Unlocking the potential of bile acids in synthesis, supramolecular/materials chemistry and nanoscience

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The Maitra group has explored a variety of chemistry with bile acids during the past 15 years and these experiments have covered a wide variety of chemistry—asymmetric synthesis, molecular recognition, ion receptors/sensors, dendrimers, low molecular mass organo and hydrogelators, gel–nanoparticle composites, *etc.* Some of what excites us in this field is highlighted in this perspective article

Introduction

Bile acid science has a history of more than a century with continuing importance in biology and medicine. This class of compounds has gained considerable attention in supramolecular chemistry in recent years.[1] Bile is produced by all vertebrates, and bile salts are among the most important physiological constituents. Structurally modified bile acids have pharmacological potential to act as carriers of liver-specific drugs, absorption enhancers and as cholesterol lowering agents. Bile salts are natural biosurfactants which act as solubilizer and emulsifier for cholesterol, lipids and proteins in the intestine.[2] The most abundant among the human bile salts are cholate, chenodeoxycholate and deoxycholate, and they are normally conjugated with either glycine (75%) or taurine (25%). Conjugation increases the water-solubility of bile salts under physiological conditions. All primary bile acids seem to have three features in common: (i) they are the major end products of cholesterol metabolism, (ii) they are secreted into the bile largely in a conjugated form and (iii) the conjugates are membrane impermeable, water soluble, amphiphilic molecules. They have a remarkable ability to transform lamellar arrays of lipids into mixed micelles.

Though the studies on bile acids and their salts started in the beginning of the 19th century,[3–5] the current scientific phase of bile acid research began in the nineteen fifties.[6] Detection and characterization, extensive metabolic studies and detailed physicochemical studies were embarked upon during this period. Several orphan nuclear receptors have recently been shown to bind bile acids (cholic and chenodeoxycholic acids), including the farnesoid X receptor (FRX), the LXRα receptor and the CPA receptor.[7] There is a growing body of evidence that bile salts are involved in the control of high-density lipoprotein (HDL) and low density lipoprotein (LDL) metabolism. Bile acids secreted by male sea lamphrey act as sex pheromones.[7]

In recent years, bile acids and their derivatives have been used extensively in supramolecular chemistry, materials chemistry and nanotechnology.[8] The slightly curved shape of the bile acid backbone (Fig. 1), and the availability of a variable number (up to 3) of hydroxyl groups and their differential chemical reactivity

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Uday Maitra

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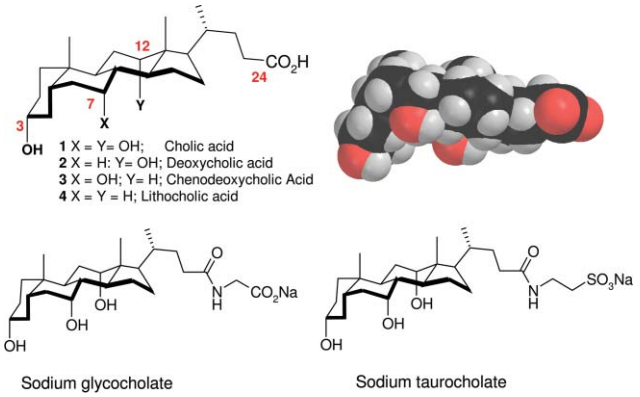

Fig. 1 Representative structures of common bile acids and their conjugates.

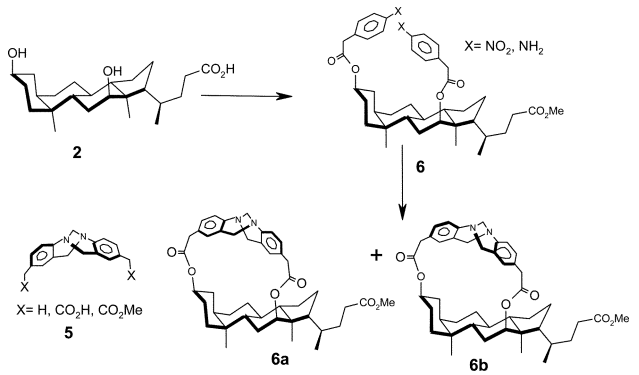

Fig. 2 Templated synthesis of Tröger's base analogues.

have been exploited by a number of research groups, including us, in diverse areas of chemistry like templates/chiral auxiliaries for asymmetric synthesis, molecular and ionic receptors, supramolecular host–guest systems, chiral dendritic species, artificial light-harvesting systems, foldamers/protein mimics, low molecular mass organo/hydrogelators, *etc.* The variety of 'games' we have played with bile acids are described in the following sections.

Bile acid derivatives as chiral auxiliaries/templates in asymmetric synthesis

Achieving high levels of stereoselectivity is one of the major challenges in modern organic synthesis. Over the years a wide collection of chiral auxiliaries and catalytic methods have evolved for a variety of asymmetric organic reactions with varying degrees of success. The transfer of chirality through the use of chiral auxiliaries has been proved to be an effective way for preparing homochiral molecules. Facially amphiphilic chiral bile acids with a rigid backbone, a unique disposition of hydroxyl groups and being inexpensive prompted us to explore them as chiral auxiliaries. Our approach involved (i) bringing the two reacting groups together so as to facilitate the geometric requirements and (ii) shielding one face of the reacting group using a planar aromatic moiety. The unique disposition of hydroxyl groups of the bile acids was exploited to meet both the requirements.

Asymmetric synthesis of molecules like Tröger's base analogues remained a challenge for many years because of their rapid racemization under acidic conditions, which are also needed for their synthesis.[9,10] Our idea of exploring bile acid as a chiral template in asymmetric synthesis led us to execute the first asymmetric synthesis of a Tröger's base analogue on a bile acid template.[11] Deoxycholic acid **2**, because of the optimum distance between the hydroxyl groups at 3 and 12-positions, was selected as an ideal template, which was converted to **6** and the coupled Tröger's base unit was obtained in 2.5 : 1 ratio (Fig. 2). Slow crystallization of the minor diastereomer **6b** took place from the diastereomeric mixture. The structure of **6b** was unambiguously proved by single crystal X-ray analysis. The cleaved product from **6b** afforded the Tröger's base analogue in a homochiral form.[11] The diastereoselectivity was further improved by fine tuning the tether lengths of the two fragments. This work illustrated that the optimum geometric control was responsible for the observed stereoselectivity.

The Diels–Alder reaction has provided numerous, and unparalleled solutions to a diverse range of synthetic puzzles provided by nature in the form of complex natural products. By the time we initiated our work, the literature was enriched with a vast number of approaches towards chiral auxiliary based asymmetric synthesis.[12,13] However, the utility of abundant, chiral and inexpensive bile acids remained unexplored. We envisaged new chiral auxiliaries derived from bile acid. Our approach for the design of the new molecular scaffold relies on placing a suitable aromatic group at C-7 thereby introducing a new element of steric control and imposing an additional restriction to the transition state (Fig. 3). Interestingly, only the *endo* product (99%) was isolated when the reaction was performed at −80 °C using $BF_3{\cdot}Et_2O$ as Lewis acid with 88% de (Fig. 3).[14] The reaction product was isolated, and the chiral auxiliary was regenerated by iodolactonization mediated cleavage of the mixture of **7a**–**7b**.

