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Unprecedented Chiral Molecular Recognition in a C_3-Symmetric Environment

Sung-Gon Kim, Kyung-Hyun Kim, Junyang Jung, Seung Koo Shin,† and Kyo Han Ahn*

Contribution from the Department of Chemistry, Center for Integrated Molecular Systems, Division of Molecular and Life Science, Pohang University of Science and Technology, San 31 Hyoja-dong, Pohang 790-784, Republic of Korea

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Abstract: The enantiomeric recognition of α-chiral primary ammonium ions has been studied with benzene-based tripodal tris(oxazoline) receptors. Contrary to the literature and our expectation, a good level of chiral discrimination is observed with one of the tripodal receptors, which provides a C_3-symmetric chiral environment on guest binding. The chiral discrimination has been found to be general in the case of α-aryl substituted guests, suggesting $\pi-\pi$ interactions as an important factor. This result raises a question with respect to the origin of the chiral discrimination since little steric or electronic difference is expected between the diastereomeric inclusion complexes. Binding studies by NMR titration and isothermal titration calorimetry show that the chiral discrimination results from the different thermodynamic stabilities between the diastereomeric complexes and that the host−guest complex formation is driven by favorable enthalpy changes with a minor negative contribution by entropy changes. The X-ray crystal structures for both of the diastereomeric inclusion complexes are resolved, which unambiguously show the binding mode and provide clues on the origin of the chiral discrimination. Bond angle analyses indicate that the minor complex experiences a larger steric strain, which is discernible when it is viewed from "three-body" interactions between the host and the guest. The guest and oxazoline phenyl rings are well stacked, indicating interplay of the $\pi-\pi$ interactions. The $\pi-\pi$ interactions are believed to stabilize host−guest complexes, thereby endowing the highly flexible receptors with a substantial enantio-discrimination.

Introduction

Molecular recognition of biologically important substrates by artificial receptors has been a subject of intense research interest for a better understanding of the recognition phenomena in nature as well as for potential applications to separation processes, catalysis, sensing, and biochemical studies.[1,2] Chiral discrimination is a particularly intriguing molecular interaction, which involves preferred recognition of an enantiomeric molecule out of its racemic mixture. Compared to achiral molecular recognition, chiral discrimination requires additional constraint, that is, an effective chiral environment. Much effort has been devoted to implementing artificial receptors with substantial differences in the steric and electronic interactions in their diastereomeric inclusion complexes. Most of the receptors developed so far provide a C_1- or C_2-symmetric environment, with notable examples such as chiral crown ether derivatives.[3,4] Attempts at the chiral recognition of α-chiral primary organoammonium ions with receptors of higher symmetry, particularly

* To whom correspondence should be addressed. Fax: +82) 54-279-3399. Tel: +82) 54-279-2105. E-mail: ahn@postech.ac.kr.

† Fourier Transform Ion Cyclotron Resonance Laboratory, Department of Chemistry, POSTECH.

(1) For a special issue on molecular recognition, see: *Chem. Rev.* **1997**, *97*, No. 5.

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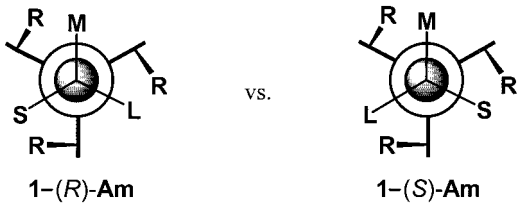


1−(*R*)-**Am** 1−(*S*)-**Am**

Figure 1. Schematic diagrams of diastereomeric inclusion complexes between tripodal receptor **1** and *a*-chiral primary ammonium ions (**Am**). R represents the oxazoline substituents and points upward.

C_3 or D_3, have been unsuccessful.[5] Consequently, it has been believed that the chiral recognition in these environments may not be feasible.[5a,5c] Herein, we wish to report the unprecedented chiral discrimination in a C_3-symmetric environment. In addition, the origin of this unusual chiral discrimination has been elucidated from different binding studies and X-ray crystallographic analyses for both of the diastereomeric inclusion complexes.

