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Photo-Induced Switchable Binding Behavior of Bridged Bis(β-cyclodextrin) with an Azobenzene Dicarboxylate Linker

YU LIU[1,*], SHU KANG[1], YONG CHEN[1], YING-WEI YANG[1]
JURRIAAN HUSKENS[2]
[1]*Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P.R. China;* [2]*Laboratory of Supramolecular Chemistry and Technology and Strategic Research Orientation "Nanofabrication", MESA+ Institute for Nanotechnology, University of Twente, 217, Enschede 7500 AE, The Netherlands*

Key words: azobenzene, bridged bis(cyclodextrin), photoisomerization, switchable binding behavior

Abstract

A bridged bis(β-cyclodextrin) (**1**) with an azobenzene dicarboxylate linker was synthesized, and its binding behavior with a fluorescent dye, acridine red (AR), was investigated by means of fluorescence spectroscopy. Due to the photo-induced conversion of the azobenzene dicarboxylate linker from the *trans*-conformer to the *cis*-conformer, **1** exhibits a different binding behavior before and after UV light irradiation, giving a stronger binding ability towards AR in the *cis* form. This switchable binding behavior of **1** may open a new channel to the design of azobenzene-linked dimeric receptors as photo-induced molecular devices.

Introduction

Azobenzene derivatives are expected to provide useful applications for optical switching [1] and image storage [2] devices, because their photoisomerization can induce changes of various chemical and physical properties such as the absorption spectrum, dielectric constant, and refractive index. Among them, cyclodextrin (CD)/azobenzene derivative systems attract extensive interest because CDs can form inclusion complexes with azobenzene derivatives via host–guest recognition, and the photoisomerization of azobenzene groups can control the inclusion and exclusion of guest molecules [3]. These machinelike switching motions have been widely applied to molecular shuttles, motors, and information storage in various matrices [4–6]. As early as 1979, Ueno *et al.* prepared the azobenzene-capped β-CD to regulate the binding ability of β-CD by light [7]. At 1998, they further synthesized the azobenzene-bridged bis(β-CD) and investigated its photoisomerization in aqueous solution [8]. Recently, Matsui *et al.* reported that the azobenzene-coated nanotubes could be immobilized onto α-CD SAMs on a patterned Au substrate via host–guest recognition and detached via UV irradiation due to the photoisomerization of azobenzene groups [9]. Tian *et al.* reported a light-driven rotaxane molecular shuttle containing an azobenzene or a stilbene unit, and the *cis–trans* photoisomerization of the photoswitchable unit resulted in the motion of the CD macrocycle on the track [10, 11]. More recently, we reported the inclusion complexation behavior of azobenzene-modified CDs with aliphatic alcohols [12] as well as the self-assembly of CD/azobenzene complexes [13]. Compared with mono-modified CDs, bridged bis(CD)s are well documented to greatly enhance the original binding ability of native CDs through the cooperative binding of dual hydrophobic cavities located in close vicinity with a guest molecule. Therefore, we here report the preparation of a new bis(β-CD) with an azobenzene dicarboxylate linker (Chart 1) and the investigation of the photoisomerization of the azobenzene linker and its effect on the conformation and binding behavior of azobenzene-bridged bis(β-CD). These studies will be useful for the design of photo-driven molecular devices and machines.

Experimental

Material

β-CD of reagent grade (Shanghai Reagent Works) was recrystallized twice from water and dried in vacuo at 95 °C for 24 h prior to use. *N*, *N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under a reduced pressure prior to use. Dicyclohexylcarbodiimide (DCC) was commercially available (Shanghai Reagent Factory) and used without further purification. Disodium hydrogen phosphate and sodium dihydrogen phosphate were dissolved in distilled, deionized water to make a 0.1 M phosphate buffer solution of pH 7.20 for spectral measurements.

