Chapter 5
Chemosensors for Water Contaminants Based on Chromophore-Appended Cyclodextrins

Hiroshi Ikeda

Contents

Abstract The development of new chemical sensing methods for the recognition of molecules or ions in water is an important theme in many fields including environmental, biological, and clinical applications and simple methods for detecting organic molecules in water is desired. Chemosensors have been attracting considerable attention among the variety of methods for detecting chemical species. Many kinds of chromophore-appended cyclodextrins have been reported for chemosensors. Here, we review the molecule-sensing abilities of chromophore-appended cyclodextrins as chemosensors. First, turn-off fluorescent chemosensors using chromophore-appended cyclodextrins are discussed. The fluorescence intensities of turn-off fluorescent cyclodextrin chemosensors always decrease upon analyte addition,

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and the analyte-induced variation of the fluorescence intensities of the turn-off fluorescent cyclodextrin chemosensors depend on a analyte. The sensitivities of the turn-off cyclodextrin chemosensors roughly only depend on the binding affinity for a analyte. Next, dye-appended cyclodextrins are discussed as color-change chemosensors, which are effective for detection by the naked eye. Then, turn-on fluorescent chemosensors using chromophore-appended cyclodextrins are discussed. The fluorescence intensities of turn-on fluorescent cyclodextrin chemosensors increase upon addition of special analytes, which have a comparatively spherical shape. The turn-on fluorescent β-cyclodextrin chemosensor is not sensitive to bile acids, which are strongly bound by β-cyclodextrin. The shape and size of analytes have a greater influence on the fluorescence intensity than the binding affinity. Finally, chromophore-appended cyclodextrins for detection of anion or cation species are discussed.

Abbreviations

AdCOOH	Adamantanecarboxylic acid
AdOH	Adamantanol
$AdNH_2$	Adamantanamine
Bor	Borneol
CA	Cholic acid
Cam	Camphor
CD	Cyclodextrin
CDCA	Chenodeoxycholic acid
c-HexOH	Cyclohexanol
c-OctOH	Cyclooctanol
DCA	Deoxycholic acid
DNS-L-Leu-βCD	*N*-dansyl-L-leucine-appended β-cyclodextrin
DNS-D-Leu-βCD	*N*-dansyl-D-leucine-appended β-cyclodextrin
DNS-L-Phe-βCD	*N*-dansyl-L-phenylalanine-appended β-cyclodextrin
DNS-D-Phe-βCD	*N*-dansyl-D-phenylalanine-appended β-cyclodextrin
DNS-L-Val-βCD	*N*-dansyl-L-valine-appended β-cyclodextrin
DNS-D-Val-βCD	*N*-dansyl-D-valine-appended β-cyclodextrin
Fen	Fenchone
Ger	Geraniol
HDCA	Hyodeoxycholic acid
LCA	Lithocholic acid
Men	Menthol
NC0αCD	(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin
NC0βCD	(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin
NC0γCD	(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin
NC4βCD	(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended β-cyclodextrin

NC4γCD	(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended γ-cyclodextrin
Ner	Nerol
UDCA	Ursodeoxycholic acid

5.1 Introduction

Chemical sensing plays an important role in chemical, clinical, biological, environmental, and security tests. In the field of environmental science, it is well-known that mercury, lead and cadmium are toxic to living organisms, and the detection of them in the environment has been well studied. The detection of organic molecules such as benzene, halomethane, and agricultural chemicals in water is also important; therefore, simple methods for detecting organic molecules in water is desired.

Among the variety of methods for detecting chemical species, chemosensors have been attracting considerable attention (de Silva et al. 1997; Lavigne and Anslyn 2001; Anslyn 2007; Mirsky and Yatsimirsky 2011; Prodi et al. 2011; You et al. 2015). The concept of a "chemosensor" was introduced by Czarnik (Czarnik 1993; Desvergne and Czarnik 1997). Previously wording of organic chemists to refer to new molecular indicators as "sensors" has been criticized because Webster's dictionary defined a sensor as a mechanical device sensitive to light, temperature, radiation level or the like. Czarnik defined a fluorescent chemosensor as a compound of abiotic origin that complexes to an analyte reversibly with a concomitant fluorescent signal transduction wherein it constitutes only the active transduction unit of a sensor. Changes in fluorescence intensity or color changes of chemosensors produced by the interaction of chemosensors with analytes can be detected with the naked eye. Chemosensors also have advantages including portability, operational simplicity, rapid response and cost effectiveness.