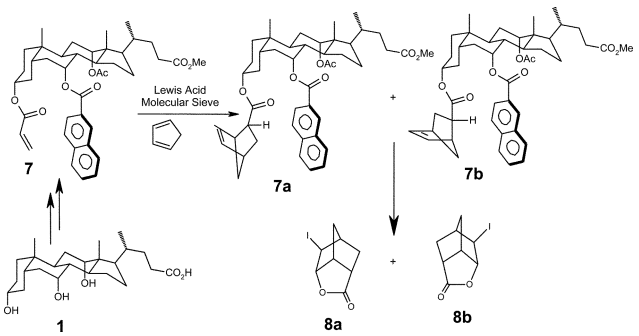

Fig. 3 Diastereoselective Diels–Alder reaction.

Optically active α-hydroxy carboxylic acids are versatile building blocks in the synthesis of chiral natural products and have gained enormous interest in recent years. Chiral auxiliaries based on sugars, terpenes and amino acids have been extensively used in which these templates were functionalized with reactive and shielding sites with 1,2 or 1,3-relationships. The 3 and 7 hydroxyl groups on the bile acid are formally in a 1,5-relationship, but because of the A–B *cis*-ring junction the distance between them is shorter.[15] Modification of compound **7** to install an α-keto ester at C-3 led to precursor **9**, and this was conveniently reduced with $NaBH_4$ to yield **9a**–**9b** in an 85 : 15 ratio.[16] It was explained based on the possible co-ordination of the metal ion (Li^+) to the two

carbonyl oxygens of keto ester **9c** (Fig. 4) thereby allowing the preferential hydride attack from the *Si*-face of the carbonyl group. The esters were removed under mild condition to yield the optically active mandelate. The de was further improved to 99% when the α-keto ester was attached at C-7.

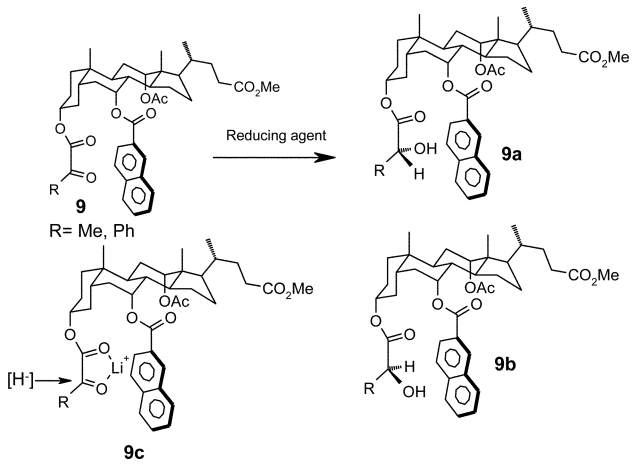

Fig. 4 Diastereoselective synthesis of α-hydroxyacids.

Chiral auxiliaries and catalysts derived from optically active 1,1′-binaphthyl-2,2′-diol (BINOL) have been utilized extensively in asymmetric synthesis in recent years.[17] Central to the success of this chemistry is the availability of homochiral BINOL. Even though a number of methods are available for its resolution,[18] only a few attempts to synthesize BINOL or its derivatives by asymmetric synthesis were reported in the literature at the time when we initiated our work. A few approaches which have appeared since then do not use an inexpensive source of chirality and these are also not recovered at the end of the synthesis. We reported the diastereoselective synthesis of 1,1′-binaphthyl-2,2′-diol on a 7-deoxycholic acid template (Fig. 5).[19] 2,7-Dihydroxy naphthalene derivatives were used as substrates and attached to the steroidal skeleton using appropriate spacers based on molecular modelling results. The de in the coupling reaction was increased from 65 to 99% by optimizing the spacer.

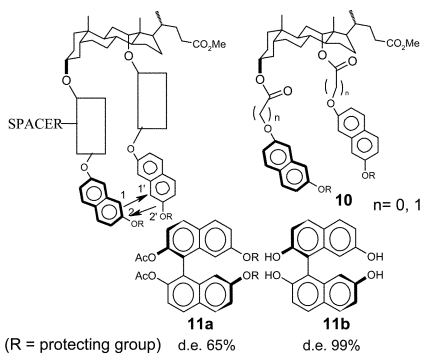

Fig. 5 Templated diastereoselective synthesis of BINOL analogues.

Bile acid based crown ethers and macrocycles: cation and anion receptors

The binding and recognition of ions with synthetic systems have received enormous interest in supramolecular chemistry as both anions and cations play many important roles in biological processes. The construction of artificial receptors, in which the molecular recognition process triggers a signal transduction, is of critical importance for extending the scope of supramolecular chemistry, and for producing devices such as molecular sensors.[20] By combining molecular recognition with an appropriate photophysical process, conceptually new sensing systems may be created. Because of their unique ability of size selective binding of cations, crown ethers[21] are of great importance in catalysis, ion transport, chromatography, chromogenic reagents and photoresponsive devices. Though there have been several reports on chiral crown ethers designed for enantioselective binding,[22] crown ethers built on bile acid backbone were not known until our first report on one step synthesis of a chola-crown **12a** from cholic acid (Fig. 6).[23] Compound **12a** showed moderately high binding affinity for K^+ and Rb^+ compared to other metal ions like Na^+, Cs^+ *etc.* This one step reaction was low yielding, presumably because of the ester on the side chain. We subsequently made 24-norcholacrown **12b**, and independently coupled azacrown ethers to a hydroxyl group through a short spacer (*e.g.* **12c**).[24]

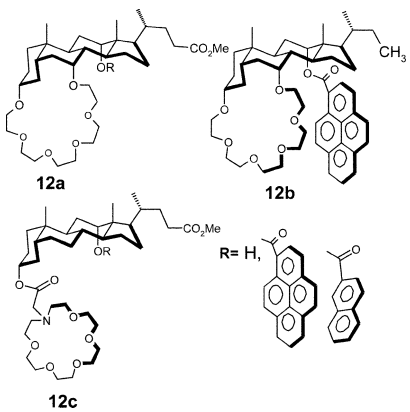

Fig. 6 Bile acid-based crown ethers.

Recently, this strategy has been refined with the use of chenodeoxycholic acid as a scaffold, and we have made sensor **13** (Fig. 7) using a modular approach. In this molecule, a

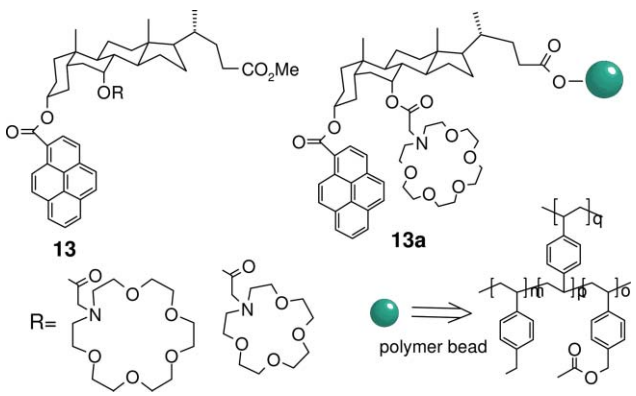

Fig. 7 Cation sensors immobilized on Merrifield resin.

through-space photoinduced electron transfer (PET) from the N-atom to the excited fluorophore unit quenches the fluorescence ("off" state). Once the crown unit complexes a cation, the PET is inhibited, and the fluorescence turns "on". Fluorescence titration with different salts with a methanolic solution of **13** showed a significant increase in the fluorescence intensity only upon the addition of K^+. Using this sensor, <0.2 μM of K^+ can be detected in 4 : 1 toluene–acetonitrile, and K^+ can selectively be sensed in MeOH.[25] This inspired us to demonstrate a simple, general, and effective strategy to immobilize such sensors on polymer beads and use them in aqueous environments. Such a molecular device attached to a polymer bead and capable of sensing cations can have practical applications for qualitative detection and quantitative determination of metal ions. Fluorescence microscopy was chosen as the method of choice for the binding measurements. Bead **13a** was stirred with $KClO_4$ (500 μM) in acetonitrile–toluene (1 : 4), and the fluorescent microscope images clearly showed that upon treatment with $KClO_4$ the fluorescence intensity of **13a** increased due to the *inhibition* of PET upon K^+ binding (Fig. 8). Reversibility of the fluorescence enhancement was also confirmed. But the detection of K^+ in a *polar* solvent remained a challenge, as sensor **13a** after treatment with $KClO_4$–MeOH did not show any fluorescence enhancement. This is not unexpected since Merrifield resin does not swell in polar solvents like MeOH, and thus the metal ion is unlikely to penetrate into the resin to be complexed by the sensor. Naturally, Merrifield resin was replaced by Tentagel® as it is known to swell in polar solvents.[26] These beads were shown to sense K^+ in water at about 90 mM. Clearly, there is further scope to improve the detection sensitivity to physiologically relevant K^+ concentrations. We believe that this strategy can be applied for a wide range of sensors and can be of practical importance.

