ARTICLE

Photochromic Properties of β-Cyclodextrin Dimer Linked by Dithienylethene

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(Dated: Received on April 23, 2006; Accepted on May 15, 2006)

A β-cyclodextrin dimer tethered by photoswitchable dithienylethene moieties was synthesized as a potentially tunable receptor. The dimer exhibits pronounced photochromic properties. Irradiation of the dimer in open form with UV light at 254 nm resulted in immediate photocyclization to the pink closed form; the colorless open form could be regenerated by irradiation with visible light of wavelength >460 nm. The reaction kinetics of the forward photoprocess were also studied. To investigate the binding ability of the dimer in open and closed forms, a fluorescence titration was performed. It was found that the stability constant for the binding of TSPP (meso-tetrakis (4-sulfonatophenyl)porphyrin) by the closed form of the dimer is a factor of 5 higher than that of the open form.

Key words: β-cyclodextrin dimer, Photochromic properties, Fluorescence spectroscopy

I. INTRODUCTION

One of the ultimate challenges in chemistry is to obtain external control over molecular properties. This is especially true for the synthesis of receptor molecules for which binding affinity towards specific substrates can be altered by external stimuli [1]. In all of the host compounds considered for implementation in tunable receptors, cyclodextrins (CD) are of special interest because of their ability to form complex hydrophobic substrates in aqueous solutions, which leads to their extremely large number of applications from drug delivery devices [2] to enzyme mimics [3]. Work in this field was initiated in the late 1970s by Ueno *et al*., who modified cyclodextrins with photoswitchable azobenzene moieties to obtain tunable supramolecular receptors in which the binding affinity and selectivity could be altered by irradiation with light [4]. From then on, a variety of metal- and photoswitchable host molecules has been reported in the literature [5-8].

Recently cyclodextrin dimers with tunable linkers have caught more attention [9-12]. It is well known that bridged bis(β-cyclodextrin)s with simple tethers show significantly enhanced molecular binding abilities toward a large variety of guest molecules in comparison with parent cyclodextrin [13-16]. Indeed, with bis(β-cyclodextrin)s the orientation and separation of the two cyclodextrin moieties in a single molecule can be adjusted by altering the conformation of the bridging chain, which gives rise to the most effectively stabilized "sandwich" complex in aqueous solution. In order to obtain tunable cyclodextrin dimer host molecules, β-CD have been tethered with metal chelating [10], photoswitchable [9], and photocleavable [17] tethers. However, all these dimers either display marginal differences in binding properties or are destroyed irreversibly when stimulated.

The use of a photoswitchable tether may be the most suitable choice for the synthesis of a tunable cyclodextrin dimer. Ueno *et al*. produced a photoswitchable cyclodextrin dimer by tethering two β-CD cavities with an azobenzene linker [5-8]. However, no guest molecules were found displaying selectivity for one of the two configurations of the dimer.

Mulder *et al*. reported a tunable β-CD dimer tethered at the secondary sides by a dithienylethene moiety [18]. Dithienylethenes are able to undergo thermally irreversible, fatigue resistant, photochromic cyclization reactions between a relatively flexible open form and a rigid closed form [19]. This subtle difference in flexibility between the two forms of dithienylethenes was used to achieve a surprisingly large difference in binding affinity (factor 35) between the open and closed states of the dimer for binding a porphyrin guest molecule.

Furthermore, Liu *et al*. have synthesized some oligo(ethylenediamine) tethered β-cyclodextrin dimers in order to elucidate the recognition mechanism as controlled by the simultaneous operation of the available weak interaction [11]. The dimers only showed a little difference in binding abilities towards the guest molecules.

