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Published in:
 Chemical Communications

DOI:
[10.1039/b208692a](https://doi.org/10.1039/b208692a)

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Document Version
 Publisher's PDF, also known as Version of record

Publication date:
 2002

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Mulder, A., Jukovic, A., Lucas, L. N., van Esch, J. H., Feringa, B. L., Huskens, J., & Reinhoudt, D. N. (2002). A dithienylethene-tethered beta-cyclodextrin dimer as a photoswitchable host. *Chemical Communications*, 75(22), 2734-2735. <https://doi.org/10.1039/b208692a>

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A dithienylethene-tethered β -cyclodextrin dimer as a photoswitchable host

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Received (in Cambridge, UK) 5th September 2002, Accepted 4th October 2002

First published as an Advance Article on the web 22nd October 2002

The binding of TSPP by a dithienylethene-tethered β -cyclodextrin dimer can be altered reversibly by irradiation with light.

Recently, cyclodextrin dimers of which the binding properties can be altered by external stimuli have received considerable attention.^{1,2} Such dimers give access to controllable selectivity and, ideally, enable the release of encapsulated guest molecules at will. This has led to the synthesis of β -cyclodextrin dimers with photocleavable linkers¹ and dimers tethered *via* linkers that are able to chelate around a metal ion.² However, these dimers are either destroyed irreversibly or display marginal differences in binding properties when stimulated. Here we report our findings on a photoswitchable cyclodextrin dimer consisting of two β -cyclodextrin cavities tethered *via* their secondary sides by a dithienylethene unit (**3**). Dithienylethenes are able to undergo thermally irreversible, fatigue resistant, photochromic cyclization reactions between a relatively flexible open and a rigid closed form.³ Dithienylethenes have been used previously for the synthesis of switchable saccharide⁴ and alkali metal ion⁵ receptors. In the open form, the two thiophene rings are capable of folding into a parallel conformation, enabling the (possibly cooperative) interaction between the thiophene-appended moieties.^{4–6}

Scheme 1 depicts the synthesis of dimer **3**. An amide coupling between diarylethene 5,5'-dicarboxylic acid⁷ **1** and β -cyclodextrin amine⁸ **2** using HBTU as the coupling agent, and subsequent deprotection of the primary hydroxy groups using trifluoroacetic acid, gave dimer **3a** in 34% overall yield. The dimer was characterized by ¹H and ¹³C NMR spectroscopy and MALDI-TOF spectrometry.[†]

The absorption spectrum of dimer **3a** is shown in Fig. 1. Dimer **3a** has an absorption maximum at 265 nm in water. Upon irradiation at 313 nm, the colorless aqueous solution turns red and a visible absorption band appears in the UV–vis spectrum at 528 nm, which is attributed to the closed form **3b** of the dimer. The ratio of **3a** to **3b** in the photostationary state under irradiation with 313 nm light was determined to be 30:70 (¹H

NMR). The photostationary mixture is stable at room temperature in the dark. The absorption spectrum returned to that of **3a** after irradiation with visible light ($\lambda > 460$ nm). The inset in Fig. 1 shows the absorption at 528 nm during alternate irradiation with 313 nm light and visible light ($\lambda > 460$ nm). The switching process is completely reversible and no decomposition of the photochromic unit occurs during irradiation.

We chose meso-tetrakis(4-sulfonatophenyl)porphyrin (TSPP) as a guest molecule to study the binding properties of the open and closed form of dimer **3**. It is well known that TSPP forms a 1:1 syn-complex with β -cyclodextrin dimers, whereby the meso-phenyl rings are penetrated deeply into the β -CD cavities.⁹

The binding of TSPP by the open and closed forms of dimer **3** was studied using isothermal titration microcalorimetry.[‡] Fig. 2 shows the net heat evolved per injection *versus* the molar ratio of guest and host. The titration of TSPP to the open form of the dimer, **3a**, gave a binding curve typical of a 1:1 complex formation. This titration curve could be well fitted with a 1:1 binding model using the association constant, *K*, and the binding enthalpy, ΔH° , as independent fitting parameters (see Table 1).

