Helix-dimer–Random-coil Thermal Switching Process of Ethynylhelicene Heptamer Highly Sensitive to Its Environment

Hiroki Sugiura[1] and Masahiko Yamaguchi*[1,2]
[1]*Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University,*
Aoba 6-3, Sendai 980-8578
[2]*Tohoku University 21st Century COE Program CRESCENDO, Sendai*

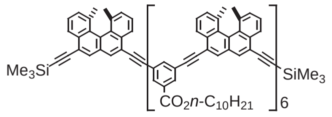
(Received July 3, 2006; CL-060744; E-mail: yama@mail.pharm.tohoku.ac.jp)

An acyclic ethynylhelicene heptamer reversibly switches its structure in solution between a helix dimer at low temperatures and random coils at high temperatures. The structural change can be repeated by alternating heating and cooling. The process monitored by CD exhibited various patterns of $\Delta\varepsilon$/time profiles depending on changes in temperature, concentration, and solvent type. This single compound provides diverse outputs upon thermal input.

The switching between two different states of a molecule is of great interest because such reversible changes have various potential applications.[1] Much attention has been focused recently on the conformational changes of synthetic helical oligomers and polymers,[2–5] which undergo helix–helix or helix–random-coil transformations as induced by temperature changes,[2] photoirradiation,[3] solvent addition,[2a,4] or complexation with chiral molecules.[5] External stimuli (input) induce structural changes, which can be detected by UV, NMR, fluorescence, optical rotation, or CD as output. If the process is reversible and reproducible, it can be used as a molecular switch. Most conventional studies have used single-stranded helical compounds, which are formed by intramolecular interactions. Switching between double helix and random coils could be attractive, because of the following reasons: 1) a larger structural change can provide a larger change in output particularly by CD provided that an optically active compound is used; 2) helix formation is a bimolecular reaction, which contains both intra- and intermolecular interactions, and therefore should be sensitive to the environment; 3) DNA and analogs undergo double-helix–random-coil transition, and such a structural change of synthetic molecules with different structures would provide a clue for understanding the functions of biological polymers.

The reversible transformation of artificial double helical polymers or oligomers, however, is rare in spite of a number of studies known to use natural DNA,[6] peptide,[7] or polysaccharide,[8] and their analogs.[9,10] Lehn examined double-helix–single-helix reversible structural changes using achiral oligopyridines by NMR, which are induced by the addition of metal cation[11] or temperature change.[12] Recently, Yashima et al. reported that oligoresorcinols fold into double helices in water, whereas random coil in methanol.[13] Luh et al. found that poly(bisnorbornene) forms DNA-like double helix, supercoil, and ladder structures.[14] Properties of the double-helix–random-coil switching of artificial optically active molecule is not well understood yet.

We previously reported that an optically active ethynylhelicene heptamer **1** (Chart 1) formed a helix dimer, most probably a double helix, and its unfolding rate to form two random coil monomers was highly dependent on an aromatic solvent at 5 µM.[15] Folding, however, was not observed at this concentration, and the helix dimer was regenerated only when the solution was concentrated to a small volume. It was considered that the folding, a bimolecular reaction, could be accelerated at higher concentrations without considerably affecting the unfolding process, a monomolecular reaction. As expected, the thermal switching of **1** between a helix dimer and two random coil monomers proceeded at 1 mM. The process being highly reproducible exhibited an extremely large change in the intensity of the Cotton effect, which is an advantage as a chiroptical switch.[16] Moreover, various patterns of $\Delta\varepsilon$/time profiles were obtained as output against thermal input using **1** depending on changes in concentration, temperature, and solvent type.



1

Chart 1.

The thermal switching of **1** was conducted in toluene at 1 mM by repeating the cycles of heating at 55 °C and cooling at 10 °C every 30 min, which was monitored by CD, $\Delta\varepsilon$ at 370 nm (Figure 1). An extremely large change in $\Delta\varepsilon$, that is, $-200/+1600$ cycles, was obtained with the heating/cooling cycle of 55/10 °C, and the $\Delta\varepsilon$/time profile was highly reproducible over six cycles. In our previous study,[15] we assigned $\Delta\varepsilon =$ approximately $+2000$ to the helical dimer structure and $\Delta\varepsilon =$ approximately -200 to the random coil structure. The folding process (blue line), being a bimolecular reaction, was highly dependent on concentration between 0.25 and 1 mM as indicated by the shape, whereas the unfolding process was not strongly affected by the concentration (red line). The $\Delta\varepsilon$ values obtained after cooling at 10 °C for 30 min also considerably differed by the change in concentration: +700 at 0.25 mM, +1250 at 0.5 mM, and +1600 at 1 mM.

