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Synthesis of a novel uracil-2,6-diaminopyridine-lithocholic acid conjugate that self-assembles into a cyclic dimer

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ABSTRACT

Synthesis and self-association studies of a uracil-2,6-diaminopyridine-lithocholic acid conjugate are described. The dimeric supramolecular structure is characterized by NMR spectroscopic, ESI-MS, and size exclusion chromatographic studies.

There has been considerable interest in recent years in the design of self-complementary molecular structures which can assemble through hydrogen bonding to form well-defined supramolecular systems.[1] Self-assembly allows access to novel supramolecular architectures with remarkable structural variety, such as linear, cyclic or three dimensional arrays, with interesting applications that are difficult to obtain through conventional synthesis.[1,2] The groups of Meijer[3] and Zimmerman[4] have developed a variety of heterocyclic complexes employing a combination of self-complementary hydrogen bonding arrays.

Nucleobases have also been exploited for the construction of supramolecular assemblies. Between the two major nucleobase binding motifs present in nucleic acids, the GC (guanine-cytosine) couple has received much attention from chemists due to its strong degree of interaction.[5] However, AT/AU (adenine-thymine/adenine-uracil) couples have also been examined for self-assembly. Sessler and coworkers have reported self-assembling structures in which AT/GC nucleobases are connected through a very rigid 1,8-diethynylanthracene spacer.[6] The studies highlighted the role of steric influence in hydrogen bond mediated self-assembly as the AT derived complex was found to form more stable dimers compared to the corresponding GC derived complex. Gokel et al. reported self-assembled dimeric structures derived from crown ethers containing nucleotide bases.[7]

Bile acids have proved to be promising candidates in the field of molecular recognition due to their unique molecular architectures.[8] In this particular area, cholaphanes which are bile acid-based macrocycles have received much attention.[8a,c] The synthesis of cholaphanes requires a crucial cyclization step that usually gives low yields. Our group has been able to overcome this problem by using the Cs-salt methodology for the synthesis of head-to-head cholaphanes.[9]

As a part of our interest in bile acid-based systems,[10] we report herein for the first time, the non-covalent synthesis of a head-to-tail cholaphane which involves self-assembly of a bile acid-based derivative containing 2,6-diaminopyridine and uracil residues. 2,6-Bis(acylamino)pyridine derivatives are known to bind uracil/thymine analogues via three hydrogen bonds in non-polar solvents.[11] However, to the best of our knowledge, there is no report on 2,6-diaminopyridine-uracil/thymine-based self-assembled systems.

The synthesis of lithocholic acid derivative **6** containing uracil and 2,6-diaminopyridine units is outlined in Scheme 1. 3α-*O*-Formyllithocholic acid[9d] **1** was coupled with 2,6-diaminopyridine to afford amine **2** in high yield, which was subsequently reacted with lauroyl chloride to give bile acid derivative **3**. This was followed by hydrolysis of **3** with LiOH to afford compound **4**, which on treatment with bromoacetyl bromide gave **5**. Reaction of **5** with uracil in DMF afforded compound **6** in 72% yield.

Compound **6** was expected to form self-assembled structures because of the complementary 2,6-diaminopyridine and uracil units. However, the nature of assembly (dimer, trimer, etc., or polymeric aggregates) could not be envisaged merely on the basis of its structural features. Initial evidence for self-assembly of **6** came from ^{1}H NMR spectroscopic studies carried out at 298 K in $CDCl_3$ (Fig. 1). The ^{1}H NMR spectrum of **6** (10 mM, $CDCl_3$) clearly indicated the formation of a self-assembled structure involving

