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Fragmentation of molecule-induced γ-cyclodextrin nanotubular suprastructures due to drug dosage

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ABSTRACT

The guest–host concentration has already been proved to be a very important factor in the drug delivery process. In the present work we demonstrate the formation of compound induced γ-cyclodextrin nanotubular suprastructure. The nanotubes formed are found to be highly sensitive to the concentration of the guest molecule. The increasing concentration of the compound in solution initiates a competition toward their existence inside the core of the nanotubes affecting the extent of nanotubular cluster formation. The hydrogen bonding responsible for the building of the cyclodextrin nanotubes is found to be partially disrupted because of this increasing competition. The continuous replacement of the guest molecules inside the nanochannels is supposed to be responsible for the instability in some of the hydrogen bondings that develop during the primary and the secondary interactions between the formed nanotubes resulting into fragmentation of the suprastructures. The steady state and time-resolved fluorescence experiments coupled with fluorescence anisotropy and atomic force microscopy illustrate the guest concentration dependence of the formation of the γ-cyclodextrin nanotubes.

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1. Introduction

It is well known that cyclodextrin (CD) and its derivatives can incorporate appropriately sized guest molecules selectively through weak interactions like hydrophobic interaction, van der Waals force and hydrogen bonding [1–3]. The supramolecular assembly in CD chemistry has intrigued increasing interest of chemists due to their potential to serve as molecular devices together with their properties as functional materials [4–9]. Li and co-workers found that nanotubes of β- and γ-CD incorporated with a rod-like molecule could be formed just through supramolecular assembly [5]. Pistolis and co-workers studied in extension to the findings of Li et al. and corroborated the results by investigating the size-effect of certain molecular homologues on the formation of nanotubes with γ-CD [10,11]. α-, β- and γ-CDs are known to undergo self-aggregation in aqueous solution [12]. Among the cyclodextrins, α- and γ- form spherical aggregates, whereas β- forms fiber-like assemblies [12]. Since this phenomenon is more pronounced in case of β-CDs, which affects its solubility in water, more studies have been done over that aspect [13–15]. Guest induced nanotubular suprastructures in the cases of α- and γ-CDs form elongated rod-like structures.

Depending on the relative sizes of the CDs and the guest molecules, more than one guest can be accommodated inside a single CD cavity [16–18]. If the guest molecule is long enough, several cyclodextrins can be threaded along its length [19–22]. Formation of well-structured nanorods has been observed with β-, and γ-CDs because of their ample cavity space as compared to that for α-CD [5–11,16]. Cyclodextrin-based aggregates have been widely investigated with microscopies such as STM, AFM, SEM, TEM, and fluorescent microscopy to obtain the direct morphology and structure of samples [23,24]. He et al. reported about various types of cyclodextrin aggregates, aggregates of cyclodextrin rotaxanes and polyrotaxanes, cyclodextrin nanotubes and their secondary assembly [23]. Miyake et al. explained the formation process of cyclodextrin necklace on a molecular level through the analysis of hydrogen bonding [24]. They reported that most CDs are arranged in head-to-head or tail-to-tail conformation through secondary–secondary or primary–primary hydrogen bonding. Wen et al. showed that the nanotube could be formed between the drug cinchonine and β-cyclodextrin in solution when they were mixed together and sonicated for about 1 h. They used fluorescence anisotropy methods to characterize the number of cyclodextrins in the nanotube and also used quantum mechanical AM1 calculation to imply that hydrogen bonds played an important role to stabilize the nanostructure [25].

With these building prospects of the formation of cyclodextrin nanotubes and their growing applications in targeted drug delivery we proceeded to investigate the host–guest complexation between *trans*-2-[4-(N,N-dimethylamino)styryl]benzothiazole (DMASBT) (Scheme 1) and γ-CD. Although formation of molecule-induced cyclodextrin nanotubes has previously been reported, a key challenge in the science of drug delivery remains incomplete without knowing the impact of the drug concentration on the growth of

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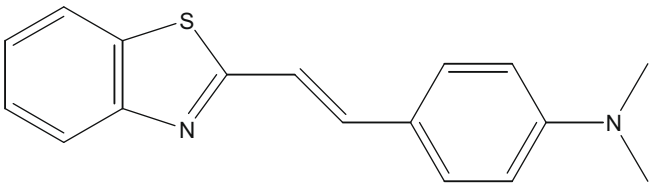

Scheme 1. Representative structure of DMASBT.

the drug induced nanotubes. We could not find reports explaining this phenomenon in details in spite of our prolonged search. Guests of similar size as that of DMASBT [29] are known to exist in couples inside a nanocapsule created by two γ-CD molecules connected head-to-head through hydrogen bonding [5–8]. It seems pretty obvious that the formation of these nanotubular clusters must get affected by the change in the concentration of the molecules that induces their formation.

Fluorescence spectroscopy coupled with atomic force microscopy can serve as a very effective tool to understand this effect. The steady state and time-resolved fluorescence can tell us about the encapsulation of the guest molecules through a well-established procedure (see later), whereas steady state fluorescence anisotropy can let us know about the orientation and the ordered arrangement of the fluorophore, and the atomic force microscopy can give us a clearer view of the whole system so as to confirm our propositions [25–27]. The drug concentration has been proved to have profound effect on the nanotubular suprastructures formed by α-CD where the space constraint is a major factor [27]. γ-CD has more cavity space and thus the guest dynamics may become prominent in this case.

