Micropolarity around a Zwitterionic Solvatochrome Covalently Fixed in the Cavity of Bowl-Shaped Cyclophanes

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Bowl-shaped bimacrocyclic cyclophanes with a zwitterionic solvatochrome embedded in the cavity were synthesized and the micropolarity around their intracavity functionality in various solvents was estimated by using the absorption wavelengths of the chromophore, the solvent effects on which were found to be dependent on the properties of the cyclophane framework.

Hydrophobicity around the catalytic functionality at the active site of enzymes has been recognized as one of the origin of the unique features of the enzymatic reactions. The micropolarity of the active sites has been investigated by means of complexation[1] or covalent fixation[2] of various chromophoric or fluorophoric probes. The latter method has the advantage that it is not affected by the equilibrium and that the structure of the observed species is more definite. The micropolarity of the cavity in the synthetic receptors, however, has been scarcely investigated by use of a covalently bonded chromophore although there have been a number of examples using the complexation methods.[3,4] Recently, we have reported the synthesis and complexing behavior of the water-soluble bowl-shaped cyclophane **1** (Figure 1).[5] It seems particularly interesting whether the functionality embedded in the cavity is provided with a highly hydrophobic microenvironment by the surrounding macrocycle like that of the active site of enzymes. Here we report the synthesis of cyclophanes **2** and **3** bearing a solvatochrome covalently bonded to the cavity and the estimation of the micropolarity around the embedded chromophore. The solvent effects on the absorption wavelengths of the intracavity chromophore are also delineated.

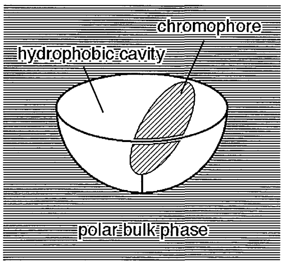
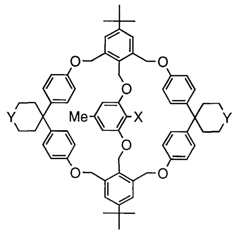
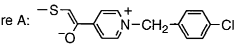


Figure 1. Schematic drawing of a bowl-shaped molecule bearing a chromophore in highly polar solvents.

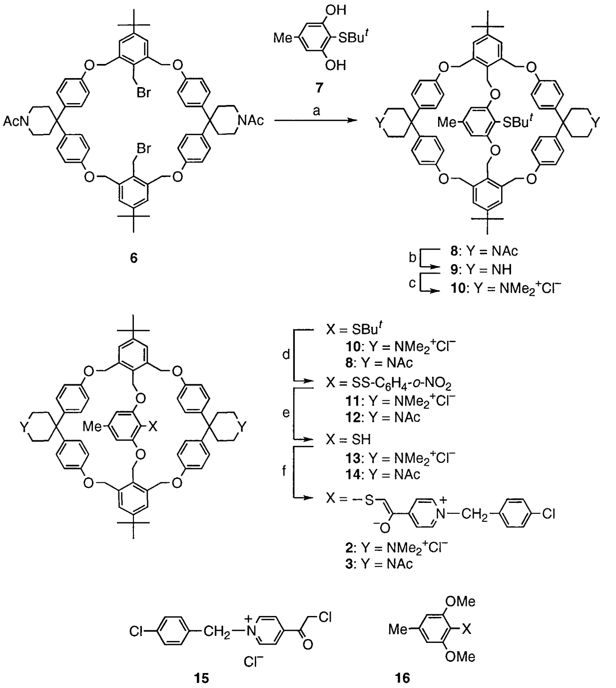


1: X = H, Y = $NMe_2^+Cl^-$
2: X = chromophore A, Y = $NMe_2^+Cl^-$
3: X = chromophore A, Y = NAc

chromophore A:



As a solvatochrome covalently bonded to the cavity, we have chosen a zwitterionic solvatochrome consisting of pyridinium and enolate moieties (denoted as chromophore A hereafter), which has been usefully employed for the estimation of micropolarity around the cysteine-SH group of the enzymes such as glyceraldehyde 3-phosphate dehydrogenase.[6] Compound **2** with two charge centers on the peripheral positions was designed as a water-soluble cyclophane bearing chromophore A. The syntheses of **2** and its neutral analog **3** are summarized in Scheme 1. The water-soluble cyclophane **10** was prepared by the procedure similar to that for **1**[5a] and converted to thiol **13** via the unsymmetrical disulfide **11**.[7] Compound **14** without charge centers was similarly synthesized from sulfide **8**. The reaction of thiols **13** and **14** with pyridinium salt **15** followed by treatment with sodium carbonate afforded cyclophanes **2** and **3**, respectively. Compound **2** with charge centers was soluble in water as well as in other organic solvents whereas the neutral compound **3** was not soluble in water and only slightly soluble in methanol.



