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Self assembly in custom designed cyclodextrins

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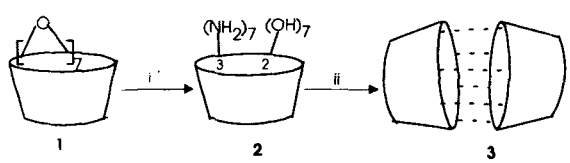
Synthesis of the first custom designed cyclodextrins obtained by a nucleophilic attack on hepatkis-2,3-epoxy-β-cyclodextrin is reported. This novel cyclodextrin provides amine functionalities in addition to hydroxyl groups for chemical processes. Spectral evidence shows that the cavity in this new cyclodextrin is flexible and it self assembles into a dimer under specific conditions.

Cyclodextrins[1], widely investigated in the last decade[2,3,4] as complexing agents, catalysts and enzyme mimics are limited in their utility due to rigidity of structure and availability of only hydroxyl groups for useful chemical processes. Attempts to ameliorate this situation have achieved limited success[5] especially with regard[6] to its catalytically important[7] secondary side. The synthesis[8] of a key intermediate, hepatkis-2,3-epoxy-β-cyclodextrin (**1**) has opened a route to custom designed cyclodextrins which can furnish a variety of functional groups on the "secondary" side of the molecule. We now report the synthesis of first of these new cyclodextrins which provide amine functionalities in addition to hydroxyl groups. Spectral evidence shows that the cavity in this new cyclodextrin is flexible and it self assembles into a dimer under specific conditions.

A new β-cyclodextrin containing seven hydroxyl and amine groups each on the secondary side is synthesized as shown in scheme 1 by stirring heptakis(2,3-epoxy)-β-cyclodextrin (**1**) with a large excess of aqueous ammonia solution for 6 days at room temperature. It is then filtered and evaporated to dryness under reduced pressure to yield heptakis(3-amino-3-deoxy)-β-cyclodextrin (**2**). The crude compound **2** is dissolved in water, pH adjusted to 3 with HCl, precipitated with acetone, the clear solution decanted out, the remaining material redissolved in water and finally evaporated to dryness under reduced pressure at 60 °C to obtain a yellow solid. The structure of this solid, based on ^{13}C NMR and mass spectral evidence is proposed as **3**.

Scheme 1



Conditions: i: aq. NH_3, 6d; *ii:* H_2O/HCl, pH 3, evaporate to dryness at 60°C

The ^1H NMR spectrum of **3** shows a doublet at 4.98 ppm for the anomeric proton with $J_{1,2}$ = 5.6 Hz indicating a $^1C_4$ conformation[9] which is expected due to stereochemical and conformational changes that take place during the formation and the ring opening of a cyclodextrin epoxide. A computational chemistry investigation carried out[10] to examine the two possible chair conformations indicate that the $^1C_4$ conformation is 16.8 Kcal/mole more stable than the $^4C_1$ conformation, which is consistent with the ^1H NMR spectrum. The ^{13}C NMR spectrum of **3** shows only six signals for carbon atoms indicating a seven fold symmetry (Figure 1a). The ES mass spectrum of **3** (Figure 2) shows a peak at 2256.1 which represents a formula of $C_{84}H_{154}O_{56}N_{14}$ suggesting a dimeric form **3**. Peaks at 2239.1, 2221.7 and 2205 represent the loss of two hydroxyl groups and ammonia respectively from the dimer. The peak at 1128.1 with a relative abundance of 100% represents a molecular formula of ($C_{42}H_{77}O_{28}N_7$) a monomer formed due to the dissociation of the dimer. Peaks at 1111.1 ($C_{42}H_{76}O_{27}N_7$) and 1094.2 ($C_{42}H_{55}O_{26}N_7$) represent the loss of one and two hydroxyl groups from this monomer. The sharpness of the ^{13}C NMR spectrum (Figure 1a) indicates that this sample is homogeneous and not a mixture of the monomer [whose peaks (Figure 1b), as explained later, are broad and distorted] and dimer. The exact mass determined by a high resolution FAB mass spectrum for this monomer peak is 1128.4883 which agrees very well with theoretical value (1128.4895) $C_{42}H_{77}O_{28}N_7$ for **2**.

