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A New Twisted Dual Hydrogen Bond Acceptor Featuring Amidine Functionality for Chiral Recognition: A High Level of Enantioselection of Diol Derivatives

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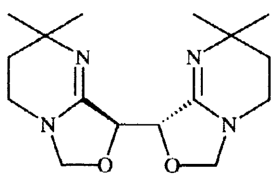
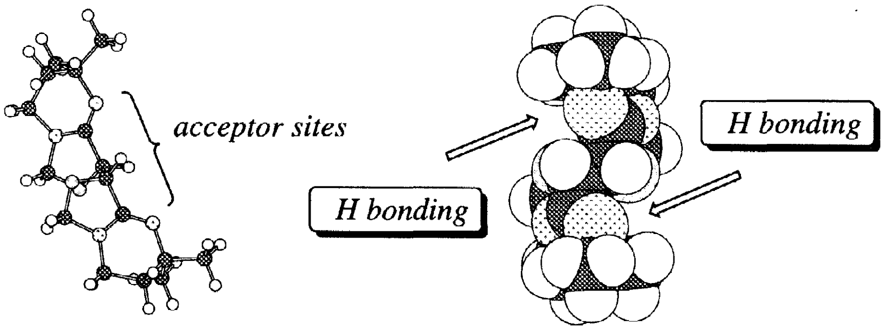
Abstract: The C_2 amidine derivative *(S,S)*-**1**, as a twisted chiral dual acceptor for hydrogen bonding, was designed and synthesized. Enantioselective binding between *(S,S)*-**1** and a series of diol enantiomers was investigated by NMR spectroscopy. High enantioselection above 1.0 kcal/mol was achieved in $CDCl_3$. The association mode based on dual N···HO interactions was confirmed by intermolecular NOEs. © 1997 Elsevier Science Ltd. All rights reserved.

The generation of enantioselectivity in the molecular complexation continues to be an intriguing subject in the area of artificial molecular recognition. A high level of enantioselection was achieved through a rational design of the molecular system utilizing multiple hydrogen bonding as the driving force for stereoselective complexation.[1] In all systems created, directionality and strength of hydrogen bonding between complementary functionalities are the key factors responsible for generating enantioselectivity. The preliminary *ab initio* calculation in this laboratory indicated that the interaction between the imino nitrogen of N^{im}-methylformamidine and hydroxyl hydrogen of methanol was remarkably strong and directive.[2] Our approach to chiral recognition is to exploit the complementarity of twists in dual hydrogen bonding.[3] The above computational study expanded this approach and thus led to the design of a new C_2 structure of chiral amidine derivative *(S,S)*-**1** illustrated below. In this paper, we report the synthesis of *(S,S)*-**1** and its enantioselectivity toward diol enantiomers through dual N···HO interactions in $CDCl_3$.

The present chiral host shows the binding surface when it adopts conformation as depicted in the figure (right).[4] Dual hydrogen bonds to the two amidine units embedded in this molecular surface are characterized in terms of the torsion between them, the sense of which reflects the absolute configuration of *(S,S)*-**1**. This hydrogen bonding array forces the enantiomeric pair of the dual hydrogen bond donor such as a diol to orientate in a different sense of twist upon complexation. Due to the difference in the interactions depending on the stereochemistry, the transient diastereomers thus formed differ in their stability.



(S,S)-**1**



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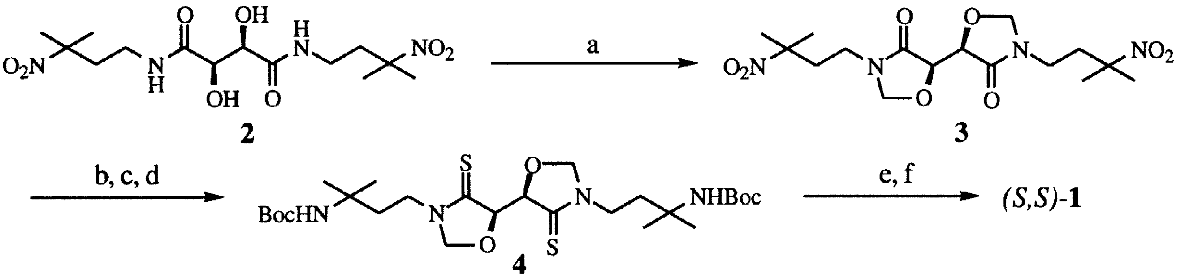
Scheme 1 describes a synthesis of *(S,S)*-**1**. *N,N'*-Dialkyltartramide derivative **2** prepared by a simple aminolysis of *(R,R)*-dimethyl tartrate with the corresponding amine was made to react with dimethoxymethane in the presence of boron trifluoride etherate. The bis five-membered lactam **3** thus obtained was subjected to hydrogenolysis catalyzed by Raney Nickel. After the protection of the amino groups with a *tert*-butoxycarbonyl group (Boc), the lactam derivative was converted to the tiolactam through the reaction with Lawesson's reagent.[5] The intramolecular cyclization following deprotection of the amino functionality of the thiolactam derivative **4** was accomplished by a treatment with mercury (II) salt, yielding *(S,S)*-**1** as a crystalline product.[6]

