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Published on Web 08/04/2007

Versatile and Practical Macrocyclic Reagent with Multiple Hydrogen-Bonding Sites for Chiral Discrimination in NMR

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Abstract: Bifunctional macrocycles **1**−**4** and diamide **5** were designed and synthesized. NMR studies demonstrated that, among them, receptor **1** functions as the best chiral solvating agent (shift reagent), which is effective for a wide range of chiral compounds having a carboxylic acid, oxazolidinone, carbonate, lactone, alcohol, sulfoxide, sulfoximine, sulfinamide, isocyanate, or epoxide functionality. The addition of only 5 mol % (69 μg, 0.15 mM) of **1** splits the enantiomeric signals of sulfoxide **13**. The excellent performance of **1** as a chiral solvating agent, such as versatility, signal sharpness, high splitting ability, high sensitivity, wide detection window, and synthetic accessibility, is reported. NMR studies revealed that the principal binding site of **1** is the two amide NH groups of the lower segment and that the additional binding site is the pyridyl nitrogen. The V-shaped arrangement of the two 2,6-diacylaminopyridine moieties as constructed in **1** was found to be much more effective for binding a variety of compounds than the parallel alignment of the two binding motifs as constructed in **4**. The NO_2 group in **1** enhanced not only the binding ability but also the degree of enantioselectivity. Unexpectedly, the comparisons between **1** and **3** enabled us to find the importance of the relative orientation of the binaphthyl moiety; the orthogonal disposition of the binaphthyl moiety in **1** most effectively brings about the differential ring-current effect on the chiral guest molecule bound, which leads to the high degree of chiral discrimination in NMR.

Introduction

Because of increasing opportunities for asymmetric synthesis, a quick and facile way of determining the enantiomeric purity is required. Chiral solvating agents and shift reagents essentially have good potential for this purpose because the enantiomeric purity can be determined just by adding the reagent to a chiral compound in a small amount of deuterated solvent.[1,2] In a rare but ideal case, a catalytic amount of reagent is enough for chiral discrimination in NMR. Therefore, chiral solvating agents have an advantage over chiral derivatizing agents,[3] which are used in excess for derivatization before analysis, and over chiral HPLC, which consumes much more solvent.

Various types of chiral solvating agents or shift reagents have been reported, such as lanthanide complexes,[2,4] cyclodextrins,[5] crown ethers,[6] calixarenes,[7] porphyrins,[8] and others.[1,9−11] Although a few of them are commercially available, the lanthanide complexes often cause signal broadening particularly at a high magnetic field because of the paramagnetic metal, and sometimes form precipitates via a ligand exchange, while crown ethers are effective only for amines. In many cases, a large amount of reagent is needed to give rise to signal splitting.[1,2]

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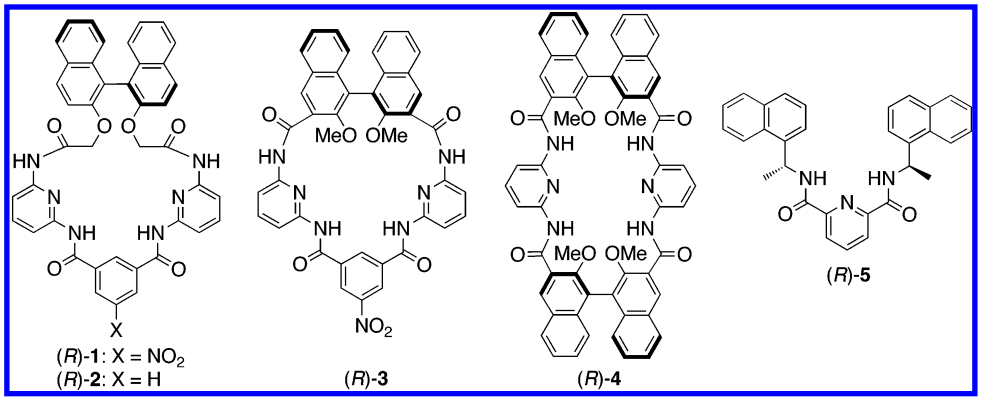
Chart 1. Chemical Structures of Reagents **1**−**5**



To find practical utility, the ideal performance needs to be pursued, such as versatility, signal sharpness, high splitting ability, high sensitivity, wide detection window, and synthetic accessibility.

