

Available online at www.sciencedirect.com



Tetrahedron Letters 46 (2005) 551-553

Tetrahedron Letters

Synthesis of a water-soluble molecular tweezer and a recognition study in an aqueous media

Hisao Nemoto,^{a,*} Tomoaki Kawano,^a Nobuo Ueji,^a Nobutaka Sakamoto,^a Takaaki Araki,^a Norikazu Miyoshi,^b Ichiro Suzuki^a and Masayuki Shibuya^a

^aDepartment of Molecular Design and Synthesis, Division of Pharmaceutical Sciences, Graduate School of The University of Tokushima, Sho-machi 1-78, Tokushima 770-8505, Japan

^bDepartment of Chemistry, Faculty of Integrated Arts and Sciences, The University of Tokushima,1-1, Minamijosanjima-cho, Tokushima 770-8502, Japan

Received 1 November 2004; revised 28 November 2004; accepted 1 December 2004

Abstract—Synthesis of a 1,10-diphenanthryl all-*trans* fused perhydrophenanthrene derivative and a recognition study in an aqueous media were carried out. A water-soluble derivative recognized certain benzene derivatives with 10^4-10^5 M^{-1} of binding constant. © 2004 Elsevier Ltd. All rights reserved.

During the last quarter of the century, recognition studies using artificially designed molecular tweezers¹ involving a pair of electron sufficient aromatic plates have been demonstrated. $^{2-21}$ In most of these publications, including our previous paper,² recognition studies between an electron-deficient aromatic compound and a pair of electron-sufficient aromatic plates were carried out in organic solvents. Kreb and Jørgensen argued that the value of 490 M^{-1} reported by them was the highest recorded value for the binding constant under those conditions.³ Until now, it was considered that these recognitions could be based on strong π - π interactions.³ Accordingly, neither molecular recognition of electronsufficient aromatic compounds as an analyte, nor recognition study in aqueous solvent²² has been reported until now. In other words, when tweezers were used as a host molecule, other typical interactions such as a hydrophointeraction between aromatics, were bic not demonstrated.

In this letter, we report the synthesis of a water-soluble molecular tweezer 1, and its recognition study in an aqueous media (Fig. 1). The cavity between two phenanthrenes of 1 is perfectly hydrophobic, and the addi-



Figure 1.

tional ionic groups are conformationally located far from this cavity.

First, we synthesized the diacid **10** from the diketone 2^2 as shown in Scheme 1. Reduction of **2** was carried out with AlH₃²³ in THF at 0 °C for 10 min, which gave a pure equatorial diol **3** in 61% yield along with a mixture of its diastereomers. The obtained purified major diastereomer **3** was treated with a mixture of acetic anhydride, pyridine, and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in dichloromethane at 0 °C for 13 h to give the diacetate **4** in 88% isolated yield. Two tolyl moieties of **4** were oxidized² with *N*-bromo succinimide (NBS), CaSO₄/H₂O, and pyrodinium chlorochromate (PCC) to obtain the dialdehyde **5** in 55% overall yield. The Honnor–Emmons–Wittig reaction of **5** was performed with diethyl benzylphosphate/NaH in THF at reflux for 8 h.

Keywords: Molecule recognition; Tweezers; Perhydronaphthacene; Water soluble; Binding constant; Hydrophobic interaction.

^{*} Corresponding author. Tel./fax: +81886337284; e-mail: nem@ph. tokushima-u.ac.jp

^{0040-4039/\$ -} see front matter @ 2004 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2004.12.002





This resulted in the production of *trans*-distyrene **6** in 82% yield. Treatment of **6** with succinic anhydride and DMAP gave the diacid **7** in 91% yield. The diacid **7** was transformed into the diester **8** with 2-(trimethylsilyl)ethanol, 1-dimethylaminopropyl-3-ethyl carbodiimide hydrochloride salt (EDC · HCl), and DMAP in 71% yield. Oxidative cyclization of two bis-styryl moieties²⁴ of **8** was carried out by a mercury lamp with iodine and propene oxide in argon-bubbled benzene for 4 h to give the bis-phenanthrene **9** in 44% yield. Finally, deprotection of 2-silylethyl moieties of **9** with tetrabutylammonium fluoride in *N*,*N*-dimethylformamide (DMF) was carried out to give the diacid **10** in 86% yield.