In order to determine the thermodynamic binding parameters for the binding of TSPP by the closed form of the dimer, **3b**, calorimetric titrations were performed using the photostationary mixture of the dimer. The titration curve (Fig. 2, below) shows the presence of two superimposed binding curves, as witnessed by inflection points around 0.3 and 1.0. Fitting of this titration curve using the composition of the photostationary state mixture of **3** (**3a**:**3b** = 30:70) and the binding parameters, *K* and ΔH° (Table 1), of the binding of TSPP by the closed form, **3b**. The calculated heats evolved per injection for the complexation of TSPP by the open (dashed line) and closed (dotted line) forms are plotted in Fig. 2.

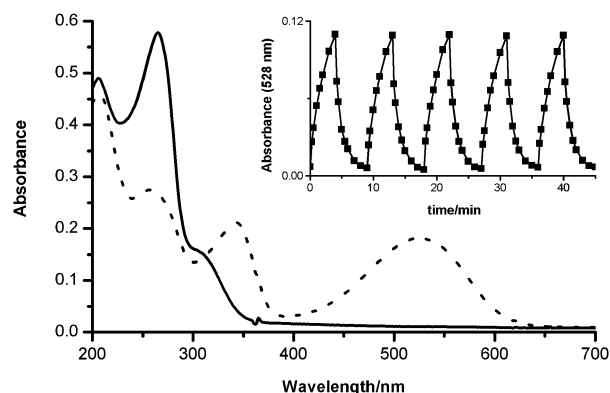
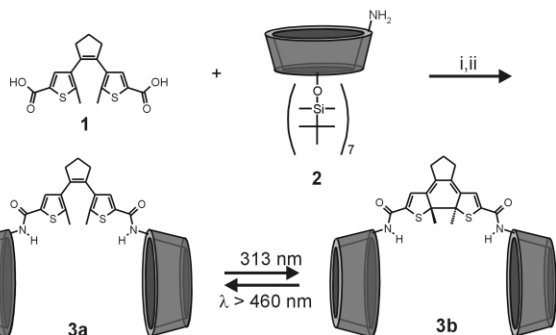


Fig. 1 Absorption spectral change of **3** in water (2.0×10^{-5} M) by photoirradiation; **3a** (—), **3** in the photostationary state under irradiation with 313 nm light (---). The inset depicts the absorption at 528 nm during alternate irradiation with 313 nm and >460 nm light.



Scheme 1 Synthesis of β -cyclodextrin dimer **3**: i, HBTU, DIPEA, DMF, 34%; ii, TFA, 99%.

The stability constant found for the binding of TSPP by the open form of the β -cyclodextrin dimer, **3a**, is a factor 35 higher compared to the binding of TSPP by the closed form, **3b**. The thermodynamic parameters show that this distinct difference in binding strength stems from the difference in the enthalpy of binding. The values determined for the binding enthalpy indicate that TSPP is tightly bound in the open form of dimer **3**, whereas the binding by the photogenerated closed form is far less effective. This tight binding of TSPP by **3a**, however, is partly counteracted by an unfavorable entropy of binding. Apparently, in the open form the conformational freedom of the dimer is restricted by the binding of TSPP, possibly the dimer is locked in the parallel conformation, which results in a negative value for the entropy of binding. The complexation of TSPP by the closed form gives a typical positive value for the entropy of binding likely as a result of the liberation of complexed water molecules.

Fig. 3 shows the photodirected release of TSPP from **3** as monitored by UV-vis spectroscopy. Irradiation at 313 nm of a mixture of TSPP and **3a** in water resulted in the liberation of TSPP, while **3a** was switched to **3b**. The absorption of complexed TSPP decreased during irradiation and simultaneously an increase in the absorption of free TSPP was observed. Conversely, uptake of TSPP was achieved by irradiation of **3b** with visible light (data not shown). The concentration range for effective photo-triggered release of guests from **3** is determined by the binding strength of the host-guest complexes of the open and closed forms.