Scheme 1

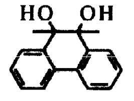


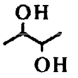
a) $CH_2(OCH_3)_2$, $BF_3 \cdot OEt_2$, CH_2ClCH_2Cl, reflux, 65%; b) H_2/Raney-Ni (W-4), 715 psi, EtOH, rt; c) $(Boc)_2O$, $CHCl_3$, rt, 81% from **3**; d) Lawesson's reagent, toluene, 90 °C, 81%; e) CF_3COOH, rt; f) $(CF_3COO)_2Hg$, THF, rt, 48% from **4**.

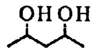
To demonstrate the efficacy of the newly constructed binding surface in generating enantioselectivity, complexation of *(S,S)*-**1** with different diol enantiomers containing 1,2-, 1,3- and 1,4-diol was examined by ^{1}HNMR spectroscopy. On addition of *(S,S)*-**1** to a $CDCl_3$ solution containing the diol derivative, a large downfield shift indicating the hydrogen bond formation with *(S,S)*-**1** was observed for the resonance of the hydroxyl protons.[7] The shift change of these sensor nuclei was monitored during the titration experiment to collect data required for establishing the binding isotherm. Titration was conducted keeping the concentration of the diol enantiomer constant.[8] A series of data obtained was subjected to a curve fitting procedure based on the non-linear least squares method assuming 1:1 stoichiometry for complexation. The association constants and limiting shift differences due to the complexation are listed in Table 1. A correlation coefficient above 0.999 was obtained in all cases. In confirmation of 1:1 binding stoichiometry, Job's plot using the calculated limiting shift of a diol in the complex resulted in a symmetrical convex curve with a maximum at a 1:1 mixing ratio of *(S,S)*-**1** to the diol enantiomer.

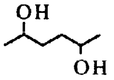
As summarized in the table, *(S,S)*-**1** exhibited the enantioselectivity toward all types of diol derivatives examined. The enantioselection exceeding 1.0 kcal/mol was achieved for the interaction with an enantiomeric pair of **5** and that of **7**. The binding and enantioselectivity in the present system were enhanced when temperature decreased. For example, association constants and enantioselectivity determined for the *(S,S)*-**1**-*trans*-**5** system at 263K were $K_{SS} = 10735\ M^{-1}$ and $K_{SS}/K_{RR} = 11.8$. A van't Hoff plot[9] based on the data obtained for this complexation system at four different temperatures indicated $\Delta H_{SS} = -12.4$ kcal/mol, $\Delta S_{SS} = -28.6$ e.u., $\Delta H_{RR} = -9.8$ kcal/mol and $\Delta S_{RR} = -23.5$ e.u. These large enthalpy changes in both diastereomeric complexations were ascribable to the formation of dual N···HO bonds. It should be noted that the difference in the binding enthalpy reaching 2.6 kcal/mol overcame the untoward loss in entropy and resulted in governing the high level of *(S,S)*-selectivity exerted by *(S,S)*-**1** toward **5**.

Table 1 Thermodynamic parameters for enantioselective interaction between *(S,S)*-**1** and the different diol enantiomers in $CDCl_3$.

5 

6 

7 

8 

Substrate	Config.	Δδ^a ppm	K^b M^{-1}	Config.	Δδ^a ppm	K^b M^{-1}	Temp. K	Δ(ΔG) kcal mol^{-1}
5	*(S,S)*	5.65	675	*(R,R)*	4.83	103	298	1.11
6	*(S,S)*	4.04	41	*(R,R)*	3.66	34	298	0.11
7	*(S,S)*	4.93	445	*(R,R)*	4.12	61	292	1.15
8	*(S,S)*	4.54	55	*(R,R)*	3.79	18	293	0.65

a) Shift difference in the resonance of hydroxyl protons; $\Delta\delta = \delta_{complex} - \delta_{free}$. b) Errors in association constants were below 5% except for a *K* value for *(S,S)*-**7**. The error in this case was 7%.

