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Visual Enantiomeric Recognition of Amino Acid Derivatives in Protic Solvents[1,†]

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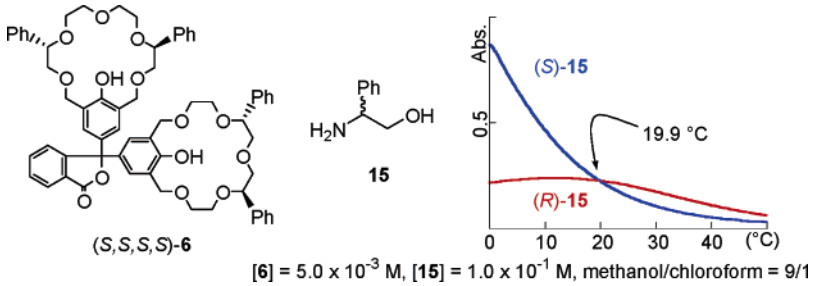

Various types of chiral host molecules **2**−**7** based on a phenolphthalein skeleton and two crown ethers were prepared for use in visual enantiomeric recognition, and we examined their enantioselective coloration in complexation with chiral amino acid derivatives **9**−**22** in methanol solution. Methyl-substituted host (*S*,*S*,*S*,*S*)-**3** showed particularly prominent enantiomer selectivity for the alanine amide derivatives **11** and **12**. A combination of methyl-substituted host (*S*,*S*,*S*,*S*)-**3** with guest (*R*)-**11** or (*R*)-**12** developed a purple color, whereas no color development was observed with (*S*)-**11** or (*S*)-**12**. On the other hand, phenyl-substituted host (*S*,*S*,*S*,*S*)-**6** showed deeper coloration with a wide range of (*S*)-*β*-amino alcohols compared to that seen with host (*S*,*S*,*S*,*S*)-**6** and the corresponding (*R*)-*β*-amino alcohols at 0 °C. Furthermore, absorbance inversion temperatures (AIT) were observed within the range of 0−50 °C in many cases.

Introduction

Since the enantiomeric recognition of chiral compounds was pioneered by Cram and co-workers in the early 1970s,[2] much attention has been focused on this topic of chemically and biologically important guests, and various kinds of host molecules have been synthesized.[3] Some of these host molecules can discriminate enantiomers on the basis of a color change; therefore, such molecules might be useful as rapid sensors for determining the absolute configurations of asymmetric guest compounds.[4]

Molecular recognition in protic solvents, especially in aqueous media, is another attractive topic since noncovalent forces derived from electrostatic interaction are weakened according to the dielectric constant (ϵ) of the solvent. In addition, the designed formation of hydrogen bonds between two molecules is especially difficult in protic solvent since a large number of solvent molecules can act as a hydrogen donor and/or acceptor.[5]

We have been investigating whether ditopic receptors consisting of phenolphthalein (one of the most popular pH indicators) and two crown ethers could be used to recognize the length of guest diamine or triamine molecules and indicate this information through the development of a purple color.[6] The mechanism of color development by phenolphthalein in the aqueous alkaline

† This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka.

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(1) A preliminary communication of part of this work has published: Tsubaki, K.; Nuruzzaman, M.; Kusumoto, T.; Hayashi, N.; Wang, B.-G.; Fuji, K. *Org. Lett.* **2001**, *3*, 4071−4073.

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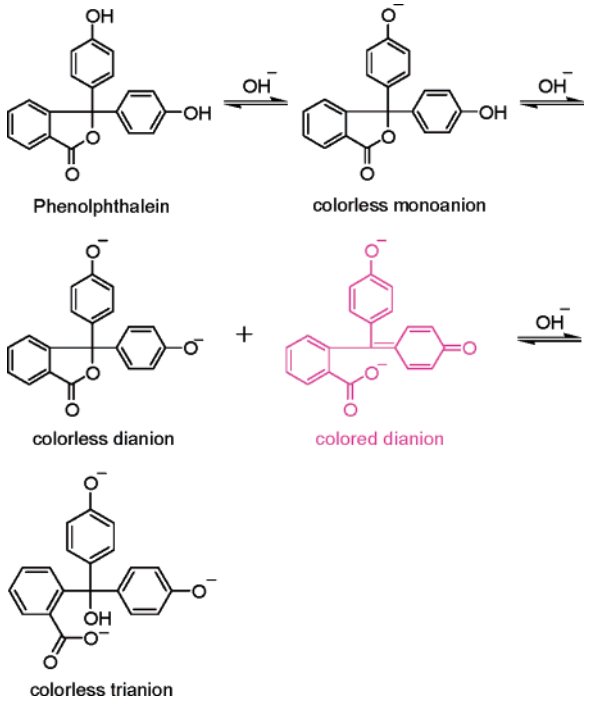
SCHEME 1. Mechanism of Color Development of Phenolphthalein in the Aqueous Alkaline Region[7]



region, as revealed by Tamura et al.,[7] is as follows: (i) monoanion of phenolphthalein is colorless, (ii) two types of dianion (colored carboxylate form and colorless lactone form)[8] are present, and (iii) in the strong alkaline region, Michael addition of hydroxide takes place to give the corresponding colorless trianion (Scheme 1). In the present paper, we report the visual enantiomeric recognition of amino acid derivatives using chiral hosts **2**−**7** in methanol media as well as changes in this phenomenon with a change in the temperature (Figure 1).

Results and Discussion

Syntheses of Chiral Host Molecules (*S,S,S,S*)-2−5 and 7. The chiral hosts **2**−**5** and **7**, containing two methyl or phenyl groups in each crown ether, were synthesized according to Scheme 2. Key chiral tetraethylene glycol subunits (*S,S*)-**24**−**28** were prepared from (*S*)-ethyl lactate or (*S*)-mandelic acid.[9] Ring-closing reactions were carried out on **29**[10] with chiral tetraethylene glycol subunits (*S,S*)-**24**−**28** under sodium hydride and potassium tetrafluoroborate to give the corresponding crown ethers (*S,S*)-**30**−**34** in moderate yields. Crown ethers **30**−**34** were treated with *t*-BuLi and allowed to react with phthalic anhydride at −78 °C to afford (*S,S,S,S*)-**35**−**39** in moderate to good yields (40−92%). Finally, reductive deprotection of the allyl groups proceeded smoothly using either 10% palladium on carbon and *p*-toluenesulfonic acid in ethanol−water[11] or sodium borohydride and a catalytic amount of tetrakis(triphenylphosphine)palladium in methanol[12] to afford (*S,S,S,S*)-**2**−**5** and **7** in excellent yields (91−100%).

