THREE-DIMENSIONAL CYCLODEXTRIN: A NEW CLASS OF HOSTS BY TREHALOSE CAPPING OF β-CYCLODEXTRIN

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ABSTRACT

In order to obtain better abiotic receptors for analytical and kinetic applications, the new capped derivative of cyclomaltoheptaose (CDTH) was synthesized by reaction of 6,6'-dideoxy-6,6'-di(S-cysteamine)-α,α'-trehalose with 6A,6D-dideoxy-6A,6D-diiodo-cyclo-maltoheptaose. The CDTH-ACS (anthraquinone-2-sulfonic acid sodium salt) system was investigated. by ^{1}H NMR spectroscopy and by i.c.d. (induced circular dicroism), and a deep inclusion of ACS inside the CDTH cavity, with an association constant about six times larger with respect to ACS - β-CD system was found.

1. INTRODUCTION

The functionalization of cyclodextrin can modify and improve some features of this class of molecules, such solubility, stability and selectivity, when forming inclusion complexes. By replacing one or more -OH groups at a desired position and with appositely designed substitution group, multisite recognition systems have been obtained [1]. An improvement can be obtained by introducing groups able to coordinate metal ions: the metal can be one more recognition site when coordinating guest are recognized by the cavity. In this class of complexes, some of them have shown to behave as chiral discriminating agents, and their use in LEC chromatography has been described [2, 3].

Capped cyclodextrins have been synthesized as well and their properties have been investigated. Among the capping groups, porphyrins [4], cyclopeptides [5], the azobenzene [6] and other aromatic moieties have been used [7]. The expansion of the hydrophobic region in comparison with the CD parents have been underlined. This increase in the hydrophobicity has resulted in larger association constants with different guests, in comparison to the CD parents [6, 7]. However, in all the capped cyclodextrins reported until now, the carbohydrate cavity hasbeen coupled with capping moieties with completely different features in comparison to CDs, as can also be seen by the short list above reported.

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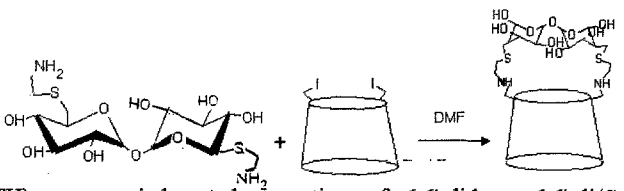
Here, we report the synthesis of the new capped derivative of cyclomaltoheptaose (CDTH). The synthesized CDTH may be considered the first example of a three-dimensional cyclodextrin for the presence of a disaccharide, which extends the carbohydrate system to a plane perpendicular to the main cavity, with a presumably increased inclusion ability with respect to the CD parent. Furthermore the presence of heteroatoms (N and S) in the two bridges between CD and TH could increase the selectivity of this class of compounds.

2. MATERIALS AND METHODS

2.1 Synthesis



The synthesis of 6A,6D-dideoxy-6A,6D-[6,6'-dideoxy-6,6'-di(S-cysteamine)-α,α'-trehalose]-β-cyclodextrin (CDTH) was carried out by reaction of 6,6'-dideoxy-6,6'-di(S-cysteamine)-α,α'-trehalose (TH) with 6A,6D-dideoxy-6A,6D-diiodo-cyclomaltoheptaose ($ADCDI_2$) [8]. according to the following scheme. The synthesis details are reported elsewhere [9]

2.2 Spectroscopic measurements

^1H NMR spectra (400MHz) were recorded on a Varian Unity 400 spectrometer and ^{13}C NMR spectra (50.33 MHZ) on a Bruker AC-200 spectrometer on D_2O solutions without a reference compound.

Circular Dichroism spectra were recorded on a JASCO J-600 spectropolarimeter at 25°C on freshly prepared aqueous solutions in phosphate buffer (0.015M) pH = 6. Quartz cuvettes of 0.1 cm pathlength were used. The ACS concentration was kept constant ($4.0\ 10^{-4}$ mole dm^3), whereas the CDTH concentration was varied such as to obtain, respectively, 1:1.5, 1:2.5, 1:4.5, 1:8, 1:15, 1:25 ACS/CDTH molar ratios. Results are reported in terms of $\Delta\varepsilon$ (molar CD coefficient) in $dm^3\ mol^{-1}\ cm^{-1}$.

2.4 Calculations

For the determination of the association constants, a graphical method was used, by the equation, not neglecting the analytical concentration of the observed component (ACS in our case) with respect to that of the other component [10].

