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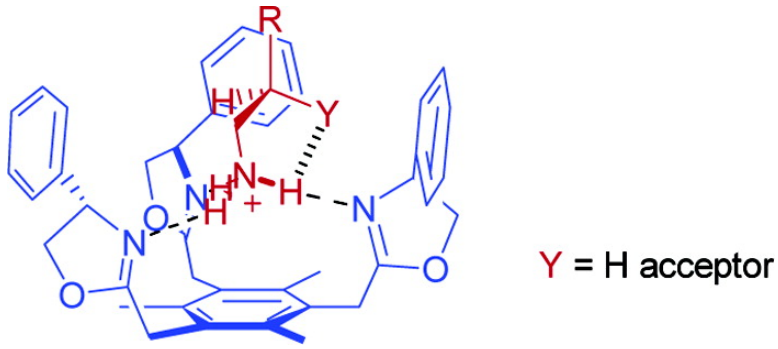

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Crucial Role of Three-Center Hydrogen Bonding in a Challenging Chiral Molecular Recognition

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Abstract: The enantio-discrimination of β-chiral primary ammonium ions is achieved by a rational approach that utilizes three-center (bifurcated) hydrogen bonding. The extraction experiments on various selected guests reveal that the bifurcated H-bonding plays a crucial role for the chiral discrimination. The X-ray data obtained for an inclusion complex substantiate such interactions. Using the bifurcated H-bonding, the chiral molecular recognition with our C_3-symmetric tripodal oxazoline receptors is extended generally toward ammonium ions of α-, β-, and α,β-chiral amines. Simple molecular models, evoking the bifurcated H-bonding, explain the chiral discrimination modes.

Introduction

It has been suggested that the three-center hydrogen bond,[1] a bifurcated hydrogen bond that involves two simultaneous hydrogen acceptors, plays an important role in determining the structure and function of molecules, ranging from inorganic to organic and biological molecules. The bifurcated H-bonding is detected in crystal structures of small molecules such as amino acids and carbohydrates,[2] as well as large biopolymers such as RNA,[3] DNA,[4] and proteins.[5] The ubiquitous nature of bifurcated H-bonding in biomolecules is further explored in the molecular recognition and self-assembly of designed molecules, together with normal two-center H-bonding.[6] The role of bifurcated H-bonding as a critical interaction in molecular recognition, however, has not been addressed yet. Designing a molecular recognition system that utilizes bifurcated H-bonding would provide further understanding of this novel molecular interaction and would expand the scope of molecular recognition by artificial receptors.

Although chiral recognition of α-chiral amines via ammonium salts has been studied extensively,[8] little progress has been made for the enantio-discrimination of β-chiral primary amines.[9] One difficulty in the recognition of β-chiral amines via ammonium ions is due to the free rotation of β-chiral substituents remote from the ammonium binding site. To overcome this problem, we propose employing bifurcated H-bonding as an auxiliary interaction that could block the free rotation of β-substituents, thereby securing a chiral environment for the guest. Herein, we wish to report our rational approach to the recognition of β-chiral primary ammonium ions through bifurcated H-bonding. The extraction experiments toward a number of selected guests reveal that the bifurcated H-bonding plays a crucial role in the chiral discrimination. The X-ray data substantiate such interactions. To the best of our knowledge, this is the first successful example that deliberately utilizes bifurcated H-bonding in chiral molecular recognition.

Results and Discussion

The tripodal oxazoline **1** and its analogues are a new and efficient receptor system, which selectively recognizes primary

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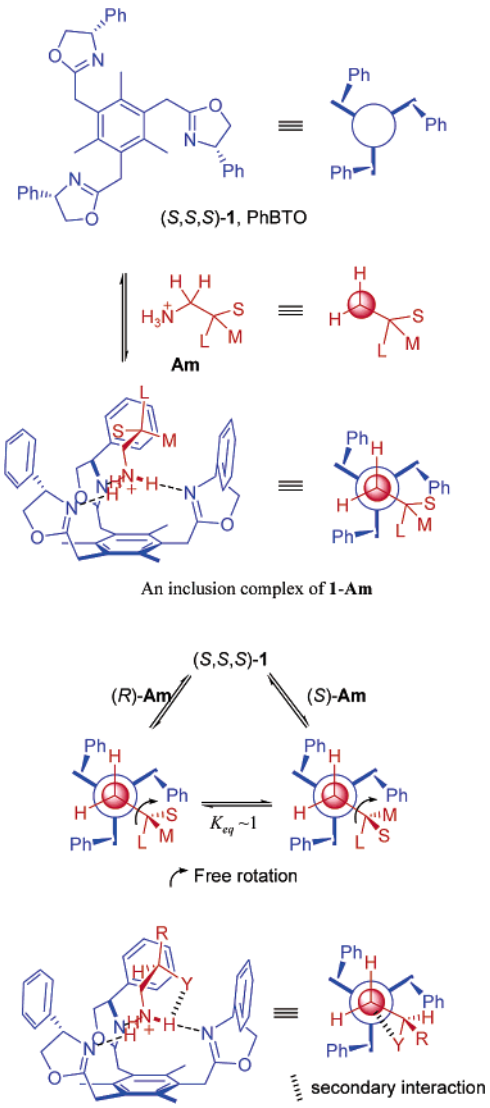