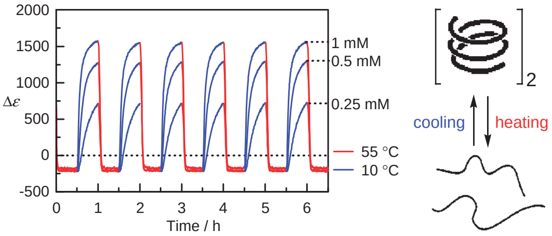


Figure 1. $\Delta\varepsilon$/time profiles of **1** in toluene at 1, 0.5, and 0.25 mM for repeating cycles of heating at 55 °C and cooling at 10 °C every 30 min.

The $\Delta\varepsilon$/time profile of **1** is also highly sensitive to temper-

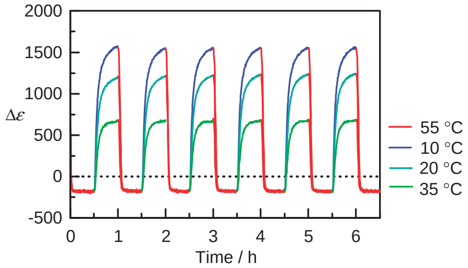


Figure 2. $\Delta\varepsilon$/time profiles of **1** in toluene (1 mM) for heating/cooling cycles 55/10, 55/20, and 55/35 °C.

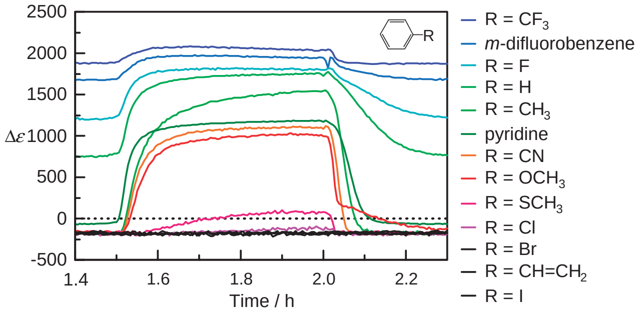


Figure 3. $\Delta\varepsilon$/time profiles of **1** for repeating cycles of 55/10 °C in various aromatic solvents.

ature (Figure 2). The heating/cooling cycles of 55/10, 55/20, and 55/35 °C in toluene provided $\Delta\varepsilon$ cycles of −200/+1600, −200/+1200, and −200/+670, respectively. The equilibrated state shifted towards the random coil by raising the temperature. The folding process as indicated by its shape was strongly affected by temperature compared with the unfolding process as observed in the concentration change (Figure 1). The heating/cooling cycles of 30/10 and 40/25 °C provided a similar profile shape with different ranges of $\Delta\varepsilon$ cycles, that is, +1500/+900 and +900/+300, respectively.[17] Note that a small change in thermal input induces a large change in the shapes of the output.

The switching of **1** in various aromatic solvents (1 mM), was dramatically affected by subtle changes of the substituent.[17] It is clearly shown, when the second switching cycles of $\Delta\varepsilon$/time profiles were compared (Figure 3). Fluorinated solvents trifluoromethylbenzene, *m*-difluorobenzene, and fluorobenzene showed high helix preferences, and thioanisole, chlorobenzene, bromobenzene, styrene, and iodobenzene showed very strong tendencies not to fold. Toluene, pyridine, benzonitrile, and anisole showed changes in similar ranges of $\Delta\varepsilon$ but have different shapes. Thus, **1** can sensitively recognize small changes in the substituents, for example, $-CH_3$, –H, $-CF_3$, and $-SCH_3$, and/or in the nature of π-electrons of the aromatic system, and provides a large change in the $\Delta\varepsilon$/time profiles. It was confirmed that helical **1** exhibits identical CD spectra in several aromatic solvents.[17] It may therefore be concluded that thermodynamic stability and transformation rate between the helix dimer and the random coils of **1** are largely different depending on its environment.

The compound **1** sensitively and reproducibly changes its structure in solution with changes in temperature, concentration, and solvent type. This is a novel switching molecule that can respond to a subtle change in its environment. It is also interesting that such an artificial oligomer exhibits a reversible thermal transformation analogous to DNA. An interesting difference, however, may be the insensitiveness of DNA to its environment, which should be essential as a biological process.

This work was financially supported by the Japan Society for the Promotion of Science (JSPS). H.S. thanks JSPS for a fellowship for young Japanese scientists.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday and also for his outstanding contribution to organic chemistry.

References and Notes

1 Reviews: a) F. M. Raymo, M. Tomasulo, *Chem. Soc. Rev.* **2005**, *34*, 327. b) B. L. Feringa, *Acc. Chem. Res.* **2001**, *34*, 504. c) A. R. Pease, J. O. Jeppesen, J. F. Stoddart, Y. Luo, C. P. Collier, J. R. Heath, *Acc. Chem. Res.* **2001**, *34*, 433.

2 Recent examples: a) T. Miyagawa, A. Furuko, K. Maeda, H. Katagiri, Y. Furusho, E. Yashima, *J. Am. Chem. Soc.* **2005**, *127*, 5018. b) A. Tanatani, A. Yokoyama, I. Azumaya, Y. Takakura, C. Mitsui, M. Shiro, M. Uchiyama, A. Muranaka, N. Kobayashi, T. Yokozawa, *J. Am. Chem. Soc.* **2005**, *127*, 8553. c) J. Tabei, M. Shiotsuki, F. Sanda, T. Masuda, *Macromolecules* **2005**, *38*, 5860.