In this context, we decided to search for a highly versatile and powerful reagent that is suitable for modern high-field NMR spectrometers and that can be synthesized easily and inexpensively.[9h] We employed hydrogen bonding as a driving force of binding and designed the hydrogen-bond-based reagents **1**−**5** (Chart 1). We envisioned that bifunctional hosts bearing both hydrogen-bond donor and acceptor sites could bind a wide range of compounds. Here, we report how we found the best reagent **1**, characterizing the properties of **1**−**5** in detail. Chiral macrocycle **1** is an extremely versatile reagent that is effective for a wide range of chiral compounds such as carboxylic acid, oxazolidinone, carbonate, lactone, alcohol, sulfoxide, sulfoximine, sulfinamide, isocyanate, and epoxide compounds. Furthermore, **1** showed high sensitivity; in a case, the addition of only 5 mol % (69 μg, 0.15 mM) of **1** resolved the enantiomeric signals.

Results and Discussion

Molecular Design. We selected 2,6-diacylaminopyridine as a binding unit, which has both hydrogen-bond donor and acceptor sites. Hamilton and co-workers have used this multiple binding motif for the recognition of thymine, barbiturate, and phosphoric acid.[12] The utility of this binding motif has also been demonstrated by other researchers.[13] Using the binding unit, we designed chiral macrocyclic structures **1**−**4**. We expected that the functional groups would be preorganized well and that the amide bonds in such environments would be solvated weakly, providing effective binding sites. Two 2,6-diacylaminopyridine moieties in **1**−**3** are arranged in a V-shape, while those in **4** are aligned in parallel. Diamide **5** was designed as a control to investigate the importance of the macrocyclic structures. The orientation of the two amide NH groups in **5** should be restricted by the intramolecular hydrogen bonds with the pyridyl nitrogen atom.[14] We introduced the NO_2 group into **1** and **3** to strengthen the hydrogen-bond donor ability of the nearest amide groups.[15] Two BINOL derivatives, having an anisotropic ring-current effect, were selected as chiral units and connected with the binding units as closely as possible to construct compact macrocyclic cavities.[16] The compounds **1**−**5**, showing resonances only at localized chemical shifts, have wide detection windows, which is suitable for the analysis of various compounds. The synthesis of **1**−**5** was quite easy and practical (Supporting Information).

NMR Study. To evaluate the chiral discrimination abilities of chiral hosts **1**−**5**, we measured NMR spectra for 1:1 or 2:1 mixtures of (*R*)-**1**−**5** and chiral compounds **6**−**17** in $CDCl_3$. The results are summarized in Tables 1 and S2−S5 (Supporting Information), where the resonances for the ^1H or ^{19}F nuclei indicated by the arrows in **6**−**17** are shown in the right column. Figure 1 compares the absolute values of the chemical shift nonequivalences ($\Delta\Delta\delta$) induced by complexation with **1**−**5**. Chemical shift nonequivalences were observed in many cases. Although macrocycles **1** and **2** with C_2 symmetry exerted a high degree of chiral discrimination, **1** bearing the NO_2 group exhibited a higher resolving power than **2** lacking the NO_2 group. It should also be noted that **1** and **2** were superior to **3**−**5** in the number of successful results (Figure 1). In particular, it was surprising to find that **3**, having the same binding domain (lower segment) as **1**, showed a diminished ability to separate the enantiomeric signals except for **7**, **12**, and **15**. Interestingly, the signal splitting pattern caused by complexation with **3** is opposite to that caused by comlexation with **1** in all cases; for example, upon complexation with (*R*)-**1** and (*R*)-**3**, the resonance for (*R*)-**7** appeared at the higher and lower field, respectively, in comparison with that for (*S*)-**7** (Tables 1 and S3). D_2-symmetric macrocycle **4**, bearing the two 2,6-diacylaminopyridine moieties in parallel, showed unsatisfactory results, and diamide **5** was much more ineffective. It is clear from Figure 1 and Tables 1 and S2−S5 that **1** can show the best performance. Molecular recognition modes leading to these differences will be addressed later.

