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Highly Sensitive Chiral Shift Reagent Bearing Two Zinc Porphyrins

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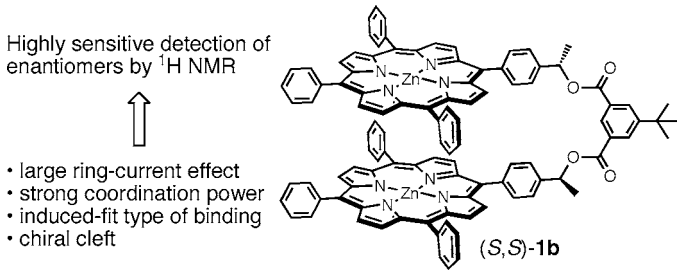
ABSTRACT



A new type of chiral receptor (*R*,*R*)- or (*S*,*S*)-1b with C_2 symmetry was synthesized. An induced-fit type of binding behavior of 1b for diamines was revealed by CD spectroscopy. NMR studies demonstrated that 1b can function as a highly sensitive chiral shift reagent for the determination of the enantiomeric purity of chiral diamines, aziridine, and isoxazoline at the microgram level.

Chiral NMR shift reagents provide a convenient way of determining the enantiomeric purity of chiral compounds without derivatization. By application of host−guest chemistry, 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. Although chiral metalloporphyrins have shown remarkable performance by taking advantage of the large ring-current effect and the strong coordination power,[5] a monomeric porphyrin is reported to be effective only for monofunctional compounds.[5b] In analyzing a chiral compound with multiple functional groups, a host molecule that can encapsulate it via multipoint interactions will perform better because of the selective formation of a 1:1 host−guest complex. Dimeric metalloporphyrins have attracted considerable attention because of their important functions such as catalysis,[7] transfer of energy or electron,[8] molecular recognition,[9−12] and chirality sensing.[13,14] The cooperative effect caused by two porphyrins plays essential roles in exerting these functions. Therefore, the concept of the cooperative effect may be useful for the design

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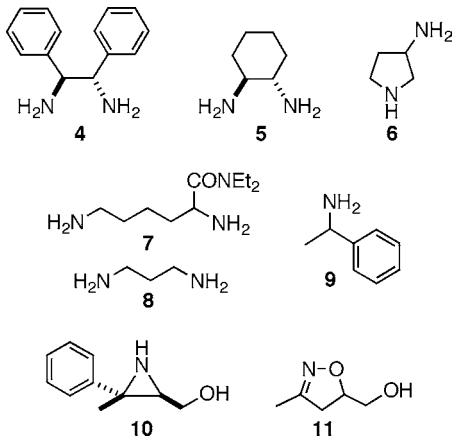
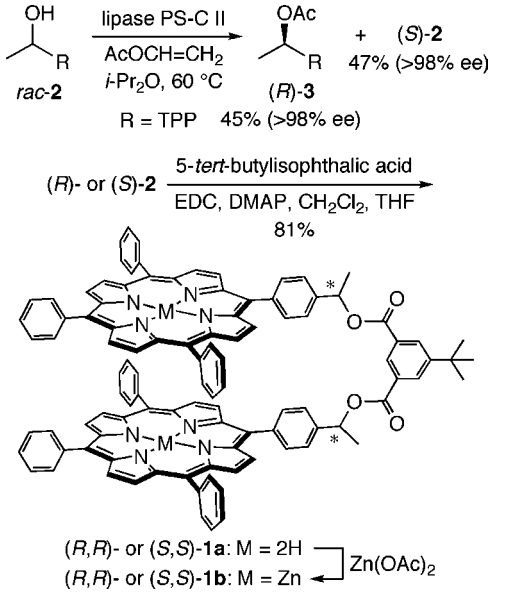
of a new chiral shift reagent; a multifunctional molecule can be encapsulated in the cleft of a diporphyrin with strong cooperative interactions. An important feature additionally required for this type of host is the appropriate conformational flexibility that enables binding of a variety of chiral molecules. Here we report that based on an induced-fit type of cooperative binding, chiral molecular tweezer (*R*,*R*)- or (*S*,*S*)-**1b** functions as a highly sensitive chiral shift reagent for bifunctional compounds.