* Author for correspondence. E-mail: yuliu@nankai.edu.cn

Synthesis of bis(β-cyclodextrin-6-yl)-3,3′-dicarboxylazobenzene (1)

To a solution of DMF(40 ml) containing 2.6 g β-CD and 0.4 g of DCC was added 0.278 g 3,3′-azodibenzoic acid (**3**) in the presence of a small amount of 4 Å molecular sieves Scheme 1. The reaction mixture was stirred for 2 days in an ice bath and another 2 days at room temperature, and then allowed to stand for several hours until the precipitate not increasing anymore. The precipitate was removed by filtration and the filtrate was poured into 300 ml of acetone. The precipitate was collected and subsequently purified on a Sephadex G-25 column with water as eluent. After the residue was dried *in vacuo*, a pure sample was obtained in 25% yield. UV/Vis λ_{max} (H_2O)/nm (log ϵ) 323 nm (4.4); ^{1}H NMR (D_2O, TMS) δ 3.27–3.82 (m, 84H), 4.91 (m, 14H), 7.22 (m, 2H), 7.67 (m, 2H), 8.06 (m, 2H), 8.46 (m, 2H); FT-IR (KBr) ν/cm^{-1} 3852, 3746, 3335, 2927, 2152, 1719, 1652, 1604, 1558, 1455, 1435, 1364, 1292, 1206, 1154, 1079, 1031, 943, 859, 758, 704, 582, 534; Anal. Calcd for $C_{98}H_{146}O_{72}N_2{\cdot}6H_2O$: C, 45.06; H, 6.10; N, 1.07. Found: C, 45.46; H, 6.20; N, 1.00.

Photoisomerization

Photoisomerization of the azobenzene units was induced by UV light irradiation (360 nm) with a 400-W high-pressure mercury-arc lamp ($\lambda \geq 290$ nm and a strong radiation at 360 nm) for 20 min.

Spectral measurements

The stability constants and Gibbs free energy changes of AR with bis(β-CD) **1** before and after irradiation were determined by using fluorescence spectrometry in phosphate buffer solution (pH 7.20) at 25 °C. Fluorescence spectra were performed in a conventional quartz cell ($10 \times 10 \times 45$ mm) on a JASCO FP-750 spectrophotometer equipped with a temperature controller. The excitation and emission slits were 5 nm.

Results and discussion

Because our repeated attempts to prepare a single crystal of **1** suitable for X-ray crystallography were unsuccessful, we performed a molecular modeling study to elucidate the possible structure of **1** and obtained its energy-optimized structure as a *trans* conformer as shown in Chart 1. Generally, the azobenzene groups can undergo reversible stereochemical rearrangements between the *trans* and *cis* conformers upon irradiation, and the direction is determined by the wavelength of the incident light [14]. As a consequence of the different electronic situations in the two conformers, the photoisomerization is always accompanied by variations of the absorption spectra. In the present case, this phenomenon is observed as well. As can be seen in Figure 1, the *trans* conformer of **1** displays a strong absorption maximum at 323 nm assigned to the π–π* transition and a weak absorption maximum at 435 nm assigned to the n–π* transition of azo group. However, after irradiating the solution of **1** with a 400-W high-pressure mercury-arc lamp for 20 min, the intensity of the π–π* absorption obviously decreased, while that of the n–π* absorption increased. This indicates that the *trans* conformer of **1** was partially converted to the *cis* conformer,

