Synopsis

Design and Synthesis of Bile Acid Derived Oligomers and Study of their Aggregation and Potential Applications

T. B. N. SATYANARAYANA
Department of Organic Chemistry

Chapter 1: Amphiphilic self-assembled systems as nanocarriers

Nanocarriers are the nanometric size molecular assemblies that are used for the transport of small molecules into their non-solvating environments. These systems find major applications as drug delivery systems (DDS) in pharmacological research. These drug delivery systems improve solubility and stability of the drug molecules through encapsulation and also offer additional advantages like target specificity and stimuli responsive release of the drug molecules. Several types of DDS are reported in the literature, which can be prepared by a variety of processing techniques. Of these, molecular self-assembled systems have attracted significant interest due to their unique properties and potential applications in drug delivery.

Chart 1: Developments in the design of amphiphilic nanocarriers
assembly has attained considerable attention due to its greater tunability and control in the preparation of nanocarriers. In this chapter we discussed about the amphiphilic nanocarriers which are prepared through self-assembly of amphiphiles through hydrophobic interactions. Several developments in the area of amphiphilic nanocarriers such as di-block polymeric systems, dendritic systems and core-shell architectures are also mentioned. We also highlighted some recent developments in the design of amphiphilic nanocarriers through supramolecular interactions and advantages of such systems.

Chapter 2: Bile acid derived dendrons and their application as nanocarriers

Host-guest chemistry is well known for dendritic systems. To understand the influence of steric crowding, dendritic effect and importance of number of hydroxyl groups on the bile acid backbone in the host-guest chemistry of bile acid dendrons, we designed and synthesized a new series of C3 symmetric systems and studied the above-mentioned objectives through extraction of polar dyes into nonpolar media. Dye extraction experiments performed using trimeric molecules suggested that only the cholate derivatives (3 and 4) showed considerable extraction of the polar dyes into chloroform; deoxycholate derivatives did not show any extraction, thus emphasizing the importance of the number of hydroxyl groups for dye extraction in these molecular architectures. The effect of steric crowding at the core of these trimeric molecules was shown by efficient extraction of the dyes with the triethylbenzene core (4) compared to the benzene core (3). Greater influence of the aggregates in the case of triethylbenzene core on the extracted dye was also manifested in the

![Chart 2: Structures of the designed molecules 1-6](image-url)
value of the induced circular dichroism signal. Surprisingly, a higher analogue in these molecular architectures showed lesser efficiency in dye extraction (on a per bile acid residue basis) compared to the trimers, suggesting a more compact structure for the higher analogue. This was supported by molecular modeling studies. Generality of these systems as nanocarriers for hydrophilic dyes was investigated by screening several other dyes and polar molecules, which are diverse in their structure and functionalities. All these experiments suggested a dependency of the extraction profile on the size of the dye molecule. This was also examined by dynamic light scattering studies, which showed larger size and wider distribution in the size of the aggregates in the case of larger dyes. We also demonstrated selective extraction of a single dye molecule from a blended food color (apple green) using one of the trimer (4) and demonstrated solvent dependent morphological changes in these compounds using electron microscopy. The self-assembly of these amphiphilic molecules at the air-water interface was studied through Langmuir monolayer studies.

Chapter 3: Design and synthesis of bile acid derived surfactants: Study of their aggregation and potential applications

Bile acids are facially amphiphilic systems and their amphiphilicity can be improved by attaching polar groups on the bile acid back bone or by synthesizing oligomeric systems which show better self-assembly compared to their monomeric units. To study and improve the amphiphilicity of bile acids, we designed and synthesized a new tripodal surfactant system, with a phosphine oxide based central core to which the bile acids were attached through the C-3 position using click chemistry. Our molecular design also offers added advantage of studying the influence of the stereochemistry at the C-3 position on the
aggregation of these molecular architectures. We synthesized trimeric systems with both cholic and deoxycholic acids attached to the central phosphine oxide core with α and β stereochemistry at the C-3 position. Aggregation of these molecules was studied by surface tension measurements, dye extraction studies and NMR. All these compounds showed aggregation at micromolar concentrations. NMR studies suggested changes in the structure of the aggregates at higher temperature and these changes were studied by DLS, which suggested thermodynamically stable monodispersed aggregates for cholic acid derivatives (13 and 15) at higher temperature. These aggregates are stable even after cooling to room temperature and with time. The aggregates of these derivatives were also characterized by atomic force microscopy. Gelation was observed in the case of α derivatives (12 and 13) in phosphate buffer (0.1 M) at pH 7.5 for both deoxy and cholic derivatives, which emphasized the influence of stereochemistry at C-3 position in these architectures. These gels were characterized by rheology experiments. Finally, the possible utility of these micellar systems as model systems to study photophysical processes was demonstrated through lanthanide sensitization experiments in these micellar solutions.

![Chart 4: Structure of the designed molecules](image)

**Chapter 4: Synthesis of oligomeric bile acid-taurine conjugates: Study of their aggregation and efficiency in cholesterol solubilization**

Bile acids are bio-surfactants that are used for the emulsification of fats, vitamins etc. in our body. Bile salts also solubilize the excess cholesterol in our body through mixed micelle formation in the bile and when the bile gets saturated with cholesterol, it leads to cholesterol gallstone formation, which needs to be treated. Ursodeoxycholic acid (UDCA) is
used as drug in some cases for the solubilization of (small) cholesterol gallstones, even though the efficiency to solubilize cholesterol is less for UDCA compared to the other bile acids (UDCA is less toxic than the others). So there is a need to develop new cholesterol solubilizing agents. Since oligomeric systems can aggregate better, we designed and synthesized two tetramer taurine conjugates, which differ in the spacer between the bile acid units. Since these conjugates are not soluble in water, their solubility and aggregation was studied in 10% MeOH/Water using pyrene fluorescence experiments. Aggregation studies suggested better aggregation for these molecules compared to their monomeric analogues. These aggregates were also characterized by DLS and electron microscopy. These systems were subsequently studied as nanocarriers for lipophilic dye molecules into aqueous media. Finally, the influence of oligomeric effect in cholesterol solubilization was investigated by cholesterol solubilization studied using these two tetramer taurine compounds and a control, sodium taurocholate. These studies suggested efficient solubilization of cholesterol by oligomers compared to monomeric analogues.

Chart 5: Structure of the synthesized tetramer taurine conjugates