Previously, a large amount of lipase (lipase PS, *Burkholderia cepacia* lipase immobilized on Celite, 900 mg) was used in the kinetic resolution of **2** (28 mg) because of the low reactivity of **2**.[15] To improve the reaction rate, here we used lipase PS-C II (the same enzyme immobilized on porous ceramic support) at higher reaction temperatures because it is reported to be highly thermostable.[16] As a result, the highest conversion was attained at 60 °C, where racemic alcohol **2** (135 mg) was completely resolved by lipase PS-C II (900 mg) into (*R*)-**3** (65 mg, 45%, >98% ee) and (*S*)-**2** (63 mg, 47%, >98% ee). The ester (*R*)-**3** was hydrolyzed to (*R*)-**2**, and (*R*)- or (*S*)-**2** was condensed with 5-*tert*-butylisophthalic acid to give (*R*,*R*)- or (*S*,*S*)-**1a**, which were converted to zinc complex (*R*,*R*)- or (*S*,*S*)-**1b**, respectively (Scheme 1).

The binding behavior of **1b** was first investigated by means of UV−vis and CD spectroscopy. The binding constants (K_a) determined by UV−vis titrations are listed in Table 1. The K_a values of **1b** for **4**−**8** were much larger

Scheme 1. Synthesis of Chiral Molecular Tweezer **1b**



than that of 5,10,15,20-tetraphenylporphyrinato zinc (TPP(Zn)) for **9**, which strongly suggests that the two amino groups in **4**−**8** were bound simultaneously in a cooperative manner to the two Zn atoms in **1b**. Table 1 also indicates that **1b** has only a poor ability to recognize the chirality of diamines **4**−**7**.

CD spectra are shown in Figure 1. While **1b** itself showed weak Cotton effects of opposite signs in the Soret region (Figure 1a), the binding of **4**−**8** amplified the bisignate CD, which can be attributed to the chiral exciton coupling between the two porphyrin chromophores.[10−14,17,18] On the other hand, the binding of chiral monoamine **9** to **1b** did not increase the CD amplitude at all (not shown). These results indicate that the binding of **4**−**8** fixed the conformation of the two porphyrin moieties in **1b** effectively. Interestingly, in the case of **4** and **5**, the signs of the exciton-coupled CD were governed by the chirality of the diamine (Figures 1c and 1d). On the other hand, in the case of **6** and **7**, the CD signs were governed by the chirality of **1b** itself (the CD

Table 1. Binding Constants of **1b** and TPP(Zn) for Amines[a]

host	guest	K_a (M^{-1})
(*R*,*R*)-**1b**	(*R*,*R*)-**4**	$(2.85 \pm 0.05) \times 10^4$
(*S*,*S*)-**1b**	(*R*,*R*)-**4**	$(2.27 \pm 0.05) \times 10^4$
(*R*,*R*)-**1b**	(*R*,*R*)-**5**	$(2.62 \pm 0.07) \times 10^5$
(*S*,*S*)-**1b**	(*R*,*R*)-**5**	$(3.06 \pm 0.18) \times 10^5$
(*R*,*R*)-**1b**	(*R*)-**6**	$(1.19 \pm 0.18) \times 10^7$
(*S*,*S*)-**1b**	(*R*)-**6**	$(9.16 \pm 2.21) \times 10^6$
(*R*,*R*)-**1b**	(*S*)-**7**	$(2.59 \pm 0.35) \times 10^6$
(*S*,*S*)-**1b**	(*S*)-**7**	$(1.83 \pm 0.27) \times 10^6$
(*S*,*S*)-**1b**	**8**	$(5.05 \pm 0.36) \times 10^6$
TPP(Zn)	(*R*)-**9**	$(2.96 \pm 0.01) \times 10^3$

[a] In $CHCl_3$ at 25 °C. The K_a values were calculated by the nonlinear least-squares method.

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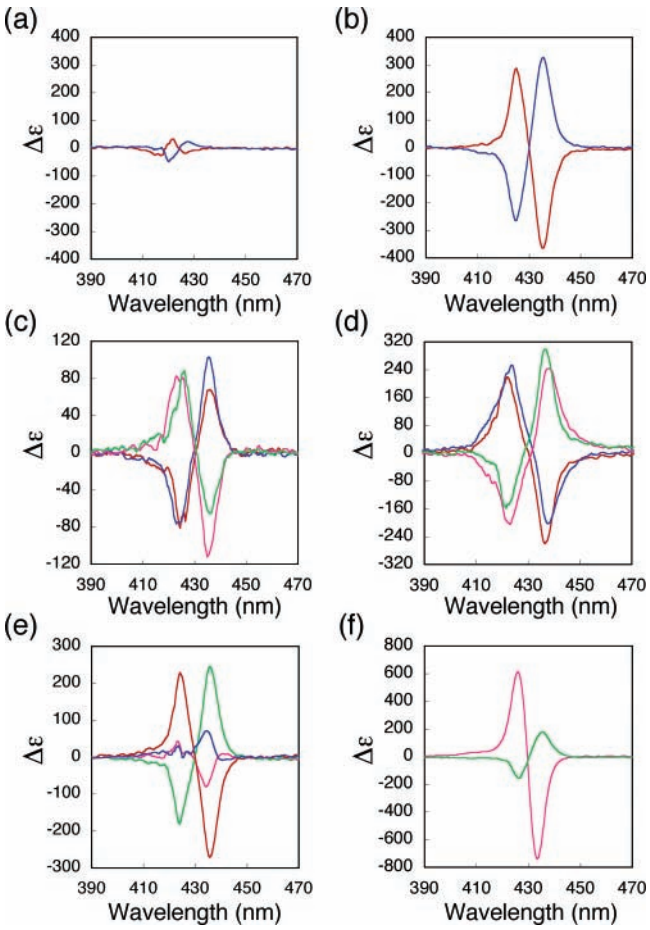

