Bile acids in asymmetric synthesis and molecular recognition

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This account summarizes the progress made in our laboratory towards the development of new uses of naturally occurring bile acids. Applications in Asymmetric Synthesis (*intra*molecular coupling, and *inter*molecular reactions) and Molecular Recognition are described with suitable examples.

NATURE is asymmetric and almost all chiral molecules present in nature are homochiral (i.e. they exist in only one of the two possible enantiomeric forms). Organic chemists have always been fascinated by the possibility of constructing natural products by total synthesis. This approach was very successful till the sixties for constructing racemic modifications of chiral natural products. The methodology for synthesizing only one (the naturally occurring form) enantiomer was not present in the organic chemists' 'toolbox' until the seventies. During the past two decades, however, asymmetric synthesis of a variety of molecules has been accomplished by chemists using an assortment of techniques. In most of these examples, the inherent chirality of natural products (such as terpenes, sugars, amino acids etc.) has played important role.

The 'lock and key' concept of Emil Fischer for explaining the specificity of enzymatic action has been known for a century. Deliberate attempts to mimic such biological processes in the laboratory with small organic molecules, however, started much later. Early work with cyclodextrins and subsequently with crown ethers were forerunner to a new area of research towards the design, synthesis, evaluation and applications of synthetic molecular receptors. Carefully designed studies on molecular receptors have provided new insight into molecular interactions. In addition, recent research has shown that many molecular receptors can be designed to have tailor-made properties and hence can be used as a variety of molecular devices including molecular sensors (see, for example, ref. 15).

1. Bile acids: their properties

Bile acids, secreted by the liver, are important metabolites of cholesterol (Figure 1). These compounds are sometimes found in the form of conjugates, specially with glycine and taurine. Most bile acids are

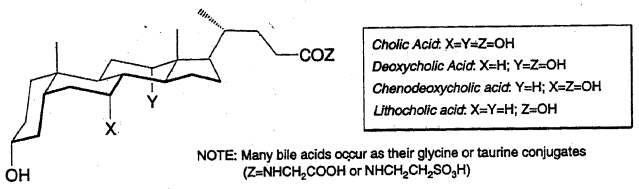


Figure 1. Representative examples of bile acids.

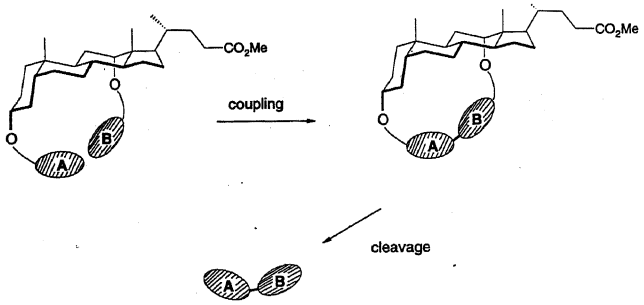


Figure 2. Schematic representation of the bile acid unit acting as a template for a coupling reaction.

characterized by two distinct faces, one being the hydrophobic top (β) face, while the other (α, bottom) face is functionalized with polar hydroxyl groups. In addition, the side chain terminates in a carboxylic acid or other polar functionality. These acids are believed to aid in fat metabolism *in vivo*[1].

A great deal of work has been carried out during the past three decades on the inclusion properties of bile acid crystals[2]. The crystals of cholic and deoxycholic acids contain channels, wherein guest molecules such as low molecular weight ketones can be trapped.

We were intrigued by the orientation of the hydroxyl groups of varying reactivity arranged on the α-face of the bile acid backbone. Until the mid-eighties, there were no reports on the use of the bile acid moiety towards the design of chiral auxiliaries and molecular receptors. We set out to develop new chemistry of bile acids, and use them for asymmetric synthesis and for the design of novel molecular receptors. The progress we have made in the past six years is summarized in this account.

2. Bile acids in asymmetric synthesis

Since the late seventies, there has been considerable progress towards achieving asymmetric synthesis of bioactive molecules[3]. Numerous chiral auxiliaries and catalysts, such as those derived from amino acids, terpenes, sugars, etc. have been utilized. Surprisingly, readily available optically pure bile acids did not receive any attention at all.

We have used bile acids in two distinct ways to induce chirality in reaction products. One approach, described in §2.1, was explored for *intra*molecular coupling processes. The other strategy (§2.2) made use of cholic acid as a chiral auxiliary for *inter*molecular reaction.