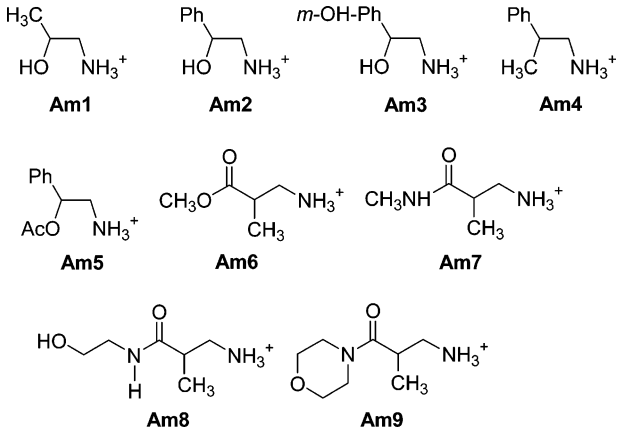
Figure 1. Schematic diagrams of diastereomeric inclusion complexes between PhBTO **1** and β-chiral primary ammonium ions (**Am**) with and without a secondary interaction.

ammonium ions through tripod H-bonding, cation-π and steric interactions.[7,10] The phenyl substituents of **1** provide a C_3-symmetric "screw-sense" chiral environment toward α-chiral primary ammonium ions. For β-chiral ammonium ions, the β-substituents can occupy one of the three "chiral sectors" provided by the receptor.[7] Although the β-substituents reside in a regional chiral environment, no enantio-discrimination is anticipated if the β-substituents rotate freely. Thus, to achieve chiral discrimination, we have introduced a secondary interaction that may hinder the free rotation of β-substituents (Figure 1).

We envisage bifurcated H-bonding as a suitable choice for the secondary interaction, because the tripod H-bonds supplied by the ammonium ion are already present in the system, and an appropriate H-bond acceptor that favorably interacts with one of the tripod H-bonds may form a bifurcated H-bond. In another sense, we may expect chiral discrimination through the bifurcated H-bonding from a guest molecule, in which the β-substituents are conformationally rocked through intramolecular H-bonding.

(10) (a) Ahn, K. H.; Kim, S.-G.; Jung, J.; Kim, K.-H.; Kim, J.; Chin, J.; Kim, K. *Chem. Lett.* **2000**, 170−171. (b) Kim, S.-G.; Ahn, K. H. *Chem. Eur. J.* **2000**, *6*, 3399−3403.

Table 1. Selective Binding of PhBTO **1** toward Racemic Ammonium Salts of β-Chiral Amines



entry	racemic guest	enantioselectivity[a]	extraction (%)[b]
1	**Am1**	63:37[c]	50
2	**Am2**	75:25	60
3	**Am3**	72:28	40
4	**Am4**	50:50	97
5	**Am5**	58:42	72
6	**Am6**	58:42	71
7	**Am7**	71:29	<5
8	**Am8**	61:39	10
9	**Am9**	83:17	<5

[a] Enantiomeric ratio of the extracted guest from excess racemic salts (10 M equiv, 0.5 M in D_2O) by PhBTO **1** (0.05 M in $CDCl_3$) at 25 °C. [b] Percentage of the ammonium salt extracted into $CDCl_3$ with respect to PhBTO **1**. [c] Major: (*R*)-isomer.

Extraction Experiments and Binding Studies. We first examined guests that have β-OH functionality, which can act as the hydrogen bond acceptor. When we carried out extraction experiments with PhBTO **1** in $CDCl_3$ toward a racemic ammonium salt of **Am1**, **Am2**, or **Am3** in D_2O at 25 °C, the receptor extracted one enantiomer preferentially over the other from the racemic mixture. In contrast, in the case of **Am4** that has no β-OH group, chiral discrimination was not observed, although PhBTO **1** extracted most of the guest into the organic phase. These results indicate that the β-OH group plays a crucial role in the chiral discrimination, presumably by forming the bifurcated H-bond. When the β-OH group was changed to β-acetoxy and β-carbomethoxy groups as in **Am5** and **Am6**, we still were able to observe enantio-discrimination, albeit with lower selectivity. From these results the β-substituents are supposed to act as H-bond acceptors in the bifurcated H-bonding. As another useful H-bond acceptor we introduced carboxamide functionality at the β-position such as in the guests **Am7**−**Am9**. In these cases, a high level of enantio-discrimination is obtained, indicating that the carboxamide functionality similarly participates in the intramolecular bifurcated H-bonding. Table 1 lists the enantioselectivities and percent extractions observed. In the cases of the guests with β-carboxamide groups, the percent extraction was poor, owing to their increased solubility in the aqueous phase.