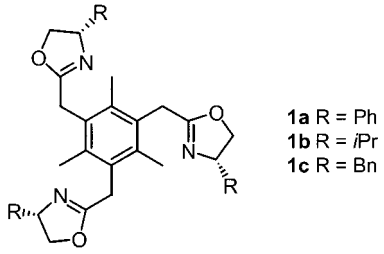
Results and Discussion

Findings. Recently, we have developed a new type of receptor system that is not only structurally simple but also is easy to derivatize, that is, benzene-based tripodal C_3-symmetric oxazoline receptors.[6a,b] It is unique in that the receptors constitute a C_3-symmetric chiral environment on binding α-chiral primary organoammonium ions. Although C_3-symmetric receptors of macrocyclic peptides and pseudopeptides have been successfully used in the chiral molecular recognition, none of these receptors provides a C_3-symmetric environment on guest binding.[7] Little steric or electronic difference is expected between the two diastereomeric host−guest complexes of C_3-symmetric receptors **1** with an α-chiral primary ammonium ion (Figure 1), as argued earlier in the case of D_3-symmetric macrocyclic receptors.[5a,5c] During our chiral recognition study with a different sector approach to overcome the symmetry problem,[8] we have unexpectedly discovered that a good level of chiral discrimination occurs by C_3-symmetric tripodal receptor **1a**[6b] toward racemic α-phenylethylammonium ion. The pronounced enantioselectivity observed by the C_3-symmetric receptor is quite contrary to the previous arguments, thus raising questions on its origin.

Table 1. Enantioselective Binding of Tris(oxazoline) **1a** toward Racemic Ammonium Salts

racemic ammonium guest	enantioselectivity[a]	extraction (%)[b]
α-phenylethylamine	71(*R*):29(*S*)	82
α-(1-naphthyl)ethylamine	70:30	99
phenylglycine methyl ester	78(*S*):22(*R*)	60
tryptophan methyl ester	67(*S*):33(*R*)	57[c]
alanine methyl ester	53(*S*):47(*R*)	41
phenylalanine methyl ester	55(*S*):45(*R*)	36

[a] Enantioselectivity of the ammonium ion extracted from excess racemic salts ($RNH_3^+Cl^-$, 10 M equiv, 0.5 M in D_2O; 0.6 M $NaPF_6$) by tris(oxazoline) **1a** (0.05 M in $CDCl_3$) at 25 °C. [b] Percentage of the ammonium salts extracted into $CDCl_3$ with respect to tris(oxazoline) **1a**. [c] Extraction at 45 °C.



When we changed the receptor to (*S*)-valinol-derived tris(oxazoline) **1b**,[6a] little enantioselectivity was observed. Other receptors such as **1c**[6b] extracted the organoammonium salt less efficiently than **1a** and showed little enantioselectivity. A further examination of different substrates has revealed that the recognition occurs usually in the case of α-aryl-substituted guests with a good level of chiral discrimination. For the racemic alanine or phenylalanine salts, however, little enantioselectivity was observed. Apparently, the $\pi-\pi$ interactions between the host and guest are playing a significant role in the chiral discrimination.[9]

The percent extraction and enantioselectivity observed are summarized in Table 1. Because the oxazoline receptors are not extracted into the aqueous salt solutions and the organoammonium salts do not partition measurably into chloroform in the absence of the receptors, the enantioselectivity of the binding process could be determined directly by measuring the enantiomeric excess of the host-extracted organoammonium salts.[3d,4e] The enantioselectivity of the binding processes can be determined, in most cases, by direct inspection of the ^{1}H NMR spectrum of the organic phase because the receptor acts as a chiral shift reagent for the guest molecules. The complexation induced large upfield shifts for guest protons, and the enantiomeric guests were differentiated by their chemical shifts.[10]

Binding Studies. In a previous study,[6b] receptor **1a** showed strong affinity toward *sec*-$BuNH_3^+$ ion ($K_a = 4.5 \times 10^6$ M^{-1}), as determined by an extraction−UV-titration method. This strong binding affinity obtained by the receptor **1a** actually led us to study chiral discrimination using its derivatives. We

(5) (a) See pages 3322−3323 in ref 2e. For unsuccessful attempts at the chiral recognition of α-chiral primary ammonium ions with C_3- or D_3-symmetric receptors, see: (b) de Jong, F.; Siegel, M. G.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1975**, 551−553. (c) Löhr, H.-G.; Vögtle, F. *Acc. Chem. Res.* **1985**, *18*, 65−72. The literature (a and c) argue that a D_3-symmetric receptor provides "three equal steric barriers" on each side of the receptor; hence, the guest binding to one of these sides makes an equivalent situation to that of a C_3-symmetric receptor. These arguments do not account for the chiral discrimination with C_3-symmetric receptors that provides a non-C_3-symmetric environment (ref 7).

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(7) The chiral discrimination with all the known C_3-symmetric receptors to date has been studied not toward ammonium ions, but toward dipeptide guests that involve amide hydrogen bonding in a "non-C_3-symmetric" environment, see: (a) Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111−5112. (b) Reference 4f. (c) Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155−163. (d) Pieters, R. J.; Diederich, F. *Chem. Commun.* **1996**, 2255−2256. (e) For a recent review on C_3-symmetric ligands used in asymmetric catalysis and chiral recognition, see: Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248−268. In this review, one C_3-symmetric tripodal receptor is mentioned but with no reference and enantioselectivity data.

