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Alkyl Capped Carbonates of β-Cyclodextrin

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Abstract. The synthesis is described of alkyl capped carbonates of β-cyclodextrin, obtained from diols activated with carbonyldiimidazole. The reaction preferentially gave monocapped derivatives which were characterized by HPLC, TLC, FT-IR and ^{13}C-NMR. These compounds are stable at pH <7, and methyl orange was found to form stronger inclusion compounds with capped β-cyclodextrin than with the parent β-cyclodextrin. Paramagnetic Gd(III) complexes were also studied, but they were found to be included into capped β-cyclodextrin as well as into β-cyclodextrin.

Key words: Capped cyclodextrins, cyclodextrin derivatives, inclusion compounds, methyl orange, paramagnetic Gd(III) complexes.

1. Introduction

In cyclodextrin (cyclic nonreducing oligosaccharide) chemistry [1], particular attention has been devoted to the synthesis of capped derivatives [2], in order to enhance the value of the stability constant of the inclusion complex, to improve catalytic properties [3] and/or to obtain, selectively, both symmetric [4] or asymmetric [5] bifunctionalized compounds. To date, several capped derivatives of β-CD have been obtained by reaction of β-CD with aromatic disulfonyl chlorides, as first reported by Tabushi [2]. This reaction also leads to A,B [6], A,C [7] and A,D [8] isomers.

This paper deals with a novel class of alkyl capped carbonate derivatives of β-CD, which are obtained via a synthetic procedure based on the use of α,ω-diols activated with carbonyldiimidazole.

2. Experimental

β-Cyclodextrin was a gift from Roquette Italia (Cassano Spinola, Italy) and before use was oven dried at 120 °C, until constant weight was reached.

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Diols, carbonyldiimidazole and pyridine ($H_2O_{max.}$ 0.0075%) were purchased from E. Merck (Germany) and used without further purification. 4,4′-Disulfonyldiphenyl capped β-CD was synthesized according to the literature [7].

IR spectra were recorded on a Perkin-Elmer model 1710 FT-IR spectrometer. ^{13}C-NMR spectra were obtained by a JEOL model EX400 spectrometer. TLC was conducted on silica gel plates 60 Merck (art. 5714); eluent CH_3CN/H_2O 70 : 30 (vol.) with anisaldehyde spray as detector.

HPLC was performed on a Waters model 501 apparatus, equipped with a Waters 410 RI detector (4×10^{-5} RI units, full scale). A Merck Hibar Lichrosorb NH_2 column (250 mm × 4 mm i.d.) was employed, with CH_3CN/H_2O 70 : 30 (vol.) as eluent (flow rate: 1 mL/min).

Gas Chromatography – Mass Spectrometry (GC/MS) analyses were conducted on a Hewlett Packard HP 5890A apparatus. UV-visible spectra were recorded on a Perkin–Elmer Lambda 15 UV-VIS spectrophotometer. The absorbance at 508 nm of 4×10^{-5} M Methyl Orange aqueous solutions, with pH adjusted to 1.25 by HCl, were measured at increasing β-CD or alkyl capped β-CD concentrations, (from 1×10^{-4} M to 5×10^{-3} M) and used for calculating the stability constants of the inclusion complexes. Test solutions were allowed to equilibrate overnight at 25 °C.

The Gd(III)–BOPTA (BOPTA: benzyloxymethylene-derivative of diethylenetriaminopentaacetic acid) complex was synthesized as previously reported [9]. The solvent water proton relaxation time (T_1) was measured on a Spin-Master Spectrometer (Stelar, Italy) at 25 °C and 20 MHz, by means of the inversion recovery technique [10].

CPK molecular modelling was performed using Insight II 2.3.5 Molecular Modeling Software on a Silicon Graphics Iris Indigo XZ4000 workstation.

2.1. Synthesis of α,ω-activated diols

α,ω-Activated diols were synthesized as previously reported [11, 12] and confirmed by GC/MS analysis.