Figure 1. (a, b) CD spectra of (*R*,*R*)-**1b** (red) and (*S*,*S*)-**1b** (blue) (a) before and (b) after addition of achiral diamine **8** (2.5 equiv) in $CHCl_3$. (c−f) CD spectra of (*R*,*R*)-**1b** in the presence of (*R*)-diamine (red) and (*S*)-diamine (pink) and those of (*S*,*S*)-**1b** in the presence of (*R*)-diamine (blue) and (*S*)-diamine (green): (c) **4** (50 equiv), (d) **5** (2 equiv), (e) **6** (1.6 equiv), (f) **7** (10 equiv).

signs in Figures 1e and 1f are the same as those in Figure 1b). In all cases, CD intensity varied considerably, depending on the chirality and the structure of the diamine. These results strongly suggest that **1b** adjusted its conformation to fit the size and chirality of the diamine.

Despite the poor chiral recognition revealed by the K_a values (Table 1), the remarkable differences in CD (Figure 1) encouraged us to explore the ability of **1b** as a chiral shift reagent. The upfield regions of ^{1}H NMR spectra of the **1b**−**5** complex are shown in Figure 2. Upon binding to (*S*,*S*)-**1b** (1 mM), all the signals of **5** were greatly upfield-shifted by the ring-current effect of the porphyrin rings, which strongly supports that **5** was located between the two porphyrins. The signals in Figure 2 were assigned by tracking the signals of (*R*,*R*)- or (*S*,*S*)-**5** by adding small amounts of (*S*,*S*)-**1b** in $CDCl_3$. Importantly, enantiomeric discrimination was observed for some of the resonances of **5** as shown by arrows in Figure 2a. Thus, a very small amount (37 μg) of enantiomer of the aliphatic diamine **5** could be detected clearly.

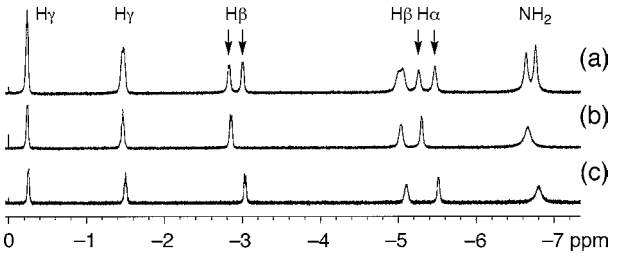

Figure 2. 600 MHz ^{1}H NMR of **5** in the presence of (*S*,*S*)-**1b** (1.06 mg, 1 mM) in $CDCl_3$ at 22 °C: (a) *rac*-**5** (74 μg, 1.0 equiv); (b) (*S*,*S*)-**5** (37 μg, 0.5 equiv); (c) (*R*,*R*)-**5** (37 μg, 0.5 equiv). The well separated signals are shown by arrows.

The signals for the protons attached to the asymmetric carbons in **4** were also resolved successfully (Figure 3a). In this case, decreasing the temperature to −40 °C slightly improved the signal separation ($\Delta\delta$ = 0.33 ppm at −40 °C, 0.29 ppm at 22 °C). Using **4** with various enantiomeric purities, we confirmed a linear correlation (r^2 = 0.995) between the theoretical and observed % ee values (Figure 3b). When 3 μg of (*R*,*R*)-**4** was added to 140 μg of (*S*,*S*)-**4** in the presence of (*R*,*R*)-**1b**, the enantiomeric purity was determined to be 94% ee by 600 MHz ^{1}H NMR measured at 22 °C, which is close to the theoretical value of 96% ee. Thus, **1b** can be used as a very sensitive chiral shift reagent to determine the enantiomeric purity of the chiral diamines at the microgram level, which is achieved by exhibiting the resonances of the diamines exclusively below 0 ppm upon tight binding. It is interesting to note that chiral discrimination is achieved between the two metal centers that are remote from the stereocenters of **1b**. We suppose that upon induced-fit binding, the remote stereocenters are used somehow to form a chiral cleft capable of causing a diastereomeric difference.