(8) Unpublished results. Part of this work was taken from the Ph.D. dissertation of Kim, S.-G. Department of Chemistry, POSTECH, 2000.

(9) In the case of phenylalanine salt, the $\pi-\pi$ stacking between the host and guest phenyl rings is found to be not possible from a molecular modeling study. For $\pi-\pi$ interactions, see: Hunter, C. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1584−1586 and references therein.

(10) For the enantioselective binding experiments and the diagnostic ^{1}H NMR peaks for each of the diastereomeric inclusion complexes, see the Experimental Section.

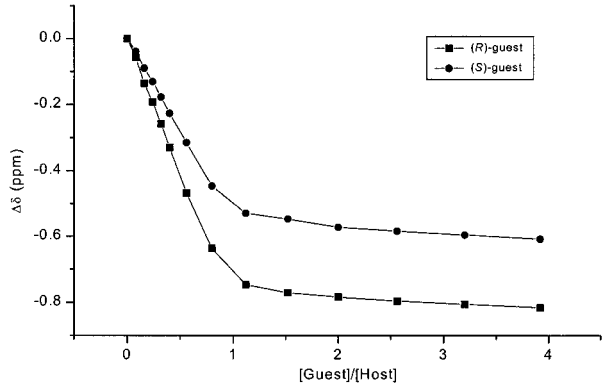

Figure 2. NMR titration curves of receptor **1a** with the perchlorate salts of (*R*)- and (*S*)-α-phenylethylamine in $CDCl_3$ at 25 °C.

obtained the binding affinity of receptor **1a** toward each enantiomeric perchlorate salt of (*R*)- and (*S*)-α-phenylethylamine [(*R*)-**Am1** and (*S*)-**Am1**] by NMR titration experiments.[11] The binding affinities are $K_a = 1.94 \times 10^4$ M^{-1} and $K_a = 6.60 \times 10^3$ M^{-1} for (*R*)-**Am1** and (*S*)-**Am1**, respectively, in $CDCl_3$ at 25 °C (Figure 2). The ratio of the K_a values (75:25) is almost identical to the selectivity ratio (71:29) determined by the extraction method.[12] Both the NMR titration experiments and the extraction method show that the inclusion complex of (*R*)-**Am1** is thermodynamically more stable than that of (*S*)-**Am1**.

To more firmly determine thermodynamic parameters for the host−guest complex formation, we carried out isothermal titration calorimetry (ITC) for the complex formation between receptor **1a** and each of the enantiomeric guests at 30 °C in CH_3CN (Figures 3 and 4).[13] The enthalpy change $\Delta H°$ is -8.97 ± 0.15 kcal mol^{-1} for the formation of the **1a**-(*R*)-**Am1** complex and -7.33 ± 0.15 kcal mol^{-1} for that of the **1a**-(*S*)-**Am1** complex. The entropy changes $\Delta S°$ are -8.9 ± 0.4 and -5.7 ± 0.1 eu for the **1a**-(*R*)-**Am1** and **1a**-(*S*)-**Am1** complexes, respectively. Thus, the formation of the major complex is preferred over the minor one by a more favorable enthalpy change with a minor negative contribution of entropy change. The overall binding enthalpies are originated from the charged tripodal hydrogen bonding, the cation−π interactions between the hydrogen-bonded ammonium ion and the benzene frame,[14] and $\pi-\pi$ interactions between the guest and host phenyl groups.

X-ray Crystal Structures. To obtain insights into the binding mode, we made an effort to obtain single crystals of both diastereomeric oxazoline **1a**-**Am1** complexes. We could resolve both structures of the diastereomeric inclusion complexes, which is a rare case in the chiral recognition area.[15] The major diastereomeric salt, (*R*)-**Am1** complex, consists of two slightly different structures, **1a**-(*R*)-**Am1**(I) and **1a**-(*R*)-**Am1**(II), in a unit cell.[16] The X-ray structure unambiguously shows that the