To get thermodynamic data for the binding process, we carried out isothermal titration calorimetry (ITC) with the

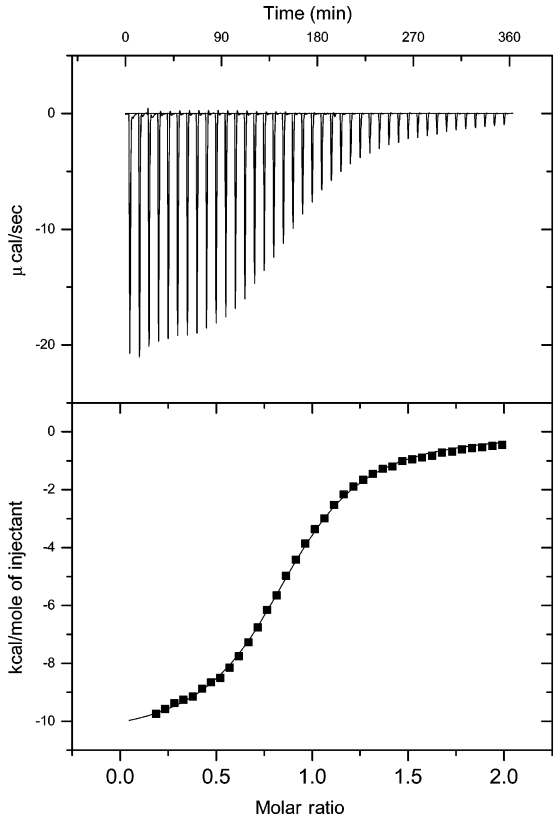


Figure 2. ITC titration plot of PhBTO **1** (1.5 mL, 0.6 mM) with (*R*)-**Am1** (perchlorate salt, 8.4 mM) in CH_3CN at 303 K.

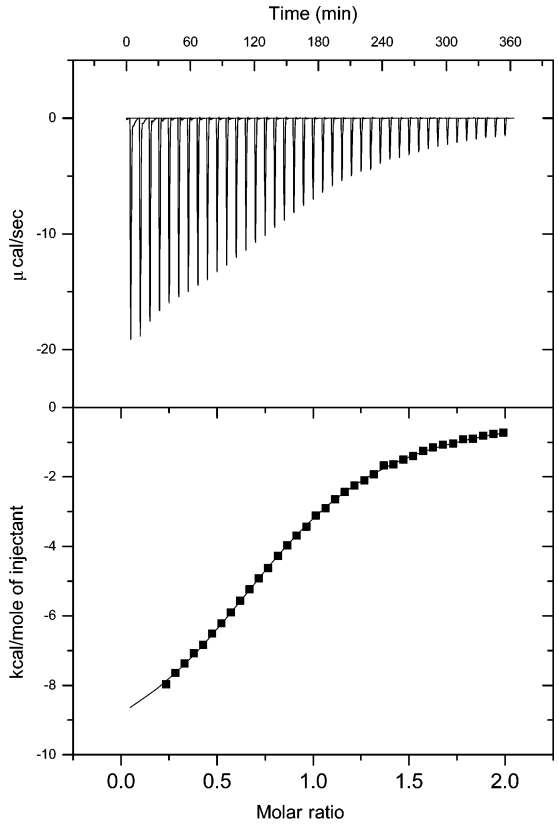


Figure 3. ITC titration plot of PhBTO **1** (1.5 mL, 0.6 mM) with (*S*)-**Am1** (perchlorate salt, 8.4 mM) in CH_3CN at 303 K.

enantiomeric guests of **Am1** (ClO_4^- salt) at 30 °C in CH_3CN.[11] The binding isotherms for the diastereomeric complexation are given in Figures 2 and 3, the slopes of which clearly indicate that formation of an inclusion complex, PhBTO **1**-(*R*)-**Am1**, is favored over the other diastereomeric complex.

In a 1:1 binding mode, the formation constants for **1**-(*R*)-**Am1** and **1**-(*S*)-**Am1** are found to be $K_a = 3.0 \times 10^4$ and 9.2×10^3 M^{-1}, respectively. Interestingly, the enthalpy changes are nearly identical within the experimental errors for both diastereomeric complexes: $\Delta H^\circ \sim -10.6$ kcal mol^{-1}. The entropy changes calculated from K_a and ΔH° values show a slight difference both with negative values: $\Delta S^\circ \sim -14.6$ and -16.8 eu for **1**-(*R*)-**Am1** and **1**-(*S*)-**Am1**, respectively. Although the binding isotherms clearly show different slopes for the two inclusion complexes, the comparison of the entropy changes cannot be made because it is within the experimental error of the enthalpy changes.