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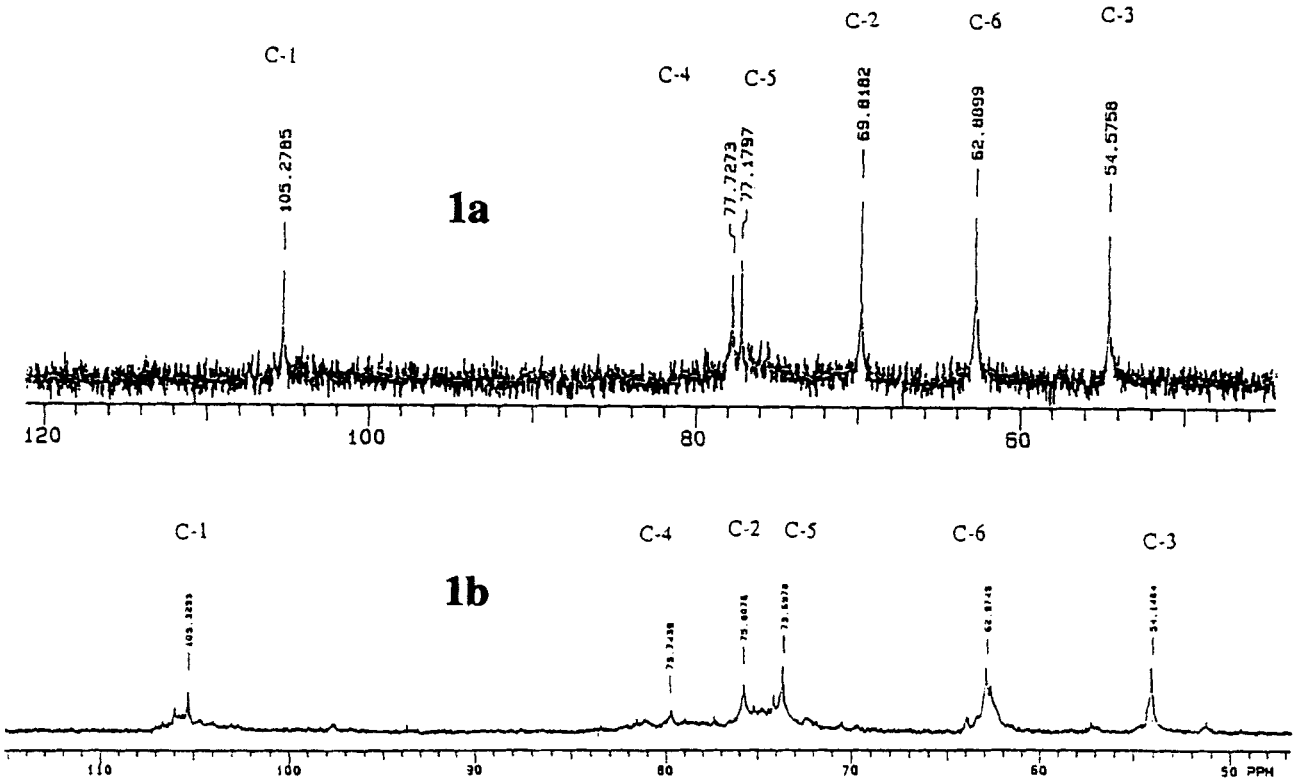

Figure 1 ^{13}C NMR spectra of a) compound **3** b) compound **2**.

The ^{13}C NMR and the high resolution mass spectra clearly establish that this compound is homogeneous and is the product expected from complete epoxide opening of **1** with ammonia.