Synthesis of the Chiral Host (*S,S,S,S*)-6. The synthetic pathway for the chiral host (*S,S,S,S*)-**6** is shown in Scheme 3. The key intermediate (*S,S*)-**42** was constructed on the basis of the known procedure.[9c,13] Thus, (*S*)-**40** derived from (*S*)-(+)-mandelic acid as a diastereo mixture was condensed with benzyl chloride **29**[10] in the presence of sodium hydride in DMF, and this was followed by deprotection of the THP groups under acidic conditions to afford (*S,S*)-**41** in 82% overall yield in two steps. Treatment of (*S,S*)-**41** with diethylene glycol ditosylate under sodium hydride and potassium tetrafluoroborate gave the corresponding crown ether (*S,S*)-**42** in 49% yield, which was converted into the host (*S,S,S,S*)-**6** via a route similar to those for the chiral hosts (*S,S,S,S*)-**2**−**5** and **7** in 95% overall yield in two steps.

Visual Enantiomeric Recognition by Chiral Hosts (*S,S,S,S*)-2−5. A preceding paper proposed that a colored complex between host **1** and triamine **8** developed because both terminal amino groups of triamine **8** bridged the two phenolic crown rings of host **1** and the inner amino group was captured as a countercation of the carboxylate, based on ring opening of the γ-lactone of host **1**.[6b] Thus, a definite chain length is required for the visualization of α,ω-diamines or linear triamines using the achiral host **1**. Derivatization of chiral guests is indispensable for meeting the above requirement. Therefore, two types of amino acid derivatives **9** and **10**−**14** were prepared.[14] Before investigating the possibility of enantiomeric recognition between chiral hosts **2**−**5** and chiral amines **9**−**14**, we examined the interaction between chiral hosts and achiral triamine **8**. When triamine **8** was added to a solution of host in methanol at 25 °C,

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(14) For the synthesis of guests, see the Supporting Information.

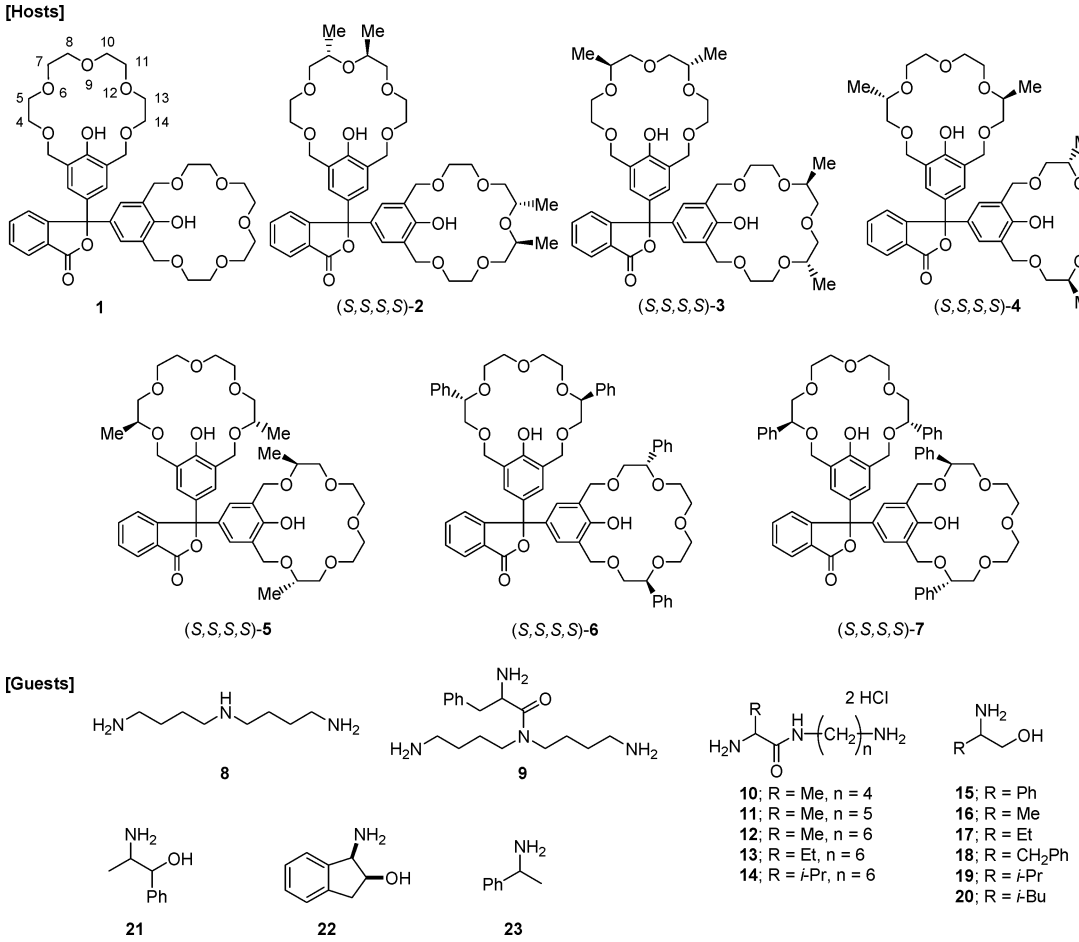

FIGURE 1. Hosts and guests.

a color change (from colorless to purple) based on an increase in the absorption band at around 570 nm was observed. The association constants (K) and molar absorption coefficients (ϵ) were determined by UV−vis titration and analyzed by the Rose−Drago method.[15] The results are summarized in Table 1.

