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Chiral Recognition of Amino Acid Derivatives by 1,1'-Binaphthalene-8,8'-diol

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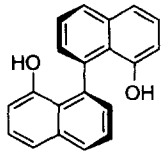
Abstract: Optically active 1,1'-binaphthalene-8,8'-diol is found to bind a variety of amines in $CDCl_3$ or C_6D_6 solution. Significant chiral recognition ($\Delta\Delta G°$ = ~1.2 kcal/mol) was observed in the valine derivative **4**. A three-point binding motif is assumed.

Chiral recognition of organic substrates through non-covalent host-guest interaction has attracted increasing attention in recent years, since the process is directly applicable to chromatographic,[1] transporting,[2] catalytic,[3] and chemosensory[4] methodology. Several examples have been reported of chiral recognition of amino acids[5], sugars[4], ammonium ions[6], and organic acids[7] using well-designed organic host molecules. We have been interested in developing the ability of 1,1'-binaphthalene-8,8'-diol (**1**) and (**2**) and its derivatives as new chiral sources.[8, 9] The excellent properties of **3** as a proton source for enantioselective protonation of enolates have been explored.[8] These compounds are also expected to function as host molecules that discriminate chirality of organic guest molecules because two hydrogen donors and/or acceptors are located in a highly asymmetric micro environment. In this paper, we report preliminary studies on chiral recognition by **1** and **2** of amino acid derivatives, amino alcohols, and amines caused.[10]



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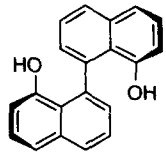

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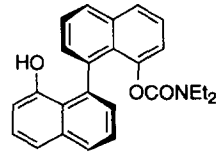

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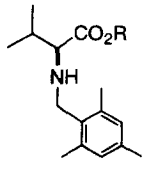
^{1}H-NMR binding studies[11] at 20 °C showed that amines **4** ~ **13** form diastereomeric complexes with enantiomers **1** (*R*) and **2** (*S*) in organic solvents. Table 1 gives the association constants, *K*a, and the difference in stability between the diastereomeric complexes, $\Delta\Delta G°$. Chiral recognition is most pronounced for the complexes of valine derivative **4** {$\Delta\Delta G°$ = 1.0~1.2 kcal/mol (enantioselectivity of ~88:12), entries 1 and 2}. The corresponding methyl ester **5** and a free amine **6** showed much reduced enantioselectivity in the binding with **1** and **2** ($\Delta\Delta G°$ ~ 0.3 kcal/mol, entries 3-5). In phenylalanine derivatives **7** ~ **9**, chirality was

scarcely recognized by **1** and **2** ($\Delta\Delta G°$ ~ 0.2 kcal/mol, entries 6-10).[12] In both amino acid derivatives, zwitterions **4** and **7** caused stronger binding than the corresponding esters **5** and **8**, respectively (entries 1 *vs* 3, 2 *vs* 4, 6 *vs* 7). Computer-assisted modeling of the binding motif of **4** and **1** was carried out by a MacroModel/MCMM conformational search[13] using AMBER*[14] force field. The most stable structure of the complex between **4** and **1** is shown in Figure 1. Characteristic features are: 1) the carboxylate moiety of **4** is hydrogen-bonded with two phenolic OHs,[15] 2) the ammonium moiety of **4** is closely located on the naphthalene ring through ammonium-π interaction,[16] 3) the *iso*-propyl group of **4** is located closely on the naphthalene ring, which could be ascribed to CH-π interaction[17] or the dispersion force. These calculation results are consistent with the observed ^{1}H-NMR phenomena in $CDCl_3$-C_6D_6 (2:1). The protons,

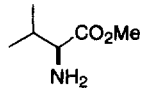
Table 1. Association Constants *K*a between Guest Compounds (**4~13**) and Host Compounds (**1**and **2**) and the Difference in Binding Energy $\Delta\Delta G°$ between Diastereomeric Complexes (T=293K).