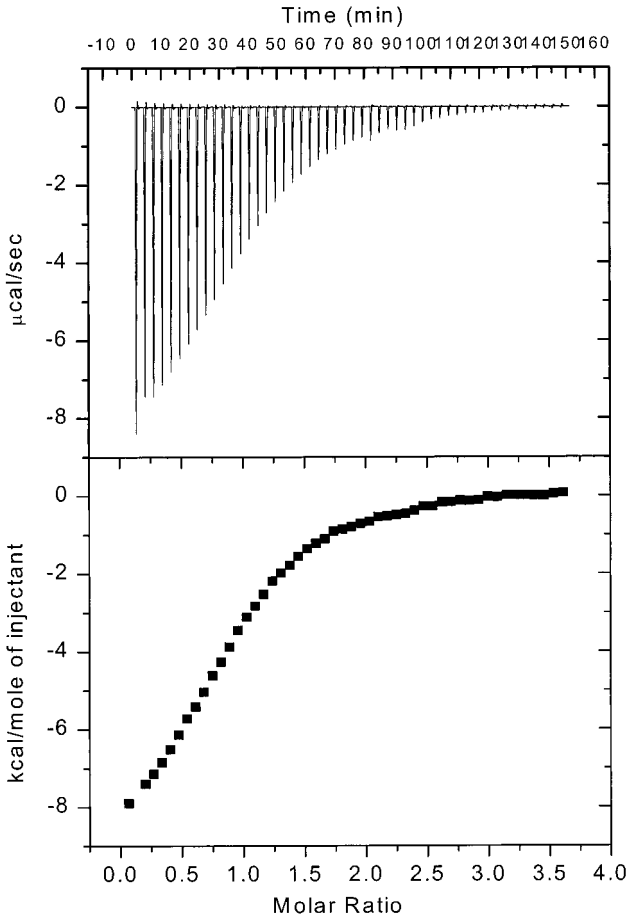

Figure 3. ITC titration data of receptor **1a** with the perchlorate salt of (*R*)-α-phenylethylamine in CH_3CN at 30 °C.

oxazoline receptor binds the ammonium ion through tripod hydrogen bonds. The phenyl substituents of the oxazoline rings form a "hydrophobic wall" that encompasses the guest in a propeller-shaped, C_3-symmetric, chiral environment. A side view of the crystal structure of the complex **1a**-(*R*)-**Am1**(I) is shown in Figure 5. The N_R-N_A distances range from 2.98 to 3.20 Å, which are close to the average hydrogen-bonded N−H−N distance, 2.98 ± 0.16 Å.[17] Values of the $N_R-N_A-N_R$ angles are within 106−123°. The complex **1a**-(*R*)-**Am1**(II) shows the N_R-N_A distances and the $N_R-N_A-N_R$ angles in the range of 2.95−3.10 Å and 102−125°, respectively. The counteranion, PF_6^-, resides outside the inclusion complex with no apparent interaction. In all cases, the guest and oxazoline phenyl rings are well stacked, suggesting a certain degree of $\pi-\pi$ interactions. The interplanar distances between the benzene carbons are in the range of 3.4−4.3 Å [**1a**-(*R*)-**Am1**(I)], 3.6−5.3 Å

(11) Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987.
(12) Job's plot indicated 1:1 complex formation. The ratio of the binding affinities was similar in a different solvent system such as $CD_3OD-CDCl_3$: $K_a = 137$ M^{-1} for (*R*)-**Am1**; $K_a = 50$ M^{-1} for (*S*)-**Am1**.
(13) Consistent thermodynamic parameters could be obtained in CH_3CN, in which K_a values of $\sim 10^4$ M^{-1} were observed. For the optimal range of K_a values that give consistent ITC data, see: Christensen, J. J.; Wrathall, D. P.; Oscarson, J. O.; Izatt, R. M. *Anal. Chem.* **1968**, *40*, 1713−1717.
(14) Oh, K. S.; Lee, C.-W.; Choi, H. S.; Lee, S. J.; Kim, K. S. *Org. Lett.* **2000**, *2*, 2679−2681 and references therein.
(15) As far as we know, three examples are known wherein the X-ray crystal structures of both diastereomeric inclusion complexes of α-chiral organoammonium ions are resolved: refs 4c and i. Davidson, R. B.; Dalley, N. K.; Izatt, R. M.; Bradshaw, J. S.; Campana, C. F. *Isr. J. Chem.* **1985**, *25*, 33−38.
(16) Crystal data for **1a**·(*R*)-$CH_3(C_6H_5)CHNH_3PF_6$: 0.20 × 0.20 × 0.20 mm^3 $C_{47}H_{51}F_6N_4O_3P$, $M_r = 864.89$, monoclinic, space group $P2_1$, $a = 11.0996(5)$ Å, $b = 19.4934(9)$ Å, $c = 20.9147(10)$ Å, $\alpha = 90°$, $\beta = 101.0440(10)°$, $\gamma = 90°$, $V = 4441.5(4)$ $Å^3$, $Z = 4$, $T = 223(2)$ K, $\rho_{calcd} = 1.293$ g/cm^3, Siemens SMART CCCD diffractometer, Mo Kα radiation, 18 213 reflections collected, 9624 independent reflections, R1 = 0.0896, wR2 = 0.2242 [$I > 2\sigma(I)$], R1 = 0.1116, wR2 = 0.2481 (all data), GOF = 1.102. Crystal data for **1a**·(*S*)-$CH_3(C_6H_5)CHNH_3PF_6$: 0.30 × 0.25 × 0.25 mm^3 $C_{47}H_{51}F_6N_4O_3P$, $M_r = 864.89$, monoclinic, space group $P2_1$, $a = 10.9878(2)$ Å, $b = 12.2344(3)$ Å, $c = 16.0947(3)$ Å, $\alpha = 90°$, $\beta = 96.8810(10)°$, $\gamma = 90°$, $V = 2148.01(8)$ $Å^3$, $Z = 2$, $T = 223(2)$ K, $\rho_{calcd} = 1.337$ g/cm^3, Mo Kα radiation, 8820 reflections collected, 5951 independent reflections, R1 = 0.0549, wR2 = 0.1258 [$I > 2\sigma(I)$], R1 = 0.0650, wR2 = 0.1361 (all data), GOF = 1.064.
(17) Kuleshova, L. N.; Zorkii, P. M. *Acta Crystallogr., Sect. B* **1981**, *37*, 1363−1366. Subscripts R and A denote the receptor and the ammonium ion, respectively.