The data in Table 1 show that the association constants (K) decreased dramatically when two methyl groups were introduced into a phenolic crown ring (compare entry 1 with entries 2−5). Furthermore, K values gradually decreased as the two methyl substituents moved from the top (positions 8 and 10, see Figure 1) to the bottom (positions 4 and 14) of the phenol crown ring (**2** > **3** > **4** > **5**). A similar tendency was observed for the molar absorption coefficient (ϵ). Consequently, the degree of coloration (absorbance) caused by the product of the molar absorption coefficient (ϵ) and the concentration of the host−guest complex changed dramatically depending on the host **1**−**5** and guest triamine **8**.

Although the molar absorption coefficient (ϵ) is supposed to be constant for each host−guest complex, its value is critically attributable to the structure of the host compound. While we do not have a clear explanation for the fluctuating molar absorption coefficient (ϵ), we speculate that ϵ reflects the position of the equilibrium between the colored and colorless dianion of the host (Scheme 1). This variable ϵ makes visual recognition unique and complicated, as described later.

Next, the enantiomeric recognition of hosts **1**−**5** with phenylalanine derivatives **9** was examined. The association constants (K) and molar absorption coefficients (ϵ) are listed in Table 2. In entry 1, the achiral host **1** was investigated to guarantee the purity of the chiral guests and the titration procedure. Small association constants were observed for the complexation of hosts **2**−**4** with enantiomeric pairs of **9**, indicating weak host−guest interaction. Almost no enantioselective recognition was observed for hosts **2**−**4**. The binding ability of host **5** was too low to determine the association constant.

During these investigations, a fundamental host−guest relationship was revealed: (i) unexpectedly large steric repulsion was observed between even the smallest methyl substituents on the phenol crown ring and the terminal primary amino group in the guest molecule, and (ii) the small differences between the association constants for achiral triamine **8** and chiral triamine **9** for each host molecule indicated that there were no additional interactions between methyl substituents on the host molecule and a chiral moiety introduced into the inner amino group of the guest molecule.

Taking this information into consideration, we next examined the visual enantiomeric recognition of chiral

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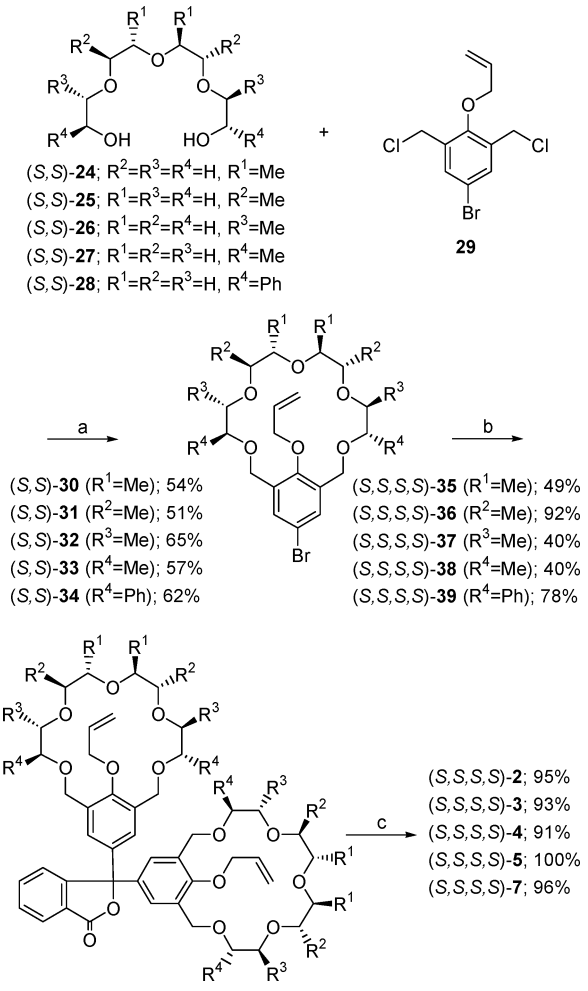
SCHEME 2. Synthetic Pathway for Chiral Hosts (*S*,*S*,*S*,*S*)-2−5 and 7[a]



[a] Key: (a) NaH, KBF_4; (b) *t*-BuLi, phthalic anhydride; (c) 10% Pd/C, TsOH[11] or $Pd(PPh_3)_4$, $NaBH_4$.[12]

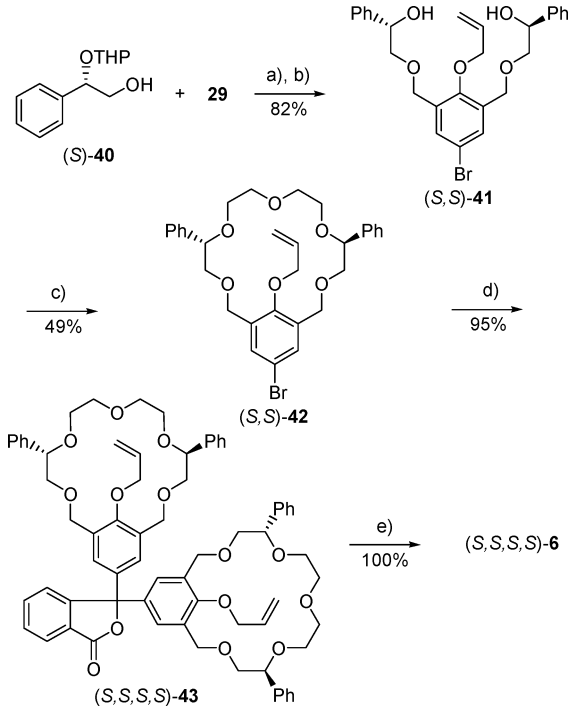
guests **10**−**14**,[16] amides of α-amino acid and linear diamine, by chiral hosts (*S*,*S*,*S*,*S*)-**2**−**5**. In this stage, guest molecules bear chiral substituents near the terminal amino group. Since relatively small association constants might be expected from the data in Tables 1 and 2, UV−vis titration experiments were carried out at 15 °C in the presence of a large excess of *N*-ethylpiperidine (NEP). In previous studies, we found that protonated *N*-ethylpiperidine ($NEPH^+$) served only as a countercation for the carboxylate anion derived from ring-opening of the benzolactone of host **1** without any interaction with the phenol crown of host **1**.[6a] The apparent association constants (*K*′) and molar absorption coefficients (ϵ) for **11** and **12** are summarized in Table 3.