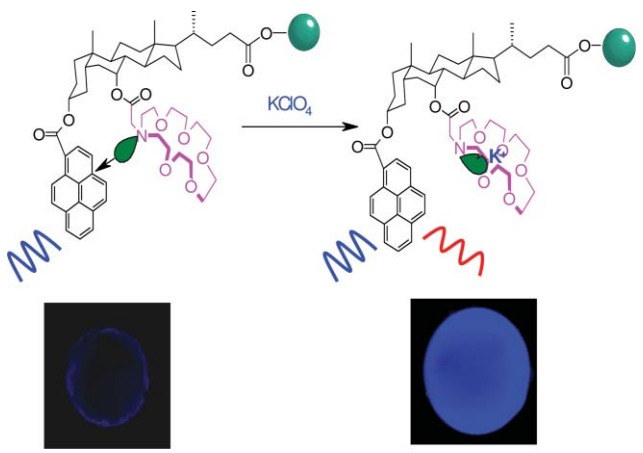

Fig. 8 Fluorescence microscopic images of sensor-attached polymer beads before and after complexation with K^+ in MeCN–toluene. Reproduced with permission from ref. 25 ©2006 American Chemical Society.

In contrast to the extraordinary success in the design of synthetic receptors for cations, the list of artificial anion receptors has grown much more slowly, even though anion inclusion complexes were observed as early as in the 1960s.[27] Anion receptor design is much more challenging than cation receptor design for a number of reasons. The larger sizes of anions imply weaker electrostatic binding interactions compared to isoelectronic cations which are smaller.[28] Anions are structurally more diverse than common cations. Finally, certain anions exist only in limited pH ranges, which places additional limitations on the design of the receptor.[29] The design, synthesis and anion binding studies of cholaphane **14** (Fig. 9) (an 'inside-out' analogue of cyclodextrin), which was achieved in two steps from cholic acid, was recently reported from our laboratory.[30] A unique feature of this cyclic dimer was that the facial amphiphilicity of the bile acid was retained because of the unprotected hydroxyl groups. Most anion receptors synthesized to date use at least some NH-donors. The cyclic dimer **14**, with only OH groups inside, resulted in the complexation of two F^- ions, as investigated using NMR titration in $CDCl_3$. An unusual C–H···F interaction was found to operate upon F^- binding, based on experimental and theoretical studies. Attempts to crystallize the dimer with and without the guest molecules resulted in two different types of polymorphs of the host.

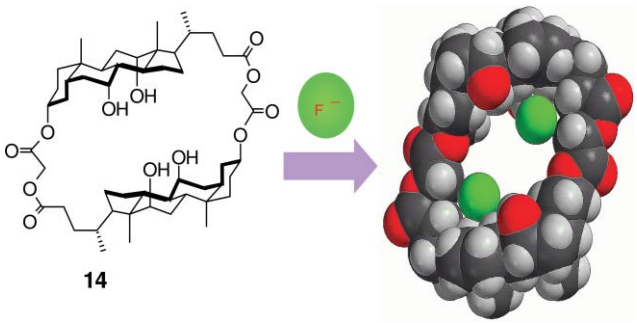

Fig. 9 A cholaphane and its minimized structure with two bound fluorides. Reproduced with permission from ref. 30 ©2006 American Chemical Society.

Bile acid based molecular tweezers[31]

The ability of certain biomolecules to recognize and bind other molecules is a key feature associated with a number of biological processes, such as enzyme activity (enzyme–substrate complexes), antibody production (immunoglobin–antigen complexes), DNA double helix formation (Watson–Crick base pairing), biosynthesis of nucleic acids, protein synthesis (transcription and translation), *etc.*[32] The past few decades have witnessed enormous growth in the efforts of chemists to understand and mimic some of these processes using systems which are easier to synthesize, manipulate and study.[33] Since the biomolecular interactions are usually noncovalent, understanding such interactions has become the central focus in diverse fields of chemistry. A variety of molecular frameworks, including natural products, have been utilized to design rigid preorganized molecular systems to create clefts, cavities, and other types of binding surfaces. Among the most popular architectures used in molecular recognition, "molecular tweezers" form an important class. These molecules are characterized by two similar or dissimilar "sticky arms" separated by a rigid or a semirigid spacer. The pioneering work by Whitlock and Zimmerman resulted in a number of molecular tweezers.[34] The first bile acid based molecular tweezer as a receptor for a number of electron deficient aromatics was reported by us.[35] Cholic acid was used as a suitable scaffold because of the optimum distance and geometric requirements between the C-3 and the C-12. Two aromatic groups attached to the hydroxyl group

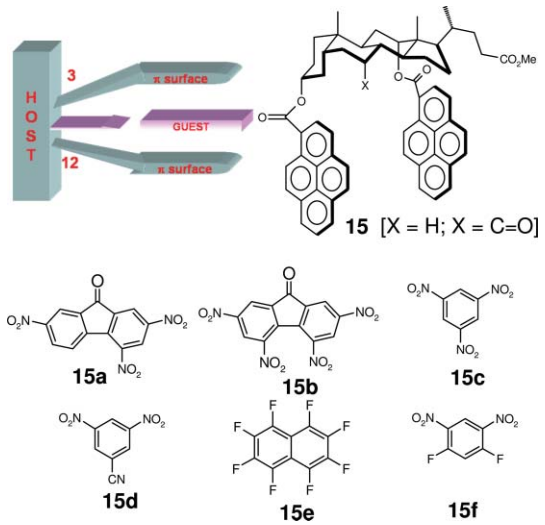

Fig. 10 Bile acid-based molecular tweezers.

thus act as the arms of the tweezer (Fig. 10). The complexation (with **15a–f**) was monitored using NMR titration experiments. Appropriate controls (1 : 1 mixture of a bile acid with one pyrene arm plus the methyl ester of pyrene carboxylic acid) showed no significant binding thereby proving that there was a synergistic effect between the two pyrene rings, and they formed sandwich type complexes. Further evidence was provided by fluorescence experiments. An interesting observation was that the tweezers upon complexation with the guests usually gave green fluorescence in $CHCl_3$, due to strong exciplex formation upon binding to the guest, while the control experiments showed blue fluorescence, which is largely from pyrene monomer emission. These could even be differentiated by holding the solutions in bright sunlight!