2.2. Alkyl capped carbonates of β-CD

In a typical experiment, 11.40 g (0.01 mol) of anhydrous β-CD were dissolved in 200 mL anhydrous pyridine; 2.36 g (0.008 mol) of activated 1,6-hexanediol were added in several portions during 1 hour, while the reaction mixture was stirred by a magnetic bar. The solution was allowed to react for 3 h at 80 °C . After this time, pyridine was removed under vacuum below 50 °C. Water (15 mL) was then added to the viscous residue, and the solution was added dropwise into a vigorously stirred CH_3CN/H_2O mixture (190 : 30 (vol.)), in order to precipitate unreacted β-CD. The solution was then concentrated and a large excess of CH_3CN was added. The resulting precipitate was recovered by filtration and freeze dried. The yield was 18.2%.

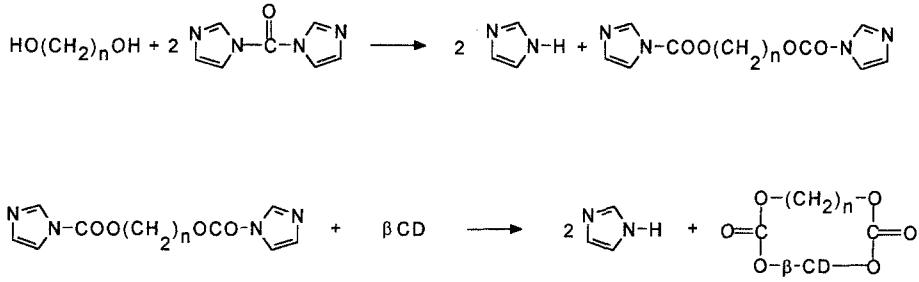

Figure 1. Synthesis of alkyl capped carbonate β-CD.

TLC showed only a spot with higher R_f (0.50) with respect to β-CD (0.26). HPLC revealed only one peak with lower retention time than the parent β-CD. FT-IR showed the carbonyl group signal at about 1750 cm^{-1}. ^{13}C NMR exhibited typical carbonate signals at about 155 ppm.

3. Results and Discussion

The synthesis is summarized in Figure 1. The reaction also proceeds for C_4, C_5, C_6 and C_{10} activated diols. The capping reaction does not give any detectable (TLC) amount of oligomeric materials, thus the intramolecular reaction, rather surprisingly, seems to be particularly favoured. This means that the intermolecular reaction is quite unlikely, even less probable than in the Tabushi reaction for rigid aromatic capped CDs. As the intramolecular reaction is more favourable than intermolecular condensation, thus also in our case it is not necessary to work under high dilution conditions to obtain capped carbonates of β-CD. On the other hand, the chain flexibility probably leads to a mixture of isomers. In fact, the ^{13}C-NMR spectrum of C_6 capped cyclodextrin (Figure 2), for example, shows two very close signals in the carbonate region and this could be accounted for by the formation of A,D and A,C isomers. CPK models showed that C_6 capped β-CD fits well in the A,D position, but the A,C isomer is also possible. With C_4 capped β-CD the A,C isomer seems to be the most favourable and in C_{10} capped β-CD the alkyl chain from carbon six of the A glucose residue can reach carbon six of the D glucose unit. Molecular models showed that the A,C linkage is unlikely to form.

Alkyl capped carbonate derivatives of β-CD act as good surfactants. The C_6 capped derivative is very soluble in water (about 25 g/100 mL), but a longer methylenic bridge generates compounds that are less soluble in water. In fact, the water solubility of the C_{10} capped carbonate is only 2 g/100 mL. The synthesised products are stable at pH $\leq$ 7, so these derivatives could be used as protecting groups in acid conditions, as they were observed to be easily hydrolysed in basic solution.

Quantitative FT-IR analysis [11] of the β-CD derivative (Figure 3) showed a degree of substitution (D.S.) very close to 2.0, thus indicating that only mono-capped substitution has occured.

