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A New Water Soluble Host Compound Possessing Two Different Hydrophobic Recognition Cavities: Calix[4]arene Derivative Conjugated with Monofunctionalized β-Cyclodextrin

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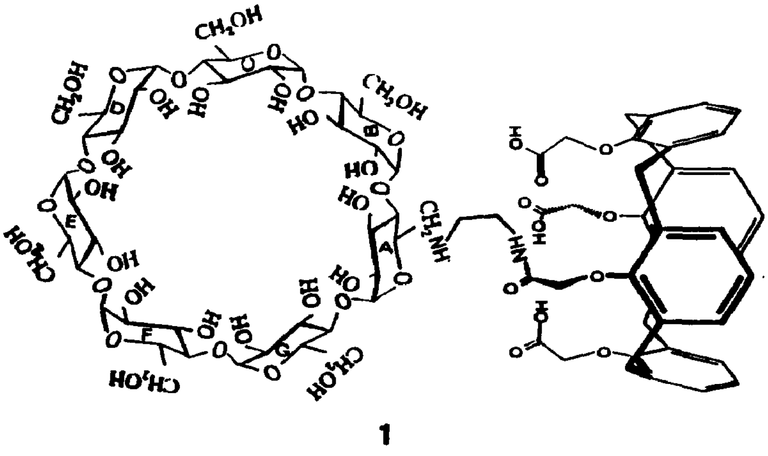
***Abstract:**: A new compound possessing two different hydrophobic cavities was obtained by the condensation of a Calix[4]arene derivative with a monofunctionalized β-Cyclodextrin . The compound has been characterized by ^{1}H NMR.*

Cyclodextrins (CDs) are cyclic oligosaccharides possessing an axial symmetry arising from the presence of six, seven or eight α-1,4-glucopyranose units (giving α, β and γ cyclodextrins, respectively). The molecular geometry of CDs is such that the interior surface of the cavity is hydrophobic (apolar) and the external surface is hydrophilic (polar). The cavity is able to form inclusion complexes with a variety of organic compounds in aqueous solution[1]. Chemical modification of CDs with various functional groups[2-5] has been extensively investigated in order to improve their complexing and catalytic abilities.

Furthermore, a number of cyclodextrin dimers have been described[6-11], some of these showing very large co-operative binding constants due to the presence of two hydrophobic cavities[9].

Calixarenes are macrocycles made up of phenolic units ortho-linked by methylene bridges forming basket-shaped cavities of various sizes which are able to form inclusion complexes with a variety of guest molecules and



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to act as enzyme mimicking systems[12]. Calixarenes have also been investigated as ion carriers[13].

The coupling of a monofunctionalized β-cyclodextrin with a calix[4]arene derivative has led to a new class of abiotic receptors characterized by two cavities both of different size and of different hydrophobicity.

Here we report the synthesis and a preliminary characterization of 25-[N-ethylamino-(N'-6-deoxycyclomaltoheptaose)]carbonylmethoxy-26,27,28-tris(hydroxycarbonylmethoxy)calix[4]arene [1].

Compound 1 was prepared according to the following procedure: 25,26,27,28-tetrakis(hydroxycarbonylmethoxy)calix[4]arene in the blocked cone structure[14] (CLX4) (mg 100) was added to a solution of 6-deoxy-6-[1-(2-amino)ethylamino]-β-cyclodextrin[15] (β-CDen) (mg 197) in DMF (ml 7) in the presence of benzotriazolyl-N-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (mg 74) and N-1-hydroxybenzotriazole (HOBT) (mg 25). The reaction mixture was stirred vigorously at room temperature overnight under a nitrogen stream. The solution was evaporated to dryness in vacuo at a temperature not exceeding 30 °C. The solid obtained was purified on a DEAE-Sephadex^R-A25 column (HCO_3^- form) which was eluted with a linear gradient of NH_4HCO_3 (0.6-2.0 mol dm^{-3}). The fractions were analyzed by TLC. The product was detected with U.V. light and the anisaldehyde reagent[16]. The purity of the product was furthermore checked by HPLC (Lichrospher 100 RP- 18, 5μm λ=272 nm with a linear gradient of water MeCN 0-30%); yield 40%; TLC (SiO_2) Rf= 0.25 (PrOH-H_2O-AcOEt-NH_3 (5:3:5:1); negative FAB/MS spectrum: 1814 $(M-H)^-$. Anal. Cal. for $C_{80}H_{106}N_2O_{45}\cdot 18H_2O$: C 44,90, H 6.69, N 1.31; found: C 45.00, H 6.61, N 1.28.

The 250 MHz ^1H NMR spectrum in D_2O is shown in fig.1.