Although TLC of **2** demonstrates a single spot with an R*f* value[11] of 0.28, its ^{13}C NMR spectrum shows broad distorted peaks for anomeric (C-1) and aglycone (C-4) carbon atoms and relatively clear signals for others (Figure 1b). An average difference of 10° in one of the torsion angles (ψ) of glycosidic linkage brings about a change of *ca* 2 ppm for anomeric and aglycone carbon atoms in the ^{13}C NMR chemical shift.[12] In keeping with the literature precedence[13] for ring of opening of the mono-epoxide of cyclodextrin, each altrose unit in compound **2** is expected to be in a distorted chair geometry and the new functionality at the 3-position is envisioned to assume a pseudoequatorial position. Since several distorted chairs can have similar energy levels and the altrose units in the new cyclodextrin are linked together, they can interconvert into other distorted chairs and produce a dynamic change in the conformation of **2**. These distorted chair geometries force the torsion angles (ψ) of glycosidic linkages to vary and thus produce broadness in the ^{13}C NMR spectral signals for the anomeric and aglycone carbon atoms. It is expected that these changes create a magnetically nonequivalent environment for each of the altrose units which explains the reason for the broadness in other peaks. The presence of such signals in the spectrum is an indication of the distortion and flexibility in the cavity of compound **2**.

When a sample of the free amine **2** is converted to **3** as described above, the ^{13}C NMR spectral signals become sharp and only six peaks are observed (Figure 1a). It is observed that sharpening of the peaks is dependent on both adjusting the pH and evaporating water under reduced pressure at 60 °C indicating that this change is not brought about by the protonation of the amine functionality. The sharpness of the signals of a sample of **3** is lost when this solution is made basic. Acidification of the

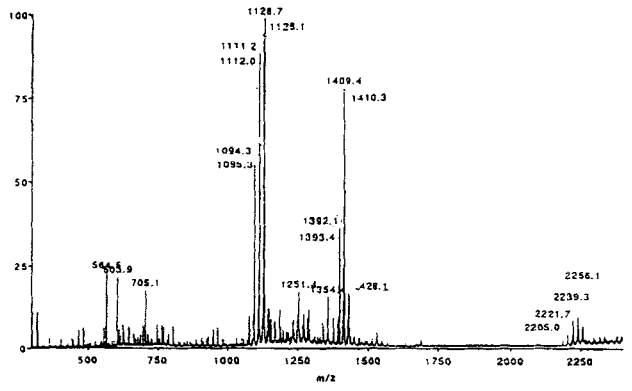

Figure 2 Low resolution mass spectrum (ES) of compound **3**.

