ORGANIC LETTERS

2006
Vol. 8, No. 17
3773−3775

Versatile and Practical Chiral Shift Reagent with Hydrogen-Bond Donor/Acceptor Sites in a Macrocyclic Cavity

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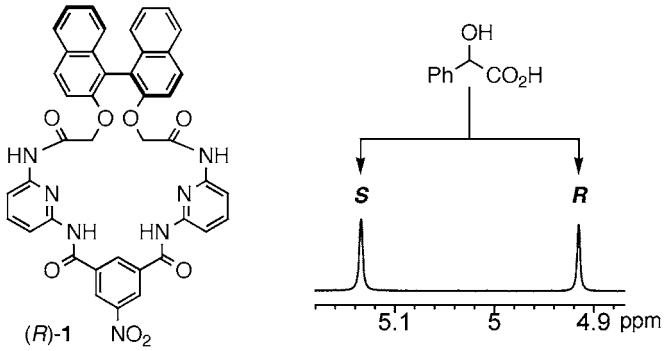
Received June 5, 2006

ABSTRACT



Bifunctional macrocycle 1 with C_2 symmetry was newly synthesized. NMR studies demonstrated that receptor 1 functions as a chiral shift reagent (solvating agent) that is highly effective for a wide range of chiral compounds having a carboxylic acid, oxazolidinone, lactone, alcohol, sulfoxide, sulfoximine, isocyanate, or epoxide functionality. Binding constants were determined to investigate the binding behavior of 1.

Because of increasing opportunities to synthesize chiral compounds, a facile and environmentally benign tool to determine their enantiomeric purities is required. Chiral shift reagents (solvating agents), using a small amount of deuterated solvent without derivatization, have great potential to achieve quick and green determination as compared with chiral HPLC or chiral derivatizing agents. Various types of chiral shift reagents such as lanthanide complexes,[1] cyclodextrins,[2] crown ethers,[3] calixarenes,[4] porphyrins,[5] and others[6] have been developed. However, few of them have been commercialized except for lanthanide complexes, which often cause signal broadening particularly at a high magnetic field because of the paramagnetic metal.

To find practical utility, a highly versatile reagent suitable for modern high-field NMR spectrometers needs to be designed carefully, which must be synthesized easily and inexpensively. In this context, we envisioned that a bifunc-

(1) (a) Fraser, R. R. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol 1. (b) Inamoto, A.; Ogasawara, K.; Omata, K.; Kabuto, K.; Sasaki, Y. *Org. Lett.* **2000**, *2*, 3543−3545.

(2) Wenzel, T. J.; Amonoo, E. P.; Shariff, S. S.; Aniagyei, S. E. *Tetrahedron: Asymmetry* **2003**, *14*, 3099−3104.

(3) (a) Wenzel, T. J.; Thurston, J. E. *J. Org. Chem.* **2000**, *65*, 1243−1248. (b) Wenzel, T. J.; Freeman, B. E.; Sek, D. C.; Zopf, J. J.; Nakamura, T.; Yongzhu, J.; Hirose, K.; Tobe, Y. *Anal. Bioanal. Chem.* **2004**, *378*, 1536−1547.

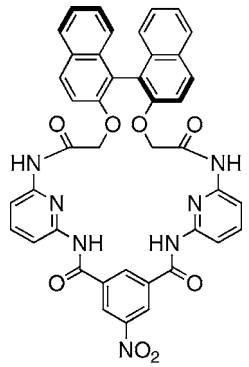
(4) (a) Yanagihara, R.; Tominaga, M.; Aoyama, Y. *J. Org. Chem.* **1994**, *59*, 6865−6867. (b) Dignam, C. F.; Richards, C. J.; Zopf, J. J.; Wacker, L. S.; Wenzel, T. J. *Org. Lett.* **2005**, *7*, 1773−1776.

(5) (a) Simonato, J.-P.; Chappellet, S.; Pécaut, J.; Baret, P.; Marchon, J.-C. *New J. Chem.* **2001**, *25*, 714−720. (b) Claeys-Bruno, M.; Toronto, D.; Pécaut, J.; Bardet, M.; Marchon, J.-C. *J. Am. Chem. Soc.* **2001**, *123*, 11067−11068. (c) Schwenninger, R.; Schlögl, J.; Maynollo, J.; Gruber, K.; Ochsenbein, P.; Bürgi, H.-B.; Konrat, R.; Kräutler, B. *Chem.−Eur. J.* **2001**, *7*, 2676−2686. (d) Ema, T.; Ouchi, N.; Doi, T.; Korenaga, T.; Sakai, T. *Org. Lett.* **2005**, *7*, 3985−3988.

