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# Visual Enantiomeric Recognition Using Chiral Phenolphthalein Derivatives

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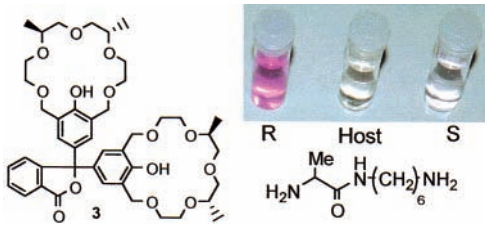
## ABSTRACT




**Optically active artificial host molecules 2–5 based on a phenolphthalein skeleton have been prepared for visual enantiomeric recognition of alanine derivatives 8 and 9. The receptor 3 discriminates (*R*)-8 and (*R*)-9 from (*S*)-8 and (*S*)-9, respectively, to develop a purple color.**

Since the enantiomeric recognition of chiral compounds was first reported by Cram in the 1970s,[1] it has attracted considerable attention, and various kinds of host molecules have been synthesized.[2] In addition, visual recognition is one of the most interesting topics in the field of supramolecular chemistry, and color-producing host molecules that can discriminate metal cations,[3] the length of guest molecules[4] and anionic species[5] have been reported. Furthermore, some of them can discriminate enantiomers on the basis of a color change in solution.[6] Hirose and Tobe[6b−d] systematically investigated complexation between chiral phenolic 18-crown-6 and 2-substituted 2-aminoethanol in chloroform solution and found that the hydroxy group of the guest and substituents at the 5 and 13 positions (Figure 1) of the phenolic 18-crown-6 play a crucial role in visual chiral recognition.

Recently, we reported that compound **1**, a hybrid molecule consisting of phenolphthalein and two loops of crown ether, could recognize the length of α,ω-diamines by developing a purple color, especially with 1,8-diaminooctane and 1,9-diaminononane.[4] We report here the visual recognition of enantiomers of alanine derivatives **8** and **9** using the chiral host **3**.

The chiral host molecules **2**−**5** were synthesized by a procedure similar to that for **1**,[4] and key chiral methyl-substituted ether subunits were prepared from (*S*)-ethyl lactate.[6c,7] Therefore, the absolute configurations of all of the host molecules **2**−**5** are (*S*,*S*,*S*,*S*). First, the interaction between hosts **1**−**5** and achiral triamine **6** was examined using UV−visible spectroscopy to obtain a fundamental host−guest relationship. With the addition of triamine **6** to

(1) (a) Helgeson, R. C.; Koga, K.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc*. **1973**, *95*, 3021−3023. (b) Helgeson, R. C.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc*. **1973**, *95*, 3023−3025.

(2) For a recent review: (a) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev*. **1997**, *97*, 3313−3361. (b) Kurtán, T.; Nesnas, N.; Li, Y.-Q.; Huang, X.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc*. **2001**, *123*, 5962−5973. (c) Kurtán, T.; Nesnas, N.; Koehn, F. E.; Li, Y.-Q.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc*. **2001**, *123*, 5974−5982.

(3) (a) Inouye, M.; Akamatsu, K.; Nakazumi, H. *J. Am. Chem. Soc*. **1997**, *119*, 9160−9165. (b) Kim, J. S.; Shon, O. J.; Ko, J. W.; Cho, M. H.; Yu, I. Y.; Vicens, J. *J. Org. Chem*. **2000**, *65*, 2386−2392. (c) Tanaka, M.; Nakamura, M.; Salhin, M. A. A.; Ikeda, T.; Kamada, K.; Ando, H.; Shibutani, Y.; Kimura, K. *J. Org. Chem*. **2001**, *66*, 1533−1537.

(4) Fuji, K.; Tsubaki, K.; Tanaka, K.; Hayashi, N.; Otsubo, T.; Kinoshita, T. *J. Am. Chem. Soc*. **1999**, *121*, 3807−3808.

(5) (a) Niikura, K.; Metzger, A.; Anslyn, E. V. *J. Am. Chem. Soc*. **1998**, *120*, 8533−8534. (b) Niikura, K.; Bisson, A. P.; Anslyn, E. V. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1111−1114. (c) Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 10438−10439. (d) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed*. **2000**, *39*, 1777−1780. (e) Lücking, U.; Rudkevich, D. M.; Rebek, J., Jr. *Tetrahedron Lett*. **2000**, *41*, 9547−9551. (f) Miyaji, H.; Sessler, J. L. *Angew. Chem., Int. Ed*. **2001**, *40*, 154−157. (g) Kato, R.; Nishizawa, S.; Hayashita, T.; Teramae, N. *Tetrahedron Lett*. **2001**, *42*, 5053−5056. (h) Lee, D. H.; Lee, K. H.; Hong, J.-I. *Org. Lett*. **2001**, *3*, 5−8.