The spectra in Table 1 are characterized by the remarkable signal separations achieved by **1**. Good enantiomeric discrimination is seen in many cases ($\Delta\Delta\delta$ > 0.15 ppm for **7**, **8**, **10**, **11**, **13**, and **14**), where the degrees of the chemical shift differences

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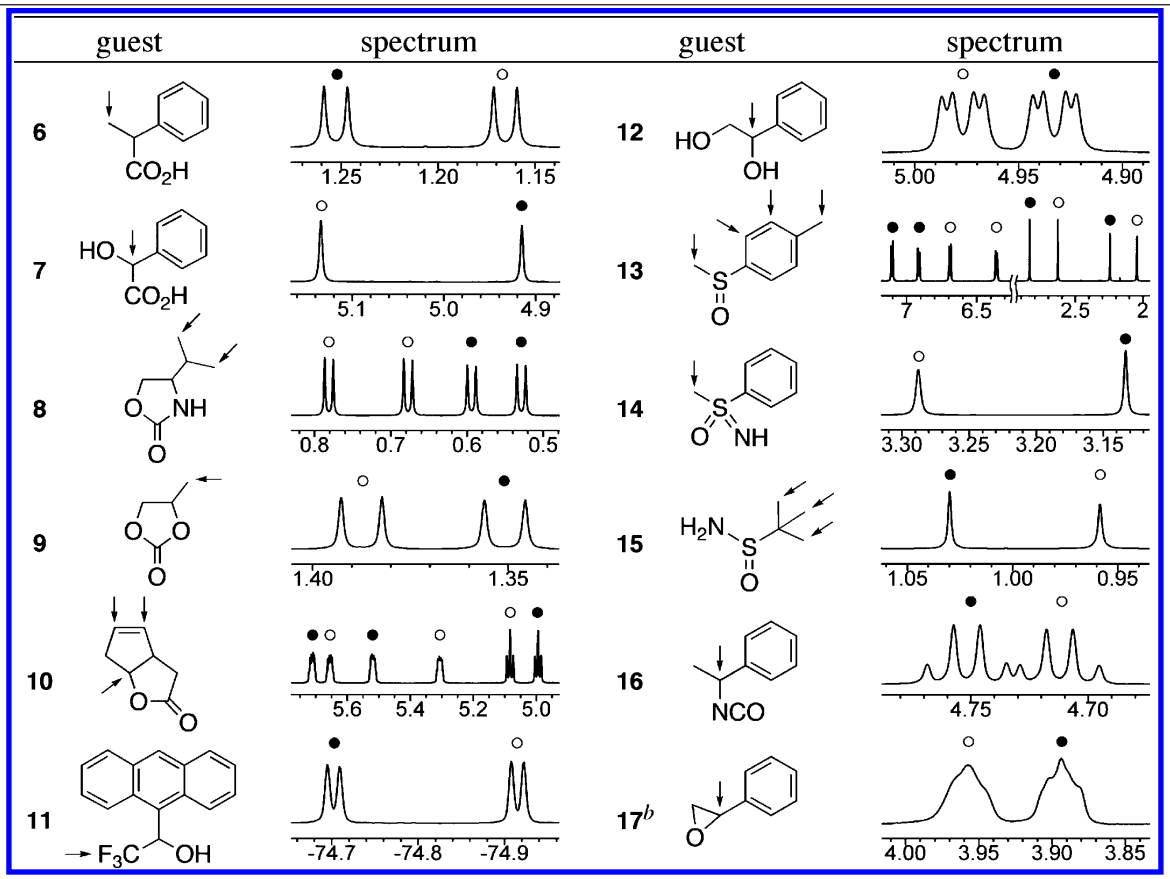
Table 1. Selected Regions of NMR Spectra of Racemic Guests **6**−**17** in the Presence of (*R*)-**1**[a]



[a] 600 MHz ^{1}H NMR of **6**−**10** and **12**−**16**; 300 MHz ^{1}H NMR of **17**; and 565 MHz ^{19}F NMR of **11** in the presence of (*R*)-**1** (15 mM, 1 equiv except for **12** and **17** (2 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, which are shown only when the signals for the enantiomers are separated well. [b] At −50 °C.

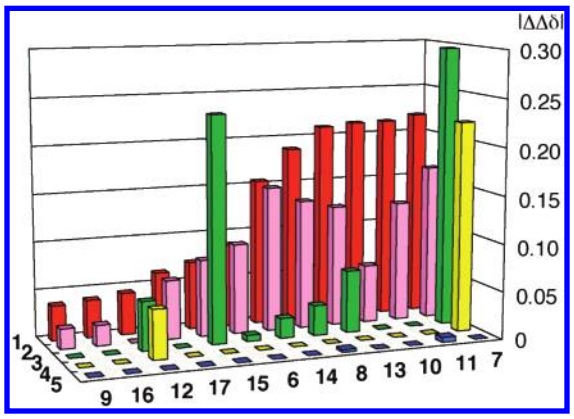


Figure 1. Comparison of the chiral discrimination abilities of **1**−**5**. The absolute values of the chemical shift nonequivalences ($\Delta\Delta\delta$) observed for **6**−**17** are indicated by the height of the vertical bars. The conditions for the measurements are shown in the footnote of Table 1. The signals used for comparison were selected arbitrarily.