2.1. Bile acids as templates for intramolecular coupling

7-Deoxycholic acid, shown in Figure 1, has two hydroxyl groups whose chemical reactivities are different. We decided to examine the possibility of attaching two reactive units to the two hydroxyl groups, and couple them to make one or more bonds. Since the bile acid moiety is chiral, it was anticipated that if the coupling generates one or more stereogenic centers, the product might be formed stereoselectively. This concept is shown schematically in Figure 2.

Our first attempt involved the coupling of two 4-substituted aniline fragments covalently attached to the chiral bile acid template. The reaction of 4-toluidine with formaldehyde and hydrochloric acid was examined more than a century ago by Julius Tröger[4]. The product from this reaction (Tröger's base **1**), and its derivatives, have recently attracted a lot of attention for their rigid *V*-shaped structure which allows one to use this structural unit as a scaffold for the design of molecular receptors[5,6]. We have demonstrated that with a suitable precursor (**2** or **3**), the template coupling does indeed occur efficiently[7], with diasteroselectivity approaching 75% (**3** producing an excess of **5a**) and with good chemical yield (Figure 3). The stereochemistry of the newly-formed stereogenic centers in the major product was unambiguously determined by a combination of chemical and spectroscopic means, including the X-ray crystallographic analysis of a single crystal (compound **4a**)[8,9].

More recently, we have shown that a similar strategy can also be employed for the asymmetric coupling of two 2-naphthol fragments (**6** to **7**) on the template (Figure 4)[10]. Chiral binaphthols are increasingly being used for carrying out a variety of catalytic asymmetric transformations, and further developmental work might lead to a *practical* template-based asymmetric synthesis of this versatile chiral unit.

2.2. Bile acids as chiral auxiliaries for intermolecular reactions

A slightly modified approach was adopted by us for using cholic acid as a chiral auxiliary for *inter*molecular reactions. We reasoned that we could make use of the 3-position of cholic acid for tethering a reactive unit, and the 7-hydroxyl group to position a flat aromatic surface for *shielding* one face of the reactive group. The target molecule (acrylate ester **8**) was synthesized readily in 7 steps from cholic acid in good overall yield. We found that the Diels–Alder reaction of **8** with cyclopentadiene at low temperature in the presence of a Lewis acid oc-

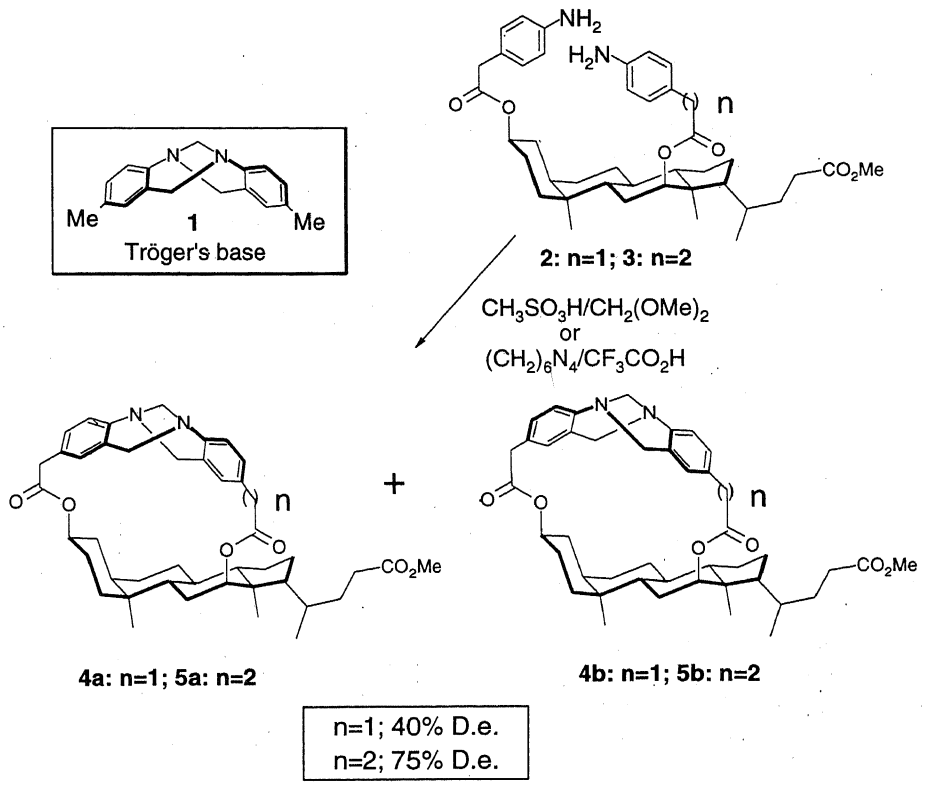


Figure 3. Template synthesis of Tröger's base derivatives on a bile acid template.