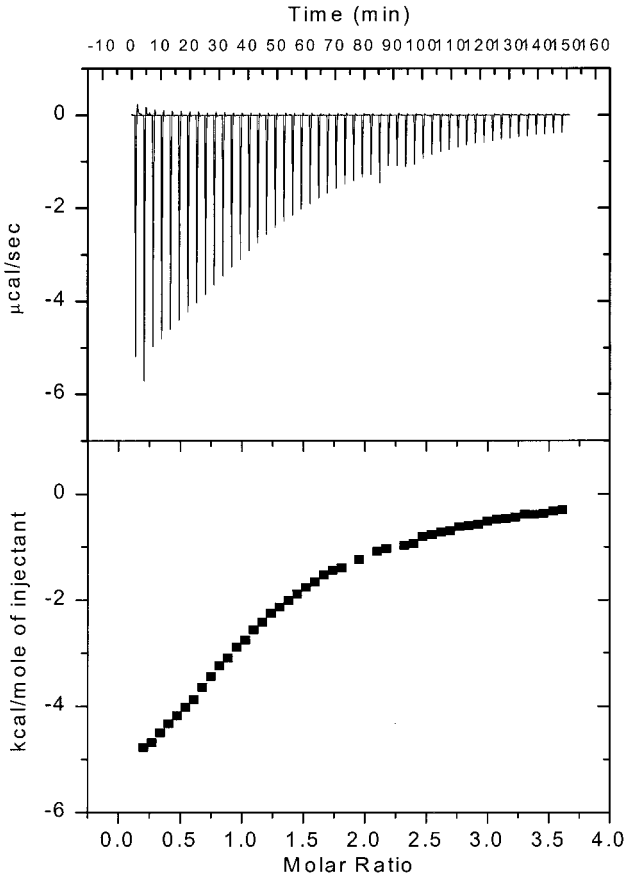

Figure 4. ITC titration data of receptor **1a** with the perchlorate salt of (*S*)-α-phenylethylamine in CH_3CN at 30 °C.

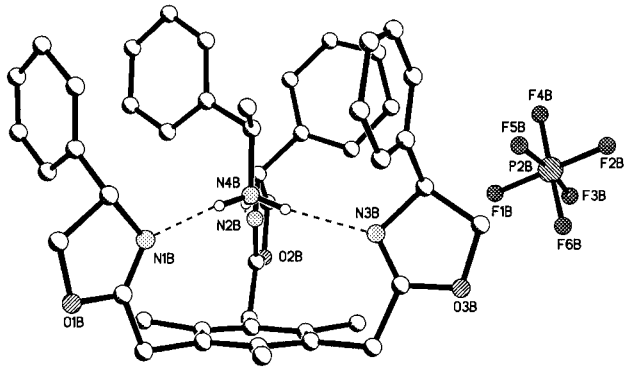

Figure 5. X-ray crystal structure of inclusion complex **1a**-(*R*)-**Am1**(I), a side view. (Hydrogen atoms are omitted for clarity, except for the three NH_3^+ hydrogen atoms.)

[**1a**-(*R*)-**Am1**(II)], and 3.4−5.2 Å [**1a**-(*S*)-**Am1**]. Among them, complex **1a**-(*R*)-**Am1**(I) shows the narrowest distance range.[18]

The minor diastereomeric complex **1a**-(*S*)-**Am1** shows a similar but slightly deviated structure from **1a**-(*R*)-**Am1**(I),[16] exhibiting the N_R-N_A distances and the $N_R-N_A-N_R$ angles in the range of 2.91−2.98 Å and 98−126°, respectively. Overall, the receptor part of complexes **1a**-(*R*)-**Am1**, particularly in the case of **1a**-(*R*)-**Am1**(I), maintains C_3-symmetry, whereas that of **1a**-(*S*)-**Am1** is somewhat distorted (Figure 6).