are even comparable to those reported for diastereomers covalently linked by chiral derivatizing agents.[3] In the case of sulfoxide **13**, all four resonances were resolved completely, one of which exhibited a paramount separation ($\Delta\Delta\delta = 0.55$ ppm). Enantiomers of fluorine-containing alcohol **11** were discriminated by ^{19}F NMR. Although the addition of 1 equiv of (*R*)-**1** to diol **12** gave a partial separation, the addition of 2 equiv of (*R*)-**1** split the signals completely. The highly reactive reagent, isocyanate **16**, could be analyzed without reaction or decomposition. Although epoxide **17** could not be differentiated by **1** at 22 °C, the signal for the proton attached to the asymmetric carbon was split well by decreasing the temperature to −50 °C (Table 1). Thus, **1** is an extremely versatile reagent that is effective for carboxylic acid, oxazolidinone, carbonate, lactone, alcohol, sulfoxide, sulfoximine, sulfinamide, isocyanate, and epoxide compounds.

When enantiomeric purities of **13** were determined by 600 MHz ^{1}H NMR, a linear correlation ($r^2 = 0.99996$) was confirmed between the theoretical and observed % ee values (Figure 2). A similar result was obtained when the same experiment was done by 300 MHz ^{1}H NMR. Therefore, **1** can be used as a reliable reagent for the determination of the enantiomeric purity. To examine a detection limit, a mixture of (*R*)-**13** (3.5 μg) and (*S*)-**13** (1.385 mg) was analyzed by 1 equiv of (*R*)-**1** (15 mM) on a 600 MHz ^{1}H NMR spectrometer. As a result, a singlet signal for the minor enantiomer could be fairly detected, and the enantiomeric purity was determined to be 99.7% ee, which is close to the theoretical value of 99.5% ee (Figure 2).

We next investigated the effect of the amount of (*R*)-**1** on the signal separation because, in principle, less than 1 equiv of reagent can be enough for the analysis. Figure 3 clearly shows that decreasing the amount of (*R*)-**1** decreased the degree of the signal separation. Nevertheless, the addition of only 5 mol

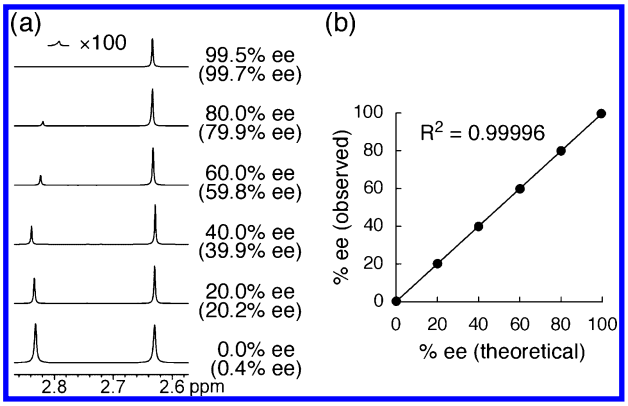


Figure 2. (a) A selected region of 600 MHz ^{1}H NMR of (*S*)-**13** (1.4 mg, 15 mM) with various enantiomeric purities in the presence of (*R*)-**1** (6.7 mg, 15 mM) in $CDCl_3$ (0.6 mL) at 22 °C. Observed % ee values calculated from the integrals are indicated in the parentheses. (b) Correlation between the theoretical and observed % ee values.

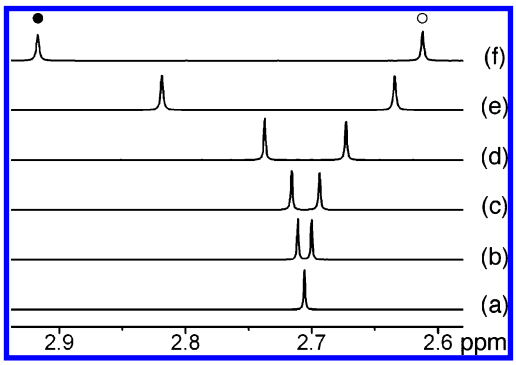
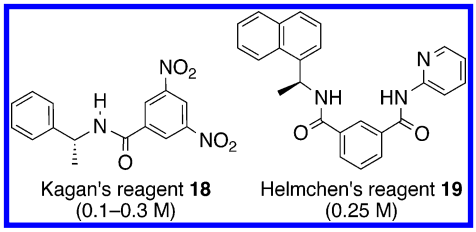