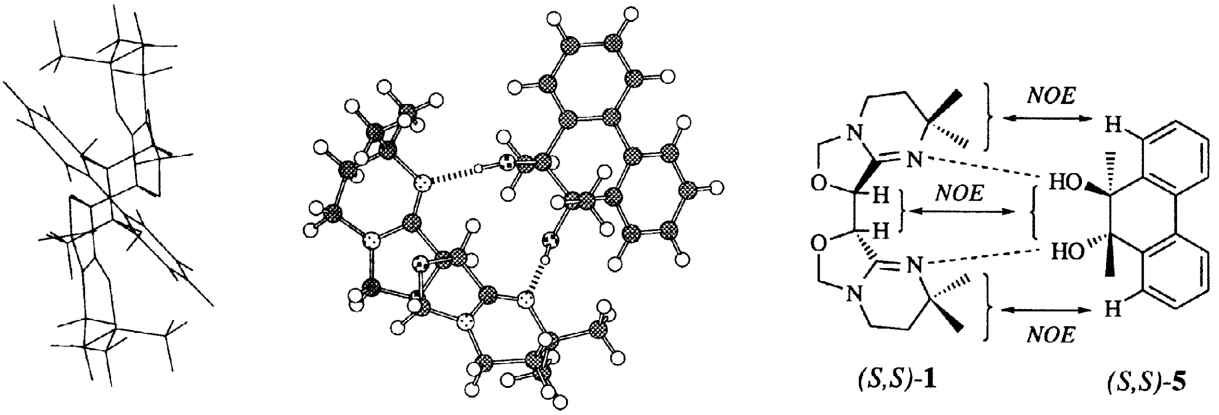


Figure 1 A proposed structure of the complex of *(S,S)*-**1** with *(S,S)*-**5** and NOE correlations observed for the complexation in solution. Perspective views of the complex (depicted on the left and in the center) were generated by Chem 3D plus, based on the calculated coordinates.[10] Left: Projection of the complex as viewed along pseudo C_2 axis from the *(S,S)*-**5** side.

The binding geometry relevant to enantioselection was clarified focusing on the complexation between *(S,S)*-**1** and *(S,S)*-**5**. On the basis of our working hypothesis, the structure consisting of dual hydrogen bonds between imino nitrogens of *(S,S)*-**1** and hydroxyl hydrogens of *(S,S)*-**5** was calculated by using the HF/3-21G* level of theory[10] as shown in Figure 1. The attribute of this complex is twist between both components, resulting from dual interactions between the twisted acceptor and donor sites. The maximum approach of one component to the other attained by eluding steric interaction and preserving the proper hydrogen bond geometry results in close contact between the binding surface of *(S,S)*-**1** and that of *(S,S)*-**5**. Resonance observed for two kinds of methyl protons of free *(S,S)*-**1** in $CDCl_3$ at 295 K appeared at 1.16 ppm as a singlet although these protons are inherently diastereotopic. Complexation with *(S,S)*-**5** rendered these isochronous nuclei magnetically nonequivalent and, thus, the limiting chemical shifts of 1.36 ppm and 1.23 ppm were assigned to two kinds of methyl protons of *(S,S)*-**1** in the complex.[11] Selective downfield shift noted for the methyl protons most likely was due to the deshielding effect based on the ring current of *(S,S)*-**5**. It should be noted that the binding geometry proposed above makes such effect possible. In a NOESY spectrum measured for a 1:1 mixture of *(S,S)*-**1** and *(S,S)*-**5** in $CDCl_3$,[12] distinct cross-peaks were observed between the protons indicated on the right of the figure. These intermolecular NOE correlations clearly demonstrated the proximity of these protons in the complex formed in solution. Thus, the NMR study confirmed the validity of the structure proposed as a core structure in dynamic complexation involving molecular motion in solution.

Molecular modeling for the diastereomeric counterpart comprised of *(S,S)*-**1** and *(R,R)*-**5** resulted in a binding motif with a different twist in the orientation of two components in comparison with the *(S,S)*-**1**-*(S,S)*-**5** system. The relatively deformed hydrogen bond geometry observed in such complexation may possibly lead to the lower binding energy relative to a more stable complexation system with *(S,S)*-**5**.

In summary, we have developed a representative of a new twisted host featuring amidine functionality that undergoes strong and selective complexation with diol enantiomers. The system described here employs a minimum set of binding interactions, but can elicit a high level of enantioselectivity. Further application of the present host to artificial molecular recognition is currently being investigated.

