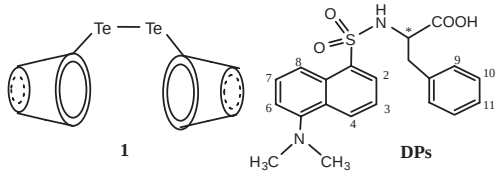
High Chiral Discrimination of 2,2′-Ditellurobis(2-deoxy-β-cyclodextrin) in Recognition of Dansyl-D/L-phenylalanine

Shu-Yan Jia, Ya-Qiong Hao, Li-Na Li, Kai Chen, Yuqing Wu,* Junqiu Liu, Lixin Wu, and Yi-hong Ding†
Key Laboratory for Supramolecular Structure and Materials of Ministry of Education, Jilin University, Changchun 130012, P. R. China
†*State Key Laboratory of Theoretical and Computational Chemistry, Institute of Theoretical Chemistry, Jilin University, Changchun 130012, P. R. China*

(Received May 30, 2005; CL-050695)

This letter demonstrates the high chiral discrimination of 2,2′-ditellurobis(2-deoxy-β-cyclodextrin) (2-TeCD, **1**) in recognizing dansyl-L-phenylalanine (DLP) and dansyl-D-phenylalanine (DDP). **1** is shown to be a very useful host in fluorescent sensing. It exhibits very good chiral enantioselectivity with a ratio of $K_L/K_D = 3.71$ in a stoichiometry of 1:1 in the chiral discrimination of DPs.



Scheme 1. Schematic structure of **1** and DPs.

The study of enantiomeric recognition of biologically important substrates has gained much attention over recent years since it can provide valuable information for understanding the mechanism of molecular recognition in biological systems, and also the opportunity for developing useful molecular devices in biochemical and pharmaceutical fields, separation processes, catalysis, and sensing.[1,2] Natural and modified cyclodextrins (CDs), as aqueous-based hosts for studying the recognition of biologic substrates, have been widely applied to chiral recognition.[3] However, studies on the recognition of chiral guests have concentrated most on native[3a,3b] and modified mono(β-cyclodextrins)[1a,3c,3d] with only a limited amount of effort hitherto devoted to the chiral recognition of β-cyclodextrin dimer[4] because of the poor matching of tether length between two cavities.[5] Liu et al. have studied the complexation inclusion of various amino acids with several cyclodextrin dimers and the enantioselectivity between 1.5–2.6 were usually found.[4b] Rekharshy et al. reported a comparative microcalarimetric and NMR spectral study on the complexation of homologous enantiomeric pairs of *N*-Cbz-D/L-aspartic and -glutamic acids by mono- and bis(trimethylammonio)-β-cyclodextrins.[5] Possessing dual hydrophobic cavities in a close vicinity via a spacer, bridged CD dimer can greatly enhance the original binding ability and molecular selectivity of parent CD through the potential cooperative interaction between two cavities and therefore be successfully employed in several areas of science and technology as an excellent enzyme mimic. The β-cyclodextrin derivative, **1**, was originally prepared as a glutathione peroxidase (GPX) mimic, and the structure was assigned unambiguously by NMR experiments, and elemental analysis.[6] The performed high substrate specificity and remarkably catalytic efficiency in catalyzing the reduction of 3-carboxy-4-nitrobenzenethiol (ArSH) as a preferential thiol substrate encourage us apply it to the enantiomeric discrimination of some biologically important substrates including phenyl ring. We, herein, report the study of **1** as a highly selective host for chiral discrimination of dansyl-modified amino acids.

To investigate the enantiomeric selectivity of **1** in chiral discrimination, dansyl-D/L-phenylalanine (DPs) are selected as the guests because of their important biological function.[1b,2] The fluorometric titration experiments were carried out with the concentration of DPs fixed at 5 μM in an methanol/water solution (v/v of methanol/water is 2%), and the concentrations of host were varied from 5 to 350 μM in aqueous solution. The emission band of the guest was excited at 340 nm with slit width of 2 nm, and the signal changes of the fluorescent emission intensity at fixed wavelength were recorded.

Figure 1 shows the fluorescent titration spectral of DDP with the addition of **1**. It is noted that the addition of a known amount of host **1** to a dilute DDP solution (5 μM) causes a significant emission enhancement, indicating that the inclusion complex is formed between **1** and DDP. The effective stability constant

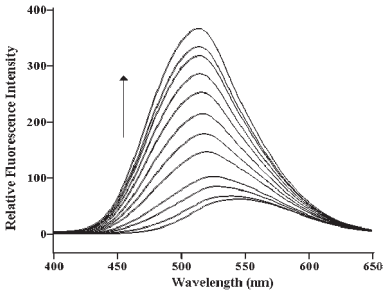


Figure 1. Fluorometric titration spectra of DDP (5 μM in methanol/water solution) with concentration changes of **1** at 20 °C.

