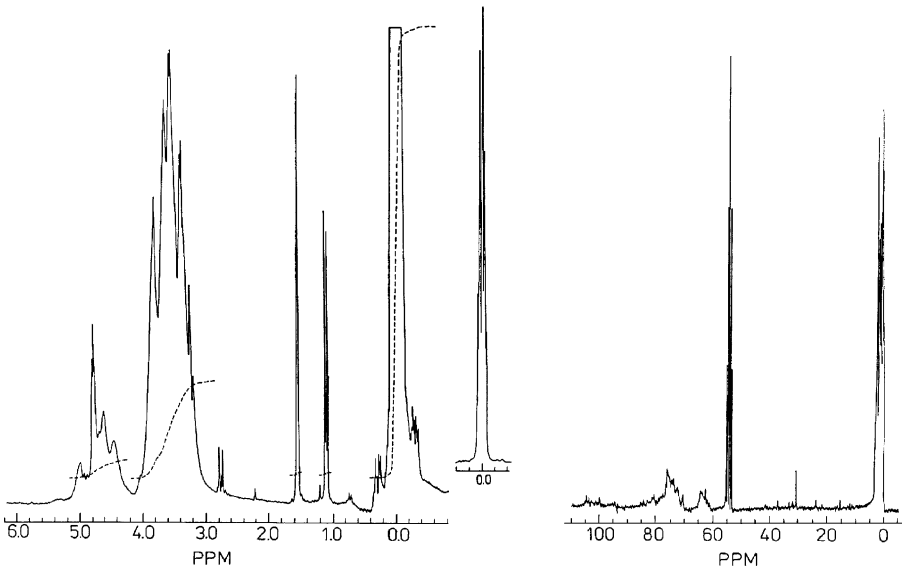


Fig. 4 ^{1}H- and ^{13}C-NMR spectra of β-CD-$Si_{3\times7}$ ($CDCl_3$ and CD_2Cl_2, respectively; 200 MHz).

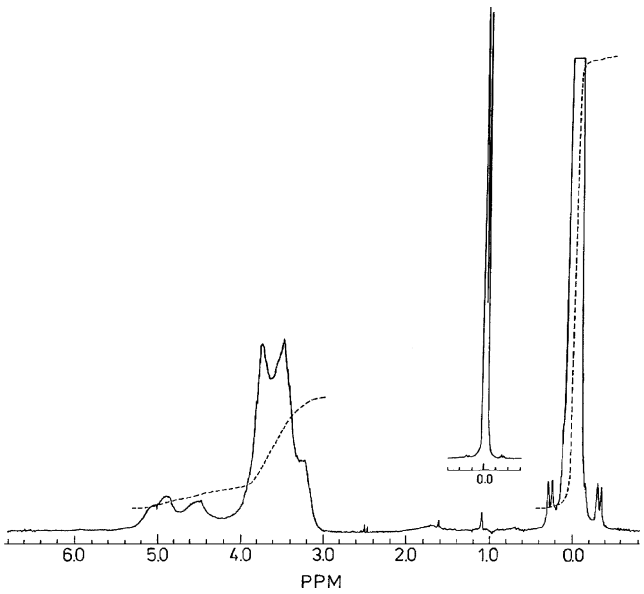


Fig. 5. ^{1}H-NMR spectrum of γ-CD-$Si_{3\times8}$ ($CDCl_3$; 200 MHz).

The higher persilylated homologues β-CD-$Si_{3\times7}$ and γ-CD-$Si_{3\times8}$ showed a decreased steric hindrance (the bulky substituents are dispersed in larger molecular volumes) and the possibility of conformational transitions on the NMR time scale (especially for γ homologue).

To confirm the total modification of the CDs, MALDI-TOF MS analysis was carried out on each of the modified CDs. However, due to experimental requirements, this analysis is not entirely appropriate for the derivatives sensitive to base or acid induced hydrolysis. MALDI-TOF analysis requires the use of a matrix that absorbs at the laser wavelength and avoids the samples degradation under laser impact. Acid matrixes such as α-cyano-4-hydroxycinnamic acid or 2,5-dihydroxybenzoic acid provide large degradation of the Si−O−C functions. An enhanced degradation was observed for α- and β-derivatives. To avoid the hydrolysis of Si−O−C groups, 2-nitrophenyloctyl ether was used as a matrix. Fig. 6 displays the mass spectrum of the γ-CD-$Si_{3\times8}$ using this matrix. The peak at $m/z = 3066$ corresponds to the pertrimethylsilylated-γ-CD, K^+. Another peak attributed to the sodium adduct is also detected, which confirms the interpretation. However, the peak observed at 2993 m/z can be attributed to the γ-CD-$Si_{3\times8}$ minus one trimethylsilyl function $+K^+$. This observation can be explained by the degradation γ-CD-$Si_{3\times8}$ during sample preparation. The spectral intensity of the degraded adduct also deserves a comment. A new molecule carrying a hydroxy function might be cationized much easier than the pertrimethylsilylated molecule, leading to a higher desorption and giving a rather high intensity signal in the spectrum.