Figure 3. 600 MHz ^{1}H NMR of *rac*-**13** (277 μg, 3 mM) in the presence of (*R*)-**1** (0−15 mM) in $CDCl_3$ (0.6 mL) at 22 °C. (*R*)-**1**: (a) no addition; (b) 5 mol % (69 μg); (c) 10 mol %; (d) 30 mol %; (e) 100 mol %; (f) 500 mol %. Filled and open circles represent (*R*)- and (*S*)-enantiomers, respectively.

Chart 2. Reagents Developed by Kagan and Helmchen



% (69 μg, 0.15 mM) of (*R*)-**1** resulted in the baseline separation of the signals for the *S*-linked methyl protons of **13**. The advantage of **1** is obvious when **1** is compared with chiral derivatizing agents, which are used in excess for derivatization prior to analysis. The progress also becomes clear when the concentration (0.15 mM) of **1** is compared with that of traditional reagents; for example, Kagan and Helmchen used reagents **18** and **19** (Chart 2) at a concentration of 0.1−0.3 M to analyze sulfoxide **13** and carboxylic acid **6**, respectively.[9a,b] Most reagents recently reported are used at 1−30 mM.[4−11] Thus, **1** is a highly sensitive reagent. On the other hand, the addition of 5 equiv of **1** brought about a wider separation (Figure 3f). Clearly, Figure 3 demonstrates that an arbitrary amount of **1** can be added to determine the % ee value, which is practical and convenient.

Molecular Recognition Modes and Important Factors for Chiral Discrimination in NMR. 1. NMR Spectroscopic Study. In view of the best performance of **1** as a chiral solvating

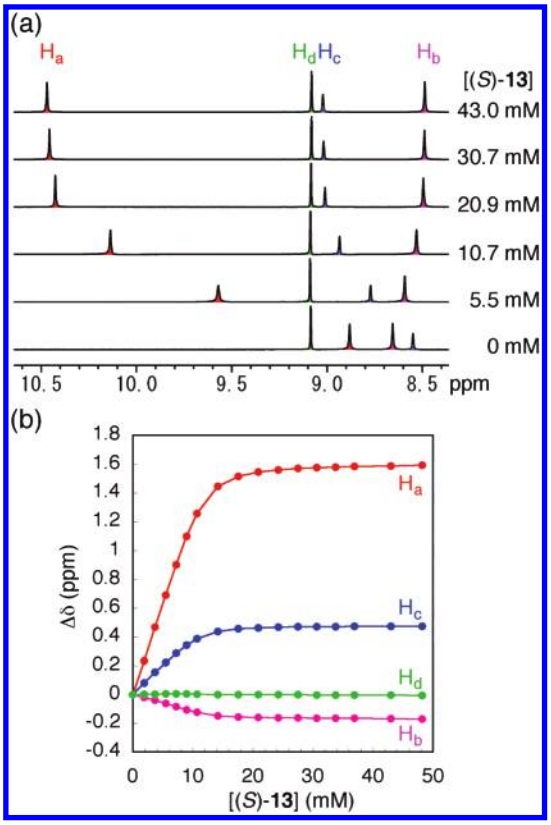


Figure 4. (a) Complexation-induced shifts ($\Delta\delta$) for the H_a–H_d protons of (*R*)-**1** (12 mM) as a function of [(*S*)-**13**] in $CDCl_3$ at 22 °C. (b) Plots of the complexation-induced shifts ($\Delta\delta$) for the H_a−H_d protons of (*R*)-**1** as a function of [(*S*)-**13**].