Herein, we described the synthesis and photochromic properties of a novel β-cyclodextrin dimer bridged on the first side by a dithienylethene tether. The photochromic properties of this dimer were studied by UV/vis spectroscopy, and the rate of forward reaction in aqueous solution was studied. Furthermore, the binding ability of the dimer with meso-tetrakis(4-sulfonatophenyl)porphyrin (TSPP) in open form as well as at photostationary state (PSS) was studied by fluo-

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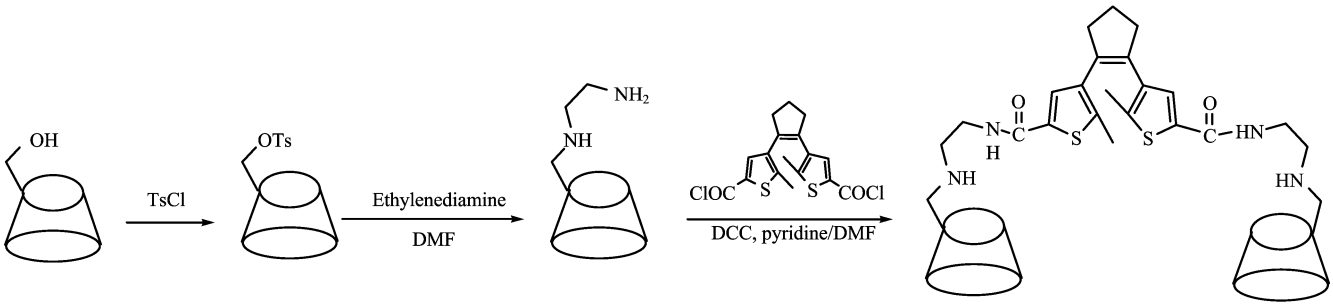


Scheme 1 Synthetic route of β-cyclodextrin dimer.

rescence spectroscopy.

II. EXPERIMENTS

A. Materials

All chemicals were reagent grade, and used without further purification unless noted otherwise. β-CD (Shanghai Reagent Works) was recrystallized twice from water. N, N-Dimethylformamide (DMF) was dried over calcium hydride for two days and distilled prior to use. Pyridine was refluxed over calcium hydride and distilled prior to use. 1,2-bis (5-carbonyl chloride-2-methylthien-3-yl)-cyclopentene was prepared [20]. Mono(6-ethylenedi-amine-6-deoxy)-β-cyclodextrin was prepared according to the procedures reported by Harada *et al.* [21]. Meso-tetrakis(4-sulfonatophenyl)porphyrin (TSPP) was synthesized [22].

All the reactions involving photochromic compounds were strictly protected from light by aluminium foil.

B. Instrumentation

^{1}H NMR was recorded with a Bruker DMX-300 spectrometer using D_2O as solvent and with chemical shift given in ppm relative to residual D_2O (4.79 ppm). IR spectra were recorded with a Bruker Vector 220 infrared spectrometer. Melting points were determined on a Yanaco melting apparatus and not corrected. The fluorescence spectra were measured by a CRT970 fluorescent spectrometer at room temperature. UV-Vis absorption spectra were measured on a Perkin-Elmer lambda 45 UV-Vis spectrophotometer. MALDI-TOF mass spectra were recorded with a BIFLEX III instrument.

C. Preparation of PSS mixtures

A solution of the open form of the dimer (0.1 mmol/L) in deionized water in a quartz bottle was irradiated with a standard lamp used for visualizing TLC plates for 30 min. UV-Vis spectra of the diluted sample were used to follow the photochromic reaction. Once the PSS reached, the sample was protected from light with aluminium foil for later use.