3.3. NMR study of the pertrimethylsilylated-α-cyclodextrin

The ^{1}H and ^{13}C chemical shifts of the pertrimethylsilylated-α-CD have been totally assigned. As the 1D 400 MHz-proton spectrum is very crowded (Fig. 3) and not directly interpretable, several other experiments, like 2D measurements (COSY, TOCSY, HSQC, HMBC) and even a 3D measurement have been carried out to resolve the remaining ambiguities and to perform the total assignation (Bax & Summers, 1986; Muller, 1979). Tables 2 and 3 give the found chemical shifts in both ^{1}H and ^{13}C spectra. For the sake of clarity, an alphabetic letter labels each glucopyranose unit to facilitate the identification of glucosidic units sequencing.

Only a few signals are easily identifiable on the 1D-proton spectrum, essentially the six anomeric protons. Almost all other glucosidic protons spread out between 3.30 and 4.20 ppm in a broad signal. Only two of them, respectively, at 4.48 and 4.40 ppm, are not included in this region. For each glucosidic unit, protons in two and three positions have been characterized without difficulties with a COSY experiment and in the corresponding spectrum (Fig. 7) we have been able to locate protons in four positions in some favorable cases. Numerous ^{13}C signals have been assigned using 2D spectrum (HSQC and HMBC) (Fig. 8). The remaining ^{1}H and ^{13}C peaks have been determined first by a TOCSY experiment and hence by a 3D correlation spectrum (TOCSY-HSQC) in order to resolve the latest remaining ambiguities.

Using the above assignations and a NOESY measurement, the connectivity between glucosidic units has been established and confirmed by 1D NOE experiments. This spectrum shows the space surrounding protons of

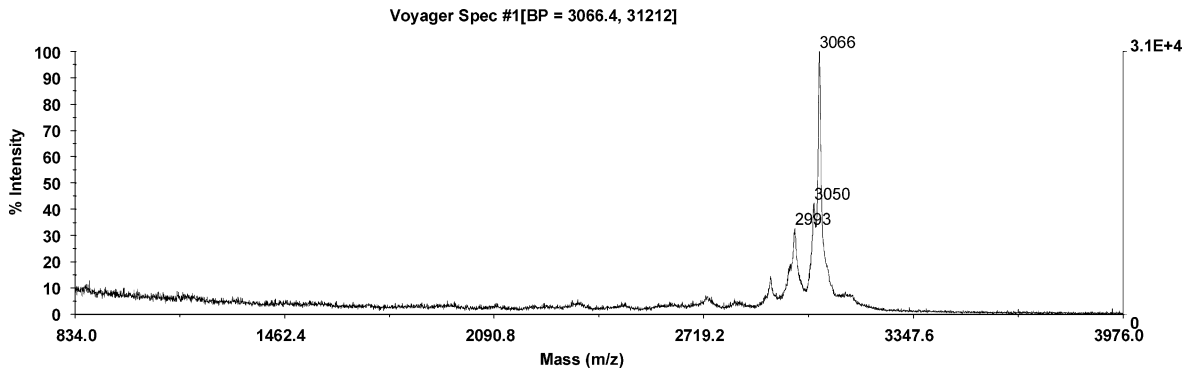
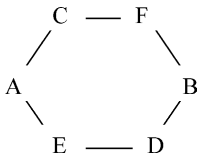


Fig. 6 MALDI-TOF mass spectrum of γ-CD-$Si_{3\times8}$ obtained with 2-nitrophenyloctyl ether as matrix ($5\cdot10^{-3}$ M in THF) (reflected mode).

