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Colorimetric recognition of the length of α,ω-diamines in water

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Abstract—Two types of host molecules based on phenolphthalein and two crown ethers have been constructed. These hosts made it possible to recognize the length of α,ω-diamines and transformed the binding events into detectable changes in color in an aqueous buffer solution.

Many supramolecular chemists have exerted considerable effort to establish useful methodologies for molecular recognition in water. In some cases, hydrophobic interaction as well as desolvation effect have been used as a driving force in the complexation of the desired molecules. Cyclodextrin derivatives[1] and rigid cages composed of aromatic rings[2] are examples of this approach. Recently, many functional host molecules based on coordinative interaction as a main driving force have been reported.[3] In contrast, it has generally been difficult to develop host molecules using hydrogen bonding, since the surrounding water molecules can act as hydrogen donors and/or acceptors and disturb the desired hydrogen bonding between two molecules. Furthermore, non-covalent forces derived from electrostatic interaction, such as coulomb force and ion–dipole interaction, are also weakened according to the dielectric constant (ε) of the solvent.[4] For all of these reasons, more effective systems for molecular recognition in water which use a combination of hydrogen bonding and some other attractive interactions have been considered.[5] We focused on the combination of convergent multiple hydrogen bonds, which provide a clear directionality between target molecules, and long-range but non-directional coulomb force between the two charges to construct a molecular recognition system in water. Specifically, we have been investigating whether phenolphthalein derivatives possessing two crown ethers could be used to recognize the length of guest α,ω-diamines and reflect this information through the development of a purple color in MeOH.[6] In the present Letter, we report the colorimetric recognition of the length of α,ω-diamines using polymer-supported host **1** and water-soluble host **2** in a completely aqueous medium (Fig. 1).

The synthetic route to polymer-supported host **1** and water-soluble host **2** is outlined in Scheme 1. Two carboxylic groups and a phenolic hydroxy group of 4-hydroxy phthalic acid (**3**) were protected by methoxymethyl (MOM) to give **4** in 93% yield. Two MOM esters of **4** were selectively hydrolyzed and treated with acetic anhydride to afford the phthalic anhydride **5** in 86% overall yield in two steps. Crown ether **6** was treated with *t*-BuLi and allowed to react with the phthalic anhydride **5** to afford **7** with a small amount of its regioisomer in 90% yield. The phenolic MOM group was removed by trimethylsilyl bromide in the presence of molecular sieves 4 Å to afford the key intermediate **8** in 94% yield.[7] To synthesize host **1**, a methoxycarbonylmethyl group was introduced to the phenolic hydroxy

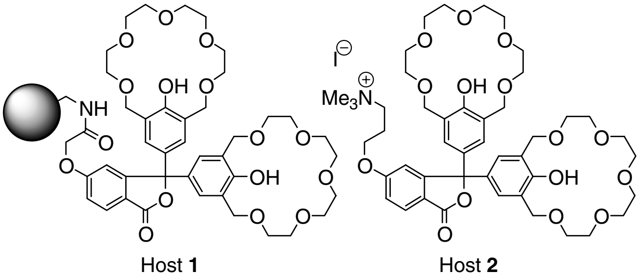

Figure 1. Structures of hosts **1** and **2**.

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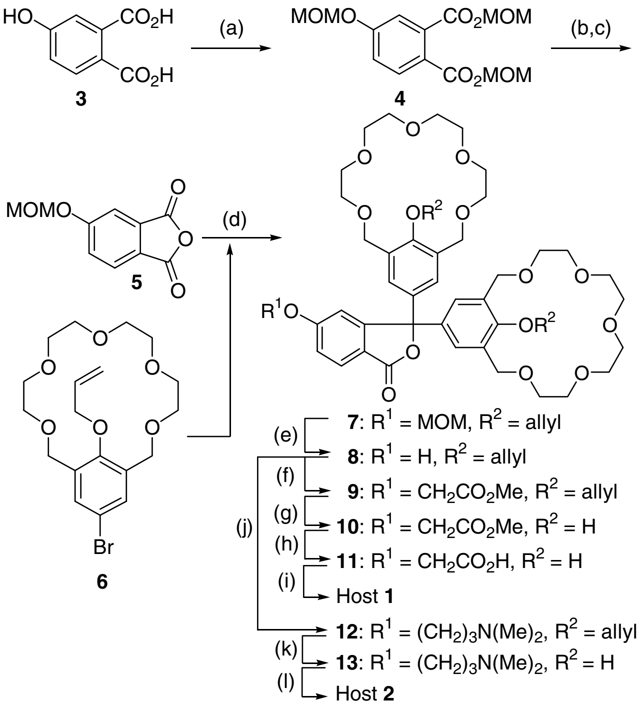