To assess the contribution of the bifurcated H-bond to the thermodynamic stability of the inclusion complexes, it is necessary to compare the thermodynamic data between two structurally related guests with and without a H-bond acceptor. But such a comparison could not be made due to the unavailability of such enantiomeric guests at the moment. Instead, a substantial contribution of the secondary hydrogen bond to the thermodynamic stability of the inclusion complexes may be inferred from a slightly higher binding affinity observed in the case of **Am2** compared to **Am4** (for racemic salts, $K_a = 2.6 \times 10^4$ and 1.8×10^4 M^{-1} respectively), the latter of which cannot have a similar bifurcated H-bonding but instead can have $\pi-\pi$ interactions.[7] A positive contribution of such a bifurcated H-bond to the thermodynamic stability may sometimes be compensated by steric strain imposed by the bifurcated H-bond, and thus a bifurcated H-bond may not necessarily result in additional thermodynamic stability. Even in such cases, however, we may observe a difference in the thermodynamic stability between two diastereomeric inclusion complexes, which can lead to chiral discrimination.

X-ray Crystal Structure for the Three-Center Hydrogen Bonding. The X-ray structure of an inclusion complex can provide further information on the binding mode in addition to the guest study. Our attempts to get single crystals from "only β-chiral" ammonium ions such as **Am1** and **Am2** had not been successful. However, we were able to obtain single crystals of (1*R*,2*S*)-norephedrine salt (**Am10**) from dichloromethane-hexane, which has additional α-methyl substituent.

The resolved crystal structure provides evidence for the presumed bifurcated H-bond, in addition to the tripod H-bonds between the ammonium ion and oxazoline nitrogens (Figure 4).[12] The β-OH group of the guest is aligned near the $N^+-H\cdots N$ bond region. The NH_3^+ and OH hydrogen atoms were located in a difference Fourier map and refined isotropically. The sum of the bifurcated H-bond angles ($\theta + \theta' + \alpha = 347.7°$)

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(12) Crystal datafor **1**·(1*R*, 2*S*)-**Am10**(PF_6^-): 0.30 × 0.30 × 0.30 mm $C_{48}H_{53}F_6N_4O_4P$, $M_r = 894.91$, monoclinic, space group P2(1), $a = 10.9999(3)$, $b = 12.3577(2)$, $c = 16.7301(3)$ Å, $\alpha = 90°$, $\beta = 93.9350(10)°$, $\gamma = 90°$, $V = 2268.82(8)$ Å^3, Z = 2, $T = 223(2)$ K, $\rho_{calcd} = 1.310$ g/cm^3, Siemens SMART CCCD diffractometer, $Mo_{K\alpha}$ radiation, 9178 reflections collected, 6596 independent reflections, $R1 = 0.0665$, $wR2 = 0.1434$ [$I > 2\sigma(I)$], $R1 = 0.0917$, $wR2 = 0.1650$ (all data), GOF = 1.106.

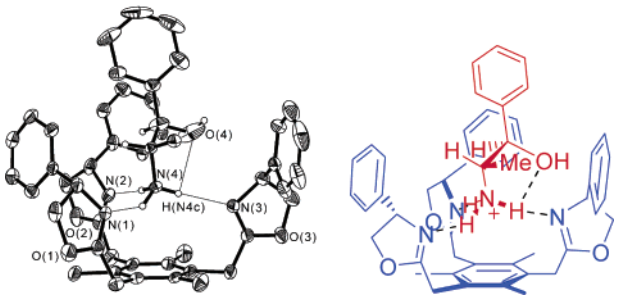
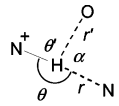


Figure 4. Crystal structure of a major inclusion complex, PhBTO **1**-(1*R*,2*S*)-**Am10**. The PF_6^- and hydrogen atoms are omitted except for some guest hydrogens.



$\theta = 173.1°$ $r = 2.14$ Å
$\alpha = 86.3°$ $r' = 2.63$ Å
$\theta' = 88.3°$ $N^+—H = 0.88$ Å

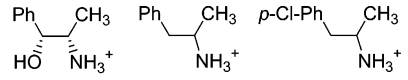
Figure 5. Bond angles and lengths of the bifurcated H-bond.