Scheme 1. Reagents and conditions: (a) K_2CO_3, DMF, r.t., 86%; (b) $LiEt_3BH$, THF, r.t., 98%; (c) CH_3I, K_2CO_3, acetone, then Dowex® 1X8-400 (Cl^-), 89%; (d) o-O_2N-C_6H_4SCl, MeOH, **11**: 81%, **12**: 96%; (e) Na_2S, MeOH, **13**: quant, **14**: 54%; (f) **15**, MeOH, then Na_2CO_3.

The relationship between the maximum absorption wavelength (λ_{max}) of the water-soluble cyclophane **2** and the polarity scale E_T^N [8] is shown in Figure 2 with filled circles and a solid line and that of the reference compound **16** without the cyclophane framework with open squares and a dotted line. It is of note that the maximum absorption wavelength of **2** in water (520 nm) is bathochromically shifted by 55 nm from that of the reference compound **16** (465 nm) in water and nearly equal to that of **16** in methanol (517 nm). By using the regression line for **16** as a calibration line, the micropolarity around the

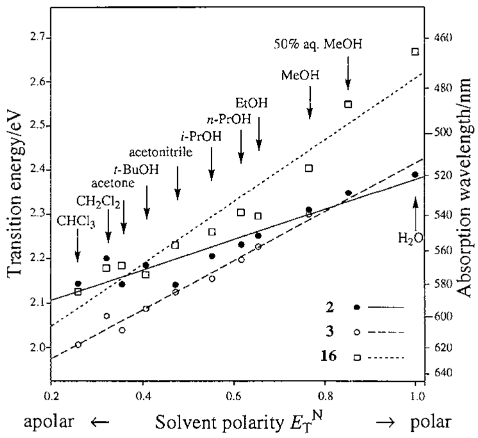


Figure 2. Maximum absorption wavelengths[9] of **2**, **3** and **16** in various solvents related to the empirical polarity scale E_T^N.

chromophore of **2** in water was estimated to be 0.70 in the E_T^N scale.

It was also found that the maximum absorption wavelengths of cyclophane **2** and the reference compound **16** have different sensitivity to the solvent polarity E_T^N; the slope of the regression line for **2** was found to be about a half of that for **16**. For the investigation of the effect of the charge centers in **2**, the maximum absorption wavelengths of the neutral compound **3** were also measured (Figure 2, open circles and a broken line). The wavelengths are bathochromically shifted in the whole region of the solvent polarity in comparison with those of **16** whereas the slope of the regression line for **3** is rather similar to that for **16** and larger than that for **2**. These results suggest that the incorporation of the chromophore within the cavity of the cyclophane induces a bathochromic shift of *ca.* 40 nm and the presence of the charge centers on the periphery of the cyclophane reduces the slope of the regression line approximately by half. The effect of the cavity can be explained by assuming that the surrounding aromatic rings limit the access of solvent molecules to the enolate oxygen of the chromophore, which results in a bathochromic shift in the whole region of the solvent polarity. On the other hand, the effect of the positive charges can be explained in terms of the electrostatic interaction between the negative enolate oxygen and the positive piperidinium nitrogen atoms. Such interaction is considered to neutralize the negative charge on the enolate oxygen to cause a hypsochoromic shift of the maximum absorption wavelength of the chromophore, especially in less polar media where the interaction is stronger. In polar media such as water, however, the electrostatic interaction between the charge centers is likely to be much less significant because they should be strongly solvated. It is consistent with the fact that the absorption maxima of **2** are almost the same as those of **3** in the range of high solvent polarity. These results indicate that the micropolarity around the intracavity functionality of **2** in aqueous media is scarcely perturbed by the positive charge centers and that the cavity can serve as a hydrophobic reaction environment for the functionality.

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