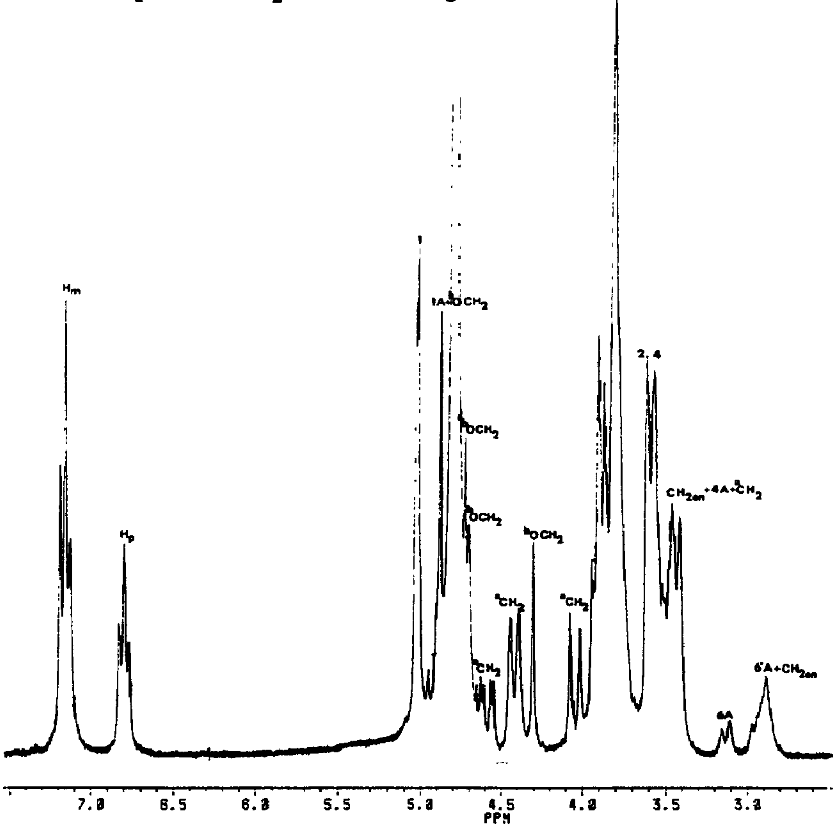

Figure 1

^{a}Bridging methylenes of CLX4 and ^{b}OCH_2 methylenes of the CLX4.

Assignments were aided by the use of 2D ^{1}H NMR COSY correlated homonuclear chemical shifts and by comparison with the CDen[15] and CLX4[14] NMR data. Although compound 1 shows appreciable solubility in water, in order to obtain homogeneous data we carried out NMR experiments in the presence of stoichiometric amounts of NaOD, since CLX4 is water soluble only in these conditions. Monosubstitution results in a loss of symmetry at the calixarene moiety. In particular the AB system relative to the four bridging methylenes, present in CLX4, is split into two different AB systems upon substitution (δ_A=4.42 ppm, δ_B=3.46 ppm J_{AB}=12.5Hz; $\delta_{A'}$=4.59 ppm, $\delta_{B'}$=4.04 ppm, $J_{A'B'}$=15.1 Hz). For the same reason the four -OCH_2- groups at the "lower rim" resonate at different fields (δ=4.87 ppm, -OCH_2CON-; δ=4,73 ppm, δ=4.70 ppm, δ=4.30 ppm -OCH_2COO^-) Also the pattern of aromatic protons is indicative of the loss of symmetry of the calixarene moiety.

Minor influences are observed in the proton chemical shifts of the CDen moiety except for one of the two ethylendiamine methylenes which is shifted downfield at δ=3.41 ppm (compared to δ=2.98 ppm of the corresponding methylene of CDen[15]).

Preliminary ^{13}C NMR experiments confirm the identity of 1 and show further evidences about the loss of symmetry occurred at the calixarene moiety.

Breslow[17] has recently claimed that the preparation of a cyclodextrin dimer doubly linked at adjacent sugar residues give rise to a rigid receptor with binding properties stronger than those of an analogous molecule with flexible linkage. Our receptor could have stronger binding properties by using the presence of a different kind of potential binding site. In fact, the amine nitrogen and /or the carboxylate groups can aid the inclusion of a hydrophobic moiety of a positive and /or negative charged organic guest. In addition, owing to the fact that preliminary results suggest that 1 binds copper(II) ion, this dimer could act as a multisite receptor for molecular recognition processes assisted by metal ions. We expect that it will be possible to employ the above reported methodology for the preparation of 1 to obtain molecules containing a greater number of cavities (two or four β–cyclodextrins linked to a calixarene group). These compounds could be able to form high stability inclusion complexes with specific substrates, and soluble calixarene derivatives as also suggested in a recent communication[18]. These studies are currently in progress in our laboratories.

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