D. Synthesis

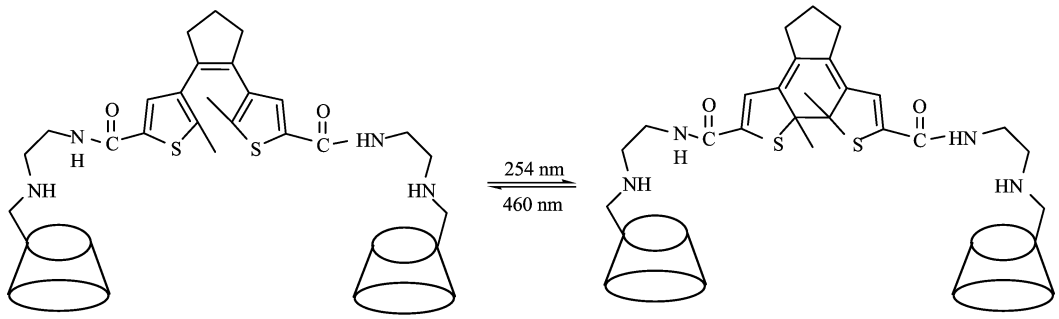
1,2-bis(5-carbonyl chloride-2-methylthien-3-yl)-cyclopentene was dissolved in dry pyridine containing dicyclohexylcarbodiimide. Mono(6-ethylenediamine-6-deoxy)-β-cyclodextrin in DMF was added to the solution at room temperature under a nitrogen atmosphere, and the resultant mixture was stirred for 3 days at 0 °C. Then the solution was allowed to warm up to room temperature and stirred for additional 2 days. The precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to dryness. The residue was dissolved in water and acetone was added to the solution to give a brown precipitate. The crude product obtained after drying was purified by column chromatography over Sephadex G25 with de-ionized water as the eluent to give a pure sample which was a bright red solid. m.p. ca. 217.3 °C (dec); ^{1}H NMR (D_2O, 300 MHz) δ: 7.67 (2H, s), 5.04 (14H, s), 3.89-3.78 (52H, m), 3.64-3.58 (28H, m), 3.25 (4H, t), 3.02-2.90 (20H, m); IR (KBr): ν: 3415.3, 2925.7, 2853.7, 1710.6, 1645.0, 1560.8, 1453.5, 1368.2, 1299.9, 1156.4, 1080.8, 1028.9, 944.2, 844.9, 753.4, 705.7, 578.3, 528.8 cm^{-1}; MALDI-TOF: m/z 2667 $[M]^+$.

III. RESULTS AND DISCUSSION

A. Synthesis and characterization of the β-cyclodextrin dimer

As illustrated in Scheme 1, the dithienylethene bridged β-cyclodextrin dimer 1 was synthesized by the reaction of 1,2-bis(5-carbonyl chloride-2-methylthien-3-yl)-cyclopentene [20] and corresponding mono(6-ethylenediamine-6-deoxy)-β-cyclodextrin. In this route, mono(6-O-*p*-toluenesulfonyl)-β-cyclodextrin was

ISSN 1003-7713/DOI:10.1360/cjcp2007.20(1).103.6



Scheme 2 Photochromic reaction of the β-cyclodextrin dimer.

prepared by the reaction of β-cyclodextrin with *p*-toluenesulfonyl chloride in aqueous alkaline solution and converted to mono(6-ethylenediamine-6-deoxy)-β-cyclodextrin by heating it in an excess amount of ethylenediamine at 70 °C for 7 h. Then the precursor was dissolved in DMF and reacted with the acylchloride in dry pyridine. It is important to maintain the mixture as anhydrous and at low temperature during the reaction, especially at the initial stage, for the purpose of avoiding undesirable products.

The dimer is poorly soluble in organic solvents. ^{1}H NMR spectra in D_2O showed a set of broad peaks around 5.0 and 4.0 ppm, which are characteristic shifts for the β-cyclodextrin protons. In addition, the signals of the thienyl hydrogen atoms appear at 7.6 ppm as a singlet. Furthermore, when the dimer was irradiated with UV light (Scheme 2), the signal of these protons underwent a very pronounced upfield chemical shift (δ=0.3 ppm). Also, the cyclopentene bridge protons occur at 3.2 ppm as a triplet. The signals of the methyl protons were overlaps with a multiplet around 3.0 ppm, which originates from the methylene group of the diamine spacer.