Scheme 1. Synthesis of hosts **1** and **2**. Reagents and conditions: (a) MOMCl, K_2CO_3, 93%; (b) LiOH, 87%; (c) Ac_2O, 99%; (d) **6**, *t*-BuLi, 90% (e) TMSBr, MS 4 Å, 94%; (f) $BrCH_2CO_2Me$, K_2CO_3, 99%; (g) $Pd(PPh_3)_4$, $NaBH_4$, 86%; (h) KOH, quant.; (i) amino PEGA resin, WSC·HCl, DMAP; (j) $MsO(CH_2)_3NMe_2$·HCl,[2e] K_2CO_3, 90%; (k) $Pd(PPh_3)_4$, $NaBH_4$, 80%; (l) MeI, 68%.

group of **8** to afford **9** in quantitative yield. After the deprotection of allyl groups under $Pd(PPh_3)_4$ and sodium borohydride (86%),[8] methyl ester **10** was hydrolyzed by KOH to afford **11**. The deprotected skeleton **11** was smoothly loaded on amino PEGA resin (amino polyethylene glycol polyacrylamide resin, 0.3–0.4 mmol/g resin, 50–100 mesh, Novabiochem) under WSC·HCl and DMAP. The effective introduction of sufficient **11** on amino groups of the resin was judged by (1) negative ninhydrin test and (2) clear and homogeneous purple coloration against aqueous sodium hydroxide solution. To construct host **2**, the introduction of a dimethylamino side chain to the phenolic hydroxy group of the key intermediate **8** furnished **12** (90%), and the deprotection of two allyl groups gave **13** in 80% yield. Finally, methylation of an amino group of **13** gave the water-soluble quaternary ammonium host **2** in 68% yield. The water-solubility of host **2** was approximately 1×10^{-1} M.

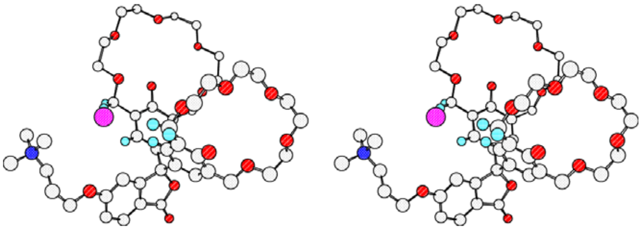


Figure 2. Structure of host **2** (stereo view). Unconcerned hydrogen atoms and a water molecule were omitted for clarity.

Colorless crystals of host **2** were precipitated from methanol-d_4 in hydrated form and the structure of host **2** was determined by X-ray analysis (Fig. 2). Interestingly, iodide anion is located among three aromatic rings, a methylene group in the crown ether, and a methyl group of the ammonium group (see Supplementary data). The distances from the iodide anion to C*H* in these moieties are within 3.36 Å, which is comparable to the sum of the van der Waals radii of hydrogen (1.2 Å) and iodine (2.15 Å). Thus, the iodide anion is captured by attractive CH–I interactions.[9]

The coloration of polymer-supported host **1** in the presence of α,ω-diamines of various lengths was investigated

