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α-CD/Crown-Appended Diazophenol for Selective Sensing of Amines

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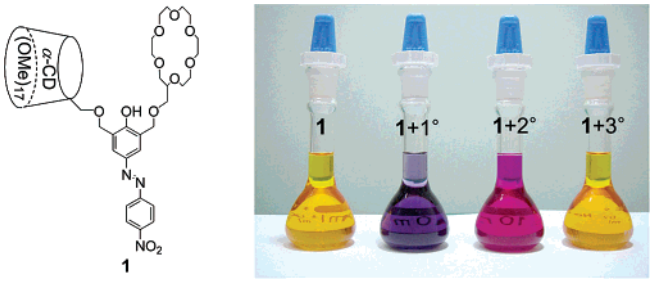
ABSTRACT



Azophenol dyes having the permethylated cyclodextrin and/or crown moieties have been synthesized. Compound 1 provides critical information on discriminating 1–3° amines with unique color changes. Addition of 1° and 2° amines to 1 shifts the absorbance maximum of 1 from 380 to ~580 and ~530 nm, respectively, but no change is observed with 3° amines. The high selectivity of 1 is mainly due to H-bonding between the ammonium H atoms of the amine and oxygen atoms of the crown-6.

One of the most pressing challenges in the design of chemosensors is discrimination for different types of biomolecules. A simple monitoring system distinguishing molecular species among amines, amino acids, or proteins would be extremely useful in environmental technology and biological technology.[1] In the particular case of discrimination among 1°, 2°, and 3° amines, the organic reaction-based *Hinsberg test* has been widely used over the past century.[2,3]

For amine sensing, visualizing macrocyclic chromophores for specific target amines have been designed,[4−11] but their low selectivity and sensitivity toward different types of amines make them impractical. With amine selectivities (1°−3°) in mind, we report herein the preparation of crown-appended cyclodextrin azophenol **1** and its selective complexation with amines.

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(1) Andreetti, G. D.; Ugozzoli, F.; Ungaro, R.; Pochini, A. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: New York, 1991; Vol. 4.
(2) Hinsberg, O. *Ber.* **1890**, *23*, 2962−2965.
(3) Solomons, G.; Fryhle, C. In *Organic Chemistry*, 7th ed.; John Wiley & Sons Inc.: New York, 2002; pp 975−976.
(4) Dix, J. P.; Vögtle, F. *Chem. Ber.* **1980**, *113*, 457−470.
(5) Dix, J. P.; Vögtle, F. *Chem. Ber.* **1981**, *114*, 638−651.
(6) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495−2496.
(7) Kaneda, T.; Umeda, S.; Ishizaki, Y.; Kuo, H.-S.; Misumi, S.; Kai, Y.; Kanehisa, N.; Kasai, N. *J. Am. Chem. Soc.* **1989**, *111*, 1881−1883.
(8) Fuji, K.; Tsubaki, K.; Tanaka, K.; Hayashi, N.; Otsubo, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 3807−3808.
(9) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522−524.
(10) Liu, C.-h. J.; Lin, J. T.; Wang, S. H.; Lin, L. G. *Chem. Sens.* **2004**, *20(B)*, 362−363.
(11) Kaneda, T. In *Crown Ethers and Analogous Compound*; Hiraok, M., Ed.; Elsevier: New York, 1992; Chapter 6.