The positions of the methyl groups on phenolic 18-crown-6 crucially affected the enantiomeric recognition toward (*R*)- and (*S*)-alanine derivatives **11** and **12**. Thus, the binding ability of host **2** is superior to those of other chiral hosts, but enantiomeric recognition was hardly observed. Among the hosts examined, host **3**, which possesses two methyl groups at positions 7 and 11 of the phenolic 18-crown-6 ring, shows prominent enantiomeric selectivity. Interestingly, Hirose and Tobe reported that the substituents at positions 5 and 13 of azo-phenolic 18-crown-6 play crucial roles in visual chiral recognition.[9c−d,17] A difference in coloration is seen in Figure 2 as well as in the UV−vis absorption spectra (Figure 3). In Figure 2, the combination of host **3** with guest (*R*)-**11** or (*R*)-**12** led to color development, while almost no color development was observed with (*S*)-**11** or (*S*)-**12**. Thus, it was easy to discriminate between enantiomers.

Furthermore, when guest **12** with different optical purities was added to the host **3** solution, a linear relationship was observed between the absorbance (λ_{max}, 574 nm) and the enantiomeric excess (ee) of guest **12**. This result clearly shows that host **3** can read the chirality of the guest and turn such molecular interactions into visual information (Figure 4).

With hosts **1**−**5** and diamine **10**, no color development was observed even under these conditions, and therefore,

SCHEME 3. Synthetic Pathway for Chiral Host (*S*,*S*,*S*,*S*)-6[a]



[a] Key: (a) NaH; (b) H^+; (c) diethylene glycol ditosylate, NaH, KBF_4; (d) *t*-BuLi, phthalic anhydride; (e) $Pd(PPh_3)_4$, $NaBH_4$.[12]

TABLE 1. Association Constants (*K*) and Molar Absorption Coefficients (ϵ) of Complexes of Hosts 1−5 with Triamine 8[a]

entry	host	K (M^{-1})	ϵ
1	**1**	2270 ± 30	5080 ± 20
2	(*S*,*S*,*S*,*S*)-**2**	274 ± 3	5900 ± 32
3	(*S*,*S*,*S*,*S*)-**3**	208 ± 4	1525 ± 18
4	(*S*,*S*,*S*,*S*)-**4**	96 ± 2	1724 ± 30
5	(*S*,*S*,*S*,*S*)-**5**	47 ± 2	806 ± 22

[a] Conditions: [host **1**]$_0$ = 5.0×10^{-3} M; [host **2**]$_0$ = 5.0×10^{-4} M; [hosts **3**−**5**]$_0$ = 1.0×10^{-3} M; 25.0 °C, MeOH.

(16) The guests **10**−**14** were used as 2HCl salts, which would deliver free amine in the presence of large excess NEP.

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TABLE 2. Association Constants (K) and Molar Absorption Coefficients (ϵ) of Complexes of Hosts 1−4 with Triamine 9[a]

entry	host	K_R (M^{-1})[b]	ϵ_R	K_S (M^{-1})[b]	ϵ_S	K_R/K_S	ϵ_R/ϵ_S
1	**1**	1658 ± 65	1987 ± 14	1645 ± 42	1940 ± 9		
2	(*S*,*S*,*S*,*S*)-**2**	169 ± 6	2702 ± 55	155 ± 2	2303 ± 15	1.1	1.2
3	(*S*,*S*,*S*,*S*)-**3**	87 ± 3	938 ± 36	62 ± 7	850 ± 30	1.4	1.1
4	(*S*,*S*,*S*,*S*)-**4**	56 ± 4	780 ± 20	49 ± 5	800 ± 25	1.1	1.0

[a] Conditions: [host **1**−**2**]$_0$ = 5.0 × 10^{-4} M; [host **3**−**4**]$_0$ = 1.0 × 10^{-3} M; [guest **9**]$_0$ = 1.0 × 10^{-1} M; 25.0 °C, methanol. [a] K_R and K_S denote association constants for (*R*)- and (*S*)-guests, respectively.

TABLE 3. Apparent Association Constants (K') of Complexes of Hosts 1−5 with Alanine Derivatives 11−12 in Methanol[a]

entry	host	guest	K'_R[d,e]	ϵ_R	K'_S[d,e]	ϵ_S	K'_R/K'_S	ϵ_R/ϵ_S
1[a]	**1**	**11**	1766 ± 106	4568 ± 123	1762 ± 68	4584 ± 102		
2[b]	**2**	**11**	2334 ± 121	890 ± 35	1554 ± 107	718 ± 24	1.5	1.2
3[c]	**3**	**11**	378 ± 15	895 ± 17	62 ± 13	630 ± 96	6.1	1.4
4[c]	**4**	**11**	148 ± 14	349 ± 29	328 ± 20	584 ± 20	0.45	0.60
5[c]	**5**	**11**	262 ± 29	320 ± 19	214 ± 17	341 ± 13	1.2	1.1
6[a]	**1**	**12**	1647 ± 55	6732 ± 113	1625 ± 62	6900 ± 123		
7[b]	**2**	**12**	2224 ± 94	1596 ± 30	1437 ± 78	1549 ± 41	1.5	1.0
8[c]	**3**	**12**	366 ± 10	1610 ± 21	65 ± 7	850 ± 30	5.6	1.9
9[c]	**4**	**12**	251 ± 10	410 ± 9	296 ± 11	781 ± 18	0.85	0.52
10[c]	**5**	**12**	208 ± 14	371 ± 15	245 ± 18	398 ± 13	0.85	0.93

