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Recognition of dihydroxynaphthalenes by a C_2-symmetric host

Hae-Jo Kim,[a] Dohyun Moon,[b] Myoung Soo Lah[b] and Jong-In Hong[a,*]

[a]*School of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, South Korea*
[b]*Department of Chemistry, College of Science, Hanyang University, Ansan, Kyunggi-Do 425-791, South Korea*

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Abstract—A functionalized C_2-symmetric host (**2**) shows high affinity and substrate selectivity for dihydroxynaphthalenes.

While recognition of sugars or aliphatic alcohols has been well studied by natural and artificial receptors,[1] relatively fewer examples of hosts for hydroxy-substituted aromatic guests have been reported,[2] even though hydrogen bonding and π–π interactions can be exploited for the efficient recognition of neutral hydroxy-substituted aromatic guests in nonaqueous solvents. Herein, a synthetic host utilizing both hydrogen bonding and π–π interactions for the recognition of dihydroxy-substituted naphthalenes is reported.

Synthesis of the functionalized oxazoline host (**2**) was carried out in three steps according to the previously reported synthetic method.[3] Conversion of terephthalic acid to acid chloride by treatment with oxalyl chloride, coupling with L-serine methyl ester in the presence of TEA and activation of the resulting alcohol with mesyl chloride, followed by cyclization in basic condition afforded the desired product, **2** in overall 30% yield.[4] Since α hydrogen in the amino acid unit is acidic, a β-elimination product was also obtained under the reaction condition[5] (Fig. 1).

The structure of **2** was confirmed by X-ray diffraction study[6] as well as by ^{1}H, ^{13}C spectra and optical properties (Fig. 2).[4]

From the crystal structure, it turns out that chiral centers on the oxazoline rings are all retained as (*S*,*S*) configuration[7] during the cyclization process even though there is a possibility of another process, elimination followed by cyclization leading to racemization.[8] No proton peaks corresponding to other stereoisomeric products were observed in the ^{1}H NMR spectra of the reaction mixture, indicating that no cyclization occurred on the elimination product.

In order to determine the guest affinity to host **2**, fluorescence titration was carried out in a reverse manner because the guests were highly luminescent (Fig. 3). When adding a solution of **2** to dihydroxynaphthalene, while maintaining the concentration of dihydroxynaphthalene constant, the fluorescence intensity decreased gradually (Fig. 4).

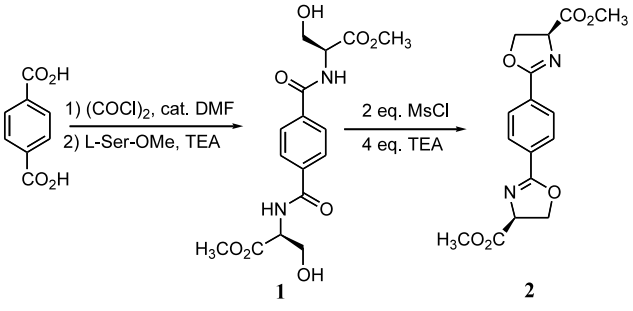

Figure 1. Synthetic scheme of the host (**2**).

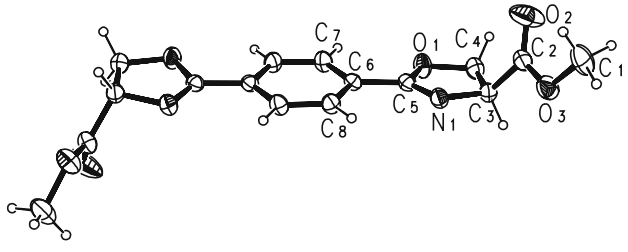

Figure 2. ORTEP drawing of **2**. Selected torsional angle (°) (bond lengths [Å]; bond angles [°]) of C_8–C_6–C_5–N_1: −5.4 (1.394, 1.477, 1.268; 119.57, 125.59).

* Corresponding author. E-mail: jihong@plaza.snu.ac.kr

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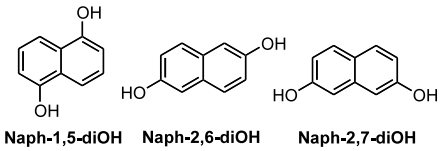

Figure 3. Guest structures.