(6) (a) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522−524. (b) Naemura, K.; Tobe, Y.; Kaneda, T. *Coord. Chem. Rev*. **1996**, *148*, 199−219. (c) Ogasahara, K.; Hirose, K.; Tobe, Y.; Naemura, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3227−3236. (d) Hirose, K.; Ogasahara, K.; Nishioka, K.; Tobe, Y.; Naemura, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1984−1993.

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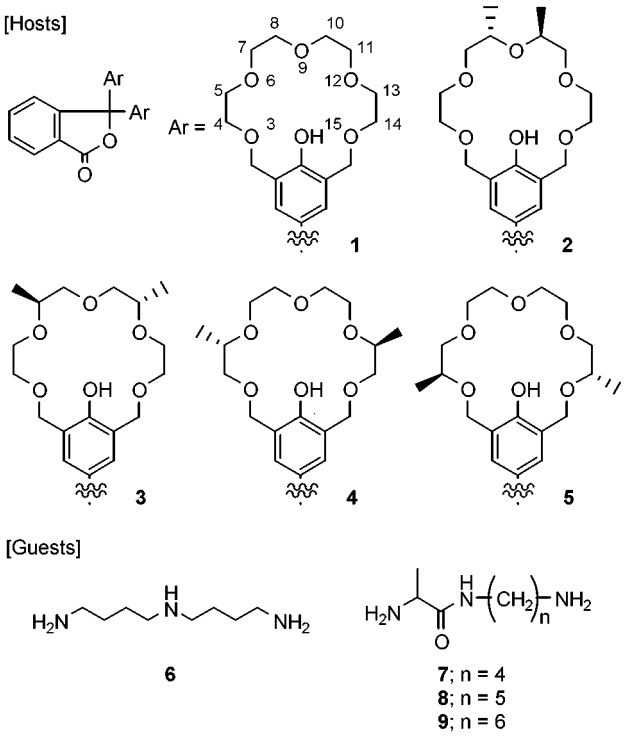


**Figure 1.** The structures of hosts **1**−**5** and guests **6**−**9**.

a solution of host in methanol at 25.0 °C, a color change (from colorless to purple) based on an increase in the absorption band at around 570 nm was observed. UV−visible titration allowed us to determine the association constants ($K$) and molar absorption coefficients ($\epsilon$), which were analyzed by the Rose−Drago method.[8] Table 1 shows that

**Table 1.** Association Constants ($K$) and Molar Absorption Coefficients ($\epsilon$) of Complexes of Hosts **1**−**5** with Triamine **6** at 25.0 °C in Methanol[a]

| entry | host | K ($M^{-1}$) | $\epsilon$ |
|---|---|---|---|
| 1 | **1** | 2270 ± 30 | 5080 ± 20 |
| 2 | **2** | 274 ± 3 | 5900 ± 32 |
| 3 | **3** | 208 ± 4 | 1525 ± 18 |
| 4 | **4** | 96 ± 2 | 1724 ± 30 |
| 5 | **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.

the association constants ($K$) decreased sharply with the introduction of two methyl groups into the phenolic crown ring. Furthermore, the $K$ values gradually increased as the two methyl substituents were separated from the phenolic rings in the crown part (entries 2−5). A similar tendency was observed for the molar absorption coefficient ($\epsilon$). Consequently, the degree of coloration (absorbance) should depend on the concentration of the host−guest complex and the molar absorption coefficient ($\epsilon$) of the complex.

We next examined the visual enantiomeric recognition of chiral guest ($R$) or ($S$)-alanine derivatives **7**−**9** using chiral

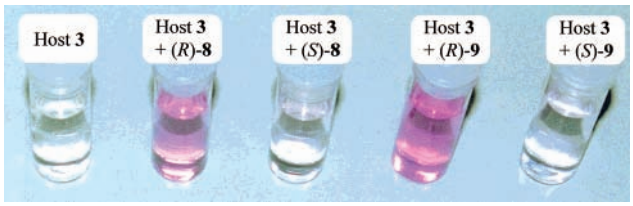


**Figure 2.** Color development by the host **3**. The concentration of host **3** was 1.0 × $10^{-3}$ M and those of guests **8** and **9** were 1.0 × $10^{-2}$ M in the presence of $N$-ethylpiperidine (5.0 × $10^{-1}$ M) in methanol.