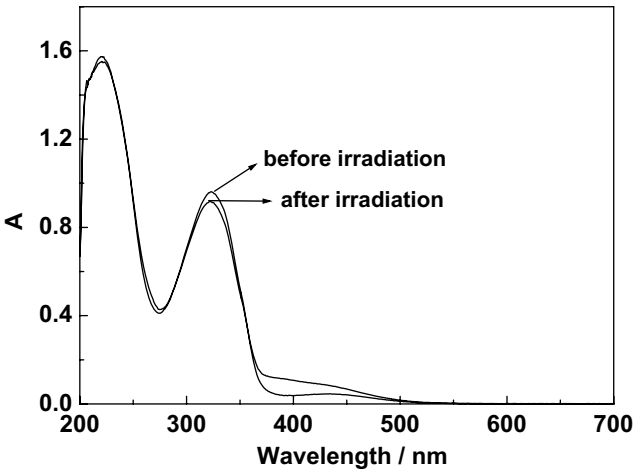
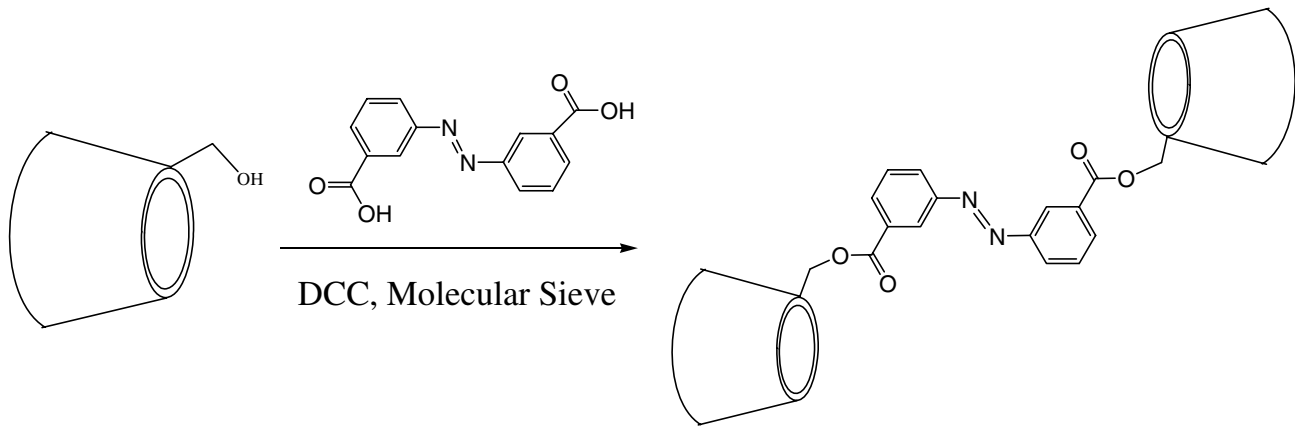
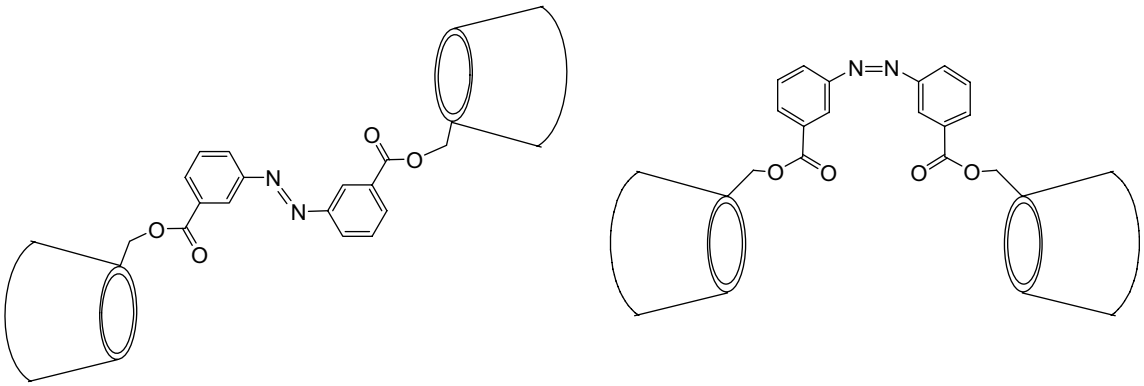


Figure 1. UV–vis spectra of **1** (3.8×10^{-5} M) in phosphate buffer solution at 25 °C (pH 7.20) before and after UV irradiation.

