Abstract

The molecular recognition behavior of versatile macrocyclic receptors, cucurbiturils (CBs) have been investigated in relation to their host-guest interaction with amphiphilic molecules, especially cationic surfactants having widespread technological importance. Construction of novel cucurbituril (CB)-adorned supramolecular micellar assemblies of a cationic surfactant, cetylpyridinium chloride (CPC), through noncovalent host-guest interactions has been demonstrated. The distinct cation receptor features and cavity dimensions of the CB5 and CB7 homologues assert that the macrocyclic hosts remain complexed with the CPC monomers and take part in the micelle formation with a shift in cmc, a unique observation in contrast to that of classical host, β-cyclodextrin, and has been characterized by photochemical, surface tension, conductivity, DOSY NMR and SANS measurements. The reversible response of these soft supramolecular micellar structures to thermal-stimuli, which project their utility for on-demand smart drug-delivery vehicles, has also been established.

Key Words: Host-guest interaction, cucurbiturils, surfactant, supramolecular-micellar assemblies, stimuli-responsive

Introduction

Supramolecular encapsulation of guest molecules through macrocyclic hosts presents a convenient pathway for modulation of molecular properties, as it can introduce pronounced effects on the physicochemical properties of the included guest.1 Host-guest interaction finds immense importance in obtaining photostability, drug delivery, catalysis, and sensor applications. Cucurbiturils (CBs), relatively new addition to the repertoire of macrocyclic hosts, are a unique class of water soluble macrocyclic receptor molecules consisting of methylene bridged glycoluril units (Chart 1).1,2 Structurally, the pumpkin-shaped CBs constitute highly symmetrical hydrophobic cages of low polarity and polarizability with two identical dipolar portal ends comprised of carbonyl functional groups.1,2 As a macrocyclic host, CBs have attracted considerable attention in recent years owing to their excellent binding abilities for varieties of guests. Among different CBs, the homologue cucurbit[7]uril (CB7, with 7 glycoluril units) forms stable inclusion complexes with several guest molecules, like organic dyes, protonated alkyl and aryl amines and cationic dyes, via a combination of hydrophobic and ion-dipole interactions.1-4 The lower homologue cucurbit[5]uril
(CB5), having a smaller cavity size, interacts with metal ions or forms exclusion complex with cationic organic guests through its highly polarized carbonyl portals. In this article, the supramolecular interactions of CB5 and CB7 hosts with a cationic surfactant, cetylpyridinium chloride, have been described in relation to the modulation in the critical micelle concentration (cmc), temperature-responsive tunability and their potential applications.

In this article, the supramolecular interactions of CB5 and CB7 hosts with a cationic surfactant, cetylpyridinium chloride, have been described in relation to the modulation in the critical micelle concentration (cmc), temperature-responsive tunability and their potential applications. With increasing CB7 concentrations, the cmc gradually increases from its normal value of 1 mM to 1.63 mM in the presence of 2 mM CB7 (Fig. 1 a-c). In contrast, the titration of NR with CPC in the presence of CB5 (1 mM), displayed a downward shift in the cmc (0.57 mM) (Fig. 1 d, e). The shift in cmc of CPC in the presence of CB5/CB7 was also confirmed by surface tension and conductivity measurements.

Considering the dimensions of the CB portals (portal diameter ~5.4 Å and ~2.4 Å for CB7 and CB5, respectively), and CPC (width of pyridinium group < 5 Å and length of hydrocarbon chain ~ 17 Å), it is apparent that the pyridinium group of CPC can be accommodated within the CB7 cavity. CPC cannot be accommodated inside the CB5 cavity, however, an exclusion complex based on ion-dipole interactions is possible. Earlier studies using cyclodextrin (CD)/CB7 hosts and other surfactant molecules have suggested that the reduction in the surfactant-monomer concentration is the prevailing mechanism for the upward cmc shift where the host-bound surfactant monomers do not participate in the micelle formation. However, a similar mechanism in the present case cannot explain the contrasting cmc shifts observed with the CB7 and CB5 hosts, which points to possible participation of the CB-bound CPC monomers in the micelle formation.
The participation of the CB hosts in the micelle structure has also been confirmed by DOSY NMR measurements. If the cucurbiturils remain attached to the CPC as inclusion or exclusion (in the vicinity of the CPC head group) complexes, the diffusion coefficients of both the CPC protons as well as the CB7 protons would get affected on micellization. The average diffusion coefficient of the –CH protons of CPC in the presence of CB5 or CB7, decreases with increasing CPC concentrations. While the diffusion coefficient of CB5 protons remain unchanged, CB7 protons show a gradual decrease even beyond the cmc (Fig. 2), indicating that the CB7-CPC unit is incorporated within the micellar assembly. However, similar studies with β-cyclodextrin (βCD) displayed such changes after an initial slight decrease, which was expected for its involvement with the monomers.5