Bile acid based adenine/biotin receptors

The design of receptors for the recognition of nucleobases using non-covalent interactions is also an area of contemporary interest.[36] A variety of receptors including macrocycles, tweezers, clefts, *etc.*, are possible with different binding modes. The hydrogen-bonding surfaces of the carboxyl and amide groups have been used extensively in synthetic receptors, and in many of these receptors this functionality has been used to bind adenine derivatives.[37] For the binding of adenine, the determination of site specificity has been considered to be an important aspect. For example, in 9-*N*-butyladenine there are two sites of binding: the Watson–Crick (WC) and the Hoogsteen (HG) sites (Fig. 11). An experimental differentiation between WC and HG binding using 6-*N*-methyl-9-*N*-ethyladenine was reported by Engel and von Hippel.[38] Considerable attention has been paid in recent years to understand HG binding in solution using the nuclear Overhauser effect (NOE) as the probe. Rebek and co-workers had performed a detailed study on the site specificity of the binding of adenine by a synthetic receptor,[39] in which both the WC and HG binding modes were shown to be operative. Sartorius and Schneider extended this method to other base pairs.[40] A bile acid based adenine receptor was designed by us based on careful molecular modelling.[41] Binding constants were estimated by NMR titration. The changes in the chemical shifts of H-2 and H-8 of *N*-butyl adenine in $CDCl_3$

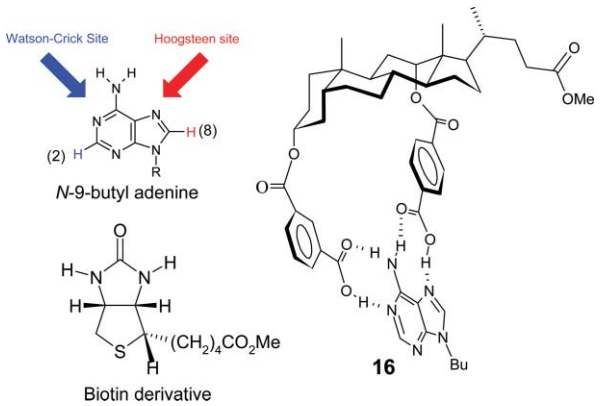

Fig. 11 Bile acid-derived adenine and biotin receptors.

were monitored and a binding constant of 3.5×10^3 M^{-1} was estimated. Control experiments using monobenzyl isophthalate and using a tweezer having an incorrect geometry of the carboxylic acids showed K_a values of 170 and 300 M^{-1}, respectively, implying cooperative participation of the acid functionalities in **16**. Biotin methyl ester was also complexed with a binding constant of 1.5×10^3 M^{-1}. In order to gain more information on adenine binding, we studied the binding of 9-ethyladenine using aliphatic carboxylic acids and the results were compared with a number of aromatic carboxylic acids. Our observations indicated that aromatic carboxylic acids prefer binding from the HG site, whereas aliphatic carboxylic acids show a binding preference from the WC site. These results were based on the predominant shift of the H-8 signal caused by aromatic carboxylic acids during the titration. The cooperative binding with the steroidal receptor was attributed to the relatively restricted rotation around the C3–O and C12–O bonds. Very recently, another report on bile acid-based receptors containing 2,6-bis(acylamino)pyridine for the recognition of uracil derivatives has appeared.[42]

Bile acid based macromolecules: design and construction of bile acid based dendrons

Dendrimers, being monodisperse, hyper-branched molecules with well-defined nano dimensions and multiple controllable functionalities have become the subject of extensive studies during the past two decades.[43] The most important features of a dendritic architecture are: (i) a central core, (ii) interior units connecting the external surface and the core and (iii) the surface end groups. Initial efforts were directed mainly on the preparation and characterization of a wide variety of dendrimers; but in recent years the attention has shifted towards the design of *functional* dendritic molecules and their applications. The ability to modulate the size, molecular weight, chemical functionalities and the position and number of functional groups in dendrimers makes them attractive candidates for a wide variety of applications including drug and gene delivery, diagnostics, catalysis, molecular recognition and light harvesting.[44,45] We designed and synthesized chiral bile acid-derived dendrons, which utilized the largest chiral repeating units in a dendritic species.[46] Kolehmainen *et al.* recently reported the synthesis of bile acid based dendritic structures.[47] The dendron initially reported by us had acetate protected bile acid backbones at the periphery, which resulted in the loss of

the facial amphiphilicity and further functionalization was also not possible. Because of the unique facial amphiphilicity of bile acids, we reasoned that it would be appropriate to re-design and synthesize dendrons with end groups resembling monomeric bile acid units and examine their potential amphiphilic properties. This was achieved using a simple nucleophilic displacement protocol.[48] Chloroacetate derivatives of carboxyl protected deoxycholic and cholic acids were synthesized and these were coupled directly with the bile salts to obtain dendritic structures (Fig. 12). Further exploration of the chloroacetate chemistry resulted in dendrons of higher generations. We also reported another approach to obtain the facially amphiphilic dendrimers by direct linkage of bile acids to the hydroxyl groups. These two approaches developed in our laboratory resulted in the synthesis of a wide variety of dendrons with multiple hydroxyl groups on the periphery.

Bile acid dendrons as normal and inverse unimolecular micelles

An important structural feature of the dendritic architectures is their resemblance to micellar structures and hence they are often described as covalently linked micelles. Micelles can solubilize guest molecules in their core, above the critical micellar concentrations (CMC) of the detergents, and this phenomenon (dye solubilization) has routinely been used to determine CMC values. With dendrimers, the "micellar structures" are maintained at all concentration ranges and thus the guest solubilization increases *linearly* with concentration. Newkome *et al.* have described such dendrimers as "unimolecular micelles".[49] Depending upon the nature of the interior, they have the ability to either solubilize a polar guest molecule in a relatively nonpolar solvent, or vice versa. Regen *et al.* have described a bile acid-based "molecular umbrella" that can change its conformation as a function of the solvent polarity.[50] Kobuke *et al.* have used an amphiphilic bile acid unit for the construction of a supramolecular transmembrane ion channel.[51] We reported the synthesis of dendritic bile acid oligomers with a remarkable ability to act as *both* normal and inverse micelles (Fig. 13) owing to the *facially amphiphilic* nature of the bile acid backbone.[52] Because of the free hydroxyl groups in the periphery, these dendrons are believed to adopt different conformations in solvents of different polarities ("adaptive dendrons"), which enable them to mimic both unimolecular normal and inverse micelles.[53] The remarkable ability of these dendrons to solubilize a non polar dye (orange OT) in a polar medium (50% MeOH–H_2O) and a polar dye (cresol red) in a non-polar medium was investigated. Control experiments proved that the dye extraction was clearly because of the dendritic architecture. We believe this property can be further exploited for potential applications.

Artificial light harvesting systems and energy transfer

Photosynthesis, one of the vital natural phenomena, involves the conversion of solar energy into chemical energy. In recent years the study of the harvesting of solar energy has received considerable attention. Since photosynthesis is a complex process, chemists