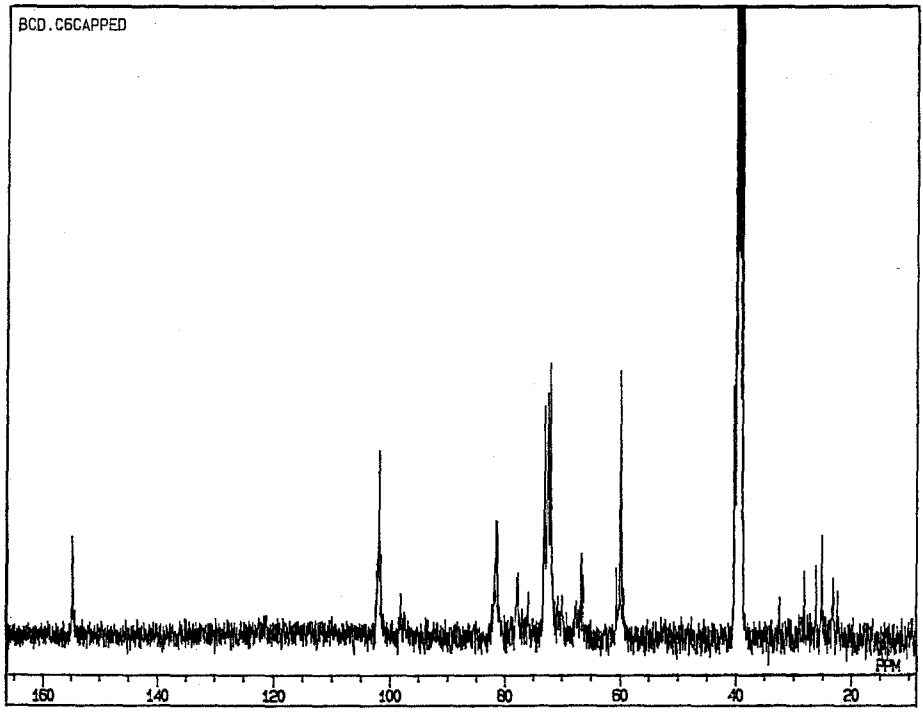

Figure 2. ^{13}C-NMR spectrum of C_6 capped β-cyclodextrin in DMSO-d_6, 400 MHz.

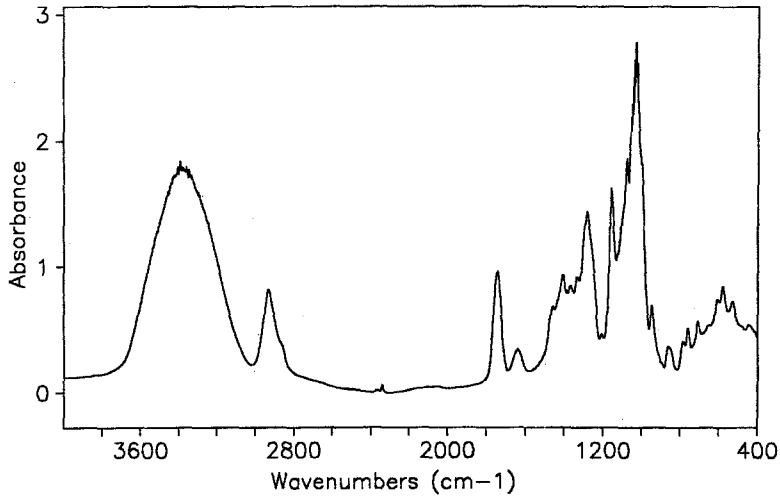

Figure 3. FT-IR of C_6 capped β-cyclodextrin, KBr pellet.

In order to obtain preliminary indications of the complexation properties of alkyl capped carbonates of β-CD, methyl orange was used as the test molecule. The visible absorbance of methyl orange solution at 508 nm decreased with increasing