Origin of the Chiral Discrimination. What then makes the difference in solid structures and also in thermodynamic

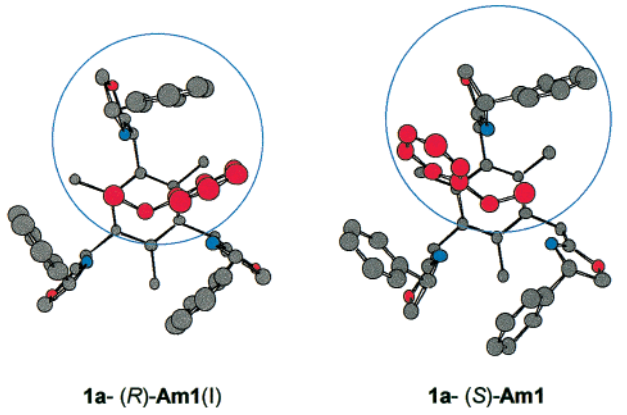

Figure 6. X-ray crystal structures of inclusion complexes **1a**-(*R*)-**Am1**(I) and **1a**-(*S*)-**Am1**, a top view. (PF_6^- and hydrogen atoms are omitted for clarity.)

stabilities between the diastereomeric complexes? We have considered the previous argument that assumes little steric or electronic difference between the diastereomeric host−guest complexes of C_3- or D_3-symmetric receptors. If we compare "two-body" interactions between the substituents of both the host and the guest, that is, those between adjacent R and S, R and M, and R and L [**1**-(*R*)-**Am** vs **1**-(*S*)-**Am** in Figure 1, R represents ligand substituents], it would be difficult to discern any steric or electronic difference between the diastereomeric complexes.[5a,5c] *However, if we look into "three-body" interactions between the host and guest, that is, those between (S, L) and R, (L, M) and R, and (M, S) and R, those interactions in one diastereomeric complex are no longer the same as those in the other* (compare those interactions in Figure 1 that correspond to the circled regions in Figure 6). The torsional strain between one oxazoline moiety and adjacent guest substituents can be viewed as part of three-body interactions; viewing it in two separate, two-body interactions is not reasonable because they are not independent from one another. Among these three-body interactions, those between (L, M) and R would cause the largest steric strain between the host and guest. The interactions between (L, M) and R in minor complex **1a**-(*S*)-**Am1** (L = Ph, M = Me, S = H; R = Ph of the oxazoline) seem to destabilize it more than those in major complex **1a**-(*R*)-**Am1**(I) do, because in the former case a larger steric strain is expected by the repulsion between M (= Me) and R groups. An examination of the bond angles between L and M in complexes **1a**-(*R*)-**Am1**(I, II) and **1a**-(*S*)-**Am1** also substantiates our explanation: The value in complex **1a**-(*R*)-**Am1**(I) is 109.4°, whereas that in complex **1a**-(*S*)-**Am1** is 114.1°, indicating that the latter, minor complex is experiencing a larger steric strain. Other bond angles of **Am1** in each of the crystal structures have similar values from each other. Selected bond angles are provided in Table 2.[19] The nonequivalent steric strain is likely to be expressed in the solid structures, expressed as a more distorted form in the case of the minor complex as compared to that of the major one. Indeed, the oxazolinyl phenyl group between L and M in **1a**-(*S*)-**Am1** is out of the propeller-shape arrangement, while that of **1a**-(*R*)-**Am1**(I) maintains it. (Compare those in the circled regions in Figure 6.)

It should be noted that the attractive $\pi-\pi$ interactions in the inclusion complexes restrict the conformational freedom of the guest and also increase the binding affinity, thereby affording

(18) For a survey of π-stacking interactions from crystal structures of organic molecules, see: Dahl, T. *Acta Chem. Scand.* **1994**, *48*, 95−106.

Table 2. Selected Bond Angles of **Am1** in the Inclusion Complexes **1a**-(*R*)-**Am1**(I), **1a**-(*R*)-**Am1**(II), and **1a**-(*S*)-**Am1**[a]

Bond Angles (deg)	
1a-(*R*)-**Am1**(I)	**1a**-(*R*)-**Am1**(II)
N(4A)−C(40A)−C(41A) 109.5(7)	N(4B)−C(40B)−C(41B) 108.8(6)
N(4A)−C(40A)−C(42A) 111.7(6)	N(4B)−C(40B)−C(42B) 111.3(7)
C(41A)−C(40A)−C(42A) 109.4(7)	C(41B)−C(40B)−C(42B) 113.8(7)
1a-(*S*)-**Am1**	
N(4)−C(40)−C(41) 108.5(4)	
N(4)−C(40)−C(42) 110.5(4)	
C(41)−C(40)−C(42) 114.1(4)	

[a] C(41) and C(42) correspond to the carbons of Me and Ph groups, respectively.

the flexible C_3-symmetric receptors a good level of enantio-discriminating ability.

