

Photo-regulated cyclization reactions of tetraazamacrocycles with azobenzene derivatives †

Wen-hao Wei, Takenori Tomohiro,* Masato Kodaka and Hiroaki Okuno

Biomolecules Department, National Institute of Bioscience and Human-Technology, 1-1 Higashi, Tsukuba, Ibaraki 305-8566, Japan. E-mail: tomohiro@nibh.go.jp

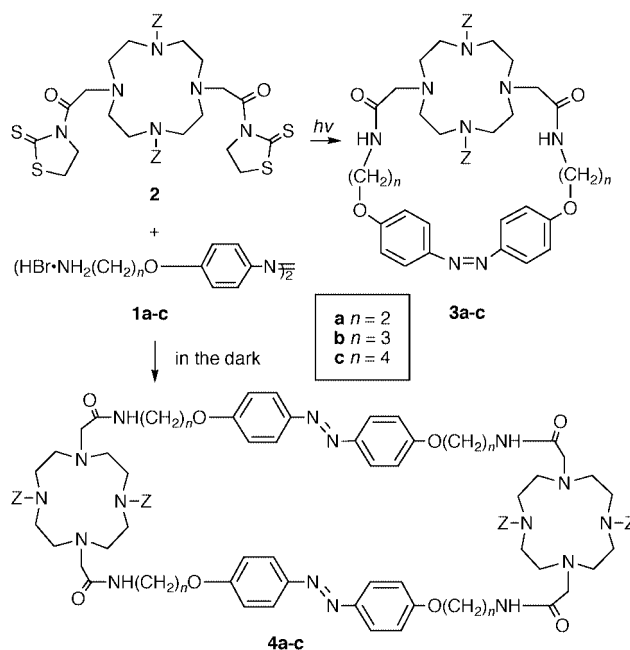
Received (in Cambridge, UK) 31st August 1999, Accepted 22nd October 1999

The cyclization reaction between **1** and **2** was carried out in high dilution and was photochemically regulated to give 1:1 (29–33 membered rings, 52–55%) and 2:2 (58–66 membered rings, 20–49%) adducts as photo-controllable compounds.

Assemblies of various controllable molecular mechanical systems have been studied in the past,^{1–5} and azobenzene derivatives have often been used as a photo-switch.^{5,6} However, preparation of cyclic compounds bearing an azobenzene moiety was difficult and the yields were usually low. Ring closure reactions have been performed by the reduction of nitrophenyl groups to azobenzene.⁶ To develop compounds capable of undergoing a reversible photochemical reaction, we synthesized two series of 1,4,7,10-tetraazacyclododecane derivatives (**3**, **4**) having an azobenzene moiety via the photochemically controlled reactions for 1:1 and 2:2 cyclization products.

The cyclization reaction between *cis*-formed azobenzene (**1**) and cyclen (**2**) derivatives was employed because the product **3** was expected to be sterically distorted in the *trans*-form, which is usually a stable form in ordinary azobenzene derivatives. The reaction was dependent on both the wavelength of light and the length of methylene chains of the linker, and it selectively proceeded to give two kinds of macrocycles; **3** as 1:1 adducts under UV irradiation (330 nm < λ < 380 nm, 52–55%) and large sized **4** in the dark (20–49%). The reactions are summarized in Scheme 1.