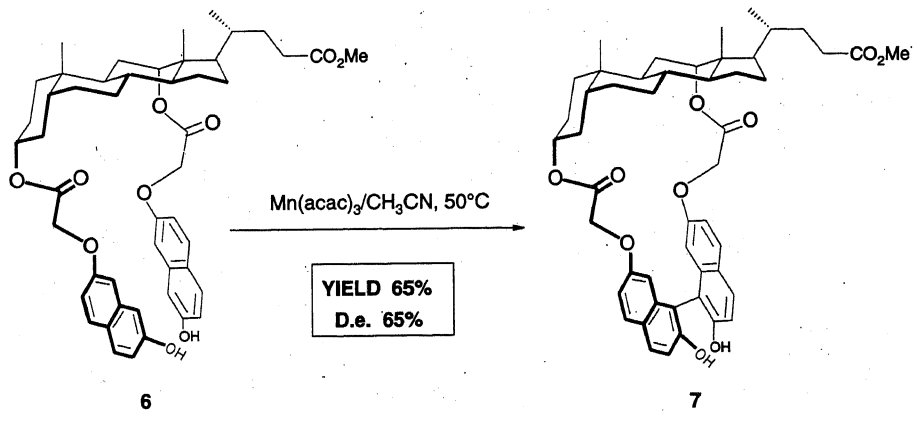


Figure 4. Template synthesis of a binaphthol unit on a bile acid template.

curred readily to give the adduct in very high yield and with diastereoselectivity approaching 90% (**9a** in excess, Figure 5). That the naphthalene ring was indeed functioning as anticipated was confirmed when the 3-acrylate ester containing an acetate at C-7 (instead of the naphthalene as in **8**) failed to show any stereoselectivity under identical conditions. The Diels–Alder product was removed from the adduct by an iodolactonization procedure, regenerating the chiral auxiliary in 88% yield[11,12].

The same strategy has also been shown to be moderately effective for the stereoselective reduction of 2-ketoesters as well. The steroidal chiral auxiliary was attached this time to pyruvic and phenylglyoxalic acids to produce **10** and **11**, respectively, and low temperature reduction with lithium borohydride resulted in 70% stereoselectivity in the diastereomeric product mixture (**12** and **13** were major products, Figure 6). The absolute configurations were assigned by comparison of spectral

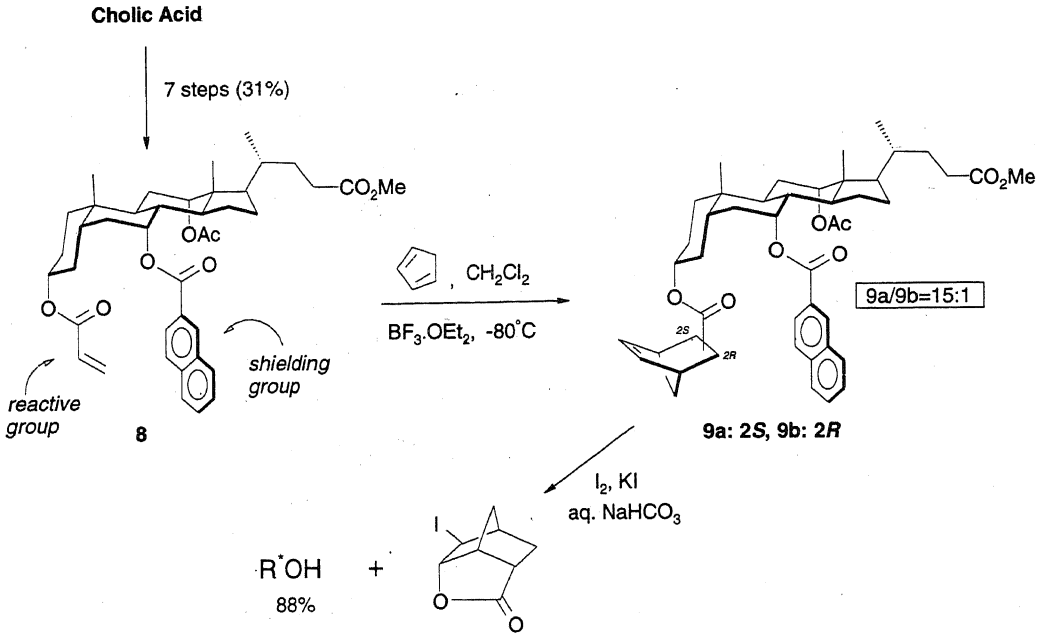


Figure 5. A cholic acid-based chiral auxiliary for asymmetric Diels–Alder reaction.