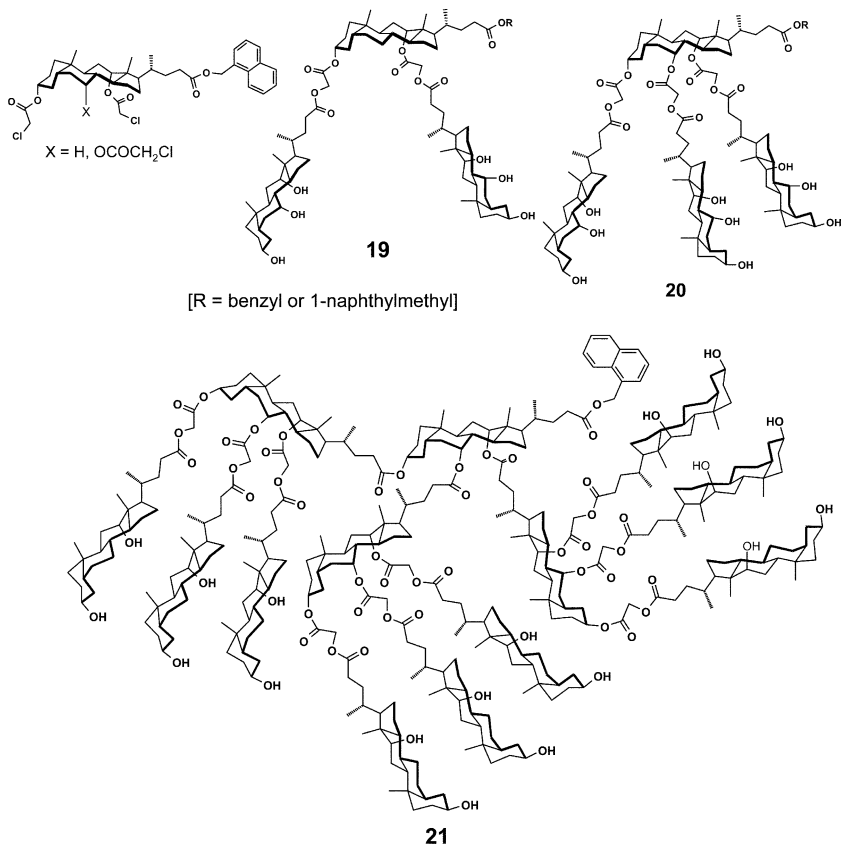

Fig. 12 Facially amphiphilic dendrons made by a divergent strategy.

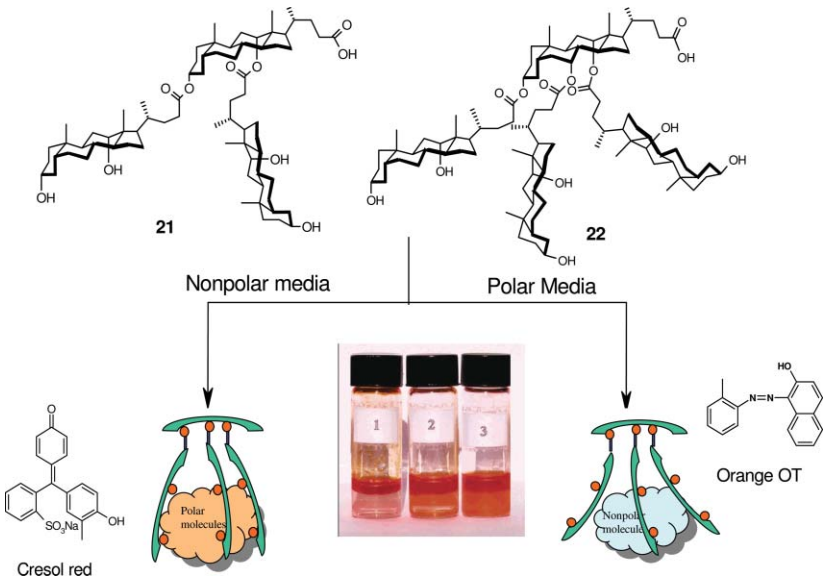

Fig. 13 Adaptive dendrons (photo shows extraction of orange OT from a hexanes to aqueous methanol). Reproduced with permission from ref. 52 ©2006 American Chemical Society.

have attempted to design efficient light harvesting materials which mimic some of the functions of the natural photosynthesis systems. Because of their architectures, dendrimers provide attractive scaffolds to hold multiple light absorbing groups ("antenna") and transfer the energy to a centrally located acceptor, through a Förster type mechanism.[54–56] In an alternative strategy, the dendritic framework can also be designed to be photoreactive. We have recently designed bile dendrimer (Fig. 14) based light harvesting mimics using multiple peripheral naproxen units as donors and a single anthracene as an acceptor.[57] Dendrons with varying number of naproxen units were studied and a linear increase of the absorption with the number of naproxen units was observed. Energy transfer from the naproxen units (donor, λ_{ex} 275 nm) to the anthracene moiety (acceptor) was monitored and it was found that the emission characteristics were chiefly that of the anthracene chromophore. As expected, control experiments using mixtures of naproxen and 9-anthracenemethanol exhibited emission characteristics only of the donor, confirming the *intramolecular* nature of the energy transfer in the dendrimer.

Bile acid based low molecular mass orgnaogelators (LMOGs): gelation of organic fluids

Gelation of organic solvents using small molecules has received enormous attention in recent years.[58] In polymeric materials gelation is believed to occur by chemical and/or physical cross-linking of polymeric chains leading to the formation of highly entangled networks, which immobilize solvent molecules. The gelation by LMOGs is mainly due to supramolecular interactions leading to the formation of fibers. Structurally diverse compounds such as derivatives of steroids, coumarins, amido alcohols, sugars, ureas, metallo complexes, amino acids, dendritic building blocks and charge transfer complexes have been studied as LMOGs. Such molecules associate intermolecularly *via* hydrogen bonding, π stacking, van der Waals interactions.[59] A number of cholesterol derivatives have also been reported to be potent gelators.[60] We discovered the first donor acceptor interaction induced gelation of organic fluids.[61] While working on bile acid functionalized molecular tweezers, we observed that bile acid derived **28** unit gelled certain organic solvents *in the presence* of 2,4,7-trinitrofluorenone (TNF **15a**). No gelation was observed with either of the pure components, and our studies showed that for optimum gelation 1 : 1 stoichiometry was needed. The gels were strongly colored because of charge-transfer between the electron donor (pyrene units) and the electron acceptor (TNF). The position of the pyrene unit on the steroid backbone appeared to be important for its gelling ability. Scanning electron micrographs (SEM) of the xerogels revealed fibrous networks, with the fiber diameters of the order of microns. The role of the bile acid unit was probed by preparing pyrene derivatives attached to alkyl chains through various linkers (Fig. 15). It is interesting to note that whereas many of these compounds (without the bile acid backbone) gelled selected solvents in the presence of TNF, some of these compounds with NHCOX linkers also gelled solvents in the *absence of TNF*. These compounds appear to form helical supramolecular aggregates through π-stacking and H-bonding interactions. More evidence for this came from studies on a chiral pyrene derived organogelator. Some of our current research activities involve the studies of chiral amplification using such chiral organogelators

Supramolecular association leading to hydrogelation

Hydrogels are of great importance because they are materials for biomedical applications, such as drug-delivery systems, tissue engineering and semi-wet biomaterials for protein microarrays.[62] The advantages of using molecular hydrogels over traditional polymeric hydrogels have been reviewed.[63] In addition to potential applications, gels are materials with intriguing features owing to the coexistence of solid (the networked fibrous structure) and liquid phases (entrapped solvent molecules). Certain bile acids/salts have been known in the literature to form gels in water under defined conditions.[64] Sodium cholate, sodium deoxycholate