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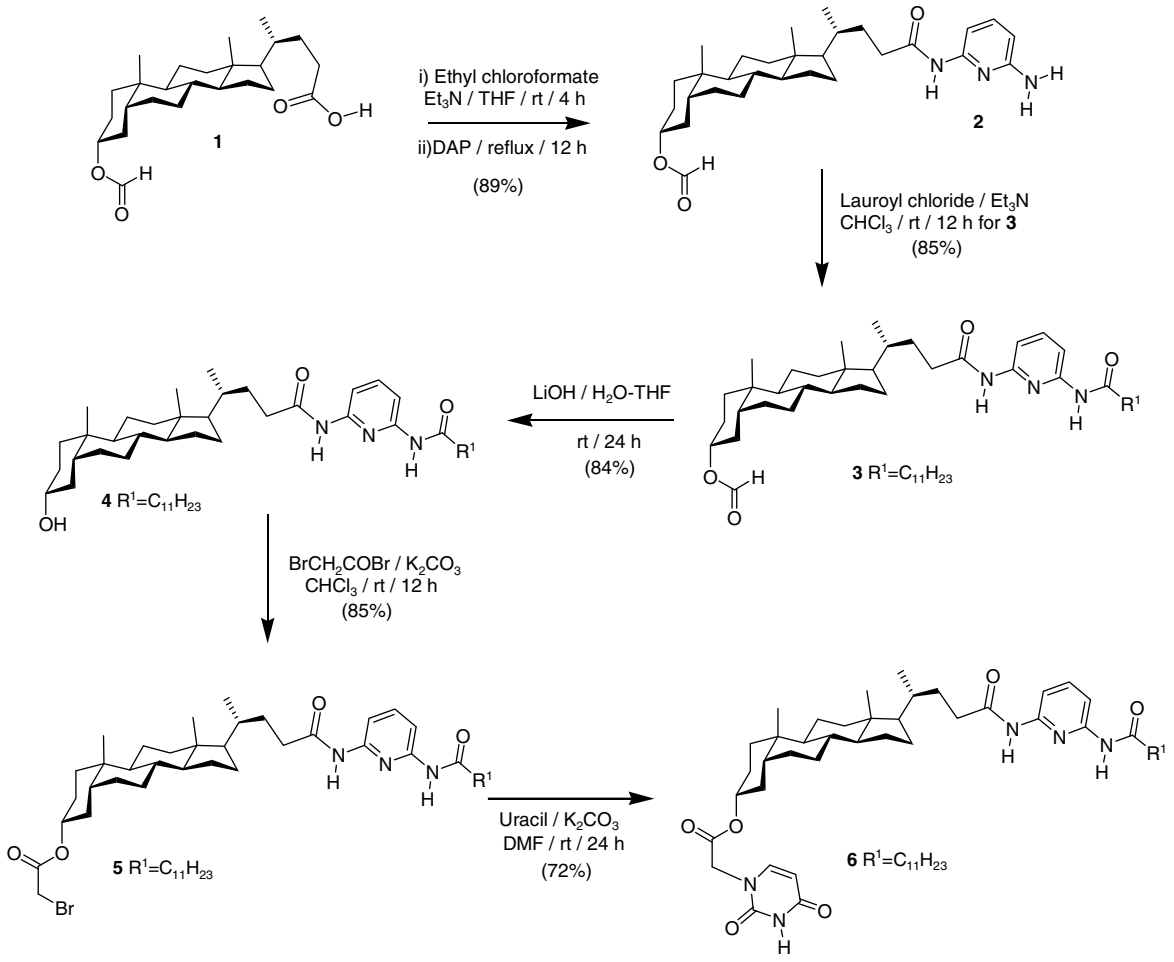

Scheme 1. Synthesis of self-assembling bile acid-based conjugate **6** containing uracil and 2,6-diaminopyridine moieties.

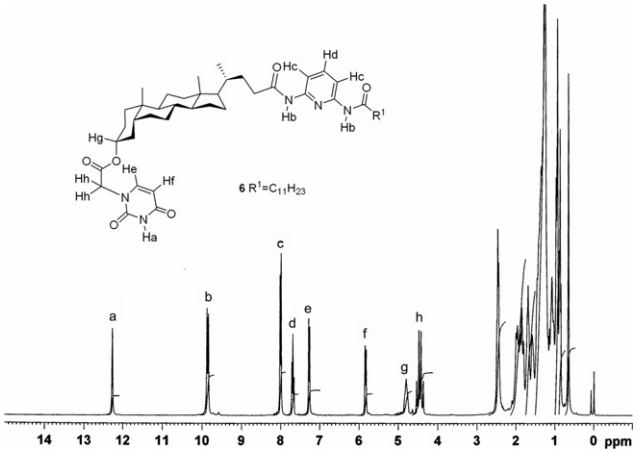

Figure 1. ^{1}H NMR (300 MHz, rt) spectrum of **6** (10 mM) in $CDCl_3$.

hydrogen bonding between the 2,6-diaminopyridine and uracil units as there was a significant downfield shift of the amide protons ($\Delta\delta \approx 2$ ppm) and the imide proton ($\Delta\delta \approx 4$ ppm) as compared to the corresponding signals in the reference compounds.[11i]

The appearance of sharp NMR signals indirectly suggests that the hydrogen bonding does not lead to polymeric aggregates. Further, the appearance of an AB quartet for the methylene protons (next to the uracil unit) indicates that free rotation of the methylene protons is restricted due to hydrogen bond formation. We studied the concentration dependence of the ^{1}H NMR spectrum of **6** in the concentration range 10–0.4 mM in $CDCl_3$. A plot of observed chemical shifts versus concentration for the imide proton is shown in Figure 2.

Upfield shifts of the imide and amide protons were observed on dilution. Plotting the changes in the chemical shift data of the imide proton upon dilution and subsequent fitting of this data to a 1:1 dimerization model with the non-linear least square regression program WINEQNMR[12] gave a dimerization constant of

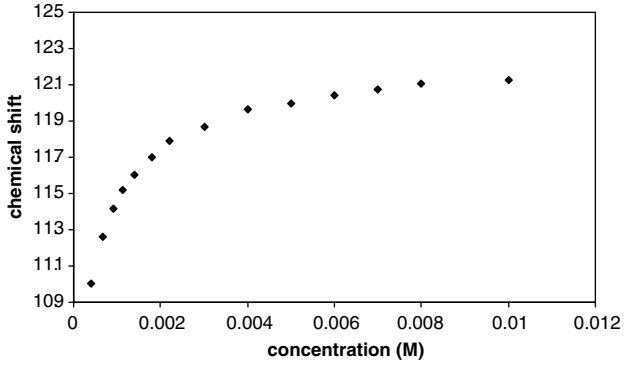

Figure 2. Dilution shift for the imide proton in **6** in the concentration range from 10 to 0.4 mM in $CDCl_3$.