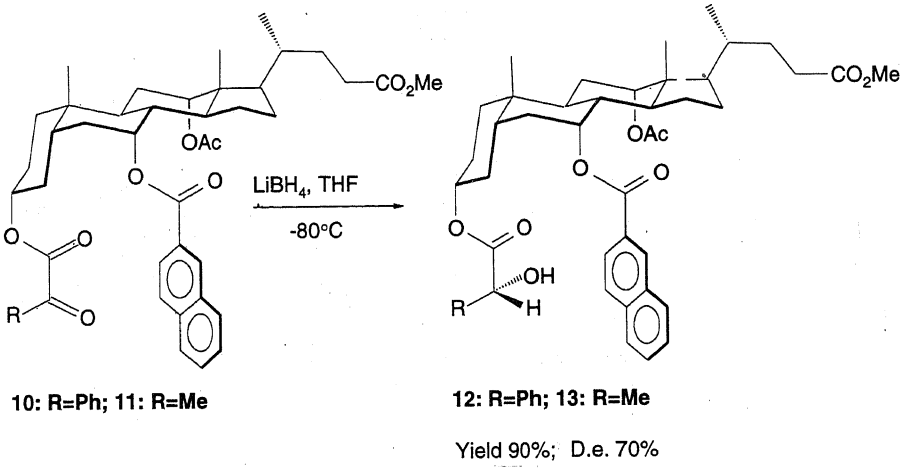


Figure 6. Asymmetric reduction of an α-ketoester on a steroidal auxiliary.

data with those of authentic samples[13]. Efforts to improve the diastereoselectivity are currently in progress in our laboratory.

3. Bile acids in molecular recognition

During the past two decades, there has been an explosive growth in research in the general area of 'Molecular Recognition' with synthetic receptors. A variety of molecular hosts have been constructed and their properties studied[14]. A number of potential applications of such designer molecules, including their use as sensors[15], can be envisaged. At the time our work was initiated, not much attention was focused on the use of bile acids for the design of molecular receptors. During the past five years, however, bile acids have been utilized by a number of groups for this purpose[16–21].

The unique arrangement of the three hydroxyl groups, along with the rigidity of the bile acid backbone, prompted us to construct novel molecular structures on the bile acid backbone capable of complexing small molecules or ions. The long term goal in this work is the development of molecular and ionic sensors, synthetic catalysts, novel organic materials, etc.