Table 2
^{1}H-NMR chemical shifts (ppm) of persilylated α-CD for each glucopyranose unit labeled from A to F

^{1}H position in the glucopyranose units	A	B	C	D	E	F
1	5.59	5.19	4.94	4.87	4.86	4.64
2	3.56	3.90	3.42	3.42	3.46	3.36
3	3.79	3.96	4.17	4.07	4.02	3.99
4	3.56	3.75	3.84	3.92	4.02	4.04
5	3.52	3.80	3.55	3.58	3.80	3.57
6	3.61	3.88	3.54	3.61	3.69	3.71
6′	3.90	3.94	3.90	3.91	4.40	4.48

each H^1 proton. For each H^1 proton one can see two correlations, the first with the vicinal H^2 and the second with a H^4 of the adjacent glucosidic unit. The following connection was found:



According to these results, one can suppose that the persilylated α-CD is probably twisted, as further demonstrated in the modeling section.

3.4. Modeling and physical properties of persilylated cyclodextrins

For amylose and their cyclic oligomers—CDs—a chair conformation of glucopyranose structural units was assigned long time ago (Casu et al., 1968). A relatively easy rotation of glucopyranose units around the C^1–O bonds is possible, giving rise to a large number of conformations by modifying the rotational angle. As proved by X-ray analysis of its inclusion complexes, the V crystalline form of amylose possesses an helical conformation (Rundle & French, 1943). The same conformation of amylose was established in water or DMSO solutions (Foster, 1965). The helical structure is stabilized through hydrogen bonds between the hydroxyl groups in two and three positions of adjacent structural units. These results were obtained by the X-ray investigation of potassium acetate/α-CD inclusion complexes (Hybl, Rundle, & Williams, 1965) or by NMR and IR analysis of amylose and CDs in DMSO solution (Casu, Reggiani, Gallo, & Vigevani, 1966).

Table 3
^{13}C-NMR chemical shifts (ppm) of persilylated α-CD for each glucopyranose unit labeled from A to F

^{13}C position in the glucopyranose units	A	B	C	D	E	F
1	97.68	95.09	97.86	98.18	100.68	103.61
2	74.16	69.88	75.95	74.86	75.08	73.09
3	72.86	74.76	77.94	76.26	74.76	72.87
4	80.88	74.61	71.61	73.60	78.77	79.40
5	70.81	80.95	70.15	72.30	73.01	72.87
6	62.16	61.70	62.72	62.00	64.11	64.33
6′	62.16	61.70	62.72	62.00	64.11	64.33

The total substitution of hydroxyl groups with bulky radicals (like trimethylsilyl groups) is expected to substantially modify the conformation of CD molecules. Moreover, in these macrocycles each glucopyranose unit is expected to play the same role that should result in a symmetrical distribution around the central axis in native CDs. In fact, as proved by the NMR spectra of persilylated CDs (Figs. 3–5), these constraints determine a strong deviation from the initial symmetry and the deviation is larger and more stable as the macrocycle is smaller.

The molecular geometry modeling was performed with HYPERCHEM program and the MM + method was used for the modeling of molecular mechanics. A slow convergence of the systems due to the relatively large number of atoms was observed.

In a structural glucopyranose unit having a chair conformation, the dihedral angles formed by the bonds adjacent to C^1 or C^4 atoms with the planes determined by three of the atoms in positions 2, 3, 5 and ring oxygen atom (Table 4) must present positive and negative values (C^1 and C^4 atoms are oriented in opposite sides of the hypothetical plane through the weight center of the unit), while for a boat conformation the angles must be either positive or negative (C^1 and C^4 atoms are located on the same side of the plane).

As one can see from Table 4, in the persilylated α-CD molecule all six structural units have shown a substantially distorted chair conformation, with very different values of homologue dihedral angles, while in persilylated β and γ oligomers it was found that one and three structural units, respectively, adopted a boat conformation.

By examination of the optimized geometry of persilylated CDs (Fig. 9), a globular shape of these molecules was evidenced. α-CD-$Si_{3\times6}$ molecule has an inner diameter (delimited by the oxygen atoms of glucopyranose units) of 0.589 nm (Table 5). The distribution of the bulky trimethylsilyl substituents in a small volume (2268.1 cm^3/mol) and the higher rigidity of the predominant chair conformations of the structural units induce a relatively high rigidity of the whole molecule. This explains why this molecule exhibits quite well resolved ^{1}H and ^{13}C-NMR spectra (Fig. 3). As the number of glucopyranose structural units increases ($n = 7$ and $n = 8$ in β- and γ-CD-Si), an increased number of units tend to adopt a more flexible boat conformation and the cyclic molecules show a twisted shape (more pronounced for the γ oligomer). The higher flexibility of seven and eight membered oligomers was also observed in NMR spectra (large peaks for anomeric atoms suggesting conformational transitions during spectrum acquisition).