[a] Conditions: (a) [host]$_0$ = 5.0 × 10^{-4} M; [NEP] = 5.0 × 10^{-2} M; 25.0 ± 0.1 °C; (b) [host]$_0$ = 5.0 × 10^{-4} M; [NEP] = 5.0 × 10^{-2} M; 15.0 ± 0.1 °C; (c) [host]$_0$ = 2.0 × 10^{-3} M; [NEP] = 5.0 × 10^{-1} M; 15.0 ± 0.1 °C. [d] K'_R and K'_S denote apparent association constants for (*R*)- and (*S*)-guests, respectively. [e] The apparent association constants (K') were determined in the following manner. K = [complex]/[host][guest][NEP] where [NEP] ≫ [host] and [guest]. Thus, [NEP] can be adequately approximated to constant ∴ $K' = K$ [NEP] = [complex]/[host][guest].

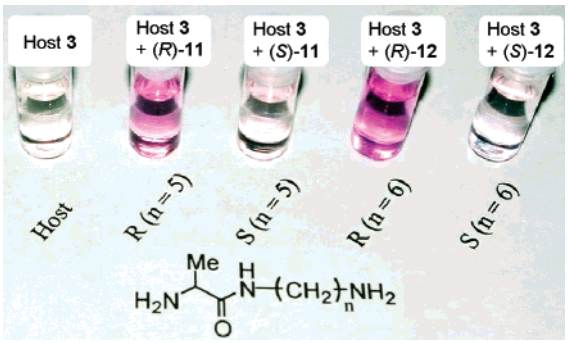

FIGURE 2. Color development by host **3**. Conditions: [host **3**] = 1.0 × 10^{-3} M, [guests **11**−**12**] = 1.0 × 10^{-2} M, [NEP] = 5.0 × 10^{-1} M, MeOH, 15.0 ± 0.1 °C.

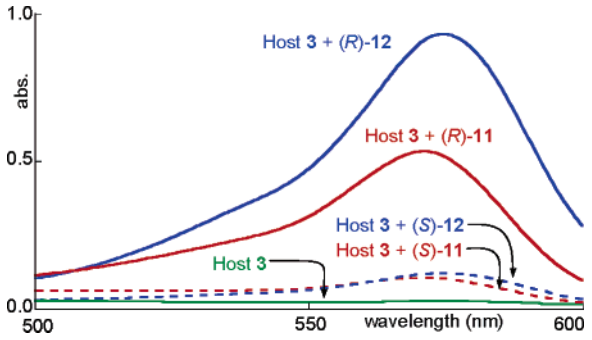

FIGURE 3. UV−vis spectra of host **3** with guests **11**−**12**. Conditions: [host **3**] = 1.8 × 10^{-3} M, [guests **11**−**12**] = 1.8 × 10^{-3} M, [NEP] = 5.0 × 10^{-1} M, MeOH, 15.0 ± 0.1 °C.

the association constants for **10** were too small to measure. Judging from the previous results with α,ω-diamines,[6] diamine **10** may develop color only weakly, since there are seven atoms between the two amino

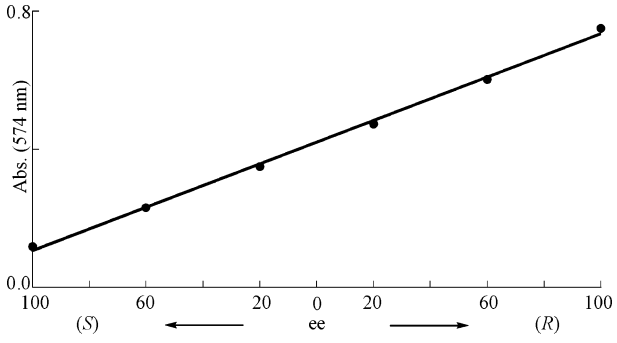

FIGURE 4. Linear relationship between the absorbance and the enantiomeric excess of guest **12**. Conditions: [host **3**] = 2.0 × 10^{-3} M, [guest **12**]$_{total}$ = 2.0 × 10^{-3} M, [NEP] = 5.0 × 10^{-1} M, MeOH, 15.0 ± 0.1 °C.

groups. The seven atoms including the amide bond are slightly shorter and more rigid than simple 1,7-diaminoheptane. This could explain why color development was not observed with diamine **10**.

An increase in the size of the substituents at the chiral center in guest molecules usually increases the extent of enantiomeric selectivity. However, no color development was observed with guest molecules **13** and **14** with larger substituents (R = Et, *i*-Pr). Only host (*S*,*S*,*S*,*S*)-**2** binds vaguely to guest **13** as measured by UV−vis titration and analyzed by the Benesi−Hildebrand method.[18] The apparent association constants and molar absorption coefficients were determined in the presence of NEP (5.0 × 10^{-1} M) by adding guest solutions (5.0 × 10^{-2} M) to 1.0 × 10^{-2} M of host **2** in methanol at 25 °C to give the following values: for (*R*)-**13**, K' = 40 M^{-1}, ϵ = 1145; for (*S*)-**13**, K' = 30 M^{-1}, ϵ = 708. These results

(18) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703−2707.

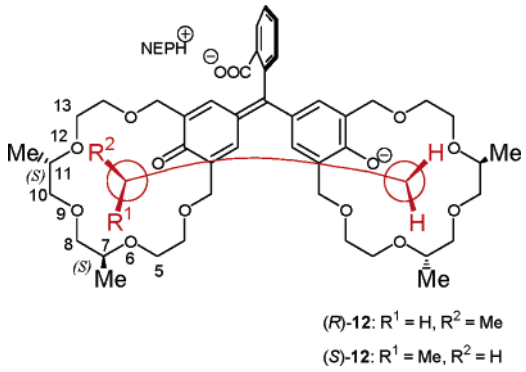

FIGURE 5. Proposed three-component colored complex.

indicated that even an ethyl or isopropyl group on the guest molecules was too bulky to form a complex under these conditions.