To further explore the utility of **1b** as a chiral shift reagent, chiral compounds other than diamines, aziridine **10**[19] and

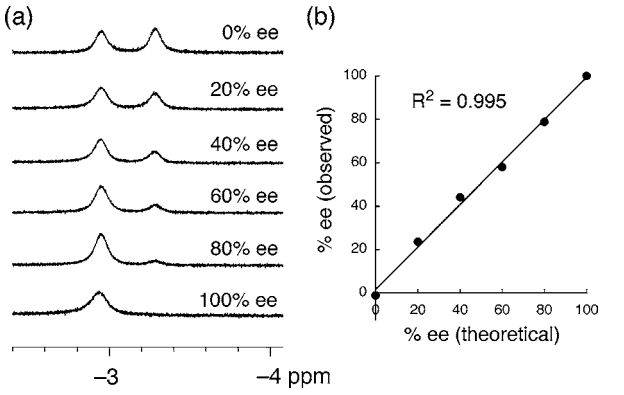

Figure 3. (a) Selected region of 300 MHz ^{1}H NMR of (*S*,*S*)-**4** (140 μg, 1 mM) with various enantiomeric purities in the presence of (*R*,*R*)-**1b** (1.07 mg, 1.0 equiv) in $CDCl_3$ at −40 °C. (b) Correlation between the theoretical and observed % ee values. The latter was calculated from the integrals in panel a.

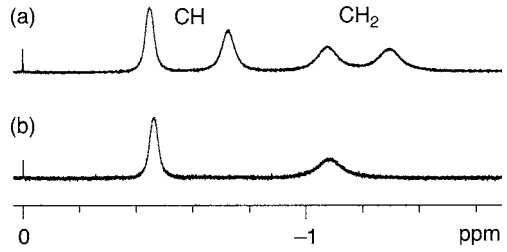

Figure 4. Selected region of 600 MHz ^{1}H NMR of **10** (107 μg) in the presence of (*S*,*S*)-**1b** (1.06 mg, 1.0 equiv, 1 mM) in $CDCl_3$ at 22 °C: (a) *rac*-**10**; (b) (2*R*,3*S*)-**10**.

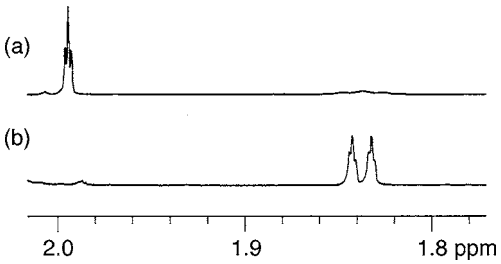

Figure 5. Selected region of 600 MHz ^{1}H NMR of **11** (75 μg) in the (a) absence and (b) presence of (*S*,*S*)-**1b** (1.06 mg, 1.0 equiv, 1 mM) in $CDCl_3$ at 22 °C.

isoxazoline **11**,[20] which are important synthetic intermediates, were next tested. Surprisingly, a high degree of enantiomeric discrimination was achieved for **10**. As shown in Figure 4, when (*S*,*S*)-**1b** (1 mg, 1 mM) was added to racemic **10**, two pairs of resonances of **10** were resolved very well at 22 °C ($\Delta\delta$ = 0.28, 0.22 ppm), which can be used to determine the % ee value with high accuracy. The methyl protons of **11** also appeared as a pair of resonances upon addition of (*S*,*S*)-**1b** to racemic **11** (Figure 5). The effective chiral discrimination of **10** and **11** may be due to the coordination of the OH group as well as the N atom.

In summary, chiral receptor **1b** functions as a highly sensitive chiral shift reagent for various bifunctional compounds; the typical concentration of **1b** is as low as 1 mM. This is due to the following unique properties of **1b**: (i) the large ring-current effect, (ii) the strong coordination power, (iii) the induced-fit type of binding, and (iv) the chiral cleft formed by imparting the chiral geometry at the remote stereocenters. The procedure is quite simple, just mixing in a small amount of $CDCl_3$, which is advantageous as compared with chiral derivatizing agents and chiral HPLC. Furthermore, a mixture of **1b** (red compound) and amine could be separated easily by silica gel column chromatography, and recovered **1b** could be used for another measurement.

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Supporting Information Available: Experimental procedures for **1**−**3**, UV−vis titrations, NMR measurements, and ^{1}H and ^{13}C NMR spectra for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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