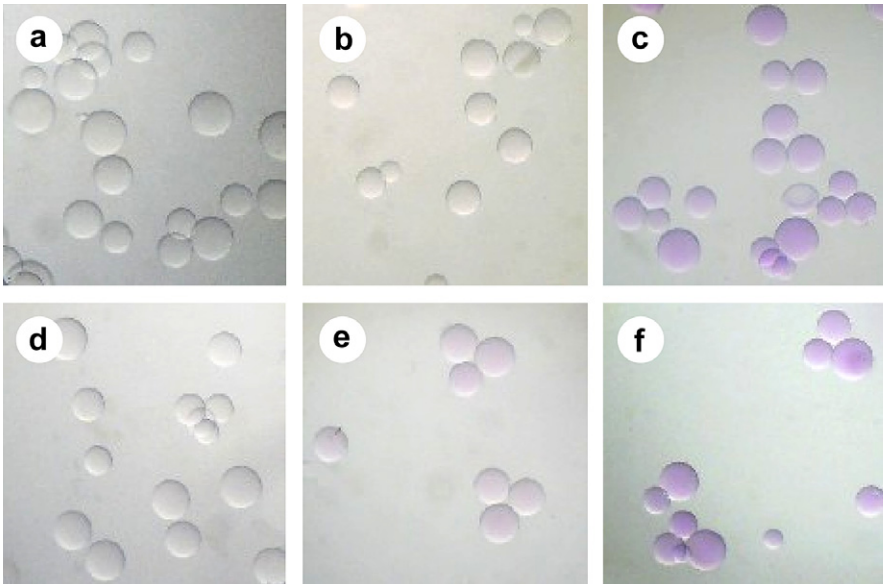


Figure 3. The coloration of polymer supported host **1** against α,ω-diamines ($n = 6$ and 9). Reagents and conditions: (a–c) MeOH, [α,ω-diamine] $= 2.0 \times 10^{-3}$ M, (a) blank, (b) $n = 6$, (c) $n = 9$; (d–f) HEPES buffer (pH 8.0, 0.6 M, titrant = NaOH), [α,ω-diamine] $= 2.0 \times 10^{-2}$ M, (d) blank, (e) $n = 6$, (f) $n = 9$.

(Fig. 3).[10] When α,ω-diamines with 7–10 ($7 \leqslant n \leqslant 10$) methylene chains were added to host **1** in methanol solution, monotonous purple coloration was observed on the beads (Fig. 3c). In contrast, for α,ω-diamines ($n \leqslant 6$), no coloration was detected (Fig. 3b). Thus, polymer-supported host **1** maintained its ability to discriminate the length of α,ω-diamines and reflected this information as a change in color. However, the degree of coloration is slight and there is only a small difference in coloration among α,ω-diamines ($7 \leqslant n \leqslant 10$). In aqueous HEPES buffer, host **1** showed almost no coloration under the same guest concentration, and nearly identical colorations were observed with a 10-fold higher concentration (Fig. 3c vs f). These results indicated that (even though the local concentration of host **1** on the bead surface should be high)[11] the side chains of amino PEGA resin may prevent complexation between the binding sites of host **1** and guests of diamines, in addition to the inherent difficulties, that is, molecular recognition using hydrogen bonding in water.

Next, we evaluated the performance of water-soluble host **2** in aqueous HEPPSO buffer at two pHs. Figures 4a and b show UV–vis spectra of host **2** with diamines of various lengths ($5 \leqslant n \leqslant 10$) at pH 7.7 and pH 7.9, respectively. While host **2** slightly responded to the pH of the solution in the absence of guest diamines, host **2** unambiguously recognized the length of diamines with a change in color that depended on the length of the diamine. Color development with host **2** and diamines was the deepest with the guest diamine of $n = 9$, and the degree of coloration was much less with both longer and shorter molecules. These phenomena could be detected by the naked eye (Fig. 4c).

To quantify the change in color development,[12] a ratiometric measurement[13] was carried out using the absorbance at 570 nm ($\lambda_{\max}$) and 390 nm at pH 7.9 (Fig. 5). This measurement showed that host **2** had greater affinity towards diamine ($n = 9$) than for those of other lengths.

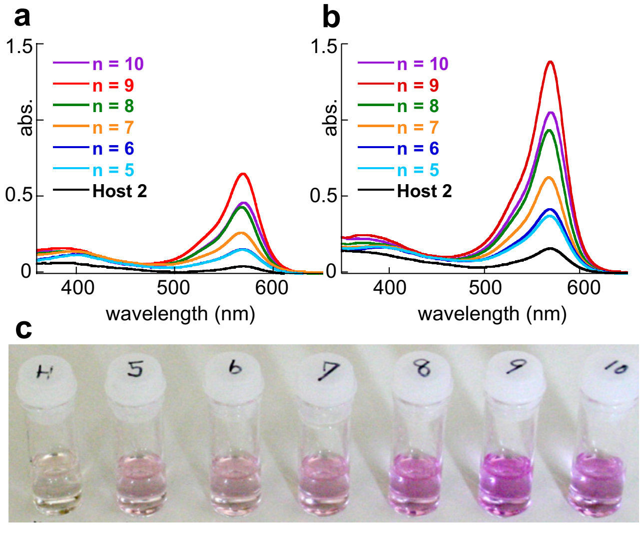
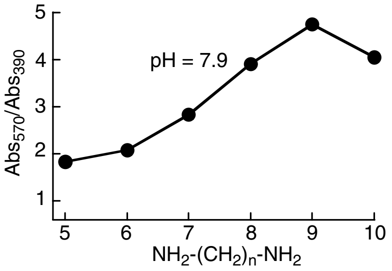