Table 2. Selected Bond Lengths and Angles of the Inclusion Complex, PhBTO **1-Am10**

bond lengths, Å		
N4−N1: 2.991	N4−O4: 2.744	N4−H(N4c): 0.879
N4−N1: 2.916	O4−N3: 3.278	N4−H(N4a): 1.136
N4−N3: 3.012		N4−H(N4b): 0.843
bond angles, deg		
N1−N4−N2: 99.36		N4−H(N4c)-N3: 173.09
N2−N4−N3: 118.62		N4−H(N4a)-N1: 147.77
N3−N4−N1: 126.73		N4−H(N4b)-N2: 176.34

shows that four atoms provide near-coplanarity, conforming to the criteria of bifurcated H-bonds:[1a] The hydrogen that participates in the bifurcated H-bonding, H(N4c), lies 0.047(5) Å below the N(3)−N(4)−O(4) plane. The H-bond distances also conform to the criteria of bifurcated H-bonds (Figure 5).[1a] The selected bond lengths and angles of all H-bonds are listed in Table 2.

Removing the β-OH group from **Am10**, as in **Am11** or **Am12**, results in negligible enantioselectivities, which manifests that the secondary H-bond interaction embedded in the crystal structure of the PhBTO **1-Am10** complex is critical to securing the necessary environment for chiral discrimination.



(1*R*,2*S*)-**Am10** **Am11** **Am12**
52:48 (72%) 52:48 (92%)

Regarding bifurcated H-bonds,[13] a charged species is involved in our case; hence, the bifurcated H-bonding seems to be energetically favored, as inferred from the similar binding affinities observed for **Am1** and α-phenylethylamine salts.

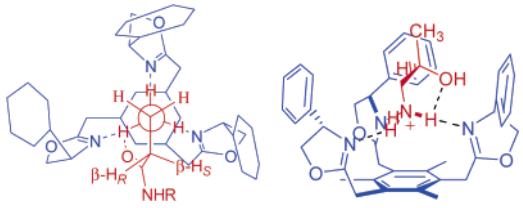


Figure 6. A top view of the optimized inclusion complex between PhBTO **1** and an ammonium ion of β-amino-carboxamide; a side view of a major inclusion complex, PhBTO **1**-(*R*)-**Am1**.

Chiral Discrimination Modes. Under the favorable bifurcated H-bonding environment, the chiral discrimination may be explained by different steric interactions between the diastereomeric inclusion complexes of guests studied. A molecular modeling study shows that there is a substantial energy difference between two diastereomeric complexes of each guest examined. Furthermore, the difference is readily recognizable by comparison of steric interactions between the diastereomeric complexes. A modeled structure in case of an achiral β-amino carboxamide is depicted in Figure 6 (the top view).[14] In the bifurcated H-bonding model, the two oxazoline groups adjacent to the β-substituents of the ammonium guest provide a pseudo-C_2-symmetric chiral environment, in which the oxazoline phenyl group adjacent to the bifurcated H-bond is positioned somewhat away from the guest. It is apparent that an enantiomeric guest with β-H_S-substituent may experience larger steric strain exerted by the nearby oxazoline phenyl group than would the enantiomeric β-H_R-substituted guest.

Thus, the minor complex PhBTO **1**-(*S*)-**Am1** seems to experience an apparent steric strain between the β-methyl group of the guest and the nearby oxazoline phenyl group, whereas that strain is reduced in the case of the major complex (Figure 6, the side view).

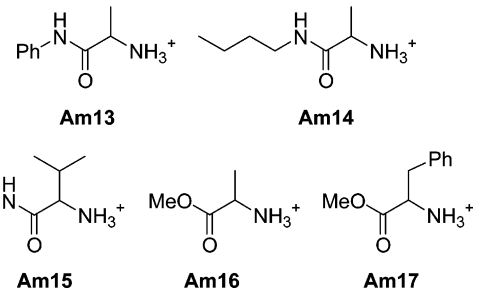
In the absence of such secondary H-bonding interactions as the case of **Am4**, the β-substituents rotate without anchoring, resulting in no difference in the thermodynamic stability between the diastereomeric complexes. Thus, we can explain the mode of enantioselection by a simple model involving the bifurcated H-bond.

Enantio-Discrimination Toward Other Substrates. On the basis of the successful chiral discrimination of β-chiral organoammonium ions through bifurcated H-bonding, we extended the concept to the α-alkyl-substituted α-chiral amines. Our previous study[7] showed that PhBTO **1** and analogues barely discriminate enantiomeric ammonium ions of α-alkyl-substituted α-chiral amines, whereas they provide good to high enantioselectivity in the case of α-aryl-substituted guests. The possible $\pi-\pi$ interactions between the receptors and α-aryl-substituted guests or simply reduced steric strain between the aryl groups seem to provide additional binding affinity and also conformational restriction to the inclusion complexes, resulting in the chiral discrimination. By introducing a bifurcated H-bond acceptor functionality into α-alkyl-substituted α-chiral ammonium ions, we may observe substantial enantio-discrimination. In fact, in the case of alanine carboxamide guests such as **Am13** and **Am14**, good enantioselection is observed, as shown in Table 3. In the case of valine-derived carboxamide **Am15**, which has a sterically more demanding isopropyl group, still

(13) For recent studies on the energetics of three-center hydrogen bonding, see: (a) Yang, J.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 9090−9091. (b) Yang, J.; Christianson, L. A.; Gellman, S. H. *Org. Lett.* **1999**, *1*, 11−13 and references therein.