hosts **2**−**5**. Since relatively small association constants might be expected on the basis of the data in Table 1, UV-visible titration experiments were carried out at 15 °C in the presence of a large excess of $N$-ethylpiperidine.[9] The apparent association constants ($K'$) and molar absorption coefficients ($\epsilon$) are summarized in Table 2. These data clearly indicate that the position of the methyl groups on the phenolic 18-crown-6 crucially affects the enantiomeric recognition of ($R$)- and ($S$)-alanine derivatives **8** and **9**. The binding ability of host **2** is greater than those of other chiral hosts, but enantiomeric recognition was hardly observed. Host **3**, which has two methyl groups at C-7 and C-11 of the 18-crown-6 ring, showed prominent enantiomeric selectivity. Interestingly, host **4** showed the reverse selectivity, which favors the ($S$)-enantiomer (entries 4 and 9). The difference in coloration is shown in Figure 2 as well as in UV−vis absorption spectra (Figure 3).

The combination of host **3** with guests ($R$)-**8** or ($R$)-**9** gave a purple color, whereas no color development was observed

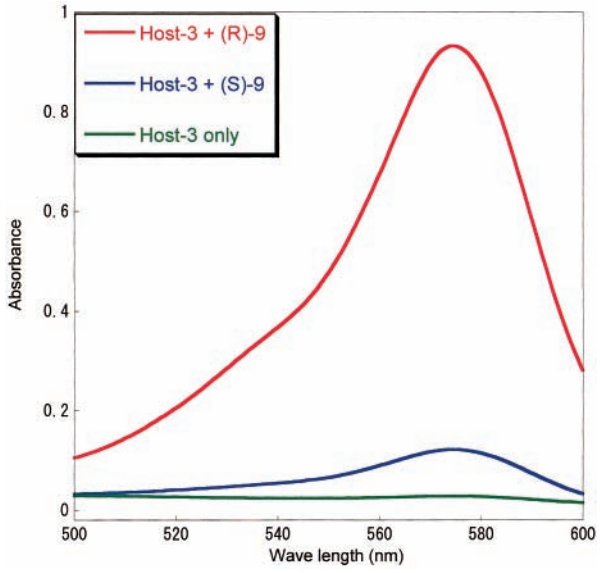


**Figure 3.** UV−vis spectra of host **3** with guest **9**. The concentration of host **3** was 1.8 × $10^{-3}$ M, and that of guest **9** was 1.8 × $10^{-3}$ M in the presence of $N$-ethylpiperidine (5.0 × $10^{-1}$ M) in methanol at 15.0 ± 0.1 °C.

**Table 2.** Apparent Association Constants ($K'$) of Complexes of Hosts **1**−**5** with Alanine Derivatives **8** and **9** in Methanol

| entry | host | guest | $K'_R$[d,e] | $\epsilon_R$ | $K'_S$[d,e] | $\epsilon_S$ | $K'_{large}/K'_{small}$ | $\epsilon_{large}/\epsilon_{small}$ |
|---|---|---|---|---|---|---|---|---|
| 1[a] | **1** | **8** | 1766 ± 106 | 4568 ± 123 | 1762 ± 68 | 4584 ± 102 | | |
| 2[b] | **2** | **8** | 2334 ± 121 | 890 ± 35 | 1554 ± 107 | 718 ± 24 | 1.5 | 1.2 |
| 3[c] | **3** | **8** | 378 ± 15 | 895 ± 17 | 62 ± 13 | 630 ± 96 | 6.1 | 1.4 |
| 4[c] | **4** | **8** | 148 ± 14 | 349 ± 29 | 328 ± 20 | 584 ± 20 | 2.2 | 1.7 |
| 5[c] | **5** | **8** | 262 ± 29 | 320 ± 19 | 214 ± 17 | 341 ± 13 | 1.2 | 1.1 |
| 6[a] | **1** | **9** | 1647 ± 55 | 6732 ± 113 | 1625 ± 62 | 6900 ± 123 | | |
| 7[b] | **2** | **9** | 2224 ± 94 | 1596 ± 30 | 1437 ± 78 | 1549 ± 41 | 1.5 | 1.0 |
| 8[c] | **3** | **9** | 366 ± 10 | 1610 ± 21 | 65 ± 7 | 850 ± 30 | 5.6 | 1.9 |
| 9[c] | **4** | **9** | 251 ± 10 | 410 ± 9 | 296 ± 11 | 781 ± 18 | 1.2 | 1.9 |
| 10[c] | **5** | **9** | 208 ± 14 | 371 ± 15 | 245 ± 18 | 398 ± 13 | 1.2 | 1.1 |