Figure 4. Colorimetric recognition of α,ω-diamines in water. (a) and (b) UV–vis spectra of host **2** with α,ω-diamines in HEPPSO buffer. Reagents and conditions: [host **2**] = 1.0×10^{-2} M, [α,ω-diamine] = 1.0×10^{-2} M. [HEPPSO] = 0.32 M, titrant = NaOH, 10 °C, (a) pH 7.7, (b) pH 7.9, (c) color development by host **2** with α,ω-diamines; [host **2**] = 1.0×10^{-2} M, [α,ω-diamine] = 1.0×10^{-2} M, pH 7.7.



n	Abs_{570}/Abs_{390}
5	1.83
6	2.08
7	2.83
8	3.92
9	4.75
10	4.06

Figure 5. The ratio of the absorbance at 570 and 390 nm.

In conclusion, we have developed two types of phenolphthalein-based hosts for molecular recognition in water. While the sensitivity was not satisfactory, these molecules, especially water-soluble host **2**, could be used to recognize the length of α,ω-diamines and transformed binding events into detectable changes in color in a buffered aqueous solution. Thus, even in a completely aqueous medium, a molecular recognition system that uses both hydrogen bonding and coulomb force could be constructed. We are currently developing more sensitive and/or fluorescent functional molecules for use in a completely aqueous medium.

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Supplementary data

Full experimental details and crystallographic information file (CIF) of host **2** (CCDC 624293). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.099.

References and notes

1. (a) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325–1358; (b) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2012; (c) Engeldinger, E.; Armspach, D.; Matt, D. *Chem. Rev.* **2003**, *103*, 4147–4174; (d) Liu, Y.; Chen, Y. *Acc. Chem. Res.* **2006**, *39*, 681–691; (e) Wenz, G.; Han, B.-H.; Müller, A. *Chem. Rev.* **2006**, *106*, 782–817; (f) Aoyama, Y.; Otsuki, J.; Nagai, Y.; Kobayashi, K.; Toi, H. *Tetrahedron Lett.* **1992**, *33*, 3775–3778; (g) Ikeda, H.; Nakamura, M.; Ise, N.; Oguma, N.; Nakamura, A.; Ikeda,

T.; Toda, F.; Ueno, A. *J. Am. Chem. Soc.* **1996**, *118*, 10980–10988; (h) Kano, K.; Kitae, T.; Shimofuri, Y.; Tanaka, N.; Mineta, Y. *Chem. Eur. J.* **2000**, *6*, 2705–2713; (i) Inoue, Y.; Miyauchi, M.; Nakajima, H.; Takashima, Y.; Yamaguchi, H.; Harada, A. *J. Am. Chem. Soc.* **2006**, *128*, 8994–8995.