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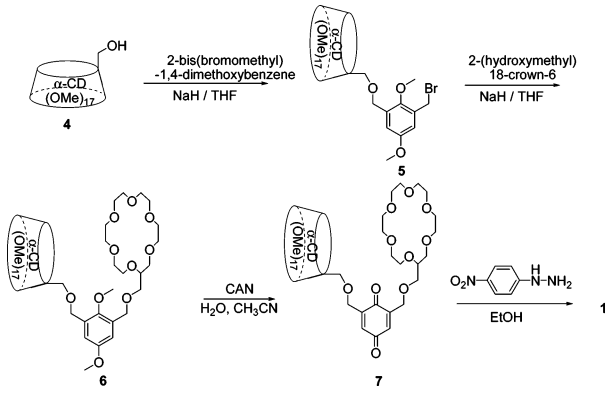
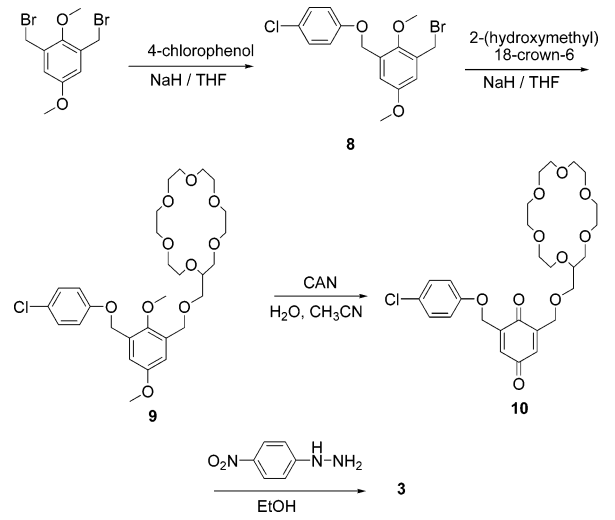
Scheme 1. Synthetic Route of Compound **1**

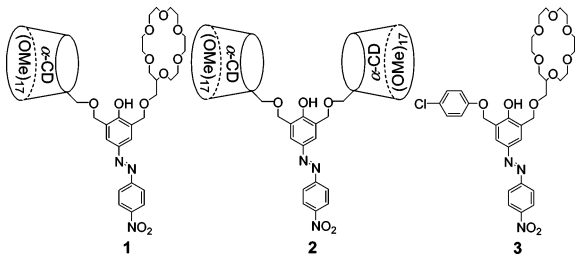


Syntheses of **1** and **3** are summarized in Schemes 1 and 2, respectively. Permethylated α-cyclodextrin-6[A]-monoal-

Scheme 2. Synthetic Route of Compound **3**



cohol[12] was reacted with 2,6-bis(bromomethyl)-1,4-dimethoxybenzene to yield the corresponding permethylated α-cyclodextrin (α-CD) in 75% yield. 2-(Hydroxylmethyl)-18-crown-6 was reacted with permethylated α-CD-appended bromomethyl-1,4-dimethoxybenzene (**5**) to give the corre-



sponding asymmetric permethylated α-cyclodextrin (α-CD) in 50% yield. Then, after the oxidation of 18-crown-6-appended permethylated α-CD with cerium(IV) ammonium

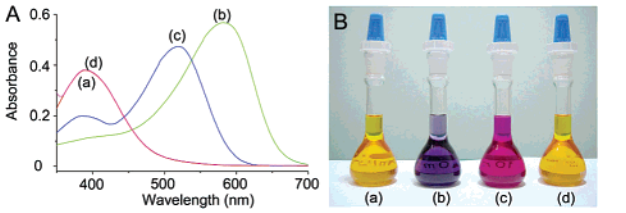


Figure 1. (A) UV−Vis spectra and (B) photographs of **1** (0.03 mM) with amines (1000 equiv) in $CHCl_3$: (a) **1**, (b) **1** + *n*-octylamine, (c) **1** + di-*n*-butylamine, and (d) **1** + tri-*n*-butylamine.

nitrate (CAN), treatment with *p*-nitrophenylhydrazine gave desired **1** in 30% yield. **3** was also synthesized in 25% yield by methods similar to those used for **1**. **2** was prepared by adaptation of procedures reported earlier.[12,13] The structures of **1**−**3** were confirmed by ^{1}H NMR, MALDI-TOF mass spectroscopy, and microanalysis (see Supporting Information).