The inner diameters delimited by glucopyranose oxygen atoms in persilylated CDs are smaller than the corresponding

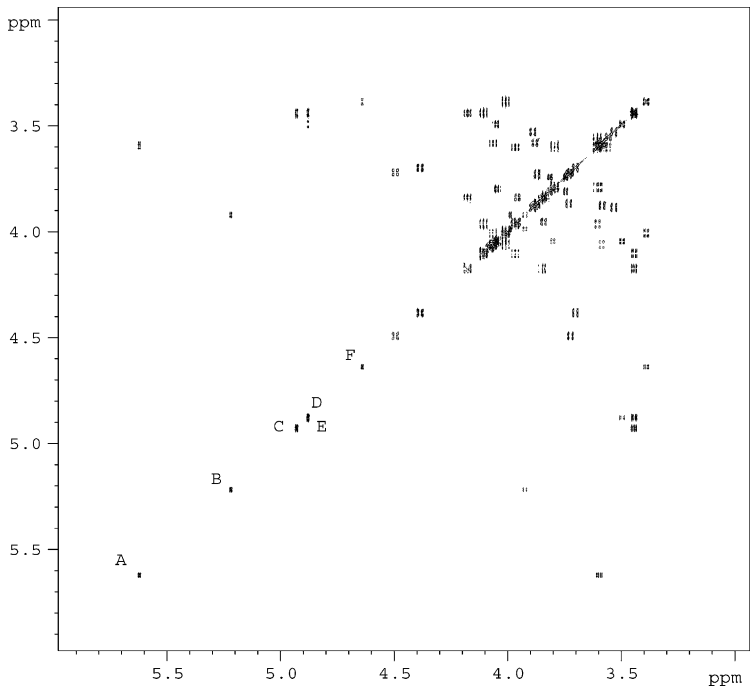


Fig. 7. 600 MHz COSY spectrum recorded with field gradients and multiquanta filtering on a 0.5 mmol solution of α-CD-$Si_{3\times6}$ in CD_2Cl_2. Recovery delay: 1s; memory size for acquisition in F2 dimension: 2K and in F1 dimension: 512W; memory size for the 2D-spectrum: 2K × 2K; number of scans: 1 (dummy scans: 16); spectral width: 2048 Hz. All other parameters settled as Brüker recommendations.

values of native CDs (Saenger, 1976) and are not in a direct proportionality to cycle dimension (Table 5). Thus, a noticeable difference in inclusion behavior between native and persilylated CDs has to be expected.

The calculated values of the decomposition temperature of persilylated CDs are in good agreement with the experimental values, except for the γ oligomer where the experimentally found lower decomposition phenomenon has to be correlated with the presence of trace amounts of water complexed in CD cavity (see also the IR spectrum in Fig. 2).

The molecular weights of persilylated CDs were determined by SEC (Table 6). The SEC curves