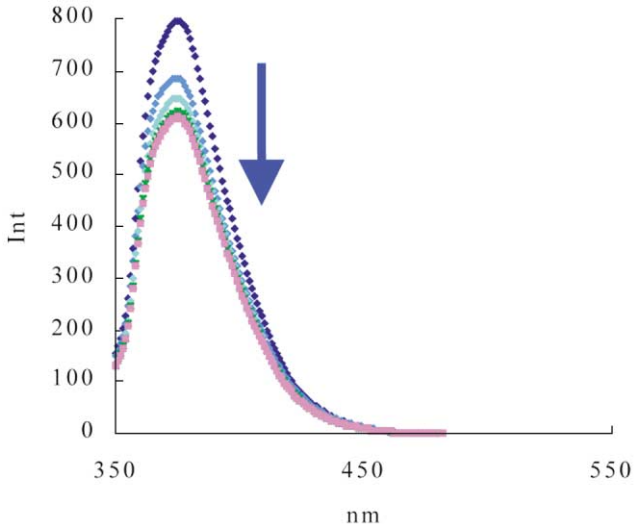

Figure 4. Typical emission spectra ($\lambda_{ex}=347$ nm, 0.20 mM in $CHCl_3$) of Naph-2,6-diOH at 298 K upon addition of **2**.

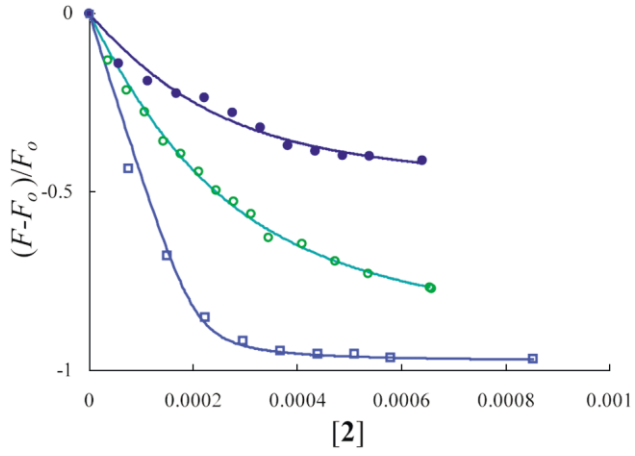

Figure 5. Fluorescence titration of dihydroxynaphthalenes (Naph-diOH) with **2** at 298 K, [Naph-diOH] = 0.20 mM, $[\mathbf{2}]_o = 15$ mM. (Open circle) Naph-1,5-diOH; (filled circle) Naph-2,6-diOH; (open rectangle) Napht-2,7-diOH.

Normalized fluorescence intensity ($\Delta F/F_0$) versus [**2**] was analyzed by the nonlinear regression method implemented in Sigma Plot 4.0.[9] The results are shown in Fig. 5.

Observed dissociation constants for 1,5- and 2,6-dihydroxynaphthalenes are in the range of submillimolar affinity; however, they are in the range of micromolar affinity (more than 20-fold increase) in the case of 2,7-dihydroxynaphthalene, as summarized in Table 1.

This highly selective binding affinity toward 2,7-dihydroxynaphthalene is thought to originate from the structure of the guest appropriate for aromatic stacking and hydrogen bonding interactions with the host. As suggested by the computational modeling (Fig. 6),[10] the naphthalene ring of the guest perfectly matches the phenyl ring of the host with an interplane distance 3.378 Å for the maximum π–π stacking interaction. In addition, the two hydrogen bonds between OH of the guest and ester C=O of the host are rather linearly arranged (D–H···A angle/distance = 173°/1.780 Å and 154°/1.802 Å). However, the hydrogen bonds with 1,5- and 2,6-dihydroxynaphthalenes (D–H···A angle/distance = 144°/1.904 Å and 144°/1.904 Å, 167°/1.771 Å and 146°/1.833 Å) are more deviated from the linearity. Further, only half of the naphthyl group of 2,6-dihydroxynaphthalene matches the phenyl ring of **2**, thus presumably reducing the extent of π–π stacking interaction.

In order to verify the aromatic stacking interaction between host and guests, 1,5-dihydroxy-1,2,3,4-tetrahydronaphthalene instead of 1,5-dihydroxynaphthalene was used as the guest. Its binding affinity was in the range of millimolar concentration ($K_d = 2.1(\pm 0.25)\times 10^{-3}$ M), which corresponds to 16-fold decrease in the binding affinity.[11] Thus, it is concluded that there are substantial π–π stacking interactions between host and naphthalene guests during the binding events. ^{1}H NMR titration revealed that the OH protons of the guest were

Table 1. Dissociation constants (K_d) between **2** and guests in $CHCl_3$[a]

Entry	Guest[b]	K_d (M)
1	Naph-1,5-diOH	$1.29(\pm 0.17)\times 10^{-4}$
2	Naph-2,6-diOH	$1.09(\pm 0.45)\times 10^{-4}$
3	Naph-2,7-diOH	$5.01(\pm 3.10)\times 10^{-6}$

[a] Reverse fluorescence titration at 298 K, [guest] = 0.20 mM, $[\mathbf{2}]_o = 15$ mM.