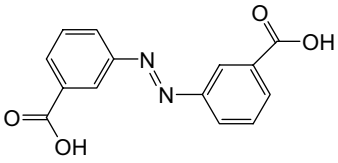


Scheme 1.



trans conformer of 1

cis conformer of 1



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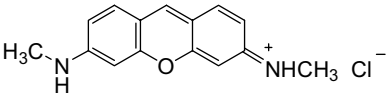

AR

Chart 1.

similar to systems reported by Ueno [8, 15], Matsui [9] and Samsonova [16]. Assuming that the *cis*-conformer shows no absorption around 320 nm, we can calculate the *cis*/*trans* ratio in **1** after irradiation to be 14:86.

After validating the photoisomerization of the azobenzene linker, we performed fluorescence titration experiments to investigate how the photoisomerization affects the binding behavior of **1**. Herein, acridine red (AR) was selected as a representative guest molecule, and the binding modes and binding constants (K) between host and guest were determined by analyzing the fluorescence changes of AR with the gradual addition of **1**. As seen from Figure 2, with the addition of a small amount of **1** (lines a–d), the fluorescence of AR slightly decreases, accompanied by an appreciable hypsochromic shift of the emission maximum (2 nm). However, with the further addition of an excess amount of **1** (lines e–i), the fluorescence of AR significantly increases, accompanied by the hypsochromic shifts of the emission maximum (2 nm). In a control experiment, the fluorescence intensity change of AR upon addition of **3** is negligible under identical conditions, which reveals that the fluorescence change of AR in the presence of **1** is attributed not to the interaction between the linker group and AR but mostly to the inclusion complexation of AR by a CD cavity.

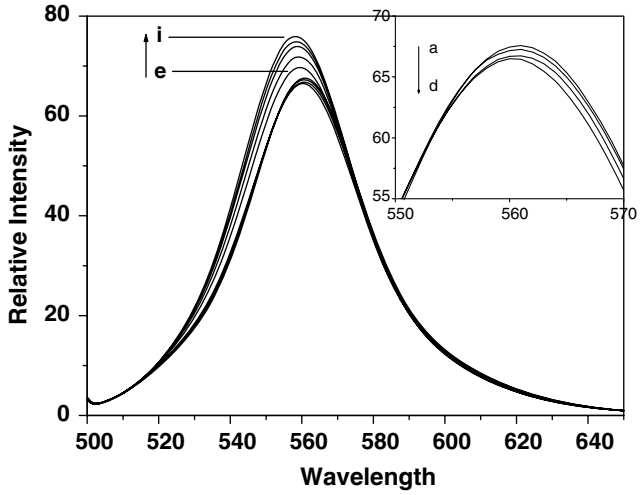

Figure 2. Fluorescence spectral changes of AR (9.5×10^{-6} M) upon addition of **1** (before irradiation) in phosphate buffer solution (pH 7.20) at 25 °C ([1] = 0, 9.6×10^{-7}, 3.8×10^{-6}, 4.8×10^{-6}, 5.8×10^{-6}, 6.7×10^{-6}, 9.6×10^{-6}, 1.2×10^{-5}, 1.4×10^{-5}, 4.3×10^{-5}, 7.2×10^{-5}, 1.0×10^{-4}, 1.3×10^{-4}, 1.6×10^{-4} M from a to i).

When analyzing the sequential changes in the fluorescence intensity (ΔF) of AR that occur upon changes of the concentration of **1**, we found that reasonable results were obtained only when a binding model assuming a 1:2 binding stoichiometry between host and guest was applied [17]. According to this binding model, the two binding sites in **1** do not behave as identical and independent binding sites, and the binding of the first AR in one CD cavity affects the binding of the second AR in the other CD cavity. The calculated Ks values for the inclusion complexation of AR with **1** are listed in Table 1, along with the Gibbs free energy changes ($\Delta G°$).

Table 1. Binding constants for the 1:2 inclusion complexation of **1** with AR

Host	Guest	K_1 (M^{-1})	$\Delta G°$ (kJ/mol)	K_2 (M^{-1})	$\Delta G°$ (kJ/mol)
β-CD	AR	2630 [a]	−19.5		
1 (before irradiation)	AR	6.76×10^4	−27.6	1.69×10^4	−24.1
1 (after irradiation)	AR	1.18×10^5 [b]	−28.9	2.94×10^4 [b]	−25.5

[a] ref. [18]. [b] apparent binding constant.