To explain this enantiomeric recognition, we considered steric repulsion between host **3** and guest **12**, since host **3** can strictly recognize the bulkiness of substituents at the α position of a terminal amino group of guests, as mentioned above. We assume that the three-component colored complex shown in Figure 5 should be generated. Thus, terminal amino groups of guest **12** bridge two phenolic crown rings of host **3** and $NEPH^+$ serves as a countercation of the carboxylate. Taking into account the steric repulsion between the methyl group at C-7 of the phenolic 18-crown-6 ring of **3** and the R^1 substituent of guest **12**, the complex between **3** and (*R*)-**12** is more stable than its diastereomeric complex. Thus, host **3** can discriminate between hydrogen and a methyl group of the guest molecule. Furthermore, this assumption can also be applied to the reverse selectivity between host **4** and guest **11** or **12** (Table 3, entries 3 vs 4 and 8 vs 9).

Visual Enantiomeric Recognition of *β*-Amino Alcohols. Although this visual recognition was accompanied by a sharp and drastic color change, the types of guest molecules were too restricted. Therefore, we next explored its broader application to other amino acid derivatives (i.e., *β*-amino alcohols). First, the visual enantiomeric recognition of chiral *β*-amino alcohols **15**−**22** with chiral hosts (*S*,*S*,*S*,*S*)-**2**−**5** was screened. Since these guest molecules lack two primary amino groups and the proper distance to bridge the two phenol crown rings of the hosts, feeble interaction and coloration might be expected. Therefore, screening of guests was carried out at low temperature (0 °C) under very highly concentrated conditions. Under these conditions, coloration based on host−guest interaction was certainly observed (Figure 6). Clear coloration gradually increased as the two methyl substituents were separated from the phenolic rings in the crown part. A similar tendency was observed in the visual enantiomeric recognition of alanine amide with 1,6-hexamethylenediamine **12** (mentioned above). However, at the point of chiral recognition, negligible differences could be perceived between enantiomeric pairs of guests by the human eye.

These data suggest that the methyl subunits on the crown ether were too sterically small to discriminate the chirality of *β*-amino alcohols. Therefore, we synthesized phenyl-substituted hosts **6** and **7**, where the phenyl group was expected to be an effective chiral barrier or attractive

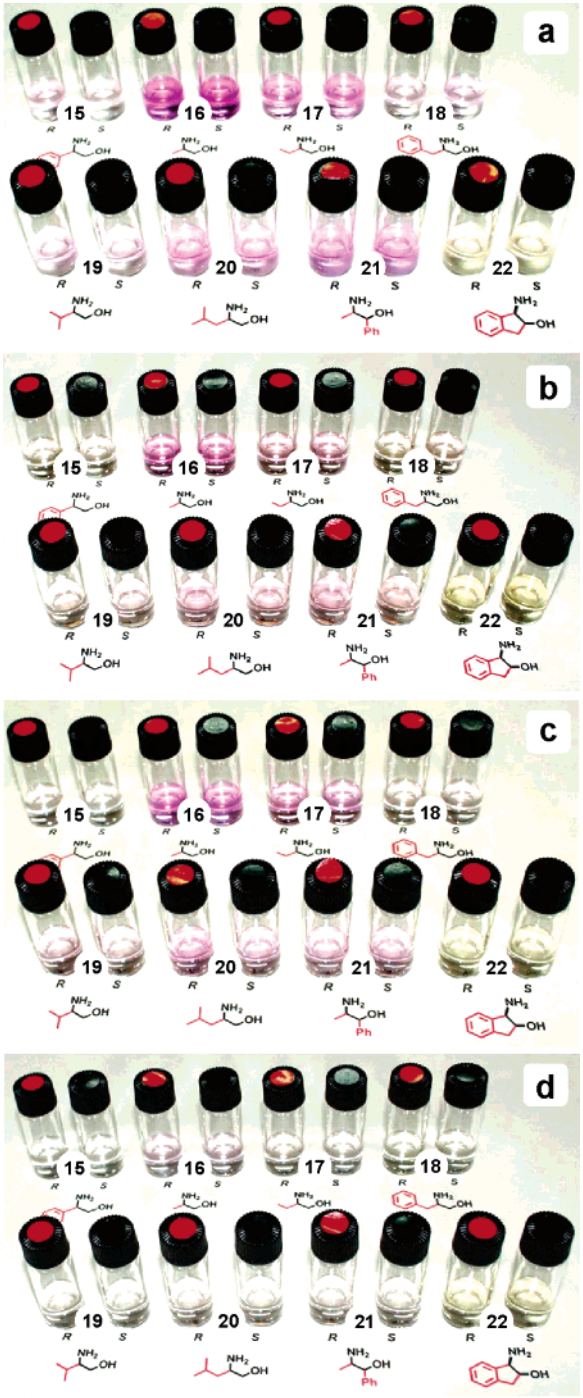

FIGURE 6. Color development by the hosts **2**−**5** with various *β*-amino alcohols. [hosts] = 5.0×10^{-3} M, (a) host **2**, (b) host **3**, (c) host **4**, (d) host **5**. [guests **15**−**22**] = 1.0×10^{-1} M in $MeOH/CHCl_3$ = 9/1 at 0 °C. Red label on the lid denotes (*R*)-configuration of guest. Key: **15**, 2-amino-2-phenylethanol; **16**, 2-amino-1-propanol; **17**, 2-amino-1-butanol; **18**, 2-amino-2-phenylethanol; **19**, 2-amino-3-methyl-1-butanol; **20**, 2-amino-4-methyl-1-pentanol; **21**, *erythro*-α-(1-aminoethyl)benzyl alcohol; **22**, *cis*-1-amino-2-indanol.

π-donor in complex with acidic hydrogen atoms of the guest molecules.

Clear coloration was observed with host **6** and *β*-amino alcohols (Figure 7a), whereas almost no coloration was detected using host **7** (Figure 7b). The coloration of host

FIGURE 7. Color development by the hosts **6**−**7** with various β-amino alcohols. [hosts] = 5.0×10^{-3} M, host **6** for **a**, host **7** for **b**, [guests **15**−**22**] = 1.0×10^{-1} M in MeOH/$CHCl_3$ = 9/1, 0 °C. Red label on the lid denotes (*R*)-configuration of guest.