2. Materials and methods

2.1. Materials

DMASBT was procured from Aldrich Chemical Company, WI, USA and was recrystallized from a mixture of ethanol and small percentage (∼10%) of *n*-hexane. Triple distilled water was used for the preparation of aqueous solution. Stock solution of DMASBT (1.001×10^{-3} M) was prepared in pure methanol, 0.1 mL of which was poured in a 10 mL volumetric flask and left for a few hours for complete evaporation of methanol before dissolving in water containing appropriate concentration of γ-CD. The final volume of solution was 10 mL and the final concentration of DMASBT was 1×10^{-5} M. γ-CD was procured from Sigma–Aldrich, WI, USA, and was used as obtained.

2.2. Methods

The absorption spectra were recorded using a Jasco V570 UV–vis spectrophotometer. Fluorescence measurements were performed using a Shimadzu RF-5301PC scanning spectrofluorimeter. The fluorescence lifetimes were measured by the method of time-correlated single-photon counting and a nanosecond spectrofluorimeter (Edinburgh Instrument, 199) was used for the purpose. A nano-LED pulsed diode powered by a pulsed diode controller (IBH) was used as the excitation light source. The excitation wavelength was 370 nm. The typical response time of this laser system was 70 ps. To calculate the lifetime, the fluorescence decay curves were analyzed by an iterative fitting program provided by IBH.

The steady state fluorescence anisotropy measurements were performed with the same Shimadzu (RF-5301PC) spectrofluorimeter fitted with a polarizer attachment. The steady state anisotropy, r can be represented as, $r = (I_{VV} - GI_{VH})/(I_{VV} + 2GI_{VH})$, where I_{VH} and I_{VV} are the intensities obtained from the excitation polarizer oriented vertically and the emission polarizer oriented in horizontal and vertical orientations, respectively. The factor G is defined as $G = I_{HV}/I_{HH}$. The AFM experiments were done using a Nanoscope II instrument (Digital Instrument Inc., USA) with lateral resolution of 1 Å and vertical resolution of 0.1 Å fitted with a Au coated probe. The surface for the sample spread was made of highly oriented pyrolytic graphite (HOPG). Droplet-evaporation or adsorption methods were used for preparing AFM samples from liquid suspensions. A droplet of liquid is deposited on freshly cleaved HOPG slide. The droplet is then carefully washed after allowing the sample to sit for about 10 min. The sample was left overnight in a dust protected environment to dry up before scanning [28].

3. Results and discussion

3.1. Fluorometric changes of DMASBT due to encapsulation

The absorption spectra of DMASBT in increasing concentration of γ-CD shows an isosbestic point at around 365 nm indicating a ground state complexation of the guest and the host. Fig. 1 demonstrates the fluorescence spectra of the twisted intramolecular charge transfer (TICT) state of DMASBT [29,30]. The hypsochromic shift of the fluorescence maxima and the concomitant increase in the fluorescence intensity confirm the encapsulation of the guest molecule inside the hydrophobic cavity of γ-CD (explained elsewhere in details) [29,30]. We tested for the nature of encapsulation of DMASBT inside the CD cavity using the Benesi-Hildebrand double reciprocal method [5–11]. However, this method is not suitable for the systems where there is a possibility of nanotube formation, since this is a multi-step process [5–8]. These observations reveal that in the present case the complexation may be of multiple-host type, i.e., numerous CDs are encapsulating the guests (most probably multiple) within the nanochannels. The lowest concentration of DMASBT (1 μM) displays a steady blue shift of the fluorescence maxima from 525 to 475 nm indicating a progressive development of hydrophobic environment around the DMASBT molecules (Fig. 2) [26,27]. The hypsochromic shift gets affected on doubling the dose of the guest molecules. The shift decreases by 10 nm indicating that probably the guest molecules are experiencing a less hydrophobic milieu. If the guest dosage is further increased (to 3 μM), then interestingly the blue shift shows some peculiarities.

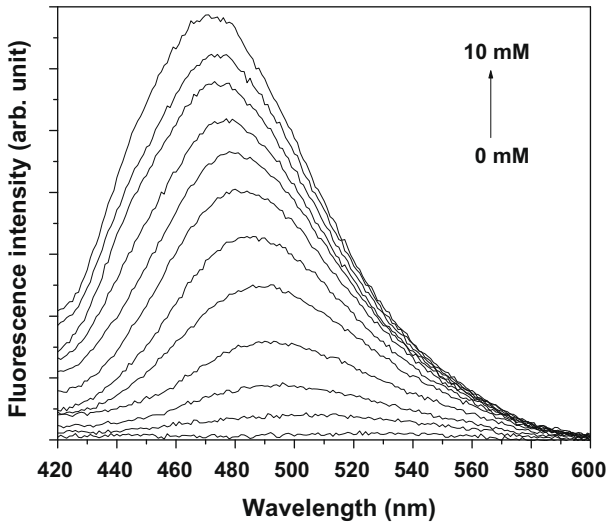

Fig. 1. Representative fluorescence spectra of DMASBT (1 μM) with increasing γ-CD concentration. The wavelength of excitation is 360 nm.

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