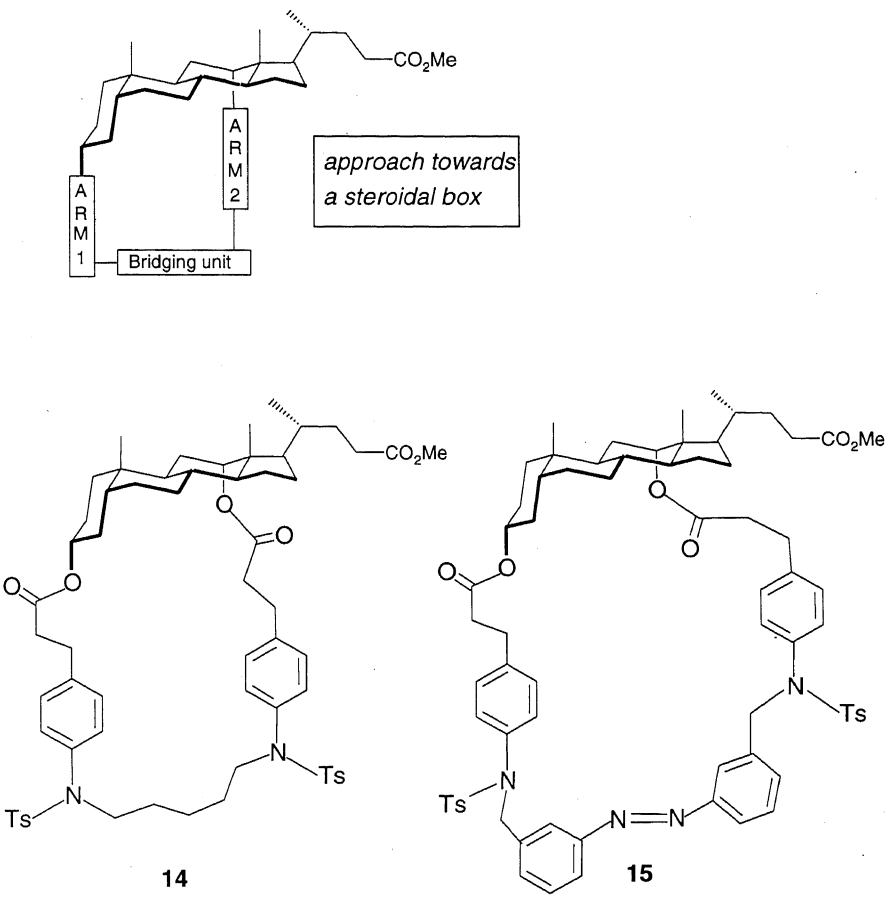


Figure 7. Molecular boxes on a deoxycholic acid scaffold.

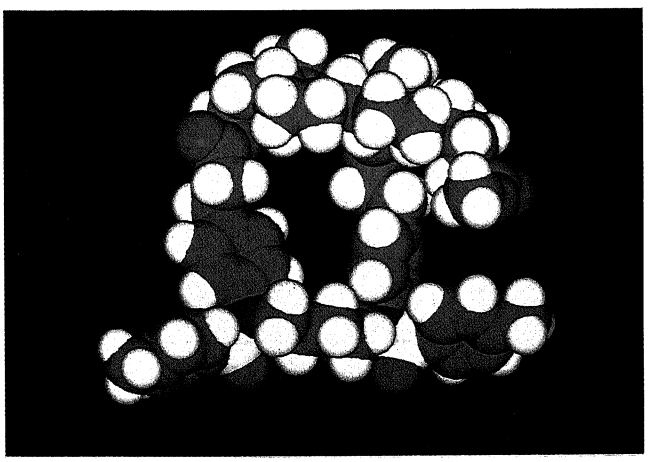
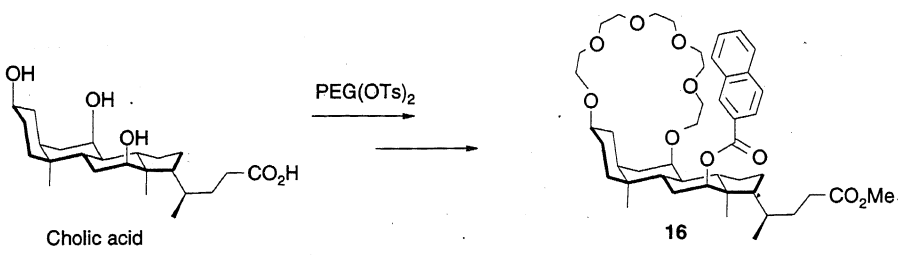


Figure 8. A space-filling representation of the INSIGHT II minimized structure of molecular box **14**. The aromatic unit attached to C-3 (left) is blocking a part of the cavity.

3.1. Molecular boxes

A simple approach adopted by us is schematically shown in Figure 7, which utilizes the two OH-handles provided by 7-deoxycholic acid. It occurred to us that by attaching two molecular 'arms' to these two handles, and finally bridging them with a third linker unit, we will be able to generate bile acid-based molecular boxes. Even though synthetically it was feasible, as we demonstrated by efficiently constructing compounds **14** and **15** (ref. 22), these boxes surprisingly did not seem to have enough room in the interior to encapsulate any 'guest' which we examined. Recent calculations[23] suggest that the two arms which were attached to the bile acid tend to adopt conformations in which one of the aromatic rings protrudes inside the cavity, thereby blocking the entry of any guest (Figure 8). Nevertheless, we believe that further work along these lines with other more rigid arms will lead to cavities capable of encapsulation of molecular guests.



Association constants in $CHCl_3$ at 25°C

M^{+}	$LogK_a(M^{-1})$
Na^+	4.31
K^+	5.43
Rb^+	5.17
Cs^+	4.64
$^tBuNH_3^+$	3.55

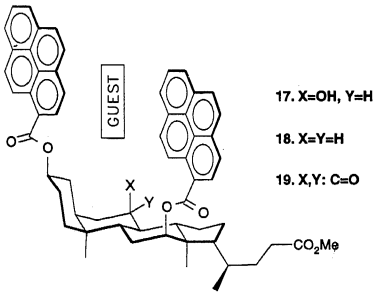
Figure 9. Cation binding with 'Chola-crown'.