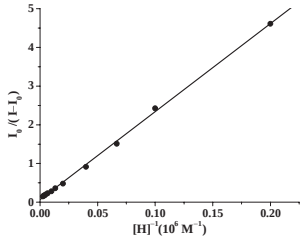


Figure 2. Estimation of binding constant for **1** with DDP in methanol/water solution at 20 °C. The plot based on the intensity changes at 519 nm with a 1:1 binding model: $I_0/(I - I_0)$ versus $[H]^{-1}$ ($R = 0.999$).

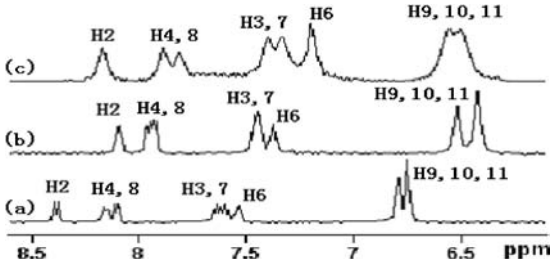


Figure 3. ^{1}H NMR shift of (a) DLP, (b) DLP/**1**, and (c) DDP/**1** in D_2O solution (with 2% CD_3OD).

(Ks) can be obtained based on the Hildebrand–Bebesi equation.[7] The linear least-squares curve fitting of the plot with $I_0/(I - I_0)$ versus $[H]^{-1}$ indicates a 1:1 binding model between the host and the guest molecules. The binding constant of DLP/**1** and DDP/**1** are 1.03×10^4 (see: Supporting Information (SI) Figures 1 and 2) and $2.77 \times 10^3\,M^{-1}$ (Figure 2), respectively, resulting a high chiral discrimination of a ratio $K_L/K_D = 3.71$. To the best of our knowledge, this ratio is rather high among the reported chiral discrimination of DPs either by proteins ($K_D/K_L = 2.64$ for α-acid glycoprotein)[2] or by native cyclodextrins ($K_D/K_L = 1.12$ and 1.46 for β- and γ-CD, respectively).[3d]

The formation of the complexes formed between DPs and **1** were characterized by ^{1}H NMR spectra (Figure 3). The ^{1}H NMR spectra of 1:1 mixture in D_2O solutions (with 2% CD_3OD) show significant upfield shifts of the guest dansyl and phenyl rings protons, indicating high shielding of the dansyl and phenyl group provided by the cyclic oligosaccharides walls upon inclusion in the CD cavity. Furthermore, broadening of DDP protons after binding with **1** is most probably the result of hindered rotation of dansyl/phenyl protons after inclusion. Additionally, inclusion differences are found between DLP and DDP in binding with **1**, which will be helpful in understanding the mechanism of enantiomeric discrimination; more pronounced upfield shifts of phenyl protons ($\Delta\delta_{9,10,11} = -0.33$ ppm) and H2 of dansyl group ($\Delta\delta_2 = -0.29$ ppm) are observed than the others ($\Delta\delta_{4,8} = -0.20$ ppm, $\Delta\delta_{3,7} = -0.16$ ppm) in DLP/**1**, indicating that the phenyl group and H2 proton in complex are more restricted in their movement as a result of deeper penetration. In contrast, the magnitude of upfield shifts in DDP/**1** illustrates different results; the upfield shifts of H2 and phenyl ring ($\Delta\delta_2 = -0.20$ and $\Delta\delta_{9,10,11} = -0.24$ ppm) are less pronounced than $\Delta\delta_{4,8} = -0.28$ and $\Delta\delta_{3,7} = -0.33$ ppm, which may correspond differently inclusion model of DDP in the bridged biscyclodextrin. Therefore, it can be concluded that the closer intermolecular contact between phenyl group and CD cavity, resulted from the geometry of phenylalanine, induces a stronger binding (larger binding constant) between DLP and **1**. Significant experimental evidences of chiral discrimination are obtained in NMR spectra between DLP/**1** and DDP/**1** complexes. The large differences in binding constants and NMR spectra between them indicate that **1** supply a more favorable microenvironment for DLP in comparison with DDP.

To get better insight of the complex between **1** and DPs, we obtained the energy-minimized structures of the complex by the molecular mechanics (MM2) method[8] (see: SI, Figure 3a). Unlike the native β-CD and γ-CD, where DPs are included in CD cavity shallowly via a strong intramolecular π–π stacking of DPs,[3d] the optimized geometry modeling in aqueous solution of the DPs/**1** demonstrates that two aromatic rings of DPs are extended in binding to the cyclodextrin cavities of the host. Meanwhile, the phenyl ring of DPs is thrown out from the one of cavities of **1**. Of note is that the chiral center of DPs was located inside of one CD cavity, which may contribute greatly to the chiral discrimination of DPs by **1**. The geometry-fit relationship between the host cavity and the guest molecule plays an important role in molecular recognition by 2-TeCD, indicating how the size and/or shape of a guest molecule fit into host cavity.