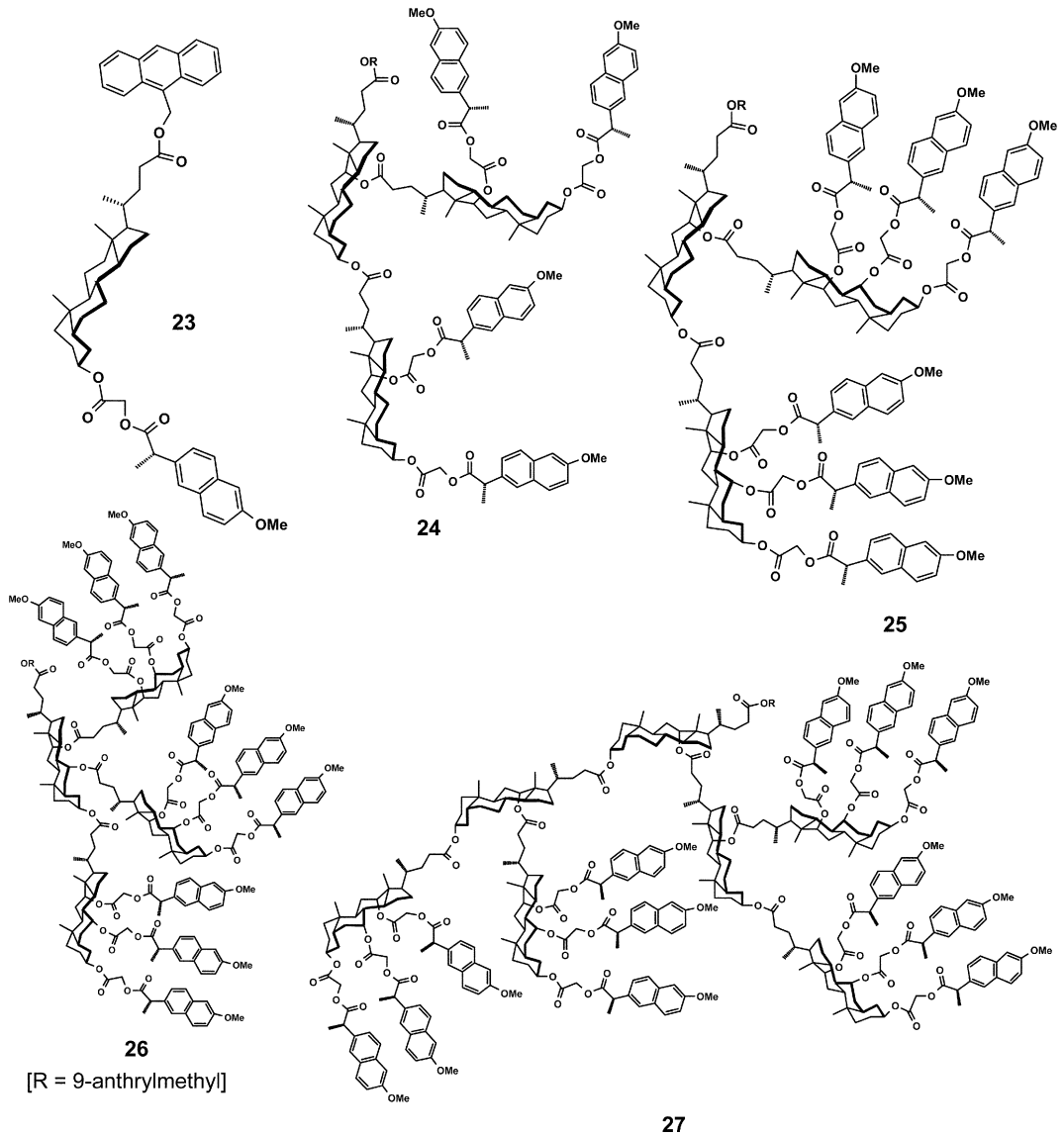

Fig. 14 Dendrons with multiple naproxen units as artificial light harvesting systems (R = 9-anthrylmethyl).

and sodium lithocholate have been shown to form gels in water. The gelation was found to be pH dependent (optimal at pH ~7), and the gels were thixotropic.

From our laboratory, we have demonstrated efficient gelation of aqueous fluids by a cholic acid trimer **29** ("tripodal cholamide").[65] These transparent gels were formed at extremely low gelator concentrations (0.02% w/v, 0.15 mM), with one gelator molecule effectively immobilizing $>10^5$ water molecules. A cryo-TEM image (Fig. 16) of the gel showed the presence of nanofibres. The formation of hydrophobic 'pockets' during gelation was inferred using ANS (8-anilino-1-naphthalenesulfonate) as a polarity-sensitive probe. A gel doped with ANS turned highly fluorescent, but only in the gel state. A thermochromic gel was subsequently developed using bromophenol blue as a dopant. The rotational dynamics of polarity-sensitive fluorescent dyes (ANS and DPH) in the gel derived from tripodal cholamide **29** was studied using time-resolved fluorescence anisotropy measurements. ANS in the gel showed two rotational correlation time (φ) components, *ca.* 13 ns (ANS bound to the hydrophobic region of the gel) and *ca.* 1 ns (free aqueous ANS). These gels appear to be excellent soft materials for futuristic applications because of their remarkable water-holding ability and the solubilization of flat, nonpolar molecules.

Since compound **29** formed gels only upon protonation, we thought it appropriate to look for simpler, monomeric cationic analogues of bile acids as potential hydrogelators. It is interesting to note that cationic bile salts have gained considerable attention during the last two decades as cancerostatic, antimicrobial, and cholesterol-lowering agents, gallstone dissolution enhancers, and DNA transfection agents.[66] We designed a number of cationic bile salts (Fig. 17) and studied their aggregation and micellar properties extensively.[67] The critical micellar concentrations of these bile salts were found to depend on the nature of the cationic head group. A number of these bile salts formed gels in aqueous solutions. Complementary scattering, diffraction, and microscopy techniques have been used extensively to provide a precise structural description of the network architecture created

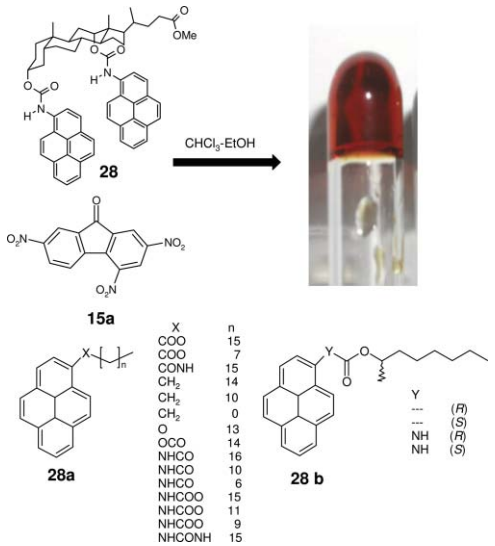

Fig. 15 Donor–acceptor interaction induced gelation.

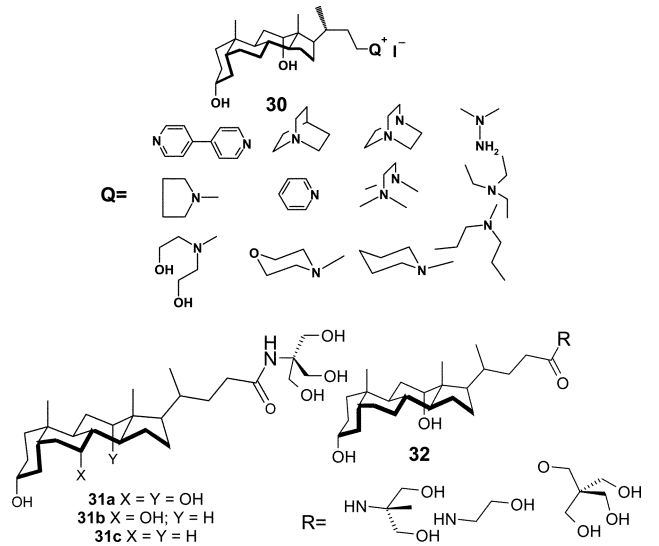

Fig. 17 Cationic and neutral analogues of bile salts.