(6) (a) Weisman, G. R. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol 1. (b) Chin, J.; Kim, D. C.; Kim, H.-J.; Panosyan, F. B.; Kim, K. M. *Org. Lett.* **2004**, *6*, 2591−2593. (c) Sada, K.; Tateishi, Y.; Shinkai, S. *Chem. Lett.* **2004**, *33*, 582−583. (d) Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc.* **2005**, *127*, 7996−7997. (e) Cuevas, F.; Ballester, P.; Pericàs, M. A. *Org. Lett.* **2005**, *7*, 5485−5487.

10.1021/ol0613665 CCC: $33.50
Published on Web 07/27/2006

tional host bearing both hydrogen-bond donor and acceptor sites could bind a wide range of compounds, giving sharp NMR signals. Here, we report that bifunctional macrocycle **1** functions as a chiral shift reagent that is effective for a variety of chiral compounds, such as carboxylic acid, oxazolidinone, lactone, alcohol, sulfoxide, sulfoximine, isocyanate, and epoxide compounds.

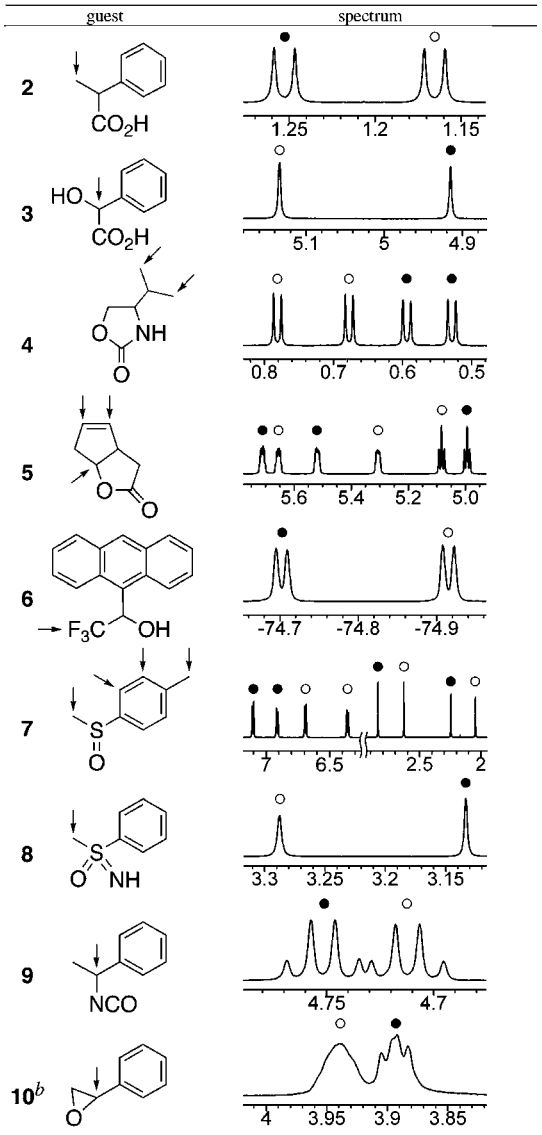


(*R*)-**1**

We selected *N*,*N*′-bis(6-acylamino-2-pyridinyl)isophthalamide as a binding unit, which has both hydrogen-bond donor and acceptor sites. Because Hamilton and co-workers had demonstrated that macrocycles having this binding unit are effective hosts for barbiturates and phosphoric acids,[7] we expected that this binding unit would also be useful for other compounds. We introduced a nitro group to strengthen the hydrogen-bond donor ability of the nearest amide groups. BINOL was selected as an inexpensive chiral unit having an anisotropic ring-current effect and connected with the binding unit as closely as possible to construct a compact macrocyclic cavity.[8] Synthesis of **1** was quite easy and practical (Supporting Information).