The binding behaviors of **1**−**3** toward various amines were investigated by UV−Vis spectrophotometry. Association constants[14] were also determined from the UV−Vis band changes upon addition of 1°−3° amines to chloroform solutions of **1**−**3** and are listed in the Supporting Information, Table S1. With **1**, the addition of 1° and 2° amines resulted in bathochromic shifts of 195 and 145 nm, respectively, as shown in Figures 1 and 2 in which the color

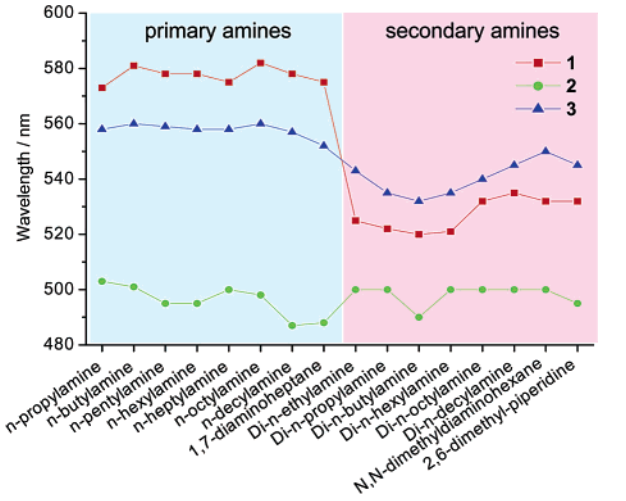


Figure 2. Absorption maxima of **1**−**3** with amines in chloroform.

changes of **1** are also noteworthy. However, addition of 3° amines to **1** gave no color change. This bathochromic shift is caused by the amine-based deprotonation of the azophenol,

(12) Jung, J. H.; Takehisa, C.; Sakata, Y.; Kaneda, T. *Chem. Lett.* **1996**, 147−148.
(13) Fujimoto, T.; Uejima, Y.; Imaki, H.; Kawarabayashi, N.; Jung, J. H.; Sakata, Y.; Kaneda, T. *Chem. Lett.* **2000**, 564−565.
(14) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

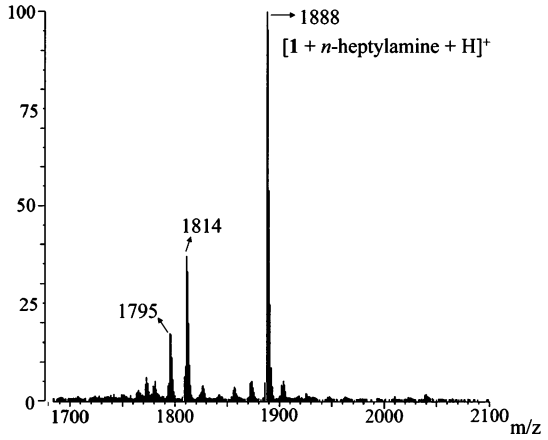


Figure 3. FAB-Mass spectrum of **1** + *n*-heptylamine in chloroform.

inducing a photoinduced charge transfer (PCT).[15] In addition, the selectivity of **1** toward the type of amines is closely related to comparable H-bonding interactions between the crown ring of **1** and the protons of the ammonium ion as well as to a critical role of the adjacent α-CD which can interact with the lipophilic alkyl chain of the amine by a hydrophobic interaction (vide infra).

The NMR spectrum of the complex **1**·*n*-heptylamine (Supporting Information, Figure S1) shows that the protons of the crown loop and C_1−H of the α-CD are seen to high-field shift. This observation is consistent with an idea that there are H-bonds between H atoms of the ammonium and the crown ring of **1** as well as hydrophobic interactions with the target amine, respectively, as mentioned earlier.

The lack of color change of **1** toward 3° amines is presumably due to a steric hindrance between the alkyl chain of the 3° amine and the α-CD.

The log K_a's of **1** for 1° and 2° amines are 4.19−4.85 and 2.02−2.32, respectively, as listed in Supporting Information, Table S1. The 1° and 2° amine selectivity of **1** was calculated to be 150−500. These results also indicate that the number of H-bonds formed between the crown ring of **1** and the protons of the ammonium ion is of critical importance to discriminate between the amines.