(14) The molecular modeling study was carried out at AM1 level using a program, PC Spartan Pro from Wave function Inc.

Table 3. Selective Binding of PhBTO **1** toward Racemic Ammonium Salts of α-alkyl-Substituted Chiral Amines



entry	racemic guest	enantioselectivity[a]	extraction (%)[b]
1	**Am13**	66:34[c]	74
2	**Am14**	61:39	20
3	**Am15**	56:44	26
4	**Am16**	53:37[c]	41
5	**Am17**	55:45[c]	36

[a] Enantiomeric ratio of the extracted guest from excess racemic salts (10 M equiv, 0.5 M in D_2O) by PhBTO **1** (0.05 M in $CDCl_3$) at 25 °C. [b] Percentage of the ammonium salt extracted into $CDCl_3$ with respect to PhBTO **1**. [c] Major: (*S*)-isomer.

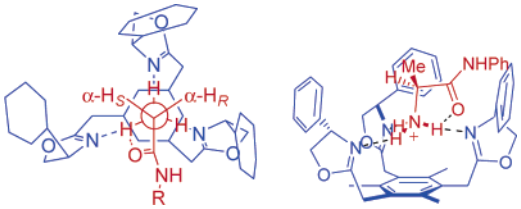


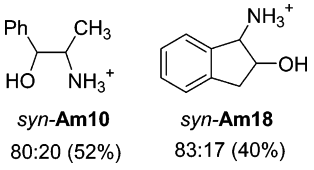
Figure 7. Top view of the optimized inclusion complex between PhBTO **1** and an ammonium ion of α-amino-carboxamide; a side view of a major inclusion complex, PhBTO **1**-(*S*)-**Am13**.

we can observe lower but appreciable enantioselection. When the ancillary group is changed to an ester, such as in guests **Am16** and **Am17**, the enantioselection also decreases probably due to weaker bifurcated H-bonding by the weaker H-acceptor ability of the ester group.

We may also explain the sense of enantioselection for these guests (**Am13**−**Am17**) by evoking a recognition model as depicted in Figure 7. In this case, the steric strain difference between the diastereomeric guests seems to be smaller in comparison with the case of the β-chiral amine guests.

From the model, we suppose that (*S*)-isomers of the amino acid derivatives (α-H$_S$-substituted guests) are experiencing smaller steric strain between the α-substituents and a nearby host phenyl group. In fact, the major extraction products of **Am13**, **Am16**, and **Am17** were confirmed to be the (*S*)-isomers by comparison with authentic samples synthesized separately. Thus, our enantiomeric receptor system may be used to assign the absolute stereochemistry of related α-chiral amino acid derivatives as well as that of β-chiral amines. Also, it would be interesting to extend our chiral recognition system to dipeptide amines in which amide functionality can participate as the bifurcated H-bond acceptor.

Having established the chiral discrimination toward α- and β-chiral amines, we have also studied α,β-disubstituted amine guests, **Am10** and **Am18**. Even higher enantioselectivity (≥80:20) is observed in these cases than for the α- or β-chiral ammonium guests studied.



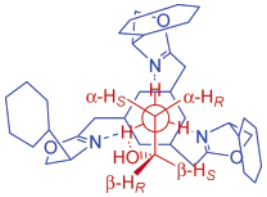
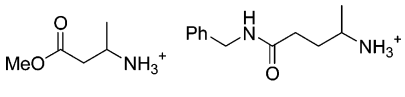


Figure 8. Top view of the optimized inclusion complex between PhBTO **1** and an ammonium ion of β-amino alcohol.

Molecular models for these guests indicate that β-substituents of the ammonium ions (the substituents at β-H$_R$/β-H$_S$ in the model) experience significant steric strain differences in the pesudo-C_2-symmetric environment, whereas α-substituents (the substituents at α-H$_R$/α-H$_S$) experience smaller differences (Figure 8). The model suggests that both the α- and β-substituents at stereotopic β-H$_S$ and α-H$_R$, particularly the substituent at β-H$_S$, experience larger steric strain than do the substituents at β-H$_R$ and α-H$_S$, respectively. Thus, in the case of ammonium guests that have "syn" α- and β-substituents, such as (1*R*,2*S*)/(1*S*,2*R*)-**Am10** and (1*R*,2*S*)/(1*S*,2*R*)-**Am18**, the β-substituents are more influential than the α-substituents for enantioselection. The steric influence of the α- and β-substituents, however, may not be synergistic because a modeling study between two diastereomeric inclusion complexes of anti-**Am10** [(1*R*,2*R*)/(1*S*,2*S*) isomers] provides a larger energy difference between the diastereomeric complexes than does the case of syn-**Am10**. Furthermore, the supposed major inclusion complex of the anti guest seems to be thermodynamically more stable than the syn. In the case of **Am18**, the π−π interactions between the phenyl moiety and the oxazoline phenyl group may be possible, and thus, in addition to steric strain, in this case electronic interactions also should be considered for chiral discrimination.