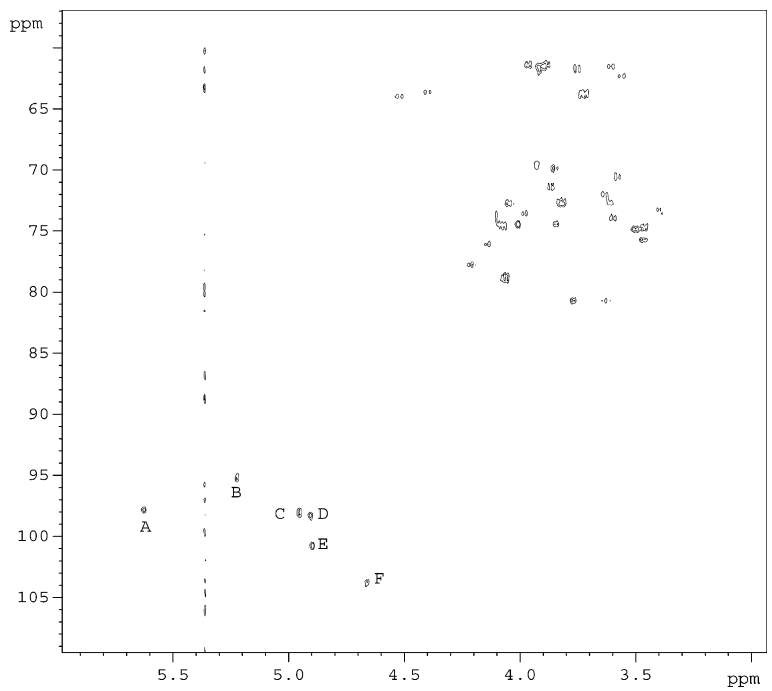


Fig. 8. 600 MHz HSQC($^1H/^{13}C$ correlation) 2D-spectrum of a 0.5 mmol solution of α-CD-$Si_{3\times6}$ in CD_2Cl_2. Recovery delay: 1s; memory size for acquisition in F2 dimension: 4K and in F1 dimension: 128W; memory size for the 2D-spectrum: 4K × 512W; number of scans: 32 (dummy scans: 40); spectral width: 3 ppm in ^1H and 53 ppm in ^{13}C. All other parameters settled as Brüker recommendations.

Table 4
Values of dihedral angles determined by the adjacent bonds of C^1 and C^4 atoms with plans determined by three of the C^2, C^3, C^5 and O atoms in persilylated CDs

Structural unit	Plan 1	Plan 2	α-CD-$Si_{3\times7}$		β-CD-$Si_{3\times6}$		γ-CD-$Si_{3\times8}$	
			Chair	Boat	Chair	Boat	Chair	Boat
I	C^2, C^1, O	C^2, C^5, O	46.8		−12.1		−67.1	
	C^3, C^4, C^5	C^2, C^3, O	−67.9		37.4		14.2.	
		C^3, C^5, O	−63.4		90.6		28.6	
		C^2, C^3, C^5	39.0		−58.8		−73.7	
II	C^2, C^1, O	C^2, C^5, O	62.6		−49.6		−58.3	
		C^2, C^3, O	−61.4		73.1		19.1	
	C^3, C^4, C^5	C^3, C^5, O	−48.2		51.9		46.4	
		C^2, C^3, C^5	45.2		−24.9		−79.7	
III	C^2, C^1, O	C^2, C^5, O	61.9		−78.0			−50.5
		C^2, C^3, O	−65.6		41.2			−20.9
	C^3, C^4, C^5	C^3, C^5, O	−15.1		21.3			−19.7
		C^2, C^3, C^5	6.9		−51.3			−39.5
IV	C^2, C^1, O	C^2, C^5, O	−18.9		−50.8		−25.4	
		C^2, C^3, O	19.6		18.2		50.4	
	C^3, C^4, C^5	C^3, C^5, O	−18.1		34.7		69.6	
		C^2, C^3, C^5	20.7		−61.8		−41.2	
V	C^2, C^1, O	C^2, C^5, O	−69.8			−13.1	3.5	
		C^2, C^3, O	69.4			−51.3	−1.1	
	C^3, C^4, C^5	C^3, C^5, O	−27.3			−28.1	16.4	
		C^2, C^3, C^5	28.1			−31.5	−14.3	
VI	C^2, C^1, O	C^2, C^5, O	−63.8		38.9			−38.9
		C^2, C^3, O	65.5		−23.0			−26.9
	C^3, C^4, C^5	C^3, C^5, O	−42.9		54.2			−32.7
		C^2, C^3, C^5	46.7		−37.9			−28.9
VII	C^2, C^1, O	C^2, C^5, O			35.0			41.6
		C^2, C^3, O			−93.9			19.5
	C^3, C^4, C^5	C^3, C^5, O			−41.2			39.8
		C^2, C^3, C^5			15.6			18.3
VIII	C^2, C^1, O	C^2, C^5, O					21.9	
		C^2, C^3, O					−59.3	
	C^3, C^4, C^5	C^3, C^5, O					−69.6	
		C^2, C^3, C^5					28.8	

are monomodal and present very low polydispersity indexes.