It is noteworthy that upon addition of *n*-octylamine, the intensity of the 380 nm absorption band of **1** decreased with concomitant increase of a new band centered at 580 nm with only one isosbestic point at 521 nm, leading to solid evidence of a 1:1 complex formation (Supporting Information, Figure S2). For the complexation ratio, we took FAB mass spectroscopy of the **1**-*n*-heptylamine complex. As shown in Figure 3, it is evident that the **1**-*n*-heptylamine complex has a 1:1 complexation ratio (1886.12 *m*/*e*, Figure 3).

To gain insight into the role of the crown unit on the amine selectivity, **2**, in which no crown ether unit was introduced,

(15) Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J. G.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573−10581.

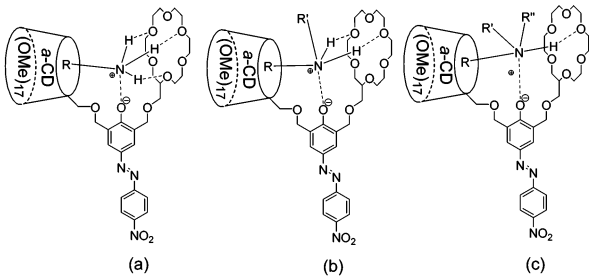


Figure 4. Proposed structures for complex formation of **1** with (a) 1° amine, (b) 2° amine, and (c) 3° amine.

was synthesized and tested for the color change upon the addition of amines. The results are given in the Supporting Information, Table S1 and Figures S4 and S5. Unlike the case of **1**, addition of 1° and 2° amines to the chloroform solution of **2** changed the color from yellow (380 nm) to pink (500 nm), respectively (Supporting Information, Table S1 and Figures S3 and S4, respectively), but lacked selectivity. On the other hand, addition of 3° amines to **2** gave no color change. These results show that the crown unit in **1** plays an important role in discriminating among the type of amines.

To elucidate the role of the α-CD in the amine selectivity, **3** with a *p*-chlorophenyl unit instead of the α-CD was prepared. Addition of 1° and 2° amines to the chloroform solution of **3** changed the color from yellow (380 nm) to pale blue (∼560 nm) and to pink (∼540 nm), respectively (Supporting Information, Table S1 and Figures S5−S7, respectively). As with **1**, no color change was noted with the addition of 3° amines. However, both binding sensitivity and selectivity of **3** toward the tested amines were found to be much lower than those of **1**. So, one can assert that the less-selective interaction and low sensitivity are related to the hydrophobic interaction between α-CD and the alkyl chain of the ammonium ion. One isosbestic point appeared in the spectrum of **3** with *n*-octylamine in $CHCl_3$, indicating the formation of a 1:1 complex as well (Supporting Information, Figure S7).

Acidity, pK_a, is also important to determine the selectivity of the acidic ligands toward the target guest molecules. The pK_a values of **1**−**3** in a solution of H_2O/1,4-dioxane (9:1 v/v) were determined to be 5.75, 5.99, and 7.30, respectively. Hence, it is noteworthy that **1** can be easily deprotonated to give rise to a phenoxide anion which develops photoinduced charge transfer through the *p*-nitrodiazophenol to provide its bathochromic shift.

According to UV−Vis, NMR, and mass spectra of the complex, we propose the complex structures of **1**-amine in Figure 4. Previously, Kaneda et al. reported on the H-bonding interactions between the crown ring of a macrocyclic chromophore and amines through an XRD study.[7,11] A 1° amine forms three-pointed perching H-bonds between the oxygen atoms of 18-crown-6 and the H atoms of the ammonium ion, and a 2° amine participates only through two-pointed H-bonding interactions.

In conclusion, we found in this study that the main factors contributing to the high selectivity of **1** toward amines are: (i) the formation of efficient H-bond interactions between the oxygen atoms of the crown loop and the H atoms of the ammonium ion of the amines; (ii) the hydrophobic interaction between the α-CD and the lipophilic tail of the amine; and (iii) acidity of the host molecule. Hence, molecule **1** reported here can be considered as an innovative tool in the discrimination of the 1°−3° amines.

Supporting Information Available: The log K_a and UV−Vis band wavelengths of **1**−**3** with amines in $CHCl_3$. Photographs for color changes of **2** and **3** with amines, and synthetic methods of **1** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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