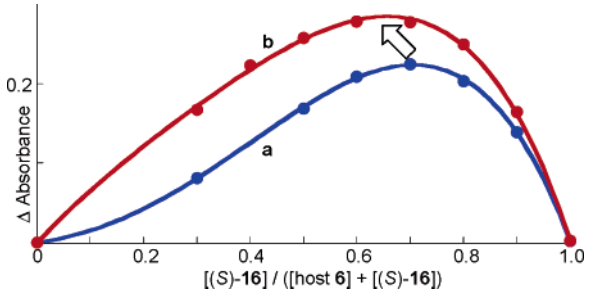

FIGURE 8. Job's plots of host **6** with (*S*)-**16** (a) in the absence of NEP (blue line) and (b) in the presence of NEP (red line). Conditions: (a) [host **6**] + [(*S*)-**16**] = 2.0×10^{-2} M, 570 nm; (b) [host **6**] + [(*S*)-**16**] = 2.0×10^{-2} M, [NEP] = 5.0×10^{-1} M, 569.5 nm, MeOH/$CHCl_3$ = 9/1, 10 °C.

6 (which has large phenyl groups at C-5 and C-13) with amines was generally deeper than that with the corresponding methyl-substituted host **4** (Figure 6c vs Figure 7a). Host **6** was selected for further investigations of enhanced functions. Figure 7a shows that coloration is sensitive to bulkiness around the amino group of the guest molecule (**18** vs **16** and **17**). Based on observation with the naked eye, the development of color between host **6** and (*S*)-guests is stronger than that between host **6** and (*R*)-guests in all cases.

Next, the stoichiometry of the colored complex formed by host **6** and guest (*S*)-**16** was determined by a Job's plot (Figure 8). The Job's plot exhibited a peak at approximately 0.7 and suggested that the host−guest ratio was 1:2 or 1:3 (Figure 8, blue line a). To clarify the stoichiometry of complex formation, the Job's plot was measured in the presence of a large excess of NEP. Figure 8 shows that under these conditions, the peak of the Job's

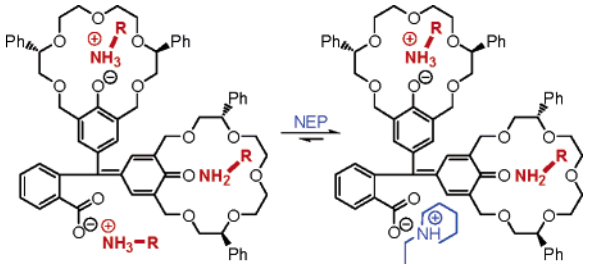

FIGURE 9. Proposed four-component colored complexes.

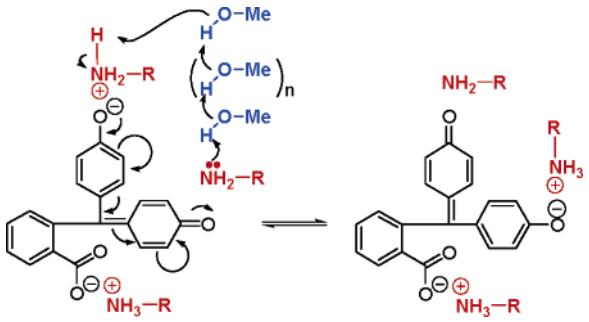

FIGURE 10. Proposed proton transfer through surrounding methanol. Crown ether parts have been omitted for clarity.

plot (red line b) shifted to 0.66. This behavior indicates that a four-component colored complex (in case a, host **6**/guest = 1:3, in case b, host **6**/NEP:guest = 1:1:2) should be generated in this solution (Figure 9). In Figure 9, these complexes are shown as canonical structures. Therefore, there may be some irrational interaction between the quinoid form of the phenolic crown ether of the host (right side) and the neutral amino group of the guest. We can interpret the actual complexes as follows (Figure 10): (i) the guest amines react with free host **6** to generate two kinds of dianions (see Scheme 1), (ii) with regard to "colored" complexes, a negative charge preferentially locates on the carboxylate, and another charge spreads over the two phenolic rings, and (iii) proton transfer takes place from the ammonium ion bound to the phenoxide form of the crown ether to the neutral amine bound to the quinoid form through intervention of the bulk solvent (methanol). Thus, both amines acquire a positive charge, depending on the time-scale of the above equilibrium. It should be pointed out, in this respect, that no coloration was observed in aprotic polar solvents such as $CHCl_3$, DMSO, and DMF.

We also found that the response of host **6** and (*S*)-**16** to temperature was completely different from that of host **6** and (*R*)-**16**.[19] Therefore, the relationship between color development and temperature was investigated. The temperature of the mixture of host **6** and guest was increased gradually from 0 °C to 50 °C over 50 min (1 °C/min), and wavelengths of absorption maxima (λ_{max}) were measured by UV−vis spectroscopy.[20] Some examples are shown in Figure 11a−h.

(19) For a recent review for temperature effect on the selectivity, see: (a) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515. (b) Cainelli, G.; Giacomini, D.; Galletti, P.; Marini, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *35*, 2849−2852.

(20) The actual variable-temperature UV spectra for a pair of diastereomeric complexes of host **6** and **15** are shown in Figure SI-1 (Supporting Information).