[a] $[host]_0 = 5.0 \times 10^{-4}$ M; [*N*-ethylpiperidine] $= 5.0 \times 10^{-2}$ M; 25.0 ± 0.1 °C. [b] $[host]_0 = 5.0 \times 10^{-4}$ M; [*N*-ethylpiperidine] $= 5.0 \times 10^{-2}$ M; 15.0 ± 0.1 °C. [c] $[host]_0 = 2.0 \times 10^{-3}$ M; [*N*-ethylpiperidine] $= 5.0 \times 10^{-1}$ 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]·[*N*-ethylpiperidine] where [*N*-ethylpiperidine] ≫ [host] and [guest]. Thus, [*N*-ethylpiperidine] can be adequately approximated to constant ∴ $K' = K$ [*N*-ethylpiperidine] = [complex]/[host]·[guest].

with host **3** and (*S*)-**8** or (*S*)-**9**. Thus, the chirality of the guest could be easily determined by the naked eye. The diamine **7** gave no color with hosts **1**−**5**, although 1,7-diaminoheptane, which has seven carbon atoms between the two amino groups, gives a purple color with **1**.[4] The seven atoms including the amide bond are slightly shorter and more rigid than those of simple 1,7-diaminoheptane. This could explain why color development was not observed with diamine **7**. A three-component complex, generated from host **3**, guest **9** and *N*-ethylpiperidine, may be responsible for the recognition of enantiomers. Thus, the terminal amino groups of guest **9** bridge two phenolic crown rings of host **3**, in such a way that the $\omega$-amino group coordinates with the phenolic oxygen atom and the α-amino group interacts with the carbonyl of quinoid form.[10] The *N*-ethylpiperidinium cation serves as a counter cation for the carboxylate that is generated from ring opening of the $\gamma$-lactone in **3**. 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 **9**, the complex between **3** and (*R*)-**9** is more stable than that with the latter's diastereomer. Thus, host **3** can discriminate between hydrogen and the methyl group of the guest molecule. This discrimination is one of the most challenging subjects in molecular recognition chemistry. Furthermore, this assumption can also be applied to the reverse selectivity seen between host **4** and guests **8** or **9** (Table 2, entries 3 vs 4 and 8 vs 9).

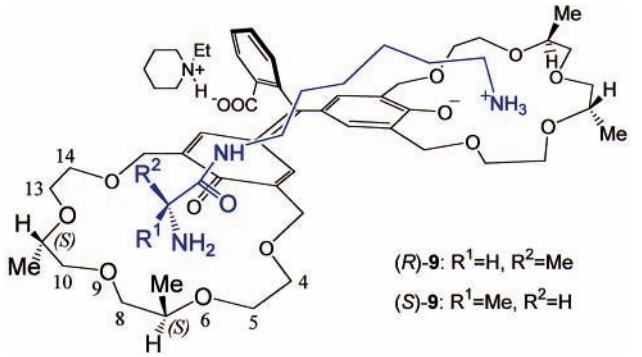


**Figure 4.** Proposed colored complex of host **3**, guest **9**, and *N*-ethylpiperidine.

In conclusion, we have developed optically active artificial host molecules based on a phenolphthalein skeleton for the visual enantiomeric recognition of alanine derivatives. Host **3** makes it possible to discriminate between hydrogen and a methyl group of guest molecules **8** and **9** with the naked eye. We are currently modifying the host structure to develop more general hosts for the discrimination of optically active amino acid derivatives.

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(7) (a) Cooper, K. D.; Walborsky, H. M. *J. Org. Chem.* **1981**, *46*, 2110−2116. (b) Huszthy, P.; Oue, M.; Bradshaw, J. S.; Zhu, C. Y.; Wang, T.; Dalley, N. K.; Curtis, J. C.; Izatt, R. M. *J. Org. Chem.* **1992**, *57*, 5383−5394.

(8) (a) Rose, N. J.; Drago, R. S. *J. Am. Chem. Soc.* **1959**, *81*, 6138−6145. (b) Hirose, K. *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *39*, 193−209.

(9) *N*-Ethylpiperidine itself gave no color; see ref 4.

(10) The $pK_a$ values are 9.19 and 10.79 for the α-amino and the $\epsilon$-amino groups.[11]

(11) Dawson, R. M. C.; Elliott, D. C.; Jones, K. M. *Data for Biochemical Research*; Oxford University Press: Oxford, 1969.