			*K*a (L/mol)		
entry	guest	solvent	**1** (host)	**2**	$\Delta\Delta G°^a$ (kcal/mol)
1	**4**	$CDCl_3$	80	11	1.2
2	**4**	$CDCl_3$ - C_6D_6 (2:1)	150	26	1.0
3	**5**	$CDCl_3$	~0	~0	-
4	**5**	C_6D_6	10	5.6	0.3
5	**6**	C_6D_6	10	9.8	<0.1
6	**7**	$CDCl_3$	41	37	<0.1
7	**8**	$CDCl_3$	~0	~0	-
8	**8**	C_6D_6	6.0	5.0	0.1
9	**9**	$CDCl_3$	~0	~0	-
10	**9**	C_6D_6	15	11	0.2
11	**10**	$CDCl_3$	8.4	11[b]	0.2
12	**10**	C_6D_6	41	34[b]	0.1
13	**11**	$CDCl_3$	15	15[c]	<0.1
14	**11**	C_6D_6	40	35	<0.1
15	**12**	$CDCl_3$	19	19	<0.1
16	**12**	C_6D_6	77	78	<0.1
17	**13**	$CDCl_3$	4.0	2.7[d]	0.2
18	**13**	C_6D_6	34	32[d]	<0.1

a) Differnce in stability between diatereomeric complexes, guest-**1** and guest-**2**.
b) *K*a between *ent*-**10** and **1**. c) *K*a between *ent*-**11** and **1**. d) *K*a between *ent*-**13** and **1**.



4 : R = H
5 : R = Me



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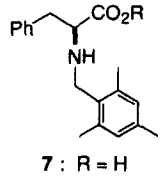
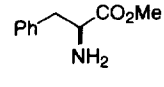


7 : R = H
8 : R = Me



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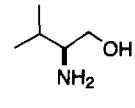

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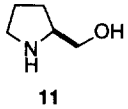

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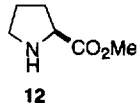

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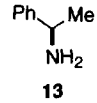

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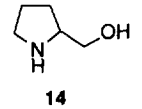

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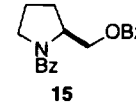

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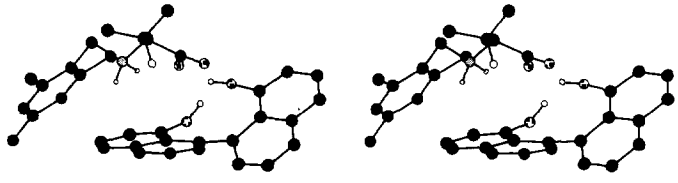
-NHC$\underline{H}_2$Ar and -CH(C$\underline{H}_3$)$_2$ of **4** (0.014 M), exhibited up-field shifts of 0.41 and 0.27 ppm, respectively, in the presence of **1** (0.037 M). Thus, a three-point binding motif can be assumed; nonetheless, the structure of the host molecule **1** is quite simple. Calculations of the most stable structure[18] of the complex between **4** and **2** indicated a lower stability than that between **4** and **1** by 0.6 kcal/mol, which is roughly consistent with the experimental results shown in Table 1, entries 1 and 2. We should note, however, the above discussions are significant only in the binding of valine derivative **4**, since the corresponding phenylalanine derivative **7** showed much reduced enantioselectivity in the binding with **1** and **2**. Amino alcohols **10, 11** and amines **12, 13** showed complex formation with **1** and **2** without noticeable chiral recognition (entries 11 ~ 18). Binding between guests and hosts is stronger in C_6D_6 than in $CDCl_3$. This implies that the major binding force is hydrogen bonding.

Figure 1



Computer-assisted binding motif (stereoview) between **4** and **1**. Hydrogens, except the interacting ones, are omitted for clarity.

We next examined optical resolution through clathrate formation with **2**. A mixture of racemic pyrrolidine-2-methanol (**14**) (110 mg, 1.1 mmol) and **2** (280 mg, 0.89 mmol) in benzene was kept at room temperature to give precipitates, which were then recrystallized twice from benzene to furnish a 1:1 complex of **11** (*S*, 98% ee) and **2** (153 mg, 36% yield). The absolute configuration and the ee were determined by its transformation into **15**.[19] The highly diastereoselective clathrate formation does not seem to originate in the diastereoselectivity of the complex formation between **14** and **2** in solution. In both $CDCl_3$ and C_6D_6 solution, **11** showed complex formation with **1** and **2**, but without noticeable chiral recognition (Table 1, entries 13 and 14).

In conclusion, we have shown the potential ability of 1,1'-binaphthalene-8,8'-diol for chiral recognition. Since the simple structure already possesses the functionalities responsible for hydrogen bonding, XH-π, CH-π, and π-π interactions, highly enantioselective recognition would be feasible through further functionalization of the structure.

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17. The calculated distance between C<u>H</u>Me$_2$ and the nearest aromatic carbons is 3.05-3.09 Å. For an excellent review on CH-π interaction, see: M. Nishio, Y. Umezawa, M. Hirota, Y. Takeuchi, *Tetrahedron*, **51**, 8665 (1995).
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