To investigate the chiral discrimination ability of **1**, we measured NMR spectra for 1:1 mixtures of (*R*)-**1** and chiral compounds **2**−**10** in $CDCl_3$. The results are summarized in Table 1. The resonances for the ^1H or ^{19}F nuclei, indicated by the arrows in **2**−**10**, showed chemical shift nonequivalences upon complexation with (*R*)-**1**. The spectra in Table 1 are characterized by the remarkable signal separations without line broadening. Good enantiomeric discrimination was achieved in many cases ($\Delta\Delta\delta$ > 0.15 ppm for **3**−**8**). In the case of sulfoxide **7**, all four resonances were resolved completely, one of which exhibited a paramount separation ($\Delta\Delta\delta$ = 0.55 ppm). Enantiomers of fluorine-containing alcohol **6** were discriminated by ^{19}F NMR. The highly reactive reagent, isocyanate **9**, could be analyzed without reaction or decomposition. Although epoxide **10** could not be differentiated by **1** at 22 °C, the signal for the proton attached to the asymmetric carbon was separated by decreasing the temperature to −50 °C (Table 1). We also found that in some cases even 0.05 equiv of (*R*)-**1** was enough to afford a baseline separation; e.g., $\Delta\Delta\delta$ = 0.03 ppm for the 4-methyl protons of **7**.

Table 1. Selected Regions of NMR Spectra of Racemic Guests **2**−**10** in the Presence of (*R*)-**1**[a]



[a] 600 MHz ^1H NMR of **2**−**5** and **7**−**9**; 300 MHz ^1H NMR of **10**; and 565 MHz ^{19}F NMR of **6** in the presence of (*R*)-**1** (15 mM, 1 equiv) in $CDCl_3$ at 22 °C. The resonances for the protons or fluorines indicated by the arrows are shown in the right column. The signals for the enantiomers were assigned by adding some amount of one enantiomer to the above solution. Filled and open circles represent (*R*)/(1*R*,5*S*)- and (*S*)/(1*S*,5*R*)-enantiomers, respectively. [b] At −50 °C.

To specify the binding sites in **1**, the complexation-induced shifts of the resonances for **1** were measured. A typical example is shown in Figure 1. Among the H_a−H_d protons designated in Figure 2, the H_a protons showed the largest downfield shift ($\Delta\delta$ = 1.59 ppm at 48 mM (*S*)-**7**), which strongly suggests that the two H_a atoms are hydrogen-bonded with the S=O group of (*S*)-**7**. The H_c signal also underwent a downfield shift ($\Delta\delta$ = 0.47 ppm). These trends were observed in all cases examined. In addition, the CO_2H signal of (*S*)-**2** and the NH signal of (*R*)-**4** also shifted downfield

(7) (a) Chang, S.-K.; Engen, D. V.; Fan, E.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 7640−7645. (b) Hirst, S. C.; Tecilla, P.; Geib, S. J.; Fan, E.; Hamilton, A. D. *Isr. J. Chem.* **1992**, *32*, 105−111.

(8) For a recent review on macrocycles, see: Gibson, S. E.; Lecci, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1364−1377.

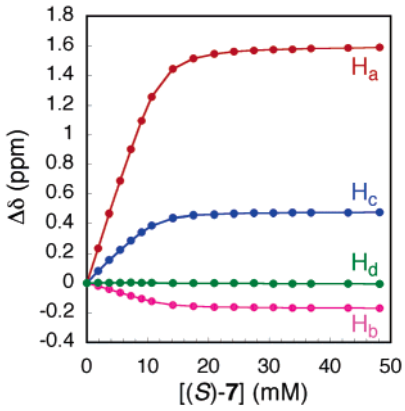


Figure 1. Plots of the complexation-induced shifts ($\Delta\delta$) for the H_a−H_d protons of (*R*)-**1** (12 mM) as a function of [(*S*)-**7**] in $CDCl_3$ at 22 °C.

by 1.9 and 1.4 ppm, respectively, when 1 equiv of (*R*)-**1** was added (Supporting Information). Therefore, it is likely that lactone **5** and sulfoxide **7** are fixed by the double hydrogen bonds and that carboxylic acids **2** and **3** and oxazolidinone **4** are fixed by the triple hydrogen bonds as represented by Figure 2, which were supported by MO calculations and the following thermodynamic analysis.