Finally, we examined chiral discrimination of PhBTO **1** toward guests **Am19** and **Am20**. The **Am19** is a suitable guest to examine the relative steric influence of α- and β-substituents as suggested by the model (Figure 8). The low selectivity observed for **Am19**, as well as **Am16** and **Am17**, supports our model that the α-substituents experience a smaller steric strain difference than do the β-substituents. The model shows that the β-substituents are in the pseudo-C_2-symmetric environment, whereas the α-substituents are not. The **Am20** may have the bifurcated H-bond in a seven-membered ring. The poor enantioselection indicates that the bifurcated H-bond, if any, is not strong enough to give appreciable chiral discrimination in this case.



Conclusions

We have achieved the enantio-discrimination of β-chiral primary ammonium ions by utilizing bifurcated H-bonding. The

extraction experiments toward a number of selected guests reveal that the bifurcated H-bonding plays a crucial role in the chiral discrimination. The X-ray data substantiate such interactions. Using the bifurcated H-bonding, the chiral molecular recognition with our C_3-symmetric tripodal oxazoline receptors is extended generally toward α-, β-, and α,β-chiral primary amines. With ample examples of bifurcated H-bonds in nature, our study demonstrates for the first time its crucial role in the field of chiral molecular recognition. Our results would also expand the scope of chiral molecular recognition by artificial receptors. A further mechanistic study and extension to other receptor derivatives are under investigation.

Experimental Section

General. The synthesis of oxazoline receptor is described previously.[10b] All the racemic organoammonium ions are synthesized from commercially available starting materials by standard procedures. NMR spectra were recorded on an AM-300 Bruker spectrometer and recorded in ppm, referenced to TMS. Deutrated solvents are purchased from Aldrich and used without further purification.

Determination of Enantioselective Binding. The enantioselectivity of the binding process was determined directly by measuring the enantiomeric excess of the host-extracted ammonium salts, because the oxazoline receptors are not extracted into the aqueous salt solutions.

The binding experiment was carried out by extracting a D_2O solution (0.5 mL) of a racemic alkylammonium salt (0.5 M**)** and $NaPF_6$ (0.6 M) with a $CDCl_3$ solution (0.5 mL, 0.05 M) of PhBTO **1**. The ammonium salts used are the corresponding HCl salts except for **Am7** (HBr salt) and **Am8** (CF_3CO_2H salt). 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 an hour in a thermostat at 25 °C. After 1 h, the whole mixture was extracted with a Vortex-Genie for 1 min and then centrifuged at 1500 rpm for 1 min.

The ^{1}H NMR analysis of the organic phase, in some cases, allowed for "direct" determination of enantioselectivity of binding because the host acted as a chiral shift reagent for extracted guest molecules (ref 7). When the direct analysis was not possible, the extracted guests were derivatized to the corresponding Mosher's amide derivatives, from which the enantioselectivity was determined by ^{1}H or ^{19}F NMR analysis. The Mosher's amides were prepared as follows: The organic phase was treated with Et_3N (4 molar equiv) followed by (*R*)-Mosher's acid chloride [4 molar equiv. of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride]. The Mosher's amide was purified by passing through a short-pad of silica gel, and subjected to ^{1}H or ^{19}F NMR analysis. The absolute stereochemistries of the major components in cases of **Am1**, **Am10**, **Am13**, **Am16**, and **Am17** were established by comparison with authentic materials prepared from both enantiomers. The absolute configurations of other compounds were not determined because both enantiomeric guests were not available.

