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SYNTHESIS AND CONFORMATIONAL STUDIES OF A NEW HOST SYSTEM BASED ON CHOLIC ACID*

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ABSTRACT. New synthetic hosts have been designed incorporating two molecules of cholic acid linked by a rigid diamine. Proton NMR studies indicate that the compounds exist in a rigid conformation with the steroid hydroxyl groups intramolecularly hydrogen-bonded. Heat or addition of methanol leads to conformational isomerism due to insertion of methanol into the cavity.

Synthetic molecular receptors command widespread interest as mimics of membrane transport agents and enzyme active sites.[1,2] The development of new host systems for the selective complexation of organic and inorganic cations and anions has mushroomed in recent years; however, examples of solution phase coordination of neutral organic molecules are few. Most of these examples involve inclusion of an aromatic hydrocarbon into the hydrophobic pocket of a water soluble cyclodextrin or cyclophane receptor.[3-6] A smaller subset of synthetic receptors possess lipophilic exteriors and hydrophilic cavities for the association of polar substrates in nonpolar media. [7-9] We report here the synthesis and characterization of a new system of the latter type designed to bind polar guests in chloroform solution.

Cholic acid forms the architectural unit for the construction of amphiphilic receptors that are chloroform soluble while possessing a cavity lined with hydroxyl groups. Cholic acid is an ideal building block for artificial receptors because of the following features: (i) rigidity of the steroid framework insures formation of a cavity, (ii) the two faces of the steroid differ dramatically in their properties--the alpha face displays three hydrogen bonding groups while the beta face is entirely hydrophobic, (iii) the cis A-B ring junction imparts a curvature to the steroid ring system, (iv) the hydroxyl group are directed convergently toward the center of the concave face, (v) the

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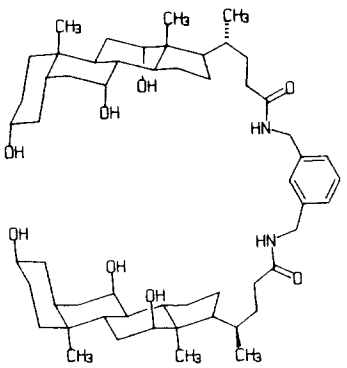
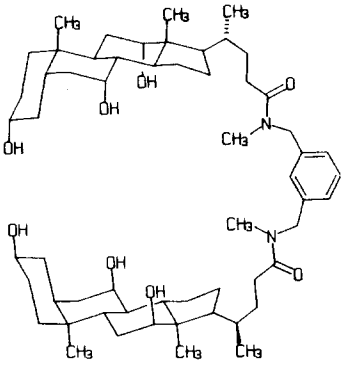
side chain carboxylate is readily derivatized, (vi) cholic acid is chiral, and (vii) it is nearly as inexpensive as cholesterol. Thus, cholic acid displays a great deal of complexity and molecular information in a readily available material.



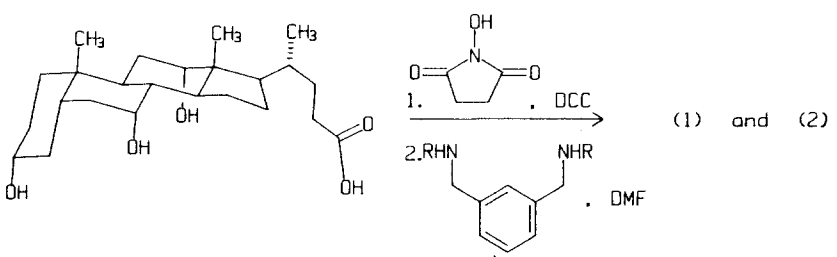
(1)



(2)

The first molecules investigated were compounds 1 and 2, bis-cholamides joined by an aromatic link. Although a number of more rigid linking groups were prepared, we became intrigued with the unusual conformational properties of the m-xylylene derivatives. Compounds 1 and 2 were synthesized as shown in Scheme I by a method analogous to that of Kunitake.[10] Both were isolated in high yield (60-80%) as white solids after flash silica chromatography (10% MeOH, $CHCl_3$). The new compounds were fully characterized by spectroscopic and analytical methods. Both compounds were chloroform soluble (0.05 M) but fairly insoluble in non-hydrogen bonding solvents such as methylene chloride.

Scheme I



Proton NMR spectra of 1 and 2 displayed resonances similar to that of cholic acid [11] and the anticipated aromatic peaks. The resonances for the protons adjacent hydroxyl groups appeared as distinct multiplets at 3.35, 3.79, and 3.90 ppm for H_3, H_7 and H_{12} respectively. However, the positions of the diastereotopic benzylic hydrogens were highly dependent upon the solvent and the presence of small quantities of polar substances such as caffeine. In pure $CDCl_3$

two doublets of doublets appear at 3.95 and 4.77 ppm. These resonances collapse to a single narrow multiplet upon addition of small quantities of CD_3OD. Figure 1 shows the 3 to 5 ppm region of the spectrum for compound 1 as a function of added methanol. Concentrations of 1 were varied between 0.02 M and 10^{-4} M with similar results. The same phenomenon was observed in the variable temperature spectrum of 1 upon warming the solution. Figure 2 indicates a few of the temperatures studied. Coalescence occurs near 29°C (300 MHz) suggesting a dynamic process with a 14 kcal/mole energy barrier.