The typical procedures are as follows. The compound **1b** was derived from 4-nitrophenol and γ -bromopropylamine hydrobromide, Br(CH₂)₃NH₂·HBr. The activated diacid derivative **2** was obtained by a condensation reaction⁷ of 1,7-dicarboxymethyl-4,10-di(benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane⁸ with TTH in the presence of WSC or DCC. According to the high dilution method, a solution of **2** (0.190 g, 0.25 mmol) in THF (75 ml) and a solution of **1b** (0.123 g, 0.25 mmol) and Et₃N (0.05 g, 0.5 mmol) in 50% THF–H₂O (75 ml) were simultaneously added to a 90% THF–H₂O solution (350 ml) at a rate of 2 cm³ min⁻¹ with vigorous stirring at room temperature. After the addition, the solution was continuously stirred for 1 hour. The solvents were removed under reduced pressure. The residue was dissolved in CH₂Cl₂ followed by washing with 1 M K₂CO₃, dil. HCl (15 ml) and H₂O. The products were isolated by TLC. When the reaction was carried out under UV light irradiation provided by a 500 W super high-pressure Hg lamp through a color glass filter (UV-D36B, 330 nm < λ < 380 nm), a 1:1 cyclic product **3b** was predominantly isolated in 52% yield. In the dark **3b** was not detected on an alumina TLC plate, and a 2:2 cyclic product **4b** and a 1:1 “acyclic” intermediate [$R_f = 0.18$ MeCN–MeOH–Et₃N (8:1:0.1), m/z (FAB) 868.0 (M + H)⁺] were isolated in 49 and 8% yields. When the reaction was carried out under common



Scheme 1

laboratory illumination, **3b** produced only a 13% yield. Analogous observations were made in the reaction of **1a** and **2**. Compound **3a** yielded 51% under UV irradiation but produced nothing in the dark. In contrast to **1a** and **1b**, **1c** reacted with **2** in the dark to produce **3c** and **4c** at 27 and 20% yields, but under UV irradiation, **1c** reacted with **2** and yielded **3c** at 55%. UV spectra of the unclosing intermediate ($n = 3$) showed that the *trans*-form [$\lambda_{\max}(\text{MeOH})$ 359 nm (ϵ 24560 dm³ mol⁻¹ cm⁻¹)] accounted for more than 90% in the dark, and that **1a–c** form only *trans*-isomers in the dark at room temperature.⁹ Under UV irradiation through a UV-D36B filter, these compounds were completely converted to the *cis*-form within 2 minutes. Namely, the 1:1 ring-closure reaction depended on the distance between the two amino groups of **1** and did not proceed in the dark in the case of **3a**, **3b** ($n = 2, 3$) even though the high dilution condition is preferential to intramolecular cyclization. This was also suggested by the CPK model examinations. The 2:2 adducts (**4**) were not obtained under UV irradiation through a UV-D36B filter. The *cis*-isomer of the unclosing intermediate may be advantageous to the intramolecular cyclization.

All compounds of **3** and **4** were characterized on the basis of ¹H, ¹³C NMR, FAB-MS or MALDI TOF-MS, elemental analysis and UV–Vis absorption spectra. Typical data of **1b**, **3b** and **4b** are shown in Table 1. ¹H NMR spectra showed the different ring current effects of benzene rings. An especially large low-field shift was observed in the OCH₂ of *trans*-**3b** compared to its *cis* isomer. For methylene protons of the cyclen moiety, the signals of *trans*-**3b** appeared at a higher field in comparison to those of **2** (3.42 and 2.91 ppm). In addition, 3,5-protons of azobenzene appeared only as a broad signal. These

† Experimental data and structure of the reaction intermediate are available as supplementary data. For direct electronic access see <http://www.rsc.org/suppdata/p1/1999/3397>, otherwise available from BLDSC (SUPPL. NO. 57670, pp. 3) or the RSC Library. See Instructions for Authors available via the RSC web page (<http://www.rsc.org/authors>).