2. (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324; (b) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250; (c) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504–2505; (d) Smithrud, D. B.; Wyman, T. B.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5420–5426; (e) Inouye, M.; Fujimoto, K.; Furusyo, M.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 1452–1458; (f) Herm, M.; Molt, O.; Schrader, T. *Chem. Eur. J.* **2002**, *8*, 1485–1499; (g) Tashiro, S.; Tominaga, M.; Kawano, M.; Therrien, B.; Ozeki, T.; Fujita, M. *J. Am. Chem. Soc.* **2005**, *127*, 4546–4547.
3. (a) Ogoshi, H.; Mizutani, T. *Acc. Chem. Res.* **1998**, *31*, 81–89; (b) Borovkov, V. V.; Hembury, G. A.; Inoue, Y. *Acc. Chem. Res.* **2004**, *37*, 449–459; (c) Sirish, M.; Chertkov, V. A.; Schneider, H.-J. *Chem. Eur. J.* **2002**, *8*, 1181–1188; (d) Wright, A. T.; Anslyn, E. V. *Org. Lett.* **2004**, *6*, 1341–1344; (e) Buryak, A.; Severin, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 4771–4774; (f) Kruppa, M.; Mandl, C.; Miltschitzky, S.; König, B. *J. Am. Chem. Soc.* **2005**, *127*, 3362–3365; (g) Folmer-Anderson, J. F.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2005**, *127*, 7986–7987; (h) Aoki, S.; Zulkefeli, M.; Shiro, M.; Kohsako, M.; Takeda, K.; Kimura, E. *J. Am. Chem. Soc.* **2005**, *127*, 9129–9139.
4. (a) Israelachvili, J. N. *Intermolecular and Surface Forces*; Academic Press: London, 1991; (b) Daniel, J. M.; Friess, S. D.; Rajagopalan, S.; Wendt, S.; Zenobi, R. *Int. J. Mass Spectrom.* **2002**, *216*, 1–27.
5. (a) Meot-Ner (Mautner), M. *Chem. Rev.* **2005**, *105*, 213–284; (b) Hossain, Md. A.; Schneider, H.-J. *J. Am. Chem. Soc.* **1998**, *120*, 11208–11209; (c) Rekharsky, M.; Inoue, Y.; Tobey, S.; Metzger, A.; Anslyn, E. *J. Am. Chem. Soc.* **2002**, *124*, 14959–14967; (d) Schmuck, C.; Geiger, L. *J. Am. Chem. Soc.* **2004**, *126*, 8898–8899; (e) Mandl, C. P.; König, B. *J. Org. Chem.* **2005**, *70*, 670–674; (f) Schmuck, C.; Wich, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4277–4281.
6. (a) Fuji, K.; Tsubaki, K.; Tanaka, K.; Hayashi, N.; Otsubo, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 3807–3808; (b) Tsubaki, K.; Hayashi, N.; Nuruzzaman, M.; Kusumoto, T.; Fuji, K. *Org. Lett.* **2001**, *3*, 4067–4069; (c) Tsubaki, K.; Kusumoto, T.; Hayashi, N.; Nuruzzaman, M.; Fuji, K. *Org. Lett.* **2002**, *4*, 2313–2316.
7. (a) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515–2518; (b) Huffman, J. W.; Zhang, X.; Wu, M.-J.; Joyner, H. H.; Pennington, W. T. *J. Org. Chem.* **1991**, *56*, 1481–1489.
8. (a) Beugelmans, R.; Bourdet, S.; Bigot, A.; Zhu, J. *Tetrahedron Lett.* **1994**, *35*, 4349–4350; (b) Beugelmans, R.; Neuville, L.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1995**, *36*, 3129–3132.
9. For selected articles of anion recognition based on CH–halogen interactions, see: (a) Weiss, H.-C.; Boese, R.; Smith, H. L.; Haley, M. M. *Chem. Commun.* **1997**, 2403–2404; (b) Wallace, K. J.; Belcher, W. J.; Turner, D. R.; Syed, K. F.; Steed, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 9699–9715; (c) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2003**, *125*, 10241–10249; (d) Bryantsev, V. S.; Hay, B. P. *J. Am. Chem. Soc.* **2005**, *127*, 8282–8283; (e) In, S.; Cho, S. J.; Lee, K. H.; Kang, J. *Org. Lett.* **2005**, *7*, 3993–3996; (f) Bryantsev, V. S.; Hay, B. P. *Org. Lett.* **2005**, *7*, 5031–5034; (g) Fujimoto, C.; Kusunose, Y.; Maeda, H. *J. Org. Chem.* **2006**, *71*, 2389–2394; (h) Khatri, V. K.; Upreti, S.; Pandey, P. S. *Org. Lett.* **2006**, *8*, 1755–1758.
10. For selected examples of polymer-supported hosts. (a) Still, W. C. *Acc. Chem. Rev.* **1996**, *29*, 155–163; (b) Kubo, M.; Nishimoto, R.; Doi, M.; Kodama, M.; Hioki, H. *Chem. Commun.* **2006**, 3390–3392; (c) Nath, S.; Maitra, U. *Org. Lett.* **2006**, *8*, 3239–3242.
11. Based on the Novabiochem catalog, about 2–4 nmol of **11** is loaded on a single bead. Polymer-supported host **1** has a diameter of ca 0.1 mm as measured under a microscope. From these data, the local concentration of host **1** around the beads could be estimated to be 0.5–1 M.
12. In the previous paper,[6a] binding constants could be estimated under appropriate conditons (i.e., in the presence of large excess of *N*-ethylpiperidine). However, this method was not applicable to the present buffered aqueous solution system. Therefore, the binding constants could not be calculated.
13. (a) Tsien, R. Y.; Harootunian, A. T. *Cell Calcium* **1990**, *11*, 93–109; (b) Liu, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 90–94.