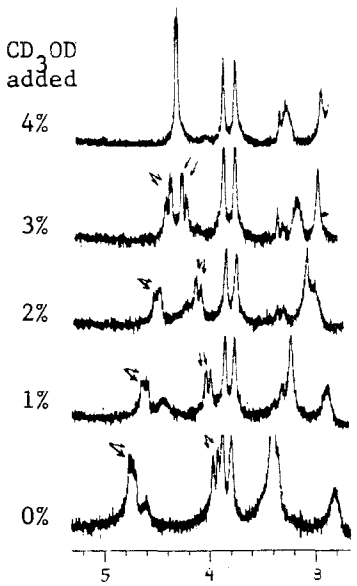


Figure 1. 300MHz spectrum of 1 in $CDCl_3$ at 294° as a function of added CD_3OD. Arrows indicate benzylic H's.

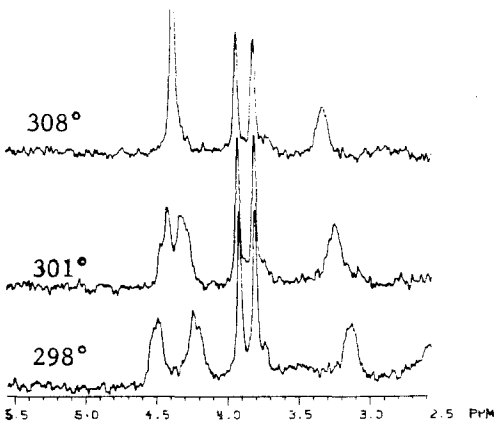
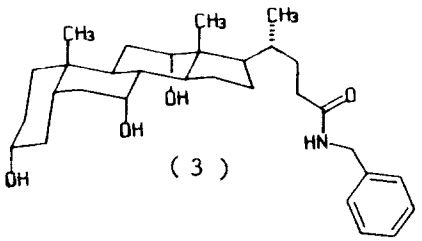


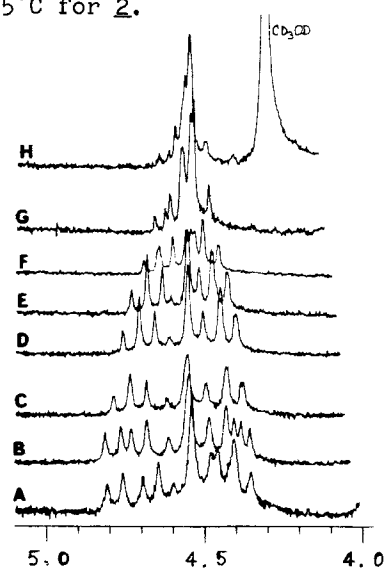
Figure 2. 300MHz variable temp. NMR study of 1 in $CDCl_3$.

An explanation consistent with the data involves solvent or temperature-induced isomerization of two conformational isomers, a closed form in which the two steroid halves of 1 are face-to-face and held together by direct intramolecular hydrogen bonding, and an open form in which rotations about bonds in the linking group are fast on the NMR time scale. Rigidity in the closed form of 1 would explain the large difference in chemical shift between the benzylic hydrogens. In a freely rotating form, these protons are likely to be in similar chemical environments. For comparison, compound 3 was prepared and investigated in the same fashion. Under all experimental conditions, the benzylic protons of 3 appeared as a narrow multiplet at 4.42 ppm. Thus, the dynamic process is a result of two cholate groups being present in the molecule.



(3)

The $CDCl_3$ solution spectrum of 2, an N-methylated analog of 1, suggests that there are at least three major conformers present at room temperature (21°C.) Incremental addition of CD_3OD produced a similar convergence of the benzylic proton signals, but now nearly an equal volume of methanol was necessary to bring about free rotation. (See Figure 3.) Variable temperature studies failed to show convergence up to 65°C for 2.



% CD_3OD added

H = 40%

G = 25%

F = 20%

E = 15%

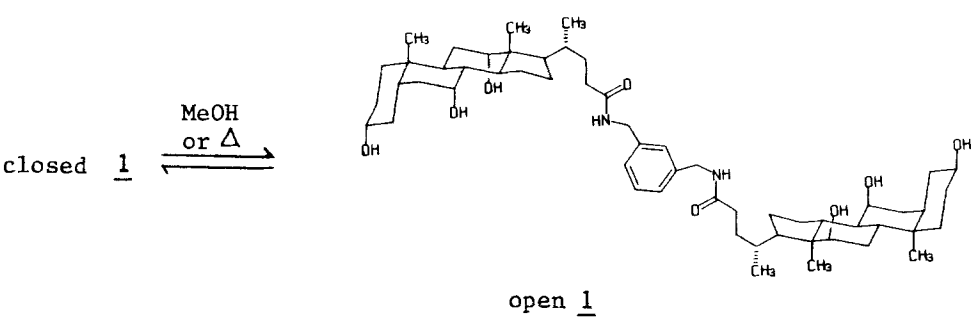
D = 10%

C = 5%

B = 2%

A = 0%

Figure 3. 300MHz spectrum of 2 in $CDCl_3$ at 294° with increments of CD_3OD added.



open 1

While conformational isomerism about the amide C(O)-N bond may account for some of the complexity of the spectrum of 2, the

interpretation most consistent with compound 1's sensitivity to the presence of a hydrogen-bonding solvent is that of intramolecular bonding of a closed form interconverting with a freely rotating form. These results suggest that this new class of synthetic hosts displays the appropriate solubility and hydrogen-bonding characteristics required for association of polar molecules such as methanol. Further studies are being directed toward the characterization of molecular complexes and the elaboration of 1 and 2 to macrocyclic analogs.

Finally, it is interesting to note that the biological function of cholic acid and other bile acids is to form inclusion complexes with hydrocarbons in aqueous solution and the excretion of cholesterol.[12] Indeed, others have mimicked this phenomenon in synthetic systems where cholic acid forms a hydrophobic pocket.[13,14] We have attempted to reverse the role of cholic acid and to take advantage of its singular features as a convergently functionalized binding group.

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