**Stimuli-responsive Tuning**

The advantages of the contrasting supra-molecular cmc shift established in CPC on using CB7 or CB5 has been explored further to demonstrate a supramolecularly tunable cmc, which has implications in drug transport, binding and release strategy, etc. The effect of increasing CB7 concentration or solution temperature on the cmc of CPC in a solution containing 1 mM

**Small-angle neutron scattering (SANS) measurements on the CB7-CPC system revealed that the micellar structure of CPC is prolate ellipsoidal with axes 34.3 Å (a) and 18.5 Å (b). However, in the presence of CB7, there is slight elongation along the major axis from 34.3 to 35.9 Å with a significant decrease in the surface charge on the micelle (0.17 to 0.10). This is very much in line with the existence of CB7 beaded CPC micelle. On the other hand, in the CB5-CPC system, though the SANS data indicated a significant reduction in the surface charge, the micellar dimensions remained unchanged, suggesting an externally embedded CB5 on the CPC micelle. Based on the above results, the positioning of the CB7/CB5 hosts in the CPC micelle can be visualized as in Fig. 3. In the case of CB5, the macrocycle remains in the periphery of the micellar structure, whereas in the case of CB7, the CB7-CPC complex is incorporated within the micellar structure leading to the formation of mixed micelles. The incorporation of CB7 at the neck of the pyridinium head group provides optimum interaction for the negatively polarized CB portals with the cationic charge of the pyridinium head group. In addition a part of the alkyl chain is included in the cavity of the macrocycle due to favorable hydrophobic interactions. The partial encapsulation of alkyl chain of CPC within the CB7-CPC complex can reduce the hydrophobicity of the alkyl chain and can lead to an increase in the cmc.5

**Fig.2:** Plot of the diffusion coefficient values for the β-CD (a), CB7 (b) and the CB5 (c) protons with CPC concentration.

**Fig.3:** Schematic representation of the distinct cucurbituril adorned micellar assemblies formed by CPC (a), in presence of CB7 (b), and CB5 (c).
CB5 has been investigated. The fluorescence titration curves progressively shifted with the addition of CB7 or increasing temperature and the corresponding \( cmc \) values demonstrated a tunable range from 0.57 to 1.6 mM (Fig. 4).5 The addition of CB7 or increase in temperature at the above discussed conditions disrupts the CB5-CPC micellar structure, which establishes a facile host/temperature-induced release mechanism having direct relevance in drug delivery applications.

The supramolecular modulation of the surfactant aggregates, envisioned in the present work is very potent and promising for pharmacological applications and for designing tunable artificial molecular devices or nanoreactors.

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References


Fig. 4: Micellization curve for the CB5 or CB7 adorned CPC surfactant and the proposed release mechanism for the CB5 assembly.

Conclusion

The established cucurbituril-adorned, thermo-responsive on/off supramolecular micellar assemblies of the cationic surfactant, CPC, is schematically shown in figure 4. While the supramolecular additive, CB5, exhibits an early micellization of CPC at \(~0.57\) mM, the CB7 host delays the same to about 1.6 mM of CPC. Response of these systems to external stimuli, such as, temperature or the combination of CB5/CB7, demonstrates a continuous tunable range for the micellization of CPC. The supramolecular modulation of the surfactant aggregates, envisioned in the present work is very potent and promising for pharmacological applications and for designing tunable artificial molecular devices or nanoreactors.