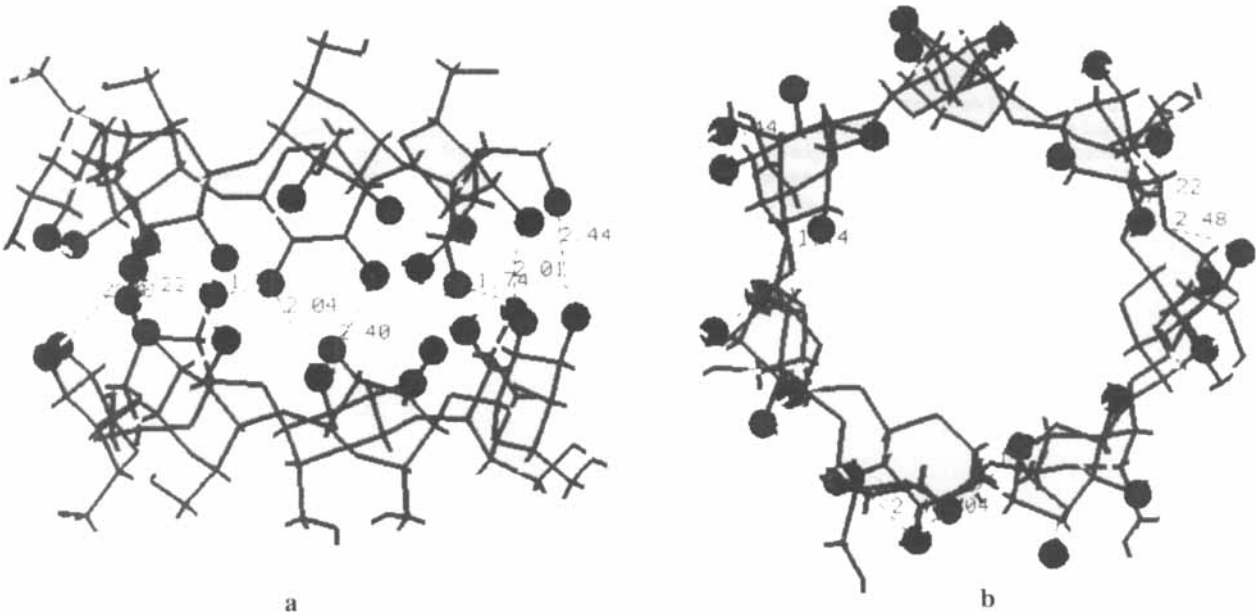

Figure 3 Structure of compound **3** obtained from computational chemistry, a) a side view showing hydrogen bonds between the hydroxyl and amine groups, b) top view showing the fit between the two units. All oxygen and nitrogen atoms at the secondary side of both units are indicated by CPK representations. (See color plate II at back of journal.)

same sample with dueterated hydrochloric acid (pH= 3) does not produce sharp NMR spectral signals unless the solvent is evaporated to dryness under reduced pressure and dissolved in D_2O. On the other hand, acidification of a sample of the free amine **2** (which gives broad ^{13}C NMR signals, Figure 1b) does not produce sharp peaks. When the sample is evaporated to dryness under reduced pressure at 60 °C and subsequently dissolved in D_2O, it shows (Figure 1a) sharp proton and ^{13}C NMR spectral signals which are lost if the solution is made basic. Thus it is noted that these NMR spectral effects are completely reversible and samples of both **2** and **3** show similar behavior.

The sharp NMR signals, observed after removal of water in acidic pH, indicate a symmetrical, rigid structure whereas broad signals seen in basic pH suggest a flexible and distorted geometry. The above described experiments clearly indicate that evaporation of water from the acidic solution of **2** locks it into a rigid structure **3**. The structure **3** can account for the symmetry in ^{13}C NMR and the mass spectral peak at 2256.1.[14] An examination of the monomeric and dimeric structures by computational chemistry[15] indicate that the dimer is 30.57 Kcal/mol more stable than two moles of the monomer. It further shows a very good fit between the two monomer units and multiple hydrogen bonds between hydroxyl and amine groups of the two units (Figure 3).

In conclusion, the high resolution mass spectrum and the ^{13}C NMR spectrum indicate that ammonia reacts with the epoxide to yield the proposed new cyclodextrin. The low resolution mass spectrum (ES), ^{13}C NMR spectra at various pH and the computational chemistry study indicate that the product self assembles when an acidic solution of the new cyclodextrin is evaporated to dryness. This new custom-designed cyclodextrin exhibits very interesting complexation and catalytic properties. It catalyzes acyl-transfer reactions of unactivated esters at physiological pH, a property which is absent in native cyclodextrins and which is expected to have important applications. These exciting properties of the new cyclodextrins will be discussed in a future article.

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10 Calculations were performed with InsightII v2.2.0 using Discover v2.9 force field and executed on SiliconGraphics Iris Indigo work station. The initial geometry of β-cyclodextrin was taken from the X-ray crystal structure, the -OH groups at the 3-position were replaced by $-NH_2$ groups and the resultant structure was energy minimized. $^1C_4$ conformation was obtained from $^4C_1$ conformation by using the "flip" routine available in the program and then minimizing the energy. All structures were energy minimized to a gradient of 0.001Kcal/mol by using conjugated gradient method.
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15 The dimer was constructed by moving two energy minimized $^4C_1$ structures facing each other and then minimizing the energy of the resultant structure as described in ref 10. Several different initial position of the units were investigated and the most stable among all the structure is reported.