Table 1 Typical data of **1b**, **3b** and **4b**

| | | δ_{H} (270 MHz; CDCl_3 ; MeSi) | | | | | 3,5-H of azobenzene | λ_{max} (MeOH)/nm ^a at 25 °C | <i>m/z</i> [M + H] ⁺ | <i>R_f</i> ^b |
|-----------|--------------|---|--------------------------|---------------------------|---------------|------|------------------------|---|---------------------------------|-----------------------------------|
| | | -OCH ₂ CH ₂ CH ₂ - | | | Ring (cyclen) | | | | | |
| | | α -CH ₂ | β -CH ₂ | γ -CH ₂ | | | | | | |
| 1b | <i>trans</i> | 4.01 | 1.85 | 2.74 | — | — | 6.92 | 356 (26600) | 319.5 (100%) | — |
| | <i>cis</i> | 3.89 | 2.00 | 2.70 | — | — | 6.75 | 319, (10900), 445 (3900) | | |
| 3b | <i>trans</i> | 4.28 | 3.35 | 1.95 | 2.86 | 2.47 | 6.98 | 362 (23000) | 850.0 (100%) | 0.55 |
| | <i>cis</i> | 3.97 | 3.37 | 1.94 | 3.37 | 3.13 | 6.73 | 316 (7460), 449 (2400) | | |
| 4b | <i>trans</i> | 3.89 | 3.53 | 1.96 | 3.42 | 2.79 | 6.80 | 356 (51800) | 1669 (100%) | 0.32 |
| | <i>cis</i> | 3.89 | 3.42 | 1.92 | 3.33 | 2.77 | 6.69 | 319 (20200), 448 (6900) | | |

^a $\epsilon/\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$ values are given in parentheses. ^b Alumina TLC eluted with 80% EtOAc–MeCN.

data suggest a dynamic shape change of **3b** and rigidity in the *trans*-isomer. The UV spectra of both **3b** and **4b** showed good photo-reversibility between two geometrical isomers. The *cis*–*trans* isomerization was accelerated by light through a Y-46 filter ($\lambda > 460 \text{ nm}$) from *cis* to *trans* or through a UV-D36B filter from *trans* to *cis*.

After deprotection of the Z groups of **3** and **4**, the complexation reactions of metal ions have been preliminarily tested, and remarkable selectivity between Cu^{2+} and Ni^{2+} was observed for the *cis* and *trans* isomers.

We greatly acknowledge financial support by the Japan Science and Technology Corporation (JST).

Notes and references

‡ List of abbreviations: TTH = 1,3-thiazolidine-2-thione, WSC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

- 1 C. Mao, W. Sun, Z. Shen and N. C. Seeman, *Nature (London)*, 1999, **397**, 144.
- 2 I. Willner, *Acc. Chem. Res.*, 1997, **30**, 347.

- 3 L. Zelkovich, J. Libman and A. Shanzer, *Nature (London)*, 1995, **394**, 790; C. Canevet, J. Libman and A. Shanzer, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2657.
- 4 A. Livoreil, C. O. Dietrich-Buchecker and J.-P. Sauvage, *J. Am. Chem. Soc.*, 1994, **116**, 9399.
- 5 S. Shinkai, T. Nakaji, T. Ogawa, K. Shigematsu and O. Manabe, *J. Am. Chem. Soc.*, 1981, **103**, 111.
- 6 S. Shinkai, T. Minami, Y. Kusano and O. Manabe, *J. Am. Chem. Soc.*, 1983, **105**, 1851; S. Shinkai, T. Nakaji, Y. Nishida, T. Ogawa and O. Manabe, *J. Am. Chem. Soc.*, 1980, **102**, 5860.
- 7 V. Jacques, M. Mesbahi, V. Boskovic and J. F. Desreux, *Synthesis*, **1995**, 1022.
- 8 Z. Kovacs and A. D. Sherry, *Synthesis*, **1997**, 762; Z. Kovacs and A. D. Sherry, *J. Chem. Soc., Chem. Commun.*, **1995**, 185.
- 9 Before starting the cyclization reaction in the dark, a solution of **1** was allowed to stand in the dark for 24 h at 30 °C, or the solution was irradiated with the Hg lamp through a Y-46 filter for 2 min and allowed to stand in the dark at 30 °C for 8 h. The UV spectra showed the absorption band of the *trans*-form rapidly reached a photo-steady state under irradiation through a Y-46 filter, but the intensity was slightly increased in the dark.

Paper 9/07030C