Conclusions

It is now evident that the chiral discrimination in a C_3-symmetric environment as shown here is actually possible, contrary to the previous perceptions. We have demonstrated that C_3-symmetric (and similarly with D_3-symmetric) receptors can provide an effective chiral environment toward α-chiral primary organoammonium ions and related guests. The X-ray crystal structures of both diastereomeric inclusion complexes are resolved, which unambiguously show the binding mode and provide clues on the origin of the chiral discrimination. The $\pi-\pi$ interactions between the receptor and guest would stabilize the inclusion complexes, thereby endowing the highly flexible receptors with good enantio-discrimination. These results would greatly expand our scope of receptor design for chiral discrimination as well as the potential application of the new receptor system to other molecular recognition areas. Studies on the applications of the unique receptor system to other biologically important amines are actively underway.

Experimental Section

General. All the oxazoline receptors are synthesized as reported previously.[6b] The racemic organoammonium chloride and perchlorate salts used are either purchased from Aldrich or synthesized by standard procedures. NMR spectra were recorded on an AM-300 or AM-500 Bruker spectrometer and recorded in ppm, referenced to TMS. Deutrated solvents are purchased from Aldrich and used without further purification.

Determination of Enantioselective Binding by Extraction Experiments. Selective binding experiments were carried out by extracting a D_2O solution (0.5 mL) of a racemic alkylammonium chloride (0.5 M) and $NaPF_6$ (0.6 M) with a $CDCl_3$ solution (0.5 mL, 0.05 M) of the tris(oxazoline) receptor. A D_2O solution of racemic guest salts and a host solution were placed in a centrifuge tube equipped with a screw cap and equilibrated for 1 h in a thermostat at 25 °C. The whole mixture was then extracted with a Vortex-Genie for 1 min and then centrifuged at 1500 rpm for 1 min. An aliquot of the organic layer was subjected to ^{1}H NMR analysis, which in most cases allowed direct determination of enantioselectivity of binding because the host acts as a chiral shift reagent for extracted guest molecules. A typical spectral change is shown in Figure 7. The diagnostic chemical shifts for the diastereomeric host−guest complexes are observed for the guest peaks: α-phenylethylamine, δ 0.37 (d, $J = 6.8$ Hz, α-CH_3 group, *S* isomer) and 0.17 (d, $J = 6.8$ Hz, *R* isomer, major); α-(1-naphthyl)ethylamine, δ 1.12 (br s, α-CH_3 group) and 0.65 (br s, major); phenylglycine methyl ester, δ 3.31 (s, $-CO_2CH_3$ group, *R* isomer) and 3.07 (s, *S* isomer, major); tryptophan methyl ester, δ 3.23 (s, $-CO_2CH_3$ group, *R* isomer) and 3.10 (s, *S* isomer, major); alanine methyl ester, δ 0.11 (d, $J = 7.3$ Hz, α-CH_3 group, *S* isomer, major) and −0.09 (d, $J = 7.1$ Hz, *R* isomer); phenylalanine methyl ester, δ 3.34 (s, $-CO_2CH_3$ group, *R* isomer) and 3.09 (s, *S* isomer, major).

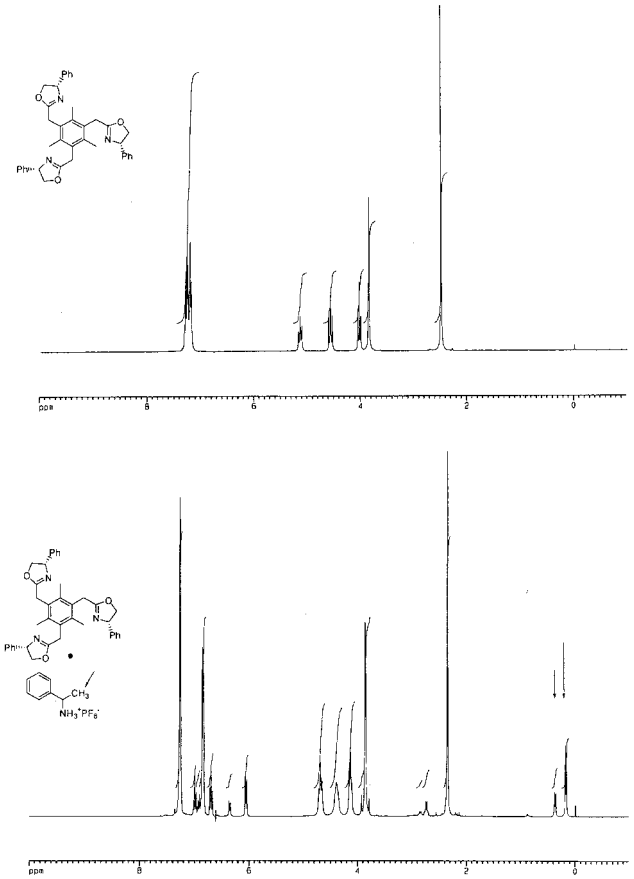

Figure 7. NMR spectra of receptor **1a** and its equilibrium complex with α-phenylethylamine salts separated from the extraction experiment.