The water-solubility of 10 was very low even though two free carboxylic acids were present. However, we incidentally attempted our binding study in a solvent more polar than CDCl₃ for comparing the obtained results with our previous result using $11.^2$ (Fig. 2) ¹H NMR of the saturated solution of 10 in several polar solvents such as acetone- d_6 , methanol- d_4 , and acetic acid- d_4 was measured. A satisfactory signal/noise range of ¹H NMR was obtained from the solution of 10 in acetic acid- d_4 , although all the NMR peaks of 10 were too broad to determine the binding constant. Finally, clear sharp peaks were observed in $CDCl_3/acetic acid-d_4$ (v/v = 3/1). This enabled us to carry out the binding study of 10 with 3,5-dinitrobenzonitrile (12). The molar ratio of the complex of 10/12 at 25 °C was determined to be 1:1 by Job plot,²⁵ which was similar to that of 11/12





in CDCl₃.² Using the titration method,²⁵ measured by ¹H NMR at 25 °C, the binding constant of **10/12** was determined to be 58 M^{-1} , which was not in a different class from the binding constant of **11/12** (34 M^{-1} at 25 °C in CDCl₃)².

Thus, the diacid **10** was transformed to bis-guanidine salt **1** as shown in Scheme 2. Condensation of **10** with 13^{26} was carried out with EDC \cdot HCl and *N*-hydroxybenzotriazol (HOBt) to give **14** in 93% yield. Finally, deprotection of four *tert*-butyloxycarbonyl groups (Boc) quantitatively yielded **1** with trifluoroacetic acid (TFA) in chloroform.

The TFA salt 1 was sufficiently soluble in both methanol- d_4 and deuterium oxide for the measurement by ¹H and ¹³C NMR. However, as no clear sharp peaks were obtained at 25 °C in each solvent, we chose UV measurement instead.

First, the UV spectra of 1 in various concentrations in water were examined and were found to be strongly influenced by the concentration. This indicates the presence of self intermolecular interactions of 1. In such a case, the binding study between 1 and a certain guest molecule could not be clearly determined based on Lambert–Beer rule alone. Unfortunately, the UV peaks indicated self interaction even at the lowest concentration for the acceptable measurable range. Therefore, we concluded that binding study of 1 in water could not be taken into account. Fortunately, the above problem was solved when solution of 1 in water/methanol (v/v = 4/1) was prepared. Difference between the UV spectra of 1 at 5×10^{-5} M and that at 2×10^{-5} M was negligible. Thus we carried out the binding study of 1 at 5×10^{-5} M.







We could not choose 12 as an analyte as it is insoluble in water/methanol. Therefore, benzene 1,3-disulfonic acid (15) and 4-methoxyphenol (16) were chosen as guest molecules as both are sufficiently soluble in water/methanol (v/v = 4/1), and the maximum UV peaktop for these two molecules was sufficiently far away from that of 1 (256 nm).

The molar ratio of both complexes of 1/15 and 1/16 were determined to be 1:1 by Job plot.²⁵ The binding constant of 1/15 was determined to be 3.3×10^4 M⁻¹ by the titration method.²⁵ Similarly, the binding constant of 1/16 was determined to be 4.0×10^4 M⁻¹. In contrast, a UV spectrum of 18 (Fig. 3) at 5×10^{-5} M⁻¹ in a watermethanol (v/v = 4/1) was not altered significantly upon titration with 15.

Therefore, we can conclude that perhydronaphthacene moiety is essential for the recognition property of 1. Additionally, the ionic interaction between guanidine moiety and either sulfonic acid or aromatic-OH could be ignored in water/methanol. The main driving force of recognition is strongly due to the elaborately designed cavity²⁷ of 1 that fits both the width and depth of the benzene ring.

In conclusion, we have designed and synthesized a water-soluble tweezer that exceeds the previous highest record of the binding constant.³ The currently obtained binding constants, 10^4 – 10^5 M⁻¹, could be a significant quantitative index for the hydrophobic interacting force of parallelly organized aromatic plates^{27,28} in an aqueous media.

Acknowledgments

This work was in part supported by research grants from Faculty of Pharmaceutical Sciences, The University of Tokushima.

Supplementary data

IR, ¹H NMR, ¹³C NMR, HRMS data of **1**, **3**, **5–10**, **13**, **14** and **18** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.002.