All persilylated CDs are thermally stable products. Their decomposition curves (Fig. 10) are similar for the first two homologues. The decomposition temperature is situated around 380 °C, a higher value as compared to the first decomposition phenomenon registered for native CDs (around 315 °C). γ-CD-$Si_{3\times8}$ presents an additional decomposition step at 275 °C. The difference in the decomposition behavior manifested by

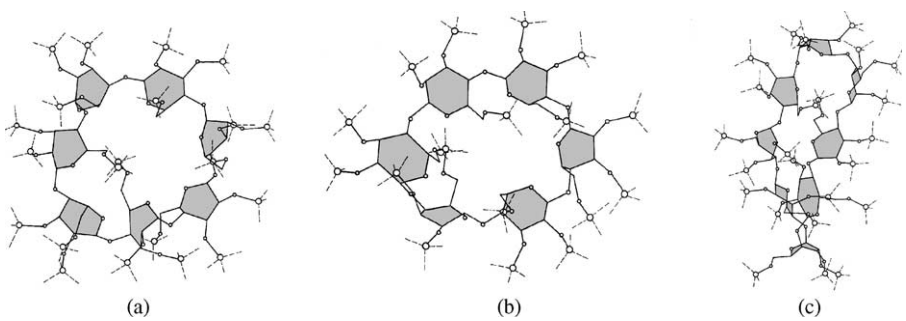


Fig. 9 The shape and conformation of (a) α-CD-$Si_{3\times6}$; (b) β-CD-$Si_{3\times7}$; (c) γ-CD-$Si_{3\times8}$.

Table 5
Characteristics of persilylated cyclodextrins as calculated from molecular geometry modeling

Characteristic	Unit	α-CD-$Si_{3\times6}$	β-CD-$Si_{3\times7}$	γ-CD-$Si_{3\times8}$
Inner diameter limited by oxygen atoms in glucopyranose units	nm	0.589	0.368	0.700
Inner diameter limited by glycosidic oxygen atoms	nm	0.948	0.930	0.870
External diameter, d_1	nm	2.058	2.274	2.503
External diameter, d_2	nm	1.910	1.989	1.936
Molecular volume effectively occupied by atoms	$cm^3\ mol^{-1}$	0.479	0.490	0.624
Total molecular volume	$cm^3\ mol^{-1}$	2268.1	2646.1	3024.0
Molar mass	a.m.u.	2272.1	2650.8	3029.5
Decomposition temperature (calculated/experimental)	°C	384.9/385	384.9/385	384.9/268 and 376

Table 6
Molecular weights of persilylated CDs

Sample code	Molecular weight			Polydispersity index (SEC)
	Calculated	M_w (SEC)	MALDI-TOF	
α-CD-$Si_{3\times6}$	2272.1	2500	-	1.009
β-CD-$Si_{3\times7}$	2650.8	2875	-	1.008
γ-CD-$Si_{3\times8}$	3029.5	3210	3027	1.007

the third term of the homologue series appears from the presence of small amounts of complexed water that determine the hydrolysis of silyl ether bonds at high temperature.

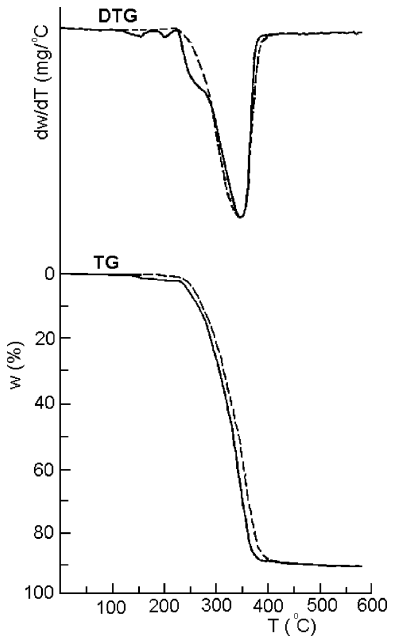


Fig. 10 TGA curves for persilylated α-CD-$Si_{3\times6}$ (dotted line) and γ-CD-$Si_{3\times8}$ (full line); β oligomer shows identical behavior with α homologue.

4. Conclusions

The synthesis and characterization of persilylated α-, β- and γ-CDs has been performed. As demonstrated by NMR analysis and structural modeling, the *n*-fold symmetry of the native molecules was found to be lost after substitution of all hydroxyl groups with bulky trimethylsilyl radicals. The well resolved α-CD-$Si_{3\times6}$ spectrum allows the full assignments of the proton and ^{13}C peaks. Furthermore, the sequence of the glucopyranose units was determined and a twisted structure was deduced by molecular modeling. The new CD derivatives are thermally stable products, soluble in non-polar solvents and they can be used as complexing compounds. Their ability to complex alkaline salts of aromatic acid in non-polar media will be reported in a subsequent paper. The values of inner diameters determined by modeling allow the assumption that their performances in this field will be quite different as compared to those of native CDs. Partially modified CDs are reported and it was shown that α-CD derivatives can be specifically modified on the primary hydroxyl face.

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