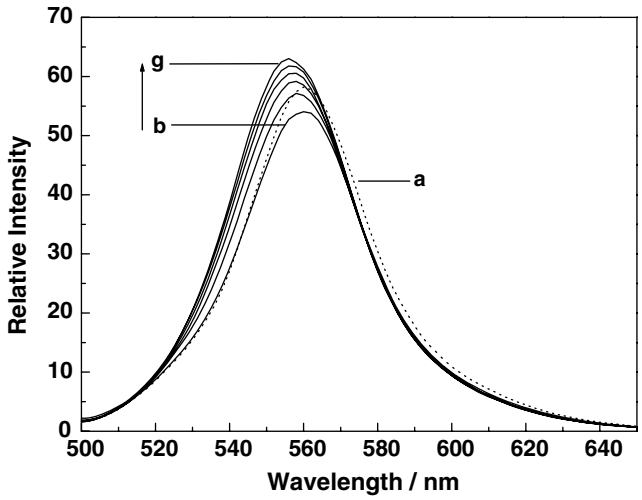

Figure 3. Fluorescence spectral changes of AR (9.5×10^{-6} M) upon addition of **1** ([1] = 0, 8.9×10^{-6}, 4.45×10^{-5}, 8.01×10^{-5}, 9.79×10^{-5}, 1.51×10^{-4}, 1.87×10^{-4} from a to g), which was irradiated by the UV light for 20 min, in phosphate buffer solution (pH 7.20) at 25 °C.

As can be seen in Table 1, the K_1 value for the inclusion complexation of AR with **1** is 26 times higher than the one with native β-CD. This high binding ability may be attributed to π–π interactions between the azobenzene substituent attached on the CD rim and the AR molecule accommodated in the CD cavity. Moreover, the hydrogen bond interactions between the –NH group of AR and the O atoms of the linker groups may be also responsible for the strong host–guest binding.

It is interesting to compare the inclusion complexation behavior of **1** before and after irradiation, because the *trans* conformer of **1** will partly convert to the *cis* conformer upon irradiation with UV light. Figure 3 illustrates the fluorescence changes of AR upon gradual addition of **1**, which is irradiated by UV light for 20 min. As can be seen in Figure 3, the fluorescence of AR decreases with the addition of a small amount of **1** (lines a–b), but significantly increases with the further addition of an excess amount of **1** (lines b–g), accompanied by the hypsochromic shifts of the emission maximum (2 nm). These phenomena also correspond to a 1:2 sequential binding model by analyzing the fluorescence changes (ΔF) of AR against the concentration of **1**. It should be noted that, because **1** exists as a mixture of *trans* and *cis* conformers after irradiation, the curve-fitting analysis could only give the apparent binding constants (K_1 and K_2) as listed in Table 1. From Table 1, we can see that, after irradiation, the K_1 and K_2 values for the inclusion complexation of AR with **1** are larger than the corresponding values before irradiation. Therefore, we can deduce that **1** adopts different binding modes before and after irradiation, as shown in Chart 2. Before irradiation, **1** exists as a *trans* conformer and complexes two AR in a two-step process. In step 1, the first AR molecule enters one CD cavity of **1** and interacts with the linker group through the π–π and hydrogen bond interactions as described above, while the other CD cavity of **1** is free. Subsequently, the second AR molecule enters the free CD cavity of **1** to complete the 1:2 inclusion complexation. After irradiation, the *trans*-conformer of **1** partly converts to the *cis* conformer that may adopt a different two-step binding process. It is well documented that bis(CD)s with a *cis* conformation always complex guest molecules through a cooperative 1:1 binding of a single guest by two hydrophobic CD cavities located in close proximity. Therefore, we deduce that, in step I, the *cis*-conformer of **1** may also adopt a cooperative binding mode upon inclusion complexation with the first AR molecule. Due to the joint contributions from the two CD cavities and the linker group, **1** exhibits a K_1 value up to 1.18×10^5 M^{-1} after irradiation, which is 44 times higher than that value for native