References and notes

1. Chen, C.-W.; Whitelock, H. W., Jr. J. Am. Chem. Soc. 1978, 100, 4921–4922.

- Nemoto, H.; Kawano, T.; Ueji, N.; Bando, M.; Kido, M.; Suzuki, I.; Shibuya, M. Org. Lett. 2000, 2, 1015–1017.
- Kreb, F. C.; Mikkel Jørgensen, M. J. Org. Chem. 2001, 66, 6169–6173.
- Harmata, M.; Murray, T. J. Org. Chem. 1989, 54, 3761– 3763.
- 5. Harmata, M.; Barnes, C. L. Tetrahedron Lett. 1990, 31, 1825–1828.
- Harmata, M.; Barnes, C. L. J. Am. Chem. Soc. 1990, 112, 5655–5657.
- Harmata, M.; Barnes, C. L.; Karra, S. R.; Elahmad, S. J. Am. Chem. Soc. 1994, 116, 8392–8393.
- Fleischhauer, J.; Harmata, M.; Kahraman, M.; Koslowski, A.; Welch, C. J. *Tetrahedron Lett.* 1997, 38, 8655– 8658.
- Maitra, U.; D'Souza, L. J. J. Chem. Soc., Chem. Commun. 1994, 2793–2795.
- D'Souza, L. J.; Maitra, U. J. Org. Chem. 1996, 61, 9494– 9502.
- 11. Maitra, U.; D'Souza, L. J.; Kumar, P. V. Supramol. Chem. **1998**, *10*, 97–106.
- Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. J. Am. Chem. Soc. 1991, 113, 201–209.
- Blake, J. F.; Jorgensen, W. L. J. Am. Chem. Soc. 1990, 112, 7269–7278; Zimmerman, S. C.; VanZyl, C. M.; Hamilton, G. S. J. Am. Chem. Soc. 1989, 111, 1373–1381.
- 14. Zimmerman, S. C.; Zeng, Z.; Wu, W.; Reichert, D. E. J. Am. Chem. Soc. **1991**, 113, 183–196.
- 15. Zimmerman, S. C.; Wu, W.; Zeng, Z. J. Am. Chem. Soc. 1991, 113, 196–201.
- 16. Zimmerman, S. C. Top. Curr. Chem. 1993, 165, 71-102.
- 17. Zimmerman, S. C. Bioorg. Chem. Front. 1991, 2, 33-71.
- Zimmerman, S. C.; Mrksich, M.; Baloga, M. J. Am. Chem. Soc. 1989, 111, 8528–8530.
- Zimmerman, S. C.; Wu, W. J. Am. Chem. Soc. 1989, 111, 8054–8055.
- Zimmerman, S. C.; VanZyl, C. M. J. Am. Chem. Soc. 1987, 109, 7894–7896.
- Muhammad, F.; Richards, N. G. J.; Guide, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.
- 22. In this publication, synthesis and the recognition study of a water-soluble tweezer was reported. However, the driving force of binding might be mainly ionic interations. Scrimin, P.; Tecilla, P.; Tonellato, U.; Vignaga, N. J. *Chem. Soc., Chem. Commun.* **1991**, 449–451.
- 23. Brown, H. C.; Yoon, N. M. J. Am. Chem. Soc. 1966, 88, 1464–1472.
- Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. J. Org. Chem. 1991, 56, 3769–3775.
- 25. Blanda, M. T.; Horner, J. H.; Newcomb, M. J. Org. Chem. 1989, 54, 4626–4636.
- The guanidine derivative 13 was prepared from piperadine and BocN=C(NHBoc)-NH-SO₂CF₃.
- 27. β-Cyclodextrin has a cone-shaped cavity. In contrast, the tweezer **1** has a rectangular-shaped cavity that is fit for the thickness of benzene ring. We carried out the recognition study of 4-methoxyphenol with β-cyclodextrin in water/ methanol (4/1), and observed no recognition.²⁹
- Smiththrud, D. B.; Wyman, T. B.; Diederich, F. J. Am. Chem. Soc. 1991, 113, 5410–5419; Ferguson, S. B.; Sanfold, E. M.; Seward, E. M.; Diederich, F. J. Am. Chem. Soc. 1991, 113, 5420–5426.
- 29. The binding constant between β -Cyclodextrin and 4nitrophenol was reported ($6 \times 10^3 \text{ M}^{-1}$ in D₂O; no recognition in methanol). Kanda, Y.; Yamamoto, Y.; Inoue, Y.; Chûjô, R.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1987**, *62*, 2002–2008.