[b] $\lambda_{ex}=298$ nm and $\lambda_{em}=450$ nm for Naph-1,5-diOH. $\lambda_{ex}=347$ nm and $\lambda_{em}=375$ nm for Naph-2,6-diOH. $\lambda_{ex}=284$ nm and $\lambda_{em}=346$ nm for Naph-2,7-diOH.

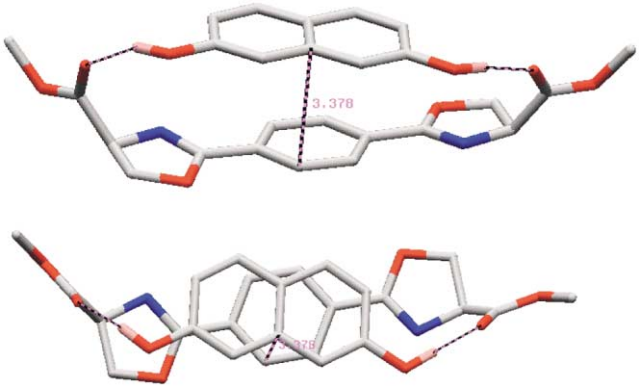

Figure 6. Energy-minimized structure for the complex between **2** and 2,7-dihydroxynaphthalene in chloroform solvation model.

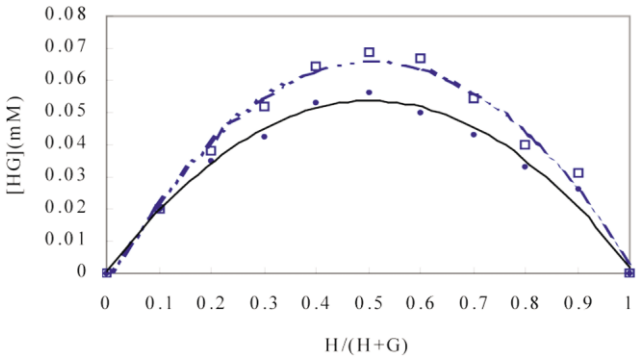

Figure 7. Job's plot between **2** and dihydroxynaphthalenes at 298 K in $CHCl_3$, [G]+[H]=0.20 mM. (Open rectangle) Naph-2,7-diOH; (filled circle) Naph-2,6-diOH.

broadened upon the addition of the host, indicating the participation of OHs in H-bond interactions with the host. Furthermore, ^{1}H NMR titrations showed the upfield shifts ($\Delta\delta = -0.017$ to -0.031 ppm) of the aromatic protons of dihydroxynaphthalenes upon addition of **2**, suggesting that the aromatic groups of **2** and dihydroxynaphthalenes are in vicinity to each other upon complexation

The stoichiometry between host and guest was determined by a continuous variation plot obtained by taking traces of fluorescent intensity (Fig. 7).[12] It was evidently shown that a 1:1 complex between host and guest was formed.

In conclusion, a functionalized C_2-symmetric oxazoline host (**2**) was shown to bind dihydroxynaphthalenes with high affinity and high selectivity. Comparing with previous hosts possessing rigidly defined cavities and concave H-bond acceptors capable of binding hydroxy-substituted aromatic guests,[2] the high affinity for dihydroxynaphthalenes and high selectivity for 2,7-dihydroxylnaphthalene by the oxazoline host (**2**) are remarkable in that **2** is acyclic and has only two rather weak H-bond acceptors and phenyl rings for the aromatic stacking interaction. The high affinity and selectivity are due to the rigid host structure, appropriately arranged H-bond accepting ester functionality and phenyl ring of the oxazoline host.

