Recognition of dihydroxynaphthalenes by a $C_2$-symmetric host

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Abstract—A functionalized $C_2$-symmetric host (2) shows high affinity and substrate selectivity for dihydroxynaphthalenes. © 2003 Elsevier Science Ltd. All rights reserved.

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 $\pi-\pi$ 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 $\pi-\pi$ 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 $\beta$ hydrogen in the amino acid unit is acidic, a $\beta$-elimination product was also obtained under the reaction condition5 (Fig. 1).

The structure of 2 was confirmed by X-ray diffraction study6 as well as by $^1$H, $^{13}$C spectra and optical properties (Fig. 2).7

From the crystal structure, it turns out that chiral centers on the oxazoline rings are all retained as (S,S) configuration7 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).](image1)

![Figure 2. ORTEP drawing of 2. Selected torsional angle (°) (bond lengths [Å]; bond angles [°]) of C8-C6-C5-N1: -5.4 (1.394, 1.477, 1.268; 119.57, 125.59).](image2)
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), 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. Thus, it is concluded that there are substantial π–π stacking interactions between host and naphthalene guests during the binding events. 1H NMR titration revealed that the OH protons of the guest were

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<td>1</td>
<td>Naph-1,5-diOH</td>
<td>1.29(±0.17) × 10^{-4}</td>
</tr>
<tr>
<td>2</td>
<td>Naph-2,6-diOH</td>
<td>1.09(±0.45) × 10^{-4}</td>
</tr>
<tr>
<td>3</td>
<td>Naph-2,7-diOH</td>
<td>5.01(±3.10) × 10^{-6}</td>
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a Reverse fluorescence titration at 298 K, [guest] = 0.20 mM, [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.
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 binding at 298 K in CHCl$_3$, [G] = [H] = 0.20 mM. (Open rectangle) Naph-2,7-diOH; (filled circle) Naph-2,6-diOH.

In conclusion, a functionalized $C_2$-symmetric oxazine 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, the high affinity for dihydroxynaphthalenes and high selectivity for 2,7-dihydroxynaphthalene by the oxazine 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 oxazine host.

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References


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$_2$Cl$_2$: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$_2$Cl$_2$ = 3:1) at 0°C.

- $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.07 (s, 4H of aromatic H), 5.00 (dd, $J$ = 11 Hz, 8.0 Hz, 2H of $C^\text{A}$), 4.76 (dd, $J$ = 11 Hz, 8.8 Hz, 2H of CH$_2$O), 4.66 (dd, $J$ = 11 Hz, 8.8 Hz, 2H of CH$_2$O), 3.86 (s, 6H of CO$_2$CH$_3$). Assignments based on HMBC.

- $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.8, 166.0 (carbonyl and oxazine), 130.3, 129.0 (aromatic), 72.0 (CH$_2$O), 69.0 (C$^\text{A}$), 53.3 (CO$_2$CH$_3$). Assignments based on DEPT32, DEPT45, DEPT135 and HMBC. $\mu$ = 333 ([M+H]).

- 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.

5. Crystal data: $C_{16}H_{16}N_2O_6$. $M_t = 332.31$, orthorhombic $C222_1$; $a = 4.4516(10)$, $b = 10.888(2)$, $c = 31.971(7)$ A, $V = 1549.6(6)$ Å$^3$, $F(000) = 696$, $Z = 4$, $\mu = 0.111$ mm$^{-1}$, $D_e = 1.424$ Mg/m$^3$, 4811 reflection measured, 1857 unique ($R_{int} = 0.0211$) with $I \geq 2\sigma(I)$. Final $R_F$ and $wR_F$ are 0.0391 and 0.1036 with absolute structure parameter of $-0.5(1)$.

6. 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 oxazine syntheses, see: (a) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. J.

9. Modified fluorescence titration equation from the 1:1 NMR titration equation was used.

\[
\frac{F_{\text{obs}} - F_0}{F_0} = \left( \frac{F_{HG} - F_0}{F_0} \right) \left( [H]_0 + [G]_0 + K_d \right) - \sqrt{\left( [H]_0 + [G]_0 + K_d \right)^2 - 4[H]_0[G]_0}
\]

where \( F_0 \) is initial fluorescence intensity, \( F_{\text{obs}} \) is observed fluorescence intensity as a dependent variable (\( H = \text{dihydroxynaphthalenes, } G = 2 \)), \( [H]_0 \) is host concentration which is constant, \( [G]_0 \) 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} \text{ M, } [H] = 1.0 \text{ mM, } [G]_0 = 20 \text{ mM in CDCl}_3 \text{ at } 298 \text{ K.}

12. Job, P. *Ann. Chim.* 1928, 9, 113–203. The complex concentration, \([HG]\) was calculated by the equation, \([HG] = \Delta F/F_0 \times [H]\).