As a reference, telluro-modified mono-β-CD, 2-acetate-telluro-2-deoxy-β-CD (TeCD, **2**, its chemical structure was showed in ESI Scheme 1c, was also used to determine an enantio selectivity of DPs and a discrimination ratio of $K_L/K_D = 1.82$ was achieved (see: SI Figures 4 and 5). It has been demonstrated that 2-TeCD enhances the chiral discrimination through the cooperative binding of its dual hydrophobic cavities located in close vicinity.

To check whether the high discrimination of 2-TeCD can be extended to other chiral probes, we performed similar experiments on dansyl-D/L-tryptophan (DTs) and pyrene-D/L-phenylalanine (PPs). Basically, high discriminations were found for DTs ($K_L/K_D = 2.02$) and PPs ($K_D/K_L = 3.84$), respectively (see: SI Figures 6 and 7). However, for the discrimination of PPs, it showed an inverse enantiomeric selectivity being in favour of D-isomer in contrast to DPs and DTs. The folding in shape and the location of PPs between two CD cavities (see: SI, Figure 3b) may be the major reason for a preference binding to PDP by **1**. Further studies on revealing the recognizing mechanism of **1** to PPs are in processing currently.

In summary, **1** has demonstrated to be a highly enantiomeric selective sensor for DPs, DTs, and PPs. It was found to be an efficient recognition for enantiomeric discrimination of probe-modified amino acids and also a useful host in fluorescent sensing. Currently, studies of the enantiomeric recognition between **1** and various native and other kinds of dansyl-modified amino acids are ongoing in our laboratory. Such kinds of studies are helpful in the future potential pharmaceutical applications of 2-TeCD in the separation, protection, and delivery of chiral drugs.

Financials support from the projects of NSFC (Nos. 20003004, 20373017, and 20473028), the Major State Basic Research Development Program (G2000078102) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT0422) are gratefully acknowledged.

References

1 a) L. Pu, *Chem. Rev.*, **104**, 1687 (2004). b) W.-L. Wong, K.-H. Huang, P.-F. Teng, C.-S. Lee, and H.-L. Kwong, *Chem. Commun.*, **2004**, 384.
2 Y. Yan and M. L. Myrick, *Anal. Chem.*, **71**, 1958 (1999).
3 a) A. Ueno, T. Kuwabara, A. Nakamura, and F. Toda, *Nature*, **356**, 136 (1992). b) K. Hamasaki, H. Ikeda, A. Nakamura, A. Ueno, F. Toda, I. Suzuki, and T. Osa, *J. Am. Chem. Soc.*, **115**, 5035 (1993). c) M. Rekharsky and Y. Inoue, *J. Am. Chem. Soc.*, **122**, 4418 (2000). d) G. Hembury, M. Rekharsky, A. Nakamura, and Y. Inoue, *Org. Lett.*, **2**, 3257 (2000).
4 a) B. Zhang and R. Breslow, *J. Am. Chem. Soc.*, **115**, 9353 (1993). b) Y. Liu, C.-C. You, T. Wada, and Y. Inoue, *J. Org. Chem.*, **64**, 3630 (1999). c) Y. Liu, Y. Chen, B. Li, T. Wada, and Y. Inoue, *Chem.—Eur. J.*, **7**, 2528 (2001). d) Y. Liu, X.-Y. Li, H.-Y. Zhang, T. Wada, and Y. Inoue, *J. Org. Chem.*, **68**, 3646 (2003).
5 M. Rekharsky, H. Yamamura, M. Kawai, and Y. Inoue, *J. Am. Chem. Soc.*, **115**, 9353 (1993).
6 a) G. Luo, X. Ren, J. Liu, Y. Mu, and J. Shen, *Curr. Med. Chem.*, **10**, 1151 (2003). b) Z. Dong, J. Liu, S. Mao, X. Huang, B. Yang, X. Ren, G. Luo, and J. Shen, *J. Am. Chem. Soc.*, **126**, 16395 (2004).
7 a) H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2703 (1949). b) F. J. C. Rossotti and H. Rossotti, "The Determination of Stability Constants," McGraw-Hill book Co., Inc., New York (1961), p 276.
8 "Hyperchem 7.01 (for windows)," Hypercube, Inc. (2002).

Published on the web (Advance View) August 6, 2005; DOI 10.1246/cl.2005.1248