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REFERENCES AND NOTES

1. For a leading review, see (a) Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.* **1993**, *22*, 383-395. Recent topics: (b) Cristofaro, M, F.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1994**, *116*, 5089-5098. (c) Gasparrini, F.; Misiti, D.; Villani, C.; Borchardt, A.; Burger, M. T.; Still, W. C. *J. Org. Chem.* **1995**, *60*, 4314-4315. (d) Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 72-74. (e) Martín, M.; Raposo, C.; Almaraz, M.; Crego, M.; Caballero, C.; Grande, M.; Morán, J. R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2386-2388. (f) Reetz, M.T.; Rudolph, J.; Mynott, R. *J. Am. Chem. Soc.* **1996**, *118*, 4494-4495. (g) Naemura, K.; Ogasahara, K.; Hirose, K.; Tobe, Y. *Tetrahedron Asymmetry*. **1997**, *8*, 19-22. (h) Dowden, J.; Edwards, P. D.; Kilburn, J. D. *Tetrahedron Lett.* **1997**, *38*, 1095-1098. (i) Das, G.; Hamilton, A. D. *Tetrahedron Lett.* **1997**, *38*, 3675-3678.
2. Dobashi, Y.; Kobayashi, K.; Dobashi, A. in preparation.
3. (a) Dobashi, Y.; Dobashi, A.; Ochiai, H.; Hara, S. *J. Am. Chem. Soc.* **1990**, *112*, 6121-6123. (b) Dobashi, Y.; Dobashi, A.; Iitaka, Y. *Tetrahedron Lett.* **1994**, *35*, 9413-9416
4. *Ab initio* calculation using the HF/6-311G** level of theory revealed that the conformer of *(S,S)*-**1** depicted in the figure was most stable *in vacuo*. Details will be published elsewhere.
5. For a review, see Cava, M. P.; Levinson, M.I. *Tetrahedron*, **1985**, *41*, 5061-5087
6. Data for *(S,S)*-**1**: mp 144-146 °C; $[\alpha]_D$ = +136.5 (c = 1.02, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.16 (s, 12H), 1.55 and 1.60 (AB system further coupled with two spins, J_{AB} = 13.2 Hz, J = 6.3 Hz, 4H), 3.17 (t, J = 6.3 Hz, 4H), 4.76 (s, 2H), 4.85 (s, 2H), 4.95 (s, 2H); ^{13}CNMR (75 MHz, $CDCl_3$): δ 29.5, 29.8, 32.2, 37.3, 50.2, 80.1, 84.3, 152.7; Anal. Calcd for $C_{16}H_{26}N_4O_2$ C, 62.72; H, 8.55, N, 18.29. Found: C, 62.65, H, 8.34, N, 18.23.
7. A trace of water in $CDCl_3$ caused fatal signal broadening for the resonance of hydroxyl protons due to chemical exchange. To remove the water completely from a solution containing a host-guest mixture, one piece of spherical molecular sieves having a ca. 3mm diameter (4AXH-6, Union Showa, Tokyo) was added into a NMR sample tubing containing a sample solution. After being stored in a refrigerator over 1 week, the signal shape of the hydroxyl protons was dramatically sharpened, permitting accurate measurement of the chemical shift.
8. A ca. 6mM solution of each enantiomer of the diol derivative was used for the titration experiment since the self-association of each diol enantiomer was negligible near this concentration. The concentration of *(S,S)*-**1** was varied from 3.0 to 36 mM for **5**, 3.0 to 48 mM for **6**, and 1.5 to 48 mM for **7** and **8**. Data were collected at six different concentrations of *(S,S)*-**1** for diol enantiomers except for **7**, for which nine different concentrations were used.
9. Temperatures used were 263, 273, 283, and 298 K. A plot of ln*K* versus 1/T gave a straight line with a correlation coefficient over 0.998 for each diastereomeric system.
10. For the conformational search of the complex, 100 ps of molecular dynamics at 300 K using AMBER* force field (MacroModel V4.5, Department of Chemistry, Columbia University, New York) was carried out. During the dynamics run, intermolecular distance constraint between the hydroxyl protons and imino nitrogens and intramolecular torsion constraint involving the OH bond were applied. 500 conformers obtained by 200 fs of sampling interval were subjected to energy minimization, affording a single conformer of the complex. Full geometry optimization of this conformer based on the HF/3-21G* level of theory was carried out by using a program package SPARTAN 4.0 (Wavefunction Inc. California).
11. Limiting chemical shifts were determined by extrapolation of the linear plot of observed chemical shifts versus % complexation, calculated using the association constant.
12. The NOESY (TPPI) spectrum using 2.0 sec of the mixing time was recorded at 500 MHz (Bruker DRX-500). The concentration of each component was 8 mM and temperature was kept at 300 K. Under these conditions, the degree of complexation was calculated to be ca. 65%.