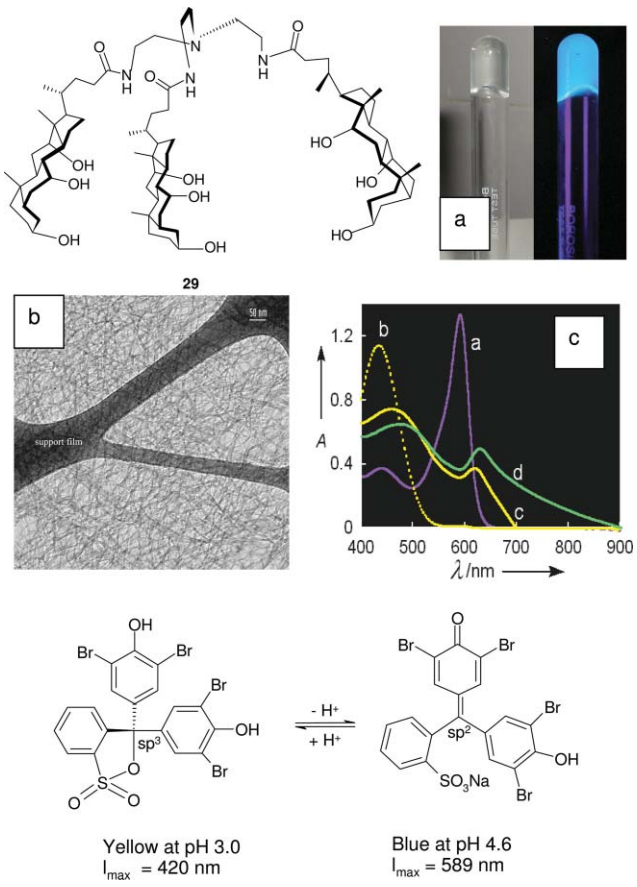

Fig. 16 (a) Photographs of gels from the tripodal cholamide **29** (5 mM in 20% AcOH–water doped with 30 μM ANS) derived colorless gel and luminescent gel (handheld long wave UV lamp); (b) cryo-TEM image of the gel (0.75 mM) in 20% AcOH–water; (c) absorption spectra (26 °C) of sodium salt of bromophenol blue (0.37 mM): (a) in neutral water, (b) in 25% AcOH–H_2O, (c) in the presence of **1** (5.25 mM) in 25% AcOH–H_2O (before forming gel) and (d) after forming gel. Reproduced with permission from ref. 65*a* ©2001 Wiley VCH.

by these gelators and its variation as a function of concentration, aging time, composition of the solvent, and type of gelator. Rheological experiments were carried out on gels derived from cationic and neutral analogues of bile acids. In the frequency sweep experiments, the elastic modulus G' was predominant, and an order of magnitude higher than the loss modulus G'', which is a characteristic behavior of viscoelastic soft solids.

In continuation of our investigation on side chain modified bile acid we synthesized phosophonic acid analogues of natural bile acids.[68] While investigating the aggregation behavior of these bile acids it was also discovered that some of the phosphonobile salts (PBS) were capable of forming pH dependent hydrogels. Since the phosphonobile salts gel at relatively low pH, a thermochromic gel was developed using congo red (CR). CR shows a violet color at pH 3.0 and turned orange-red at pH >5.2. The violet color of CR incorporated in the gel of (pH 3.3) reversibly changed to magenta–red upon heating the gel (Fig. 18). This strategy may be explored further to develop inexpensive thermal sensors.

Bile acids in nanoscience

Templated synthesis of nanotubes

Nanotubes are materials with intriguing structural parameters containing borders, inner and outer surfaces, and structured tube walls. Among the variety of nanomaterials, metal oxide nanotubes have gained a lot of attention due to their unique properties and potential applications in numerous areas such as electronic and mechanical devices.[69] Metal oxide nanotubes have been synthesized by employing a variety of strategies.[70] Sol–gel chemistry is one of the most promising ways to synthesize nanotubes of metal oxides such as silica and titania.[71] Recently, organogels were used as templates for the preparation of hollow silica nanotubes and nanotubes of transition metal (Ta, V) oxides.[72–74] Fig. 19 depicts a possible way by which hollow-nanotubes are prepared with the gel fibers as templates. Helical ribbon and double-layered TiO_2 nanotubes have been templated using cholesterol based gelators.[75,76] In all such cases, organogelators were used as templates necessitating the use of metal alkoxides as the inorganic

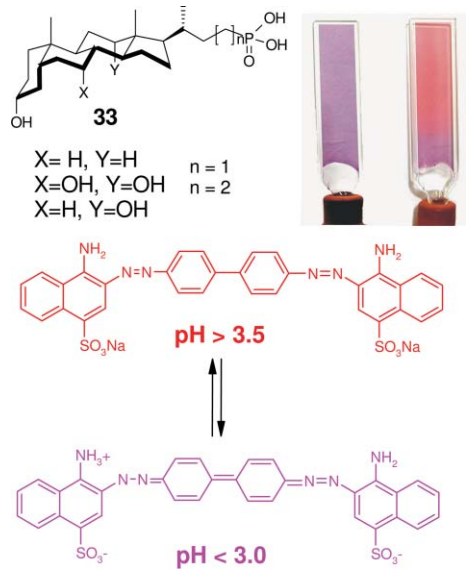

Fig. 18 Phosphonobile acids and a photo showing the color change of congo red in the gel (violet) and sol (magenta) states. Reproduced with permission from ref. 68*b* ©2005 The Royal Society of Chemistry.

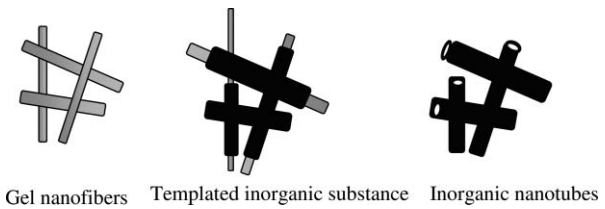

Fig. 19 Schematic representation of templated synthesis of metal oxide nanotubes.

precursors. Due to the difficulties in handling metal alkoxides, the number of metal oxide nanotubes that can be easily synthesized using organogels appears to be limited.

In order to use simple metal salts as precursors, the reactions have to be carried out in an aqueous medium in which these salts are soluble. This prompted us to use hydrogels instead of organogels as templates.[77a] After removal of the template (with ethanol) and subsequent calcination, hollow TiO_2 nanotubes were obtained. These nanotubes (ID 4–7 nm, OD 10–20 nm) had a narrow size distribution, with the lengths going up to a few hundred nanometers (Fig. 20). More recently, the **29** derived hydrogel has been used as a template to prepare CdS, ZnS and CuS nanotube and nanorods.[77b] The synthesis of the oxide nanotubes is no longer restricted to the use of inorganic alkoxides as precursors. We believe that our approach opens up new avenues to synthesize nanotubes/nanorods that were previously difficult to synthesize using traditional methods.