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References

1. (a) Lemieux, R. U. *Chem. Soc. Rev.* **1989**, *18*, 347–374; (b) Quiocho, F. A. *Pure Appl. Chem.* **1989**, *61*, 1293–1306; (c) Aoyama, Y.; Tanaka, Y.; Sugara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5397–5404; (d) Tsukagoshi, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4089–4091; (e) Inoue, M.; Takahashi, K.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 341–345; (f) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2978–2996; (g) Rusin, O.; Kral, V. *Chem. Commun.* **1999**, 2367–2368; (h) Schrader, T. *J. Am. Chem. Soc.* **1998**, *120*, 11816–11817; (i) Mizutani, T.; Kurahashi, T.; Murakami, T.; Matsumi, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *119*, 8991–9001; (j) Kim, Y.-H.; Hong, J.-I. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2947–2950.
2. (a) Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 4071–4073; (b) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *110*, 3910–3915; (c) Sijbesma, R. P.; Kentgens, A. P. M.; Lutz, E. T. G.; van der Maas, J. H.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1993**, *115*, 8999–9005; (d) Gieling, G. T. W.; Scheeren, H. W.; Israel, R.; Nolte, R. J. M. *Chem. Commun.* **1996**, 241–243.
3. (a) Kim, H.-J.; Kim, Y.-H.; Hong, J.-I. *Tetrahedron Lett.* **2001**, *42*, 5049–5052; (b) Lee, S.-H.; Yoon, J.; Nakamura, K.; Lee, Y.-S. *Org. Lett.* **2000**, *2*, 1243–1246.
4. Typical experimental and characterizations for **2** are as follows;
   To a solution of 144.6 mg (0.393 mmol) of **1** and 0.30 mL of TEA (4 equiv.) in 10 mL of dichloromethane was added dropwise 2 equiv. of methanesulfonyl chloride (100 μL, 1.29 mmol) in 5 mL of dichloromethane at 0°C under nitrogen. Resulting white suspension was stirred for additional 24 h under nitrogen. All volatiles were removed under reduced pressure. Column chromatography on a silica gel (CH_2Cl_2:MeOH=20:1, R_f=0.48) afforded the desired product as a white solid in 30% yield. Recrystallization was carried out by slow evaporation of the solution (EtOAc:CH_2Cl_2=3:1) at 0°C.
   ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 4H of aromatic H), 5.00 (dd, J=11 Hz, 8.0 Hz, 2H of C*H), 4.76 (dd, J=11 Hz, 8.8 Hz, 2H of CH_2O), 4.66 (dd, J=11 Hz, 8.8 Hz, 2H of CH_2O), 3.86 (s, 6H of CO_2CH_3). Assignments based on HMQC.
   ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 166.0 (carbonyl and oxazoline), 130.3, 129.0 (aromatic), 70.2 (CH_2O), 69.0 (C*H), 53.3 (CO_2CH_3). Assignments based on DEPT32, DEPT45, DEPT135 and HMQC.
   $[\alpha]_D^{23}$ +151.8 (c 0.485, CH_2Cl_2); Mass (FAB$^+$, m-NBA): m/z 333 ([M+H]).
5. The ratio of a cyclization product to an elimination product was 10:7 based on ^{1}H NMR spectrum after filtration of the reaction mixture through a short plug of silica gel.
6. *Crystal data*: $C_{16}H_{16}N_2O_6$, M_r=332.31, orthorhombic $C222_1$, a=4.4516(10), b=10.888(2), c=31.971(7) Å, V=1549.6(6) Å^3, $F(000)$=696, Z=4, μ=0.111 mm^{-1}, D_c=1.424 Mg/m^3, 4811 reflection measured, 1857 unique(R_{int} 0.0211) with $I>2\sigma(I)$. Final R_1 and wR_2 are 0.0391 and 0.1036 with absolute structure parameter of –0.5(1).
7. Flack x parameter=–0.4774 for (*S*,*S*), whereas it is 1.4588 for (*R*,*R*)-configuration in X-ray crystallography, which led to the conclusion of the resulting structure as (*S*,*S*)-configuration. For retention of the configuration during the functionalized oxazoline syntheses, see: (a) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J.*

Am. Chem. Soc. **1976**, *98*, 567–576; (b) Schmitz, W. D.; Romo, D. *Tetrahedron Lett.* **1996**, *37*, 4857–4860; (c) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168; (d) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399–3401.

8. Almqvist, F.; Guillaume, D.; Hultgren, S. J.; Marshall, G. R. *Tetrahedron Lett.* **1998**, *39*, 2293–2294.
9. Modified fluorescence titration equation from the 1:1 NMR titration equation was used.

$$\frac{F_{obs}-F_o}{F_o}=\left(\frac{F_{HG}-F_o}{F_o}\right)\frac{([H]_o+[G]_o+K_d)-\sqrt{([H]_o+[G]_o+K_d)^2-4[H]_o[G]_o}}{2[H]_o}$$

where F_o is initial fluorescence intensity, F_{obs} is observed fluorescence intensity as a dependent variable (H = dihydroxynaphthalenes, G = **2**), $[H]_o$ is host concentration which is constant, $[G]_o$ is guest concentration as an independent variable, and K_d is the dissociation constant in M.

10. We obtained two global minimum structures by computational calculation, MacroModel 7.0; one is a S-shaped structure like the X-ray crystal structure, the other is U-shaped. Although the host itself shows the S-shaped structure, the complex form of the host is supposed to have U-shaped structure because the rotational barrier between U- and S-shaped structure of the host is less than 5 kcal/mol in chloroform.
11. ^{1}H NMR titration was carried out because the guest was nonfluorescent, $K_d = 2.1(\pm 0.25)\times 10^{-3}$ M, [H] = 1.0 mM, $[G]_o = 20$ mM in $CDCl_3$ at 298 K.
12. Job, P. *Ann. Chim.* **1928**, *9*, 113–203. The complex concentration, [HG] was calculated by the equation, $[HG] = \Delta F/F_0 \times [H]$.