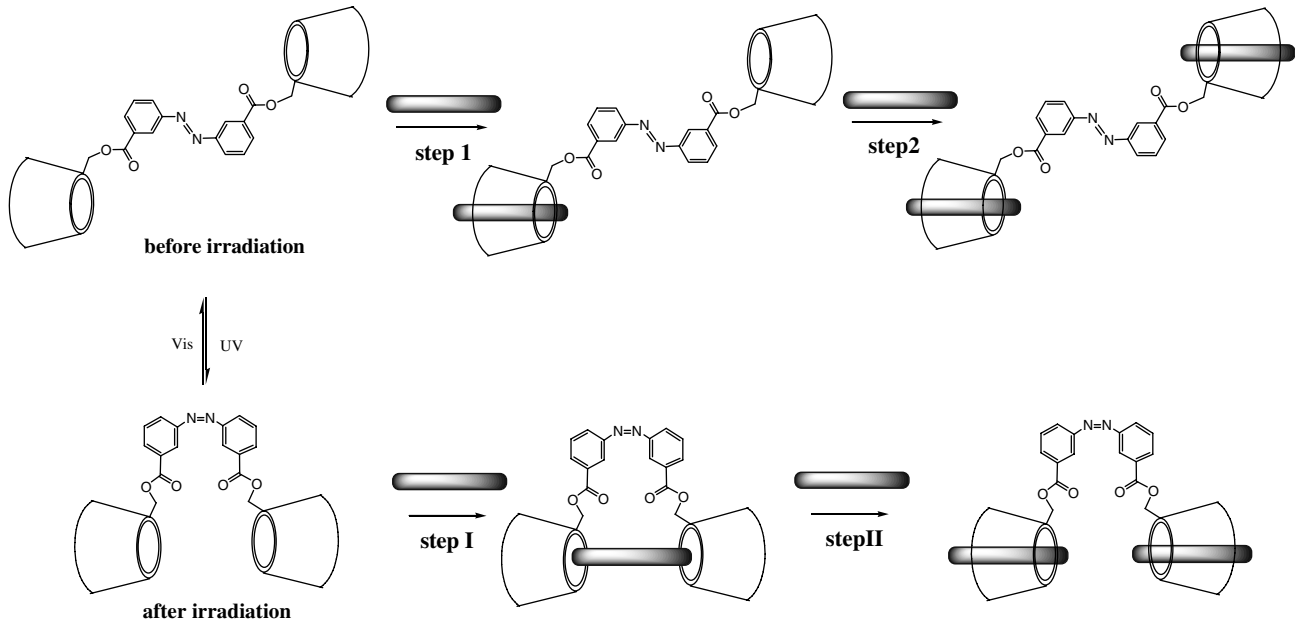

Chart 2.

β-CD. Besides the higher K_1 value, **1** also gives a higher K_2 value after irradiation ($2.94 \times 10^4\ M^{-1}$) than before irradiation ($1.69 \times 10^4\ M^{-1}$). This phenomenon should be rationalized by comparing the binding modes of **1** before and after irradiation. Before irradiation (step 2), the second AR molecule is located far away from the first one. After irradiation (step II), the first AR molecule can interact with the second AR, which is closely located, through the π–π and/or hydrogen binding interactions. These additional binding interactions further stabilize the host–guest inclusion complex and thus result in the higher K_2 value.

Conclusion

Through a comparative study of the inclusion complexation behavior of azobenzene-linked bis(β-CD) **1** before and after UV irradiation, it is demonstrated that **1** can change its conformation and thus alter its binding modes with guest molecules upon irradiation, which potentially enables **1** to act as a photo-induced molecular switch. Although this result is drawn from a rather limited variation of host–guest systems based on the functional azobenzene derivatives, this concept can potentially be extended more generally to a wide variety of bridged synthetic receptors with the azobenzene linkers and thus provide a new idea to the design and synthesis of photo-driven molecular devices.

Acknowledgments

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