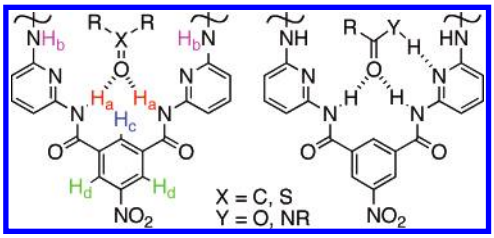


Figure 5. Double and triple hydrogen bonds between **1** and a guest molecule.

agent, we first investigated the molecular recognition behavior of **1**. 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 4. Among the H_a–H_d atoms designated in Figure 5, the H_a protons showed the largest downfield shift ($\Delta\delta$ = 1.59 ppm at 48 mM (*S*)-**13**), which strongly suggests that the two H_a atoms are hydrogen-bonded with the S═O group of (*S*)-**13**. 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*)-**6** and the NH signal of (*R*)-**8** also shifted downfield by 1.9 and 1.4 ppm, respectively, when 1 equiv of (*R*)-**1** was added. Therefore, it is likely that lactone **10** and sulfoxide **13** are fixed by the double hydrogen bonds and that carboxylic acid **6** and oxazolidinone **8** are fixed by the triple hydrogen bonds as represented by Figure 5, which were supported by the following thermodynamic analysis.[17]

2. Thermodynamic Study. The binding constants (K_a) of (*R*)-hosts for several guests were determined by NMR titrations.[18] Assuming 1:1 complexation, which was supported by

Table 2. Binding Constants and Chiral Recognition Energies between Hosts and Guests

host	guest	K_a (M^{-1})[a]	$\Delta\Delta G°$ (kcal mol^{-1})[b]
(*R*)-**1**	(*R*)-**6**	1670	−0.35
(*R*)-**1**	(*S*)-**6**	3050	
(*R*)-**1**	(*R*)-**8**	510	+0.35
(*R*)-**1**	(*S*)-**8**	280	
(*R*)-**1**	(1*R*,5*S*)-**10**	51	+0.26
(*R*)-**1**	(1*S*,5*R*)-**10**	33	
(*R*)-**1**	(*R*)-**13**	610	−0.85
(*R*)-**1**	(*S*)-**13**	2600	
(*R*)-**1**	(*R*)-**14**	170	−0.93
(*R*)-**1**	(*S*)-**14**	830	
(*R*)-**2**	(*R*)-**6**	760	−0.14
(*R*)-**2**	(*S*)-**6**	960	
(*R*)-**2**	(*R*)-**13**	140	−0.72
(*R*)-**2**	(*S*)-**13**	480	
(*R*)-**3**	(*R*)-**13**	140	+0.67
(*R*)-**3**	(*S*)-**13**	45	
(*R*)-**4**	(*R*)-**13**	—[c]	
(*R*)-**4**	(*S*)-**13**	—[c]	
(*R*)-**1**	DMSO	860	
(*R*)-**2**	DMSO	220	
(*R*)-**3**	DMSO	96	
(*R*)-**4**	DMSO	—[c]	
(*R*)-**5**	DMSO	—[c]	

[a] In $CDCl_3$ at 22 °C. The K_a values were calculated by the nonlinear least-squares method. The standard deviations were within 8%. [b] Chiral recognition energy calculated from $-RT \ln\{K_a(S)/K_a(R)\}$. [c] The K_a value was too small to determine.

Job plots (Supporting Information), we calculated the K_a values by means of the nonlinear least-squares method applied to the host's NH signal downfield shifted upon addition of the guest. Table 2 summarizes the data.

The relatively large K_a values for **1** suggest that the functional groups directed inside the cavity of **1** are preorganized well and solvated weakly, providing effective binding sites as expected. 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 5) with two exceptions, carboxylic acid and sulfoxide. When the two-point interaction systems are compared, the more polar compound, sulfoxide **13**, is bound much more strongly than lactone **10**. In the three-point interaction systems, the more acidic compound, carboxylic acid **6**, is fixed more tightly than oxazolidinone **8** and sulfoximine **14**. Table 2 also indicates that receptor **1** has a good ability to recognize the chirality of the guests.[19] For example, the K_a values for (*S*)-**13** and (*S*)-**14** are 4.3- and 4.9-fold higher, respectively, than those for (*R*)-**13** and (*R*)-**14**, the latter of which amounts to the energetic difference of −0.93 kcal mol^{-1}. The thermodynamic data for **6**, **8**, **10**, **13**, and **14** (Table 2) revealed that the signal for the enantiomer having a higher affinity for (*R*)-**1** was shifted to a greater extent than that for the antipodal enantiomer in most cases (compare Table 1 with Table S1). Exceptionally, two of the three signals for lactone **10** and the signal for the *S*-linked methyl protons of **13** did not obey this rule. Therefore, both enantioselective binding and the differential ring-current effect resulting from the binaphthyl moiety are important for chiral discrimination in NMR.