3. RESULTS AND DISCUSSION

The ^1H NMR spectrum of CDTH is reported in fig. 1a, together with its assignment, obtained by COSY spectrum. The trehalose substitution has an overall slight effect on the cavity protons, with the obvious exeception of the methilene protons of the substituted rings (6A, 6D, 6'A and 6'D). Analogously, large shifts are observed on the 6-H of trehalose, as well as on all the protons of the two cysteamine bridges. Among these eight protons, one for each bridge is at a sharply lower field with respect to the others, presumably for a cavity effect. In the 1-protons region only a peak is showed for all the seven glucopyranosinic rings of β-CD, while the two

1-protons of trehalose appear at lowerfield as two separated doublets, thus giving evidence of a loss of equivalence in this symmetric molecule, following the reaction with the cavity.
The CDTH has two secondary amino groups and can form a mono- and a di-protonated species. The CDTH was titrated by DCl and the variation was followed by ^{1}H NMR spectroscopy. These experiments shows that the two protonation constants are very similar and quite low for an amino group (log K is about eight), as tipically observed for this kind of derivatives. The ^{1}H NMR spectrum of the diprotonated species appears more complex than the unprotonated species, showing an increased asymmetry of the cavity, probably due to the formation of hydrogen bonds between the protonated nitrogens of cysteamine moities and upper rim hydroxyl groups.

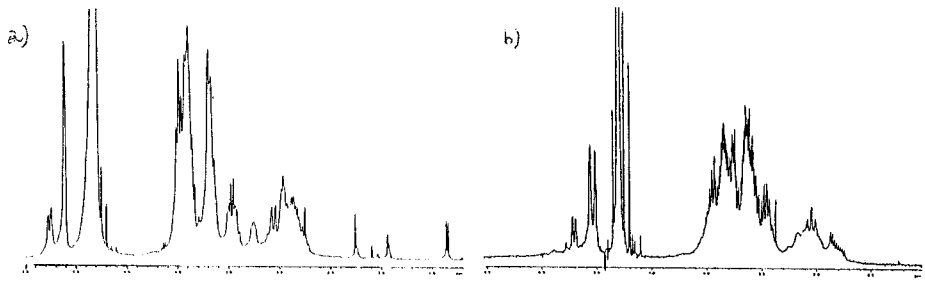


Fig. 1: a) ^{1}H NMR spectrum of CDTH; b) ^{1}H NMR spectrum of CDTH-ACS system.

^{1}H NMR spectrum of CDTH - ACS system is reported in fig. 1b. The comparison with the spectrum in fig. 1a, shows the dramatic effect that the ACS inclusion causes on the host proton chemical shifts. As expected, the 3- and 5- protons of β-CD are very affected. Furthermore, interestingly, also the trehalose protons chemical shifts are influenced, suggesting a deep inclusion of ACS inside the CDTH cavity. ROESY spectrum shows correlations between the inner protons (3,5) of the cavity with the protons of the ACS unsubstituted benzene ring, suggesting that this ring is deeply included in the CD cavity. The sulphonic group seems to be near the CD secondary OH rim, outside the cavity.
CD spectrum of CDTH shows a small positive Cotton effect ($\Delta\varepsilon = 0.54$) at 222 nm, due to the chirality of the cysteamine moieties, induced by the CD cavity. The ACS does not show a c.d. spectrum; however, if CDTH is added to an ACS solution, an i.c.d. spectrum is obtained.

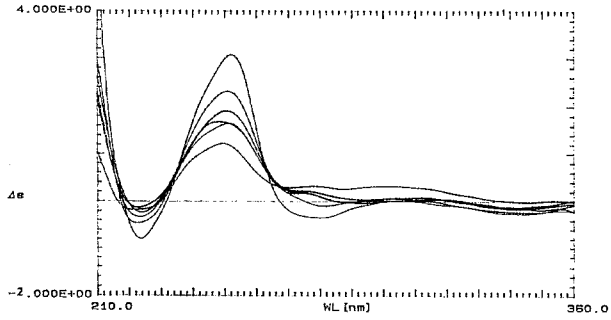


Fig. 2 - I.c.d. spectrum of CDTH - ACS system. From curve *a* to curve *f*, increasing concentrations of CDTH (see text).

In order to determine the CDTH - ACS association constant, a titration of the guest with the host was carried out, and the c.d. spectra obtained are reported in fig. 2. The positive band at 252 nm, (where the Cotton effect is stronger) corrected for the slight CDTH contribution, were used, as above described, to obtain the equilibrium constant value (Kass = 3589). This constant value is much higher in comparison to the value calculated for the ACS-β-CD complex (Kass = 598).

4. CONCLUSION

The preliminary results here reported on the new host CDTH, show its strong inclusion properties. This host can be considered the prototype of a three-dimensional cyclodextrin. By a suitable choice of the "bridge" groups, is possible to modulate the strength and the selectivity of these receptors towards specific substrates, as well as their coordinating ability towards metal ions. Work is in progress in our laboratories in order to more explore the features of CDTH, as well as to synthesize other compounds of this class.

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