3.2. Chola-crown

A variation of the molecular box approach which we examined was to build a crown ether by linking two of the three hydroxyl groups of cholic acid by a single pentaethylene glycol unit. Since cholic acid has three hydroxyl groups, we believed that a 'Chola-crown' having another available functional group (OH) will be a potentially useful system for the construction of metal ion sensors. Relative reactivity of the hydroxyl groups, and geometric considerations suggested that Chola-crown **16** shown in Figure 9 might be produced in *one* step from cholic acid. Indeed, this was found to be the case[24]. The low yield (ca. 10%) in the synthesis was acceptable since both reactants (cholic acid and pentaethyleneglycol ditosylate) are readily available. Alkali metal ion binding studies have shown that this molecule shows a slight preference for K^+ over other cations. We believe that this system will provide opportunities for the construction of potential alkali metal ion sensors.

3.3. Molecular tweezer

A variety of tweezer-like molecules have been known, which are characterized by the positioning of converging binding sites available within a single molecule. In synthetic molecular tweezers, the binding interactions commonly employed are π-stacking and H-bonding interactions. Some recently-synthesized molecular tweezers have shown high (ca. $10^5\ M^{-1}$) binding affinities



Association constants (M^{-1}) in $CDCl_3$ at 25°C

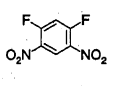
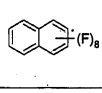
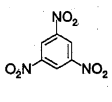
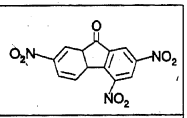
HOST				
17	6	11	47	147
18	7	15	65	165
19	8	19	83	224

Figure 10. Complexation of electron-deficient aromatic compounds with bile acid-based molecular tweezers.

towards 9-alkylated adenines[25]. We felt that the functionalization of the 3- and the 12-positions of bile acids can lead to a new class of molecular tweezers. Unlike the synthesis of molecular tweezers constructed else-

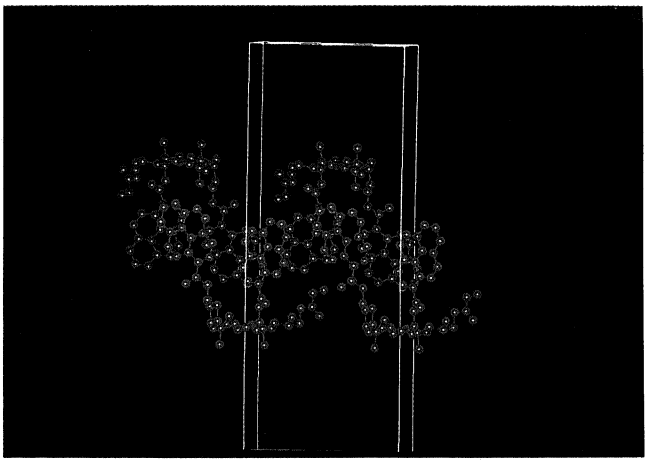


Figure 11. X-ray structure of compound **19**: view of the packing diagram down the crystallographic *c* axis.

where, this approach is rather straightforward. Accordingly, we attached 1-pyrenoyl groups to these two positions of bile acids to construct a series of three steroidal molecular tweezers (**17–19**). Molecular modelling studies showed that a family of low energy conformations (gas phase) existed in which the two pyrene units could adopt approximately parallel orientations, thereby generating a deep cleft in between. Detailed NMR titration experiments showed that electron deficient aromatic compounds shown in Figure 10 bind moderately well to these hosts in chloroform[26].

The molecular structure of a single crystal of **19** has recently been solved[27]. It is interesting to note that the conformation of the molecule is different from what we propose to be the 'binding conformation' in chloroform solution. The steroid molecules pack back to back, forming a bilayer, with the pyrene units arranged in a 'herringbone' fashion. One view of the crystal packing is shown in Figure 11.

More recently, we have immobilized the molecular tweezer to Merrified resin. Binding experiments by HPLC showed that the relative binding affinities of the immobilized host followed the pattern observed in solution. Further research in this area can possibly lead to the design of molecular filters.

Conclusions and future outlook

We have shown in this brief account how readily available bile acids can be utilized for a variety of purposes. We are currently exploring many other possibilities, such as the design of transition metal complexes using bile acid-based ligands, construction of bile acid-based dendrimers, design of host libraries based on bile acids, etc. We believe that the outcome of some of this work may possibly lead to the development of molecules of considerable interest for practical applications.

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