Gel–nanoparticle hybrid materials

Recent explosive interest in metal nanoparticles (NPs) on account of their numerous potential applications in science and technology is well known.[78,79] Among various metals, gold NPs have been studied in greater detail owing to their stability and ease of synthesis. After Brust and co-workers' report[80] on the stabilization of gold nanoparticles using alkyl thiols, several other thiol derivatives and

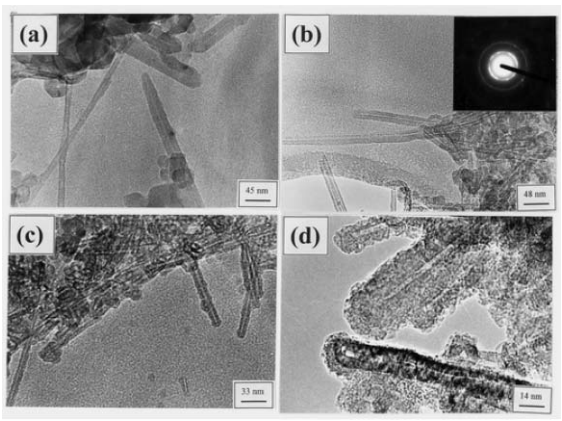

Fig. 20 TEM images of the titania nanotubes (a) as-synthesized and (b)–(d) after calcination. Inset shows the SAED pattern taken on a single nanotube. Reproduced with permission from ref. 77*a* ©2003 The Royal Society of Chemistry.

phosphine, pyridine, and selenide have been described as capping agents to stabilize gold NPs.[81] Efforts directed to design various types of organic–inorganic hybrid materials have also been intensified. We recently described the design of a novel NP–hydrogel hybrid material. We synthesized bile acid analogues with a thiol group on the side chain to stabilize metal NPs.[82] We reasoned that the specific self-aggregation modes of facially amphiphilic steroids would enable a metal NP capped by such a thiol to "lock" on to gel fiber, which is also derived from a structurally related molecule. The bile acid thiol stabilized gold NPs showed a surface plasmon resonance band at 520 nm, characteristic of a gold colloid (Fig. 21). Hydrogelator **29** was selected to explore the possible immobilization of the steroid capped NPs on a gel. Since gels derived from **29** have been extensively studied in AcOH–H_2O,

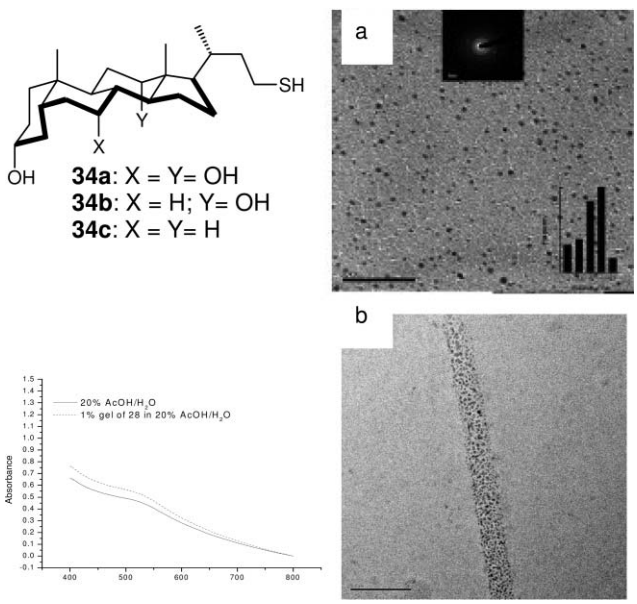

Fig. 21 Bile acid based thiols and a) TEM image of cholic thiol stabilized nanoparticles; b) AFM image of gel–nanoparticle composite; c) plasmon resonance band of thiol stabilized nanoparticles and gel–nanoparticle composite in 20% AcOH–H_2O. Reproduced with permission from ref. 82 ©2006 American Chemical Society.

the same medium was selected to study the stability of the steroid-capped NPs. The NP dispersions (>0.05 mg mL^{-1}) in 20% AcOH–H_2O were unstable beyond 5 h and separated out of the medium. In contrast, the NP–gel hybrid material was stable for several months. Therefore, the gel provides a unique stabilization/dispersibility to the NPs in this medium.

Unusual natural and unnatural bile acids

Bile acids from different species chemically differ in two respects: (i) the side-chain structure and (ii) the distribution of the number, position, and stereochemistry of the hydroxyl groups on the steroid nucleus. Several decades ago, Haslewood addressed the issue of considering the bile acid structure as an aid to the understanding of the evolutionary process.[83] The most evolved mammalian bile acids have a 5β configuration with hydroxyl groups at 3α, 7α, and 12α. An unusual 3α, 7α,16α-trihydroxy bile acid was recently isolated from storks and herons by Hagey *et al.*[84] It was named avicholic acid **35** (Fig. 22) to signify that it is a class that has to date been identified only in avian species. This bile acid was a major constituent (>90%) of biliary bile acids in the Shoebill stork and several herons. It was also suggested that 16α-hydroxy is a primitive bile acid, whereas 12α-hydroxy is a more evolved bile acid. The first chemical synthesis of avicholic acid was achieved by Iida *et al.* from chenodeoxycholic acid.[85] This synthesis utilized a dimethyldioxirane mediated 17α-hydroxylation (yield *ca.* 15%) of acetylated methyl chenodeoxycholate with an overall yield of avicholic acid of <1%. An improved synthesis of avicholic acid using a template directed biomimetic remote functional strategy was recently reported from our laboratory.[86] Recently we noticed that an unusual 16α-hydroxy derivative known as pythocholic acid **36** (3α,12α,16α-trihydroxy-5β-cholan-24-oic acid) was reported and structurally identified many decades ago from the family of snakes Biodae,[87] which includes certain primitive snakes (pythons and boas) including *Cylindrophis.* This family of snakes have pythocholic acid in their bile, as a major bile acid. Using extensive labelling studies in 1960 Bergström *et al.* reported the biosynthetic pathway and concluded that deoxycholic acid undergoes 16α-hydroxylation by the action of a 16α-hydroxylase enzyme.[88] Thus the synthesis of pythocholic acid and the study of its cholanological properties have remained unexplored for the past five decades. Hagey *et al.* recently reported the presence of 3α,7α,12α,16α-tetrahydroxy-5β-cholan-24-oic acid **37** (16α-hydroxycholic acid) which is a minor component (1.6%) in Shoebill stork's bile.[84] The first chemical synthesis and measurement of aggregation properties of pythocholic acid **36** and 16α-hydroxycholic acid **37** were carried out by us.[89] Pythocholic acid was found to exhibit unusual aggregation properties with low CMC and high cholesterol solubilization ability, while avicholic acid and cholic acid showed almost similar physicochemical properties.

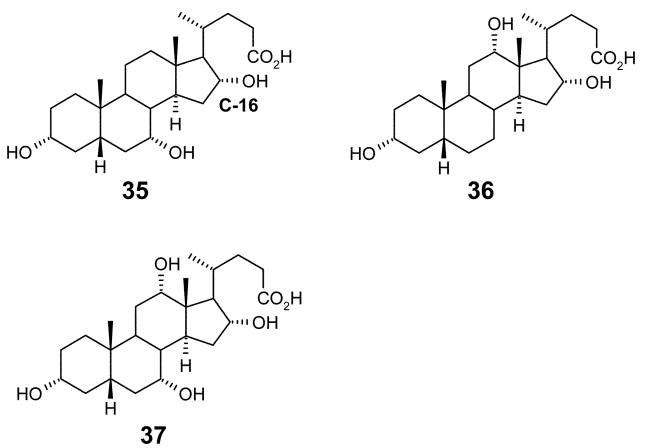

Fig. 22 16α-Hydroxy bile acids.

Summary

Facially amphiphilic bile acids provide an inexpensive source of chirality and an array of uniquely disposed hydroxyl groups with differential reactivity. This led us to design and construct a number of novel chiral auxiliaries/templates, molecular tweezers, dendrons *etc.* The discovery of the gelling ability of several bile acid derivatives inspired us to systematically design and study a large number of bile acid based hydro/organogelators. Templated synthesis of metal oxide nanotubes and gel–nanoparticle hybrid materials has provided a new edge to the use of bile acids in nanoscience. The author and his group have greatly enjoyed the chemistry they have explored, and hope that these unique molecules will continue to provide excitement in the years to come!

Acknowledgements

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