The binding constants of **1**−**5** toward achiral guest, dimethylsulfoxide (DMSO), were determined to compare the binding capacities of **1**−**5** (Table 2). The K_a values decrease in the order of **1** > **2** > **3**, and those of **4** and **5** were too small to determine. These results clearly demonstrate the importance of the double hydrogen bonds at the H_a atoms as shown in Figure 5. The larger binding constants of **1** as compared with **2** are reasonable because the H_a atoms of **1** are the better hydrogen-bond donor due to the presence of the NO_2 group. A similar effect of the NO_2 group on binding affinity has previously been reported.[15] Interestingly, the NO_2 group also contributes to the enhancement of the enantioselectivity toward **6** and **13** (Table 2), although the chiral cavities of **1** and **2** should be almost the same in size and shape. Tight binding of the guest molecule is therefore important for enantioselective binding (chiral recognition). The binding capacity of **5** was very low probably because the acidity of the amide NH protons is decreased by the intramolecular hydrogen bond with the pyridyl nitrogen.

3. Computational Calculations. To investigate the origin of the functional advantage of **1** over **3** and **4**, we performed the ab initio calculations.[20] The optimized structures are shown in Figure 6. It was first found that the size of the cavity increases in the following order: 23-membered macrocycle **3** < 25-membered macrocycle **1** < 26-membered macrocycle **4**. In addition, the V-shaped arrangement of the two 2,6-diacylaminopyridine moieties is seen in **1** and **3**, while the parallel alignment of the multiple binding motifs is seen in **4**. The distances between the hydrogen atoms of the lower amides in **1** (the H_a–H_a distance in Figure 5), **3**, and **4** are 3.65, 3.52, and 5.31 Å, respectively. Obviously, **1** and **3** have the binding site suitable for the double hydrogen bonding as illustrated in Figure 5. Thus, the V-shaped arrangement of the two 2,6-diacylaminopyridine moieties is important for interacting with a variety of functional groups.

The structures in Figure 6 also indicate that, although **1** and **3** have the same binding domain (lower segment), the latter has a smaller cavity with the two methoxy groups directed inside. This is responsible for the smaller K_a values of **3** for **13** and DMSO as compared with those of **1** for **13** and DMSO (Table 2). Furthermore, we noticed that the binaphthyl moiety in **1** is just orthogonal to the plane of the lower segment and that the relative orientation of the binaphthyl moiety in **1** differs by ca. 90° from that in **3** (Figure 6a and b). This difference can account for the results that the chiral compounds complexed

(17) The addition of 100 μL of d_4-methanol to a 1:1 mixture of (*R*)-**1** and racemic sulfoxide **13** in $CDCl_3$ (15 mM each, 600 μL) resulted in a significant decrease in $\Delta\Delta\delta$ value; the $\Delta\Delta\delta$ values for the 4-methyl and *S*-linked methyl protons of **13** were 0.039 and 0.016 ppm, respectively. The measurement of the spectrum of a 1:1 mixture of (*R*)-**1** and **13** in d_6-acetone also gave a similar result: 0.035 and 0.027 ppm. These results also support the occurrence of the hydrogen bonding between **1** and **13**.

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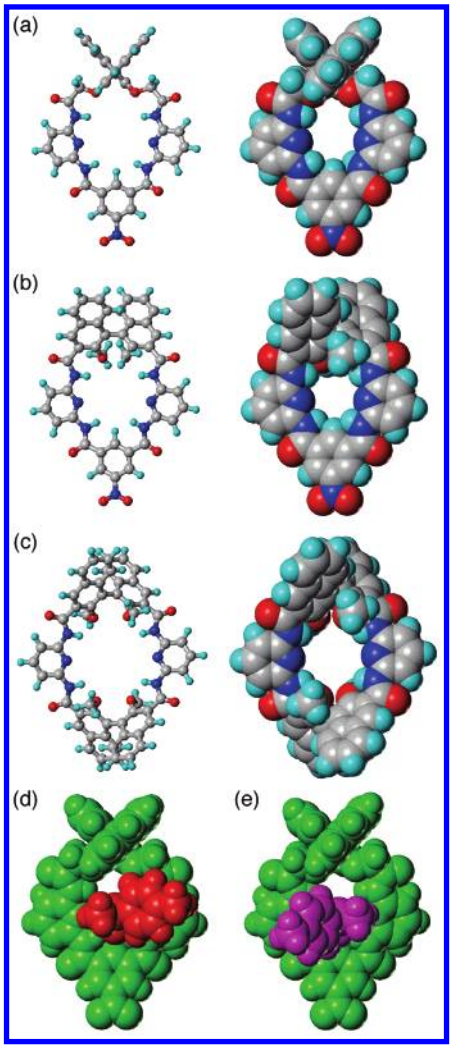