B. Absorption spectra

The absorption spectra of the open form and corresponding closed form are shown in Fig.1. The absorption spectra of the closed form was calculated from the absorption spectra obtained at the photostationary state (PSS) by using Eq.(1) for the absorbance of a mixture of two compounds at any wavelength[23].

$$A_{\rm PSS} = A_{\rm OF}(1 - C_v) + A_{\rm CF}C_v) \qquad (1)$$

where $A_{\rm PSS}$ is the absorption obtained at the PSS state, $A_{\rm OF}$ is the absorption of the open form, $A_{\rm CF}$ is the absorption of the closed form, and C_v is the conversion from open to closed isomers. $A_{\rm PSS}$ and $A_{\rm OF}$ can be determined by UV-Vis spectroscopy, and C_v can be calculated from ^{1}H NMR data by integration of the peaks for the open and closed forms.

The open form of the dimer showed strong absorption in the UV region with absorption maximum at 212 and 262 nm in water. When the solution was irradiated with 254 nm light, it resulted in an immediate increase in the visible spectral region of the absorption spectra with maxima at 527 nm and a visual change in color from colorless to pink due to the appearance of the ring-closed isomer. The reverse reaction was triggered by visible light since the closed form has a new absorption band in the 450-650 nm region (Fig.1). Subsequent irradiation of the sample with visible light of wavelengths >460 nm resulted in a reconversion into the colorless state.

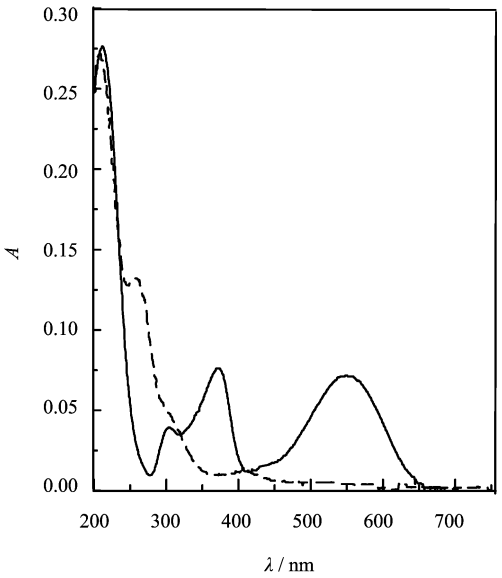


FIG. 1 UV-Vis spectra of open- (−−) and closed-form (—) of the β-cyclodextrin dimer.

The ratio of open form to closed form in the PSS under irradiation with 254 nm light was determined to be 35:65 according to the ^{1}H NMR spectrum. The photostationary mixture is stable at room temperature in the dark. The absorption spectrum of the PSS mixtures of the dimer is given by the dash-dotted line in Fig.2. UV-Vis spectra recorded before reaching the PSS shows the existence of an isobestic point near 320 nm, which indicates the lack of byproducts of the photochemical

ISSN 1003-7713/DOI:10.1360/cjcp2007.20(1).103.6

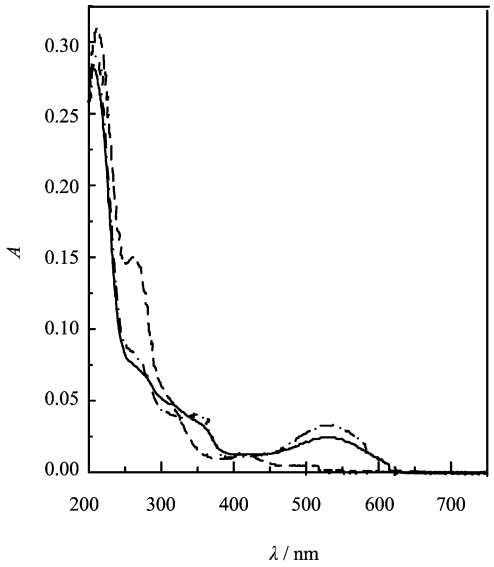


FIG. 2 UV-Vis spectra of the β-cyclodextrin dimer (−−), PSS (−·−), and that irradiated for additional 1 h after reaching PSS (—).

isomerization. It has to be added that when the closed form was irradiated by UV light at 254 nm for an additional 1 h more (after reaching the PSS), the isobestic point disappeared, thus indicating the onset of some kind of decomposition.