The diastereomeric ratio of each inclusion complexes was determined by NMR analysis for the extracted guests (the direct determination) or for the Mosher's amide derivatives in $CDCl_3$. The diagnostic peaks for each of the diastereromeric complexes are as follows: **Am1**: (^{19}F NMR) δ 7.56 [major; (*R*)-isomer] and 7.53 [(*S*)-isomer]; **Am2**: (^{1}H NMR) δ 3.35 (d, J = 1.4 Hz, $-OCH_3$ group, major) and 3.37 (d, J = 1.4 Hz); **Am3**: (^{1}H NMR) δ 5.13 (dd, J = 9.5, 8.7 Hz, β-CH group, major) and 5.32 (dd, J = 9.5, 8.7 Hz); **Am4**: (^{1}H NMR) δ 0.36 (d, J = 5.3 Hz, $-CH_3$ group, major) and 0.48 (d, J = 6.2 Hz) by the direct determination; **Am5**: (^{1}H NMR) δ 2.04 (s, acetyl group, major) and 2.07 (s); **Am6**: (^{1}H NMR) δ 0.03 (d, J = 7.1 Hz, $-CH_3$ group, major) and 0.14 (d, J = 7.1 Hz) by the direct determination; **Am7**: (^{19}F NMR) δ 7.46 (major) and 7.51; **Am8**: (^{1}H NMR) δ 1.25 (d, J = 1.1 Hz, $-CH_3$ group, major) and 1.15 (d, J = 1.0 Hz) by the direct determination; **Am9**: (^{19}F NMR) δ 7.54 (major) and 7.24; **Am10**: (^{1}H NMR) δ −0.10 [d, J = 6.8 Hz, $-CH_3$ group, major; (1*R*,2*S*)-isomer] and −0.20 [d, J = 6.8 Hz, (1*S*,2*R*)-isomer] by the direct determination; **Am11**; (^{1}H NMR) 0.35 (br s) and 0.12 (br s, $-CH_3$ group, major) by the direct determination; **Am12**: (^{1}H NMR) 0.44 (br s) and 0.21 (br s, $-CH_3$ group, major) by the direct determination; **Am13**: (^{1}H NMR) δ 0.40 [d, J = 7.2 Hz, $-CH_3$ group, major; (*S*)-isomer] and 0.24 [d, J = 7.1 Hz, (*R*)-isomer] by the direct determination; **Am14**: (^{1}H NMR) δ 0.37 [d, J = 7.1 Hz, $-CH_3$ group, major; (*S*)-isomer] and 0.15 [d, J = 6.7 Hz, (*R*)-isomer] by the direct determination; **Am15**: (^{19}F NMR) δ 7.56 (major) and 7.67; **Am16**: (^{1}H NMR) δ 0.11 [d, J = 7.3 Hz, $-CH_3$ group, major; (*S*)-isomer] and −0.09 [d, J = 7.1 Hz, (*R*)-isomer] by the direct determination; **Am17**: (^{1}H NMR) δ 3.09 [s, $-OCH_3$ group, major; (*S*)-isomer] and 3.34 [s, (*R*)-isomer] by the direct determination; **Am18**: (^{1}H NMR) 3.47 [d, J = 1.4 Hz, (1*R*,2*S*) isomer, major] and 3.43 [d, J = 1.4 Hz, (1*S*,2*R*) isomer]; **Am19**: (^{1}H NMR) δ −0.11 (d, J = 6.5 Hz, $-CH_3$ group, major) and −0.16 (d, J = 6.4 Hz) by the direct determination; **Am20**: (^{19}F NMR) δ 7.62 (major) and 7.50.

Binding Study by Isothermal Titration Calorimetry. All binding experiments were performed on an isothermal titration calorimeter purchased from Microcal Inc. A solution of PhBTO **1** in CH_3CN (1.5 mL, 0.2 mM) was filled into the calorimetry cell. A solution of perchlorate salt of (*R*)- or (*S*)-2-hydroxy-1-propanamine (**Am1**) in CH_3-CN (4.0 mM) was introduced by forty 5-μL injections, in total of 200 μL of the guest added. The solution was kept at an operating temperature of 303 K. Analysis and curve fitting were done by using the software Origin. The dilution of the guest solution in neat solvent was corrected. The perchlorate salt of **Am1**, **Am2**, and **Am4** were prepared by direct reaction of amine with $HClO_4$ in water-ethanol. After evaporation of the solvent, the salt was recrystallized from *i*-PrOH-Et_2O or *n*-BuOH−CCl_4 at 0 °C or lower temperature. The preparation of the ammonium salt solution was carried out in a glovebox.

Crystallographic Structural Determination. Single crystals were obtained as follows: The hexafluorophosphoric acid salt of 2(*S*)-amino-1(*R*)-phenylpropan-1-ol [(1*R*,2*S*)-**Am10**, (1*R*,2*S*)-norephedrine] was extracted out of an aqueous phase with a chloroform solution of PhBTO **1**. The solvent was evaporated and the resulting mixture was redissolved in dichloromethane. The solution was allowed to diffuse into hexane layer to provide suitable single crystals. A colorless crystal of approximate dimensions 0.3 × 0.3 × 0.3 mm^3, shaped as a cube, was used for crystal and intensity data collection. The NH and OH hydrogen atoms were located in the difference Fourier map and refined isotropically. The remaining hydrogen atoms were generated in idealized positions and refined in a riding model. All crystallographic data are given as the Supporting Information.

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Supporting Information Available: The X-ray crystal structure data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org. This material is available free of charge via the Internet at http://pubs.acs.org.

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