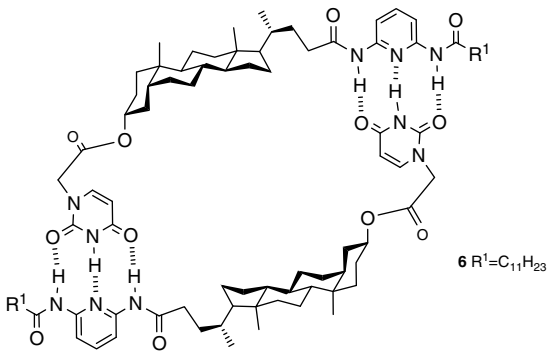

Figure 3. Self-assembly of **6** into a dimeric species.

$(1 \pm 0.1) \times 10^4\ M^{-1}$. Self-association of **6** results in head-to-tail self-assembly as shown in Figure 3.

The additional evidence for the formation of hydrogen bonds between the 2,6-diaminopyridine and uracil units was provided by two-dimensional (2D) NMR (ROESY,[13] $CDCl_3$, 300 MHz) studies (Fig. 4). The ROE contacts between the imide proton and the amide protons indicated that in solution, the uracil and the 2,6-diaminopyridine units are associated by hydrogen bonds.

Variable temperature ^1H NMR measurements at 10 mM of **6** and from 20 to 56 °C in $CDCl_3$ also revealed intermolecular hydrogen bonding. As the temperature was increased, upfield shifts of the imide proton (0.019 ppm/K) and amide protons (0.013 ppm/K) were observed.

Further direct evidence for the intermolecular head-to-tail self-assembly of the bile acid conjugate came from ESI-MS studies. In addition to the monomer peaks at *m*/*z* 802.5495 $(M+H)^+$ and 824.5256 $(M+Na)^+$, there were significant signals for the dimer at *m*/*z* 813.5145 $(2{\cdot}M+H+Na)^{2+}$ and 1626.0827 $(2{\cdot}M+Na)^+$. No signals for higher aggregates were observed.

Further evidence for dimer formation in solution came from size exclusion retention studies.[1a,14] Size exclusion chromatography (SEC) of compound **6** in THF at millimolar concentrations displayed one peak with a retention time of 23.51 min, which corresponds to a mean molecular weight (Mn) of 1623 Da (which is close to the calculated value for the dimeric species of 1603 Da).

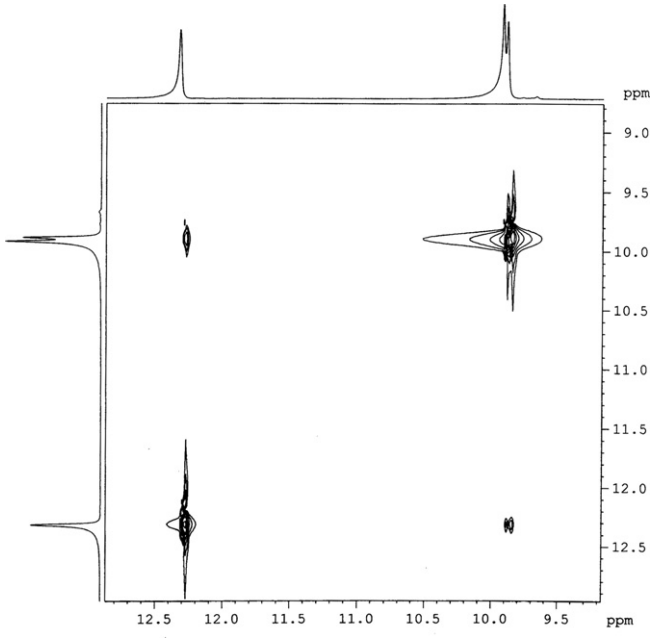

Figure 4. Portion of the two-dimensional ROESY spectrum of **6** (300 MHz, $CDCl_3$) showing ROE contacts between the imide proton at 12.12 ppm and the amide protons at 9.79 and 9.73 ppm.

In conclusion, we have shown that bile acid conjugate **6** containing uracil and 2,6-diaminopyridine units forms a stable dimer exclusively through formation of six intermolecular hydrogen bonds. Bile acids have a curved profile and the head-to-tail self-assembly creates a symmetrical cavity. Such self-assembled structures are potentially useful for selective guest encapsulation. Work is currently in progress directed towards the synthesis of deoxycholic and cholic acid-based self-assembled structures and their use for guest encapsulation.

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Supplementary data

^1H NMR, ^{13}C NMR and mass spectra of all synthetic compounds, the dimerization isotherm, the SEC chromatogram and 2-D ROESY spectrum are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.069.

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