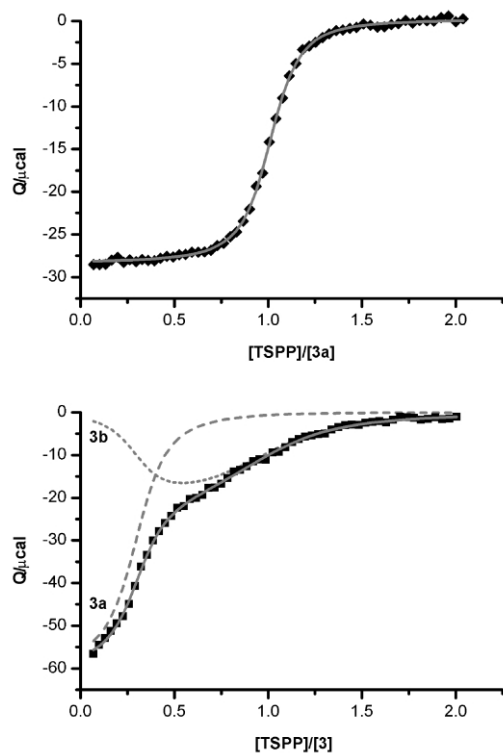


Fig. 2 Heat evolved per injection plotted against the [TSPP]/[**3**] ratio and fit (solid line) for the calorimetric titrations of TSPP to **3a** (above) and the photostationary mixture of **3** (313 nm; below) in water at 298 K. For the photostationary mixture the calculated contributions for the binding of TSPP by **3a** (---) and **3b** (---) to the heat profile are given.

Table 1 Thermodynamic parameters of the complexation of TSPP to **3a** and **3b**, as determined by microcalorimetry at 298 K

Host	K (M^{-1})	ΔG° ($kcal\ mol^{-1}$)	ΔH° ($kcal\ mol^{-1}$)	$T\Delta S^\circ$ ($kcal\ mol^{-1}$)
3a	$(3.3 \pm 0.4) \times 10^6$	-8.9 ± 0.1	-12.8 ± 0.4	-3.9 ± 0.5
3b	$(9.7 \pm 1.3) \times 10^4$	-6.8 ± 0.1	-5.3 ± 1.1	1.5 ± 1.2

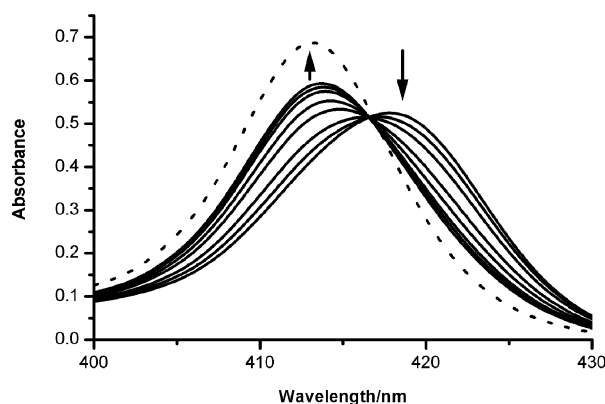


Fig. 3 Absorption spectral changes of a mixture of TSPP ($1.7 \times 10^{-5} M^{-1}$) and **3** ($1.7 \times 10^{-5} M^{-1}$) in water upon irradiation at 313 nm in time (0–25 min). The absorption spectrum of free TSPP ($1.7 \times 10^{-5} M^{-1}$) is depicted by the dotted line.

In conclusion, a new photoswitchable β -cyclodextrin dimer has been synthesized. The dimer switches upon irradiation with light and the switching process is completely reversible and fatigue resistant. In the open form, the two intramolecularly linked β -CD cavities have a certain amount of flexibility to bind TSPP tightly, while the binding is much less favorable in the photogenerated closed form. This difference in binding strength enables the controlled release of TSPP at will. Photoswitchable β -cyclodextrin dimers like **3** might find applications as photocontrollable (drug)-delivery systems, for example in photodynamic cancer therapy.^{1,10}

We gratefully acknowledge the Netherlands Organization for Scientific Research (NWO-CW) for financial support.

Notes and references

† **3a**: 1H NMR (400 MHz, 80 °C, D_2O): δ 8.19 (s, 2H), 5.61–5.53 (m, 12H), 5.20 (bs, 2H), 4.70–4.66 (m, 4H), 4.51–4.00 (m, 80H), 3.58 (m, 2H), 3.31 (m, 2H), 2.84 (m, 2H), 2.57 (s, 6H). ^{13}C NMR (400 MHz, 80 °C, D_2O): δ 166.8, 143.2, 140.3, 137.9, 136.4, 134.8, 106.5, 105.3–104.7, 85.0–84.3, 78.1, 76.6–74.8, 70.9, 63.5–63.3, 54.0, 41.8, 25.8, 17.3. MALDI-TOF MS: m/z calcd for $[M + Na]^+$ 2602.8; found 2603.2.

‡ Calorimetric measurements were performed at 298 K using a Microcal VP-ITC microcalorimeter at approx. 0.1 mM.

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