Extracted guests were also derivatized as Mosher's amides as follows. The organic phase was treated with 4 M equiv of Et_3N followed by 4 M equiv of Mosher's acid chloride, (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Mosher's amide was purified by flash chromatography and subjected to ^{1}H or ^{19}F NMR analysis for the determination of the diastereomeric excess. This procedure served as a confirmation of the direct ^{1}H NMR determination. In both procedures, absolute configurations of major components were established by comparison with corresponding authentic materials.

Binding Studies by NMR Titration. A solution of host **1a** in $CDCl_3$ (0.50 mL, 5.0 mM) was prepared in a 5 mm NMR tube. A solution of perchlorate salt of (*R*)-*a*-phenylethylamine in $CDCl_3$ (1 mL, 20 mM) was prepared. After the NMR spectrum of host **1a** was taken, the guest solution of α-phenylethylamine was added to the host solution, initially

(19) In general, the bond angles of a guest in different inclusion complexes can be variable depending on the hosts; however, since we are comparing the bond angles of enantiomeric guests included in the same host, a large deviation of a particular bond angle in one diastereomeric complex may represent a particular strain the guest feels. In the case of **1a**-(*R*)-**Am1**(II) complex, the bond angle between L and M is 113.8°, a close value to that of **1a**-(*S*)-**Am1**. A reviewer raised two related questions: (1) Why does **1a**-(*R*)-**Am1** give two forms (I, II) while **1a**-(*S*)-**Am1** gives one, and (2) since one form of former complex **1a**-(*R*)-**Am1**(I) shows similar bond angles to those of **1a**-(*S*)-**Am1**, why is the latter experiencing a larger steric strain? The origin of the different crystal packing is not certain but the phenomenon is not unusual, see: Knobler, C. B.; Gaeta, F. C. A.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 330−333. Regarding the second question, we may explain the steric strain difference between the diastereomeric complexes, **1a**-(*R*)-**Am1** and **1a**-(*S*)-**Am1**, by assuming that two structural forms (I, II) in a unit cell of complex **1a**-(*R*)-**Am1** constitute two statistical states of the complex. Although form II shows similar bond angles to those of **1a**-(*S*)-**Am1**, the other form I shows a less strained value which may lead to overall preference toward the formation of complex **1a**-(*R*)-**Am1** over **1a**-(*S*)-**Am1** during chiral discrimination.

in a 10 μL portion, and the NMR spectrum was recorded at each time; the aliquot size was gradually increased to 90 μL until a total of 490 μL of the guest solution had been added. The temperature of the NMR probe was maintained at 25 °C. Association constants were obtained by a nonlinear least-squares fitting method. A plot of the chemical shift difference of the oxazoline C*H* proton versus [guest]/[host] is shown in Figure 2.

Binding Studies by Isothermal Titration Calorimetry. All ITC experiments were performed on an Isothermal Titration Calorimeter from Microcal Inc. After running several initial experiments with different solvents, we have found that CH_3CN is the solvent of choice for our system. A solution of receptor **1a** in CH_3CN (0.2 mM) was added to the calorimetry cell. To this receptor solution, a 5 μL solution of perchlorate salt of (*R*)- or (*S*)-α-phenylethylamine in CH_3CN (4.0 mM) was injected 50 times; a total of 250 μL of the guest was added. The solution was continuously stirred to ensure rapid mixing and was kept at an operating temperature of 30 °C. The data were analyzed and fitted using the software Origin.

Crystallographic Structural Determination. Single crystals were obtained as follows: (*R*)-α-Phenylethylammonium hexafluorophosphate salt was extracted out of an aqueous phase with a chloroform solution of tripodal oxazoline **1a**, and the solvent was evaporated. The resulting mixture was redissolved in dichloromethane, and then the solution was allowed to diffuse into the hexane layer to provide suitable single crystals. Single crystals of the (*S*)-complex were also obtained similarly. All crystallographic data are given as the Supporting Information.

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Supporting Information Available: Tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for inclusion complexes **1a**-(*R*)-**Am1** and **1a**-(*S*)-**Am1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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