The binding constants (K_a) of (*R*)-**1** for several guests were determined by NMR titrations. Assuming 1:1 complexation, which was supported by Job plots (Supporting Information), we calculated the K_a values by means of the nonlinear least-squares method applied to the H_a signal downfield shifted upon addition of the guest. Table 2 summarizes the data. The relatively large K_a values suggest that the functional groups directed inside the cavity of **1** are preorganized well and solvated weakly, providing effective binding sites. The K_a values decrease roughly in the following order: carboxylic acid ∼ sulfoxide > sulfoximine ∼ oxazolidinone > lactone, which reflects the number of the hydrogen bonds between the host and guest (Figure 2) with two exceptions, carboxylic acid and sulfoxide. When the two-point interaction systems are compared, the more polar compound, sulfoxide **7**, is bound much more strongly than lactone **5**. In the three-point interaction systems, the more acidic compound, carboxylic acid **2**, is fixed more tightly than oxazolidinone **4** and sulfoximine

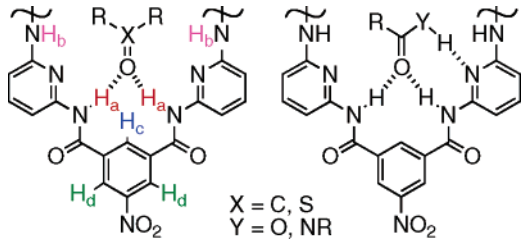


Figure 2. Double and triple hydrogen bonds between the host and guest.

Table 2. Binding Constants and Chiral Recognition Energies of (*R*)-**1** for Chiral Guests

guest	K_a (M^{-1})[a]	$\Delta\Delta G°$ (kcal mol^{-1})[b]
(*R*)-**2**	1670	−0.35
(*S*)-**2**	3050	
(*R*)-**4**	510	+0.35
(*S*)-**4**	280	
(1*R*,5*S*)-**5**	51	+0.26
(1*S*,5*R*)-**5**	33	
(*R*)-**7**	610	−0.85
(*S*)-**7**	2600	
(*R*)-**8**	170	−0.93
(*S*)-**8**	830	

[a] In $CDCl_3$ at 22 °C. The K_a values were calculated by the nonlinear least-squares method. The standard deviations were within 7%. [b] Chiral recognition energy calculated from $-RT \ln\{K_a(S)/K_a(R)\}$.

8. Table 2 also indicates that receptor **1** has a good ability to recognize the chirality of the guests.[9] For example, the K_a values for (*S*)-**7** and (*S*)-**8** are 4.3- and 4.9-fold higher, respectively, than those for (*R*)-**7** and (*R*)-**8**, the latter of which amounts to the energetic difference of −0.93 kcal mol^{-1}. It was found that in most cases the signals for the enantiomer having a higher affinity for (*R*)-**1** were shifted to a greater extent as compared with those for the antipodal enantiomer. Enantioselective binding as well as the differential ring-current effect of the binaphthyl moiety are important for the high degree of enantiomeric discrimination in NMR (Table 1).

In summary, readily accessible, bifunctional macrocycle **1** functions as a versatile chiral shift reagent that is highly effective for a wide range of chiral compounds having a carboxylic acid, oxazolidinone, lactone, alcohol, sulfoxide, sulfoximine, isocyanate, or epoxide functionality. Such a versatile organoreagent is unprecedented. The resolved signals for these chiral compounds remain sharp upon complexation with **1**, which demonstrates that hydrogen-bond-based reagent **1** is suitable for high-field NMR spectrometers. Further work is in progress to commercialize this useful compound.

Acknowledgment. We thank Prof. M. Kojima and Dr. T. Nitoda (Okayama University) for the measurement of CD and mass spectra, respectively. We are grateful to the SC-NMR Laboratory of Okayama University for the measurement of NMR spectra.

Supporting Information Available: Synthetic procedures for **1**, Job plots, determination of binding constants by ^1H NMR titration, PFG-HMBC and NOESY spectra to assign the H_a and H_b signals of **1**, copies of ^1H NMR, ^{13}C NMR, and CD spectra, and MO calculations of the complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0613665

(9) For enantioselective binding, see: (a) Famulok, M.; Jeong, K.-S.; Deslongchamps, G.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 858−860. (b) Hayashi, T.; Aya, T.; Nonoguchi, M.; Mizutani, T.; Hisaeda, Y.; Kitagawa, S.; Ogoshi, H. *Tetrahedron* **2002**, *58*, 2803−2811. (c) Oliva, A. I.; Simón, L.; Muñiz, F. M.; Sanz, F.; Ruiz-Valero, C.; Morán, J. R. *J. Org. Chem.* **2004**, *69*, 6883−6885.