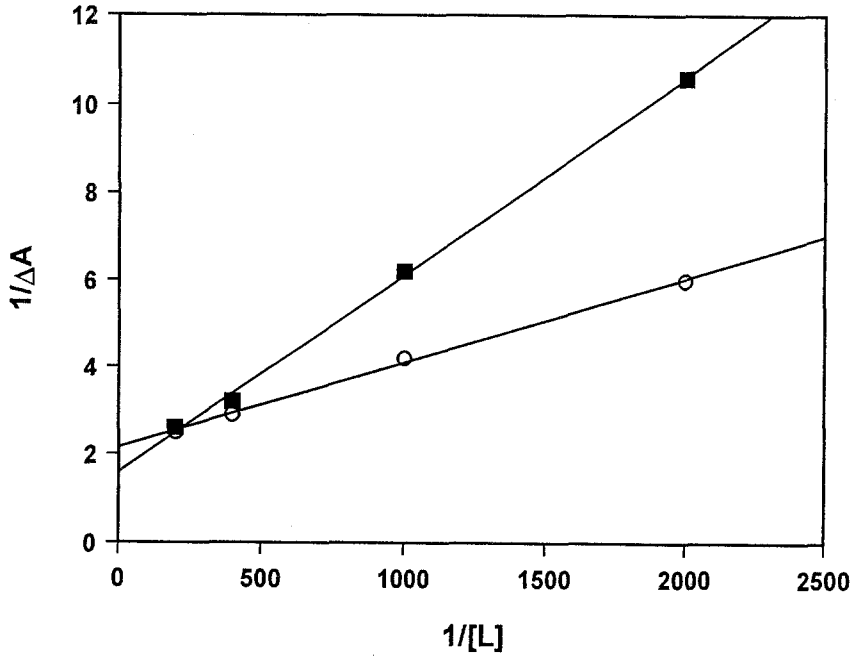

Figure 4. Benesi–Hildebrand plot for the effect of C_6 alkyl capped carbonate of β-CD (○) and of the parent β-CD (■) on the absorbance of methyl orange at 508 nm at 25 °C, pH = 1.25.

concentration of C_6 capped β-CD (or β-CD to a less extent). From the Benesi–Hildebrand equation:

$$\frac{1}{\Delta A} = \frac{1}{\Delta a \cdot K_{1:1} \cdot S_t \cdot [L]} \cdot \frac{1}{\Delta a \cdot S_t} \tag{1}$$

(where ΔA is the difference in absorbance at 508 nm, Δa is the difference in the molar absorptivities between free and complexed methyl orange, S_t the total methyl orange concentration, $[L]$ is the concentration of free β-CD). The stability constant, $K_{1:1}$, of the inclusion complex is obtained from the intercept/slope ratio of the $1/(\Delta A)$ vs. $1/[L]$ plot.

Figure 4 reports the Benesi–Hildebrand plot [13] for the effect of β-CD C_6 capped carbonate and the parent β-CD on the absorbance of methyl orange at 508 nm. The stability constant obtained from the intercept/slope ratio of Figure 4 is about 3.5 times larger for C_6 capped β-CD derivatives ($K_{1:1}$ = 1100) than for the parent β-CD ($K_{1:1}$ = 319).

Due to their high water solubility and to their potential application in imaging studies, further work was performed in order to ascertain whether the synthesized derivatives of β-CD could be used as carriers of contrasting agents for medical applications of NMR. The inclusion of paramagnetic Gd(III) complexes, which are very useful contrast agents in magnetic resonance imaging, into the cavity of C_6 capped β-CD was examined.

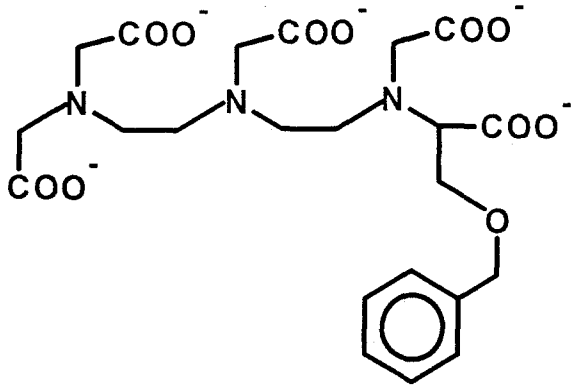

Figure 5. Structure of the benzoyloxymethylene derivative of diethylenetriaminopentaacetic acid (BOPTA).

Table I. Dissociation constants and ϵ_b values for some cyclodextrins, measured by a Spin Master spectrometer at 25 °C and 20 MHz. A: C_6-capped β-CD; B: biphenyl-capped β-CD; C: β-CD; σ: standard deviation

	A	B	C
K_d	3.03×10^{-2}	2.63×10^{-3}	3.56×10^{-2}
ϵ_b	2.43	2.33	2.05
σ	1.42×10^{-4}	1.06×10^{-4}	3.76×10^{-5}