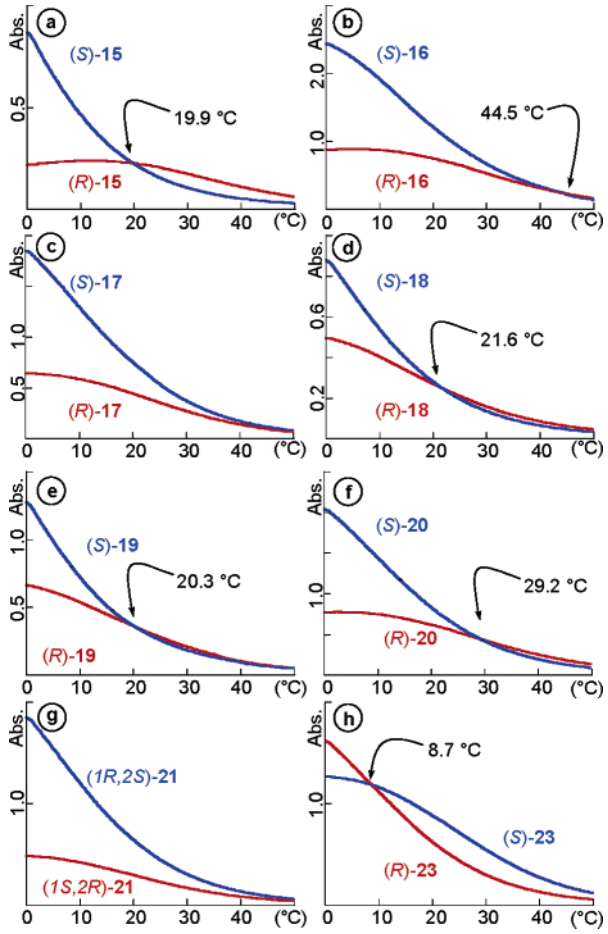

FIGURE 11. Temperature dependence of the absorbance of host **6** and guests. Conditions: [host **6**] = 5.0×10^{-3} M, [guest] = 1.0×10^{-1}, MeOH/$CHCl_3$ = 9/1, λ_{maxs} of the UV absorbance are plotted on the vertical axes (see Table 4).

As expected, the differences in color development with host **6** and (*R* or *S*)-amino alcohols **15**−**21** were enhanced as the temperature decreased. In contrast, simple amine **23** showed relatively small differences in color development. These data indicate that the hydroxy group adjacent to the amino group plays a crucial role in chiral recognition. We found absorbance inversion temperatures (AIT) in the range of 0−50 °C in many cases.[21] For example, Figure 11a shows that the absorption between host **6** and (*S*)-**15** is greater than that with (*R*)-**15** below 19.9 °C. In contrast, color development with host **6** and (*R*)-**15** is deeper above this temperature. Although this phenomenon should theoretically exist for any diastereomeric combination of a host and a guest (if their $\Delta\Delta S$ is not 0), actual observations were uncommon. We defined visual enantiomeric discrimination (VED) values to conveniently reflect the enantiomeric discrimination ability as follows:

$$\text{VED} = \text{abs(host } \mathbf{6} - (S)\text{-guest)/abs(host } \mathbf{6} - (R)\text{-guest)}$$

$$(\text{[host } \mathbf{6}] = 5.0 \times 10^{-3}\ \text{M, [guest]} = 1.0 \times 10^{-1}, \text{MeOH/CHCl}_3 = 9/1, \lambda_{max}, 0\ ^\circ\text{C})$$

TABLE 4. Wavelength of Maximal Absorption (λ_{max}), Visual Enantiomeric Discrimination Values (VED), and Absorbance Inversion Temperature (AIT)[a]

guest	λ_{max} (*S*) (nm)	λ_{max} (*R*) (nm)	VED	AIT (°C)
15	571.5	569.5	3.86	19.9
16	571.0	569.0	2.77	44.5
17	571.0	569.5	2.88	
18	571.0	569.5	1.78	21.6
19	571.0	569.0	1.92	20.3
20	571.0	569.5	2.64	29.2
21	571.0	570.0	3.83	
22	572.0	569.5	1.92	
23	571.5	572.0	0.78	8.7

[a] Conditions: [host **6**] = 5.0×10^{-3} M, [guest] = 1.0×10^{-1} M, MeOH/$CHCl_3$ = 9/1.

The VED values, λ_{max}, and AIT are listed in Table 4.

The VED values are approximately 1.8−3.8, and the discrimination of enantiomers could be easily determined by the naked eye.[22] In addition, the λ_{max} value of complex of host **6** with (*R*)-**23** is larger than those of host **6** with β-amino alcohols. This phenomenon presumably suggests that hydrogen bonding between the oxygen atom of host **6** and the −O*H* hydrogen of the guest stabilized the ground state of the colored complex.

In conclusion, we have developed phenolphthalein-based hosts with methyl- or phenyl-substituted crown ethers. Host (*S*,*S*,*S*,*S*)-**3** can discriminate the chirality of alanine amides by a color change that is discernible by the naked eye. Host (*S*,*S*,*S*,*S*)-**6** could be widely applicable as a chiral indicator for β-amino alcohols. We also observed that the strength of color development with host **6**, and (*S*)- or (*R*)-guest was reversed at the absorbance inversion temperature. Furthermore, this molecular recognition based on hydrogen bonding, Coulomb force, and ion−dipole interaction in a protic solvent is a challenging subject in supramolecular chemistry. We are currently extending this system to an aqueous medium.

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Supporting Information Available: Full experimental details, variable-temperature UV spectra for a pair of diastereomeric complexes of host **6** and **15**, and the relationship between the absorbance and the enantiomeric excess of guest **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050387U

(21) Temperature-dependent reversal of the enantiomer selectivity was reported. Naemura, K.; Fuji, J.; Ogasahara, K.; Hirose, K.; Tobe, Y. *Chem. Commun*. **1996**, 2749−2750.

(22) Because we cannot estimate the proportion of colorless complex (see Scheme 1 and ref 6b), the association constants of the colored complex between host **6** and (*R*)- and (*S*)-guests have not been determined yet. In fact, a curious relationship was observed between the absorbance (λ_{max}, 570 nm) and the enantiomeric excess of guest **15** (Figure SI-2, Supporting Information). We suppose these phenomena may be caused by the complicated equilibrium among colored **6**−(*S*)-**15**, colored **6**−(*R*)-**15**, colorless **6**−(*S*)-**15**, and colorless **6**−(*R*)-**15**.