3 Recent examples: a) H. Horiuchi, T. Fukushima, C. Zhao, T. Okutsu, H. Hiratsuka, *Chem. Lett.* **2005**, *34*, 1292. b) V. Borisenko, G. A. Woolley, *J. Photochem. Photobiol., A* **2005**, *173*, 21.

4 Recent examples: a) M. T. Stone, J. M. Fox, J. S. Moore, *Org. Lett.* **2004**, *6*, 3317. b) L. Arnt, G. N. Tew, *Macromolecules* **2004**, *37*, 1283.

5 Recent examples: a) H. Goto, H. Q. Zhang, E. Yashima, *J. Am. Chem. Soc.* **2003**, *125*, 2516. b) R. Nonokawa, M. Oobo, E. Yashima, *Macromolecules* **2003**, *36*, 6599. c) Y. Ashida, T. Sato, K. Morino, K. Maeda, Y. Okamoto, E. Yashima, *Macromolecules* **2003**, *36*, 3345.

6 C. R. Cantor, P. R. Schimmel, *Biophysical Chemistry*, W. H. Freeman and Co., San Francisco, **1980**, Vol. III.

7 a) E. Navarro, E. Fenude, B. Celda, *Biopolymers* **2002**, *64*, 198. b) S. Mondal, S. Ghosh, *J. Photochem. Photobiol., B* **2001**, *60*, 12. c) N. Abdul-Manan, J. F. Hinton, *Biochemistry* **1994**, *33*, 6773, also see reference cited.

8 a) T. Sagawa, H. Tobata, H. Ihara, *Chem. Commun.* **2004**, 2090. b) S. Ikeda, K. Nishinari, *J. Agric. Food Chem.* **2001**, *49*, 4436. c) V. Y. Grinberg, N. V. Grinberg, A. I. Usov, N. P. Shusharina, A. R. Khokhlov, K. G. de Kruif, *Biomacromol.* **2001**, *2*, 864. d) M. Ciszkowska, J. G. Osteryoung, *J. Am. Chem. Soc.* **1999**, *121*, 1617, also see reference cited.

9 Recent reviews of artificial oligonucleotides: a) C. J. Leumann, *Bioorg. Med. Chem.* **2002**, *10*, 841. b) D. Loakes, *Nucleic Acids Res.* **2001**, *29*, 2437. c) S. M. Freier, K.-H. Altmann, *Nucleic Acids Res.* **1997**, *25*, 4429.

10 Polypeptide nucleic acid: a) P. Chakraborty, U. Diederichsen, *Chem. Eur. J.* **2005**, *11*, 3207. b) A. Küsel, J. Zhang, M. A. Gil, A. C. Stückl, W. Meyer-Klaucke, F. Meyer, U. Diederichsen, *Eur. J. Inorg. Chem.* **2005**, 4317. c) D.-L. Popescu, T. J. Parolin, C. Achim, *J. Am. Chem. Soc.* **2003**, *125*, 6354.

11 M. Barboiu, G. Vaughan, N. Kyritsakas, J.-M. Lehn, *Chem.—Eur. J.* **2003**, *9*, 763.

12 a) V. Berl, I. Huc, R. G. Khoury, J.-M. Lehn, *Chem.—Eur. J.* **2001**, *7*, 2810. b) V. Berl, I. Huc, R. G. Khoury, M. J. Krische, J.-M. Lehn, *Nature* **2000**, *407*, 720.

13 H. Goto, H. Katagiri, Y. Furusho, E. Yashima, *J. Am. Chem. Soc.* **2006**, *128*, 7176.

14 H.-C. Yang, S.-Y. Lin, H.-C. Yang, C.-L. Lin, L. Tsai, S.-L. Huang, I. W.-P. Chen, C.-H. Chen, B.-Y. Jin, T.-Y. Luh, *Angew. Chem., Int. Ed.* **2006**, *45*, 726.

15 H. Sugiura, Y. Nigorikawa, Y. Saiki, K. Nakamura, M. Yamaguchi, *J. Am. Chem. Soc.* **2004**, *126*, 14858.

16 A review: a) B. L. Feringa, R. A. van Delden, N. Koumura, E. M. Geertsema, *Chem. Rev.* **2000**, *100*, 1789. Recent examples: b) H.-Z. Tang, P. D. Boyle, B. M. Novak, *J. Am. Chem. Soc.* **2005**, *127*, 2136. c) M. C. Carreño, I. García, M. Ribagorda, E. Merino, S. Pieraccini, G. P. Spada, *Org. Lett.* **2005**, *7*, 2869.

17 See supporting information, being available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) December 20, 2006; doi:10.1246/cl.2007.58