To obtain information about the interaction of the BOPTA (Figure 5) – Gd(III) complex with β-CD and its derivatives, the formation constants of the inclusion complexes were evaluated. The strength of the hydrophobic interaction has been evaluated through measurement of the solvent water proton relaxation time (T_1). In fact, the proton relaxation rate ($R_1 = 1/T_1$) increases markedly upon formation of the inclusion compound characterized by a longer re-orientational correlation time. The proton relaxation enhancement (ϵ^*) [14] is related to the dissociation constant of the inclusion complex by the following equation:

$$\frac{1}{\epsilon^*} = \frac{1}{[L]} \cdot \frac{K_d}{\epsilon_b} + \frac{1}{\epsilon_b} \tag{2}$$

K_d is the dissociation constant of the inclusion complex, ϵ_b is the ϵ^* value corresponding to the situation in which all the paramagnetic compound is totally bound by the CD. K_d and ϵ_b can be measured experimentally by titrating a solution of the paramagnetic complex with β-CD or β-CD derivatives. K_d is experimentally obtained by the slope of the $1/\epsilon^*$ vs. $1/[L]$ plot.

Table I reports the measured ϵ_b and K_d values of the Gd(III)-BOPTA complex with some cyclodextrins. Larger values of ϵ_b were obtained for 4,4′-disulfonyldiphenyl capped β-CD and C_6 alkyl capped carbonate, as ϵ_b is closely

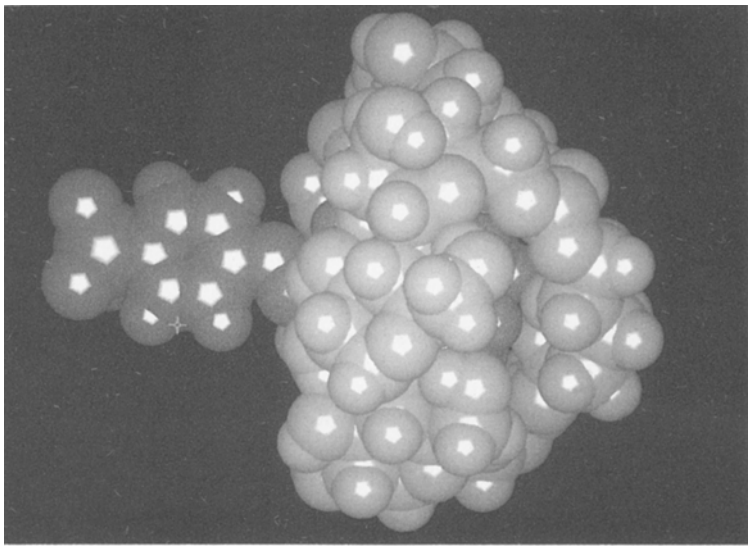

Figure 6. CPK models of the C_6 capped β-cyclodextrin inclusion compound with methyl orange.

related to molecular weight. Moreover 4,4′-disulfonyldiphenyl capped β-CD also formed an inclusion compound which was found to be more stable than that of the parent β-CD. On the other hand, C_6 alkyl capped β-CD exhibited a K_d value very close to that of the parent β-CD. The carbonate C_6 bridge on the smaller edge of β-CD was found to give no additional stabilization of the inclusion complex of β-CD with BOPTA. A tentative explanation of this fact is that only a part of the benzoyloxymethylene chain of BOPTA can penetrate into the cavity of the β-CD, due to the large steric hindrance of the rest of the molecule.

CPK models showed that the alkyl bridge of C_6 capped β-CD is situated at a longer distance from the top of the primary hydroxyl side than the aromatic bridge. For this reason, interaction of the benzoyloxymethylene moiety of BOPTA with the lipophilic bridge of the molecule is reduced, therefore its K_d is of the same order of magnitude of that as the parent β-CD. Methyl orange behaves differently because of its structure: in fact, it can fully penetrate into the C_6 capped β-CD cavity (Figure 6), thus stabilizing the inclusion complex because of its interaction with the C_6 alkyl bridge.

4. Conclusions

A general and easy method for the synthesis of β-CD capped alkyl carbonates is reported. The C_6 derivative is very water soluble and forms more stable inclusion compounds with methyl orange, at pH 1.25, than the parent β-CD molecule. However, the alkyl bridge of the capped carbonate is placed at a large distance from

the top of the cyclodextrin and very large molecules such as BOPTA complexes of Gd(III) cannot obtain extra stabilization from the C_6 alkyl bridge.

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