The rate of forward photoprocess in aqueous solution was studied for the first time. A plotting of absorption versus time fits the pattern of first order kinetics (Fig.3). We estimated the rate constant of the forward processes (k) using the following equation of the first-order kinetics.

$$\ln \frac{A_\infty - A_t}{A_\infty - A_0} = -kt \qquad (2)$$

where A_0, A_t and A_∞ are the absorbance at 527 nm at time t=0, current time t and $t\to\infty$, respectively.

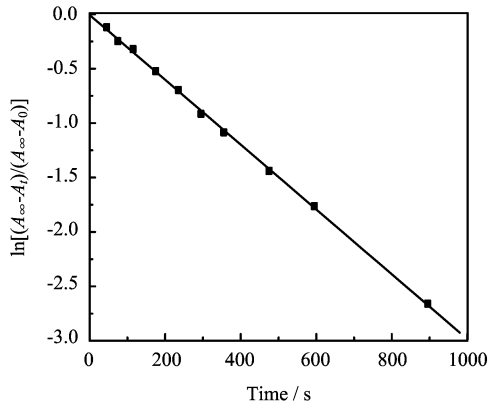


FIG. 3 Absorption of the β-cyclodextrin dimer versus time.

For the forward cyclization process (Scheme 2), the plot of absorption versus time is a straight line. This means that in this case the first-order kinetics can be applied for precise calculation of the rate constant. The rate constant was determined by using only the kinetic curves to be 2.98×10^{-3} s^{-1}.

C. Complexation studies

Complexation of the cyclodextrin dimer was carried out with meso-tetrakis(4-sulfonatophenyl)-porphyrin (TSPP). TSPP is a well-studied guest molecule for complexation by β-cyclodextrin [24] and β-cyclodextrin dimers [14,25]. Nolte *et al.* have found both 1:1 and 2:2 binding modes for the binding of TSPP by β-cyclodextrin dimers [14]. Flexible alkyl-chain-tethered β-cyclodextrin dimers displayed mostly 1:1 binding, whereas the sigmoidal shape of the fluorescence titration curve for the binding of TSPP by a relatively rigid 2,2'-bipyridine-tethered β-cyclodextrin dimer was explained by a 2:2 binding mode. To determine the binding mode of the dimer, the fluorescence titration of the open dimer and the PSS mixtures were carried out in aqueous solution and the results are shown in Fig.4. The binding of TSPP by the β-cyclodextrin cavities of the open dimer resulted in an exponential decrease in fluorescence intensity and a titration curve that corresponds to the formation of a 1:1 complex. No sigmodial character of the titration curve was observed that could imply a 2:2 binding mode. Previous studies have shown, however, that native β-CD binds TSPP in 2:1 ratio and complexes two opposite 4-sulfonatophenyl moieties [24a]. Complexation of two adjacent binding sites is sterically less favorable and gives rise to weaker complexation [26]. Therefore, it is natural to assume that the newly synthesized dimer binds TSPP in the sterically less demanding anti geometry, both in its open and closed forms.

The 1:1 inclusion complexation of a guest (G) with

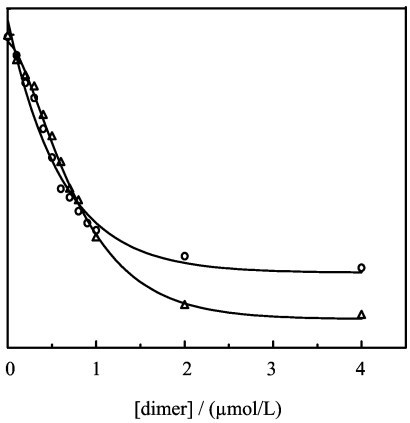


FIG. 4 Fluorescence titration curve for the complexation of TSPP (0.2 μmol/L) with the β-cyclodextrin dimer (○) and PSS mixture (△).