Figure 6. Optimized structures for (a) (*R*)-**1**, (b) (*R*)-**3**, (c) (*R*)-**4**, (d) (*R*)-**1**−(*S*)-**13** complex, and (e) (*R*)-**1**−(*R*)-**13** complex. In (d) and (e), (*R*)-**1** is shown in green, and (*S*)-**13** and (*R*)-**13** are shown in red and magenta, respectively. The geometries were optimized at the HF/6-31G* level using Gaussian 98W (Gaussian Inc.) and were drawn with Sybyl 6.4 (Tripos Inc.).

with (*R*)-**1** and (*R*)-**3** showed the opposite splitting patterns in all cases as described above (Tables 1 and S3) and that (*R*)-**1** and (*R*)-**3** showed the opposite enantiopreferences for **13** (Table 2). Furthermore, the functional advantage of **1** over **3** (Figure 1) can also be ascribed to this specific orientation of the binaphthyl moiety. For example, Figure 6d and e clearly represents how (*R*)-**1** discriminates the enantiomers of sulfoxide **13**; the S═O group of **13** is hydrogen bonded with the two amide NH groups of (*R*)-**1** at the distance of ca. 2.1 Å, and the tolyl group of (*S*)-**13** is located in the shielding region of the naphthyl moiety of (*R*)-**1**, while that of (*R*)-**13** is directed outside. These structures are consistent with the fact that the resonances for the tolyl group of (*S*)-**13** underwent a larger upfield shift in the presence of (*R*)-**1** (Table 1). Thus, the orthogonal disposition of the binaphthyl moiety in **1** is effective for having the differential ring-current effect on the chiral guest molecule bound, which leads to the high degree of chiral discrimination in NMR.

Conclusion

In summary, we have developed a readily accessible, bifunctional macrocycle **1** that can function as a versatile chiral solvating agent for a wide range of chiral compounds having a carboxylic acid, oxazolidinone, lactone, alcohol, sulfoxide, sulfoximine, isocyanate, or epoxide functionality. In a case, **1** showed high sensitivity; only 5 mol % (69 μg, 0.15 mM) of **1** was enough for the complete splitting of the enantiomeric signals of sulfoxide **13**. The resolved signals for these chiral compounds remained sharp upon complexation with **1**, which demonstrates that hydrogen-bond-based reagent **1** is suitable for high-field NMR spectrometers. Reagent **1** has excellent characteristics such as versatility, signal sharpness, high splitting ability, high sensitivity, wide detection window, and synthetic accessibility, and such a reagent is unprecedented. NMR studies revealed that the principal binding site of **1** is the hydrogen-bond donor site designated as H_a (Figure 5), where lactone **10** and sulfoxide **13** are fixed by the double hydrogen bonds. The third interaction takes place at the pyridyl nitrogen when carboxylic acid **6** and oxazolidinone **8** are bound. The V-shaped arrangement of the two 2,6-diacylaminopyridine moieties as constructed in **1** was found to be much more effective for binding a variety of compounds than the parallel alignment of the two binding motifs as constructed in **4**. The NO_2 group in **1** enhanced not only the binding capacity but also the degree of enantioselectivity. Unexpectedly, the comparisons between **1** and **3** enabled us to find the importance of the relative orientation of the binaphthyl moiety; the orthogonal disposition of the binaphthyl moiety with respect to the lower segment in **1** most effectively brings about the differential ring-current effect on the chiral guest molecule bound, which leads to the high degree of chiral discrimination in NMR. This useful compound **1** is now commercially available and will contribute widely to high-throughput research in asymmetric synthesis.

Acknowledgment. We thank Dr. T. Nitoda and Dr. T. Korenaga (Okayama University) for the measurement of mass spectra and the assistance of computational calculations, 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**−**5**, copies of ^{1}H and ^{13}C NMR spectra of **1**−**5**, NMR spectra of **6**−**17** in the presence and absence of **2**−**5**, Job plots, determination of binding constants by ^{1}H NMR titrations, PFG-HMBC and NOESY spectra to assign the H_a and H_b signals of **1**, and MO calculations of the hosts and the complexes together with the full list of authors of ref 20. This material is available free of charge via the Internet at http://pubs.acs.org.

JA073476S