ISSN 1003-7713/DOI:10.1360/cjcp2007.20(1).103.6

modified cyclodextrin (H) is expressed by Eq.(3).

$$[\mathrm{H}] + [\mathrm{G}] \rightleftharpoons [\mathrm{HG}] \quad \mathrm{K_s} \tag{3}$$

The fluorescence change (ΔI) upon addition of host, defined as ΔI=I_0(without host)−I(with host), is assumed to be proportional to the concentration of inclusion complex produced, i.e. ΔI=α[HG]. The proportionality coefficient α is taken as a sensitivity factor for the fluorescence change induced by the addition of one molar host, or a quantitative measurement of the conformational changes upon complexation. Then, the complex stability constant (K_s) is given by Eq.(4), where $[\mathrm{H}]_0$ and $[\mathrm{G}]_0$ are the initial concentrations of host and guest.

$$K_s = \frac{[\mathrm{HG}]}{[\mathrm{H}][\mathrm{G}]} = \frac{\Delta I/\alpha}{([\mathrm{H}]_0 - \Delta I/\alpha)([\mathrm{G}]_0 - \Delta I/\alpha)} \tag{4}$$

Since the initial concentrations of the host and guest are close to each other, the equation can not be simplified to a linear form. Hence, in the present work we solved Eq.(4) to give Eq.(5) and gave a curve fitting to estimate the value of K_s [27].

$$\Delta I = \frac{1}{2}\Big[\alpha([\mathrm{H}_0] + [\mathrm{G}]_0 + 1/K_s) \pm \sqrt{\alpha^2([\mathrm{H}]_0 + [\mathrm{G}]_0 + 1/K_s)^2 - 4\alpha^2[\mathrm{H}]_0[\mathrm{G}]_0}\Big] \tag{5}$$

The K_s values are 2.77×10^5 and 6.38×10^5 L/mol for the open form and PSS mixtures, respectively. Since the ratio of open/closed form is 65:35 at PSS state from the ^{1}H NMR results, the K_s value of the closed form was calculated to be 1.31×10^6 L/mol. The results fit well the observation of the fluorescence spectra changing with the different host forms (Fig.5). The difference in binding strength makes the dimer a candidate for a photocontrollable drug-delivery system, sush as in photodynamic cancer therapy [28].

IV. CONCLUSION

A β-cyclodextrin dimer linked at the first side by a dithienylethene tether was synthesized. The photochromic properties were investigated by UV-Vis spectroscopy. When the aqueous solution of the dimer was irradiated with 254 nm light, the color of solution changed from colorless to pink according to the appearance of the closed isomer. The solution can be returned to its original state by irradiation with visible light (λ>460 nm). The forward cyclization process fits first-order kinetics well with the rate constant 2.98×10^{-3} s^{-1}. The binding constants K_s determined by fluorescence titration for the dimer in open-, closed- and PSS state were 2.77×10^5, 1.31×10^6 and 6.38×10^5 L/mol, respectively.

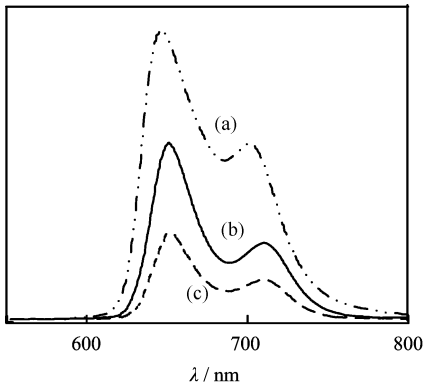


FIG. 5 Fluorescence spectra of TSPP (1 μmol/L, (a)), TSPP with addition of changed upon addition of the open form (4 μmol/L, (b)) and the PSS mixture (4 μmol/L, (c)) of the β-cyclodextrin dimer.

V. ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No.20332020, No.20472079).

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