Extensive efforts have been made to construct chemosensors that selectively interact with analytes to produce detectable changes in signals. Several chromophore-appended cyclodextrins have been prepared for this purpose. Cyclodextrin chemosensors can be used to detect colorless neutral molecules in water via changes in the intensity of their fluorescence, absorption, or circular dichroism.

Cyclodextrins are torus-shaped cyclic oligosaccharides consisting of six, seven, and eight D-glucopyranose units for α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, respectively (Fig. 5.1). Various values for the internal diameter of cyclodextrins have been reported using different estimation methods (Table 5.1) (Saenger 1980; Hall et al. 1988; Müller and Wenz 2007). Müller and Wenz calculated the minimum internal diameters of cyclodextrins by semi-empirical AM1 and PM3 calculations and showed that the stability of an inclusion complex of an α-cyclodextrin with a guest is strongly correlated with the cross-sectional diameter of the α-cyclodextrin and the guest (Müller and Wenz 2007). In aqueous solution, cyclodextrins can accommodate various organic compounds in their central cavities.

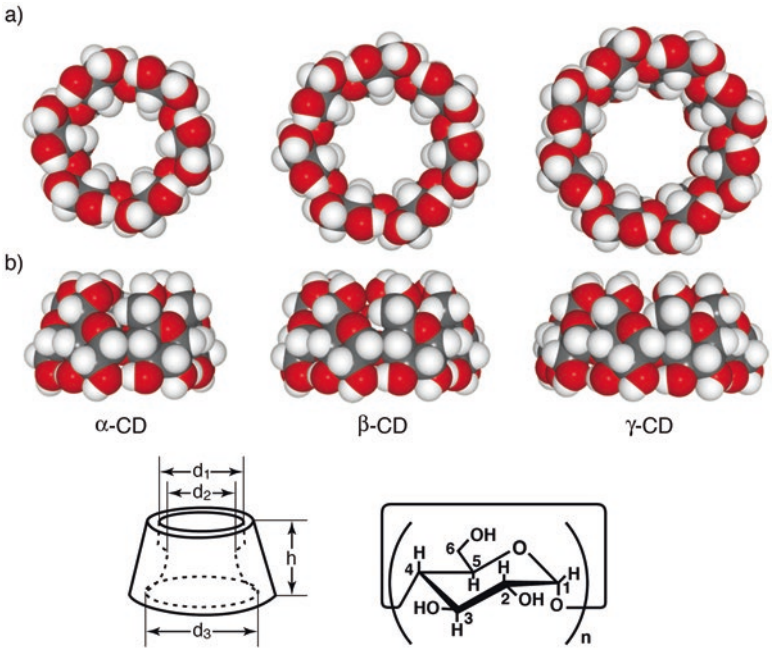


Fig. 5.1 Structures of α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD): (**a**) view from the secondary hydroxy side of cyclodextrin, (**b**) the side view of cyclodextrin

Table 5.1 Properties of cyclodextrins

	n	d_1 [Å][a]	d_2 [Å][a]	d_3 [Å][a]	h [Å][a]	d_1 [Å][b]	d_3 [Å][b]	d_2 [Å] AM1[c]	d_2 [Å] PM3[c]
α-CD	6	5.6	4.2	8.8	7.8	4.7	5.2	4.4	4.4
β-CD	7	6.8	5.6	10.8	7.8	6.0	6.4	5.8	6.5
γ-CD	8	8.0	6.8	12.0	7.8	7.5	8.3	7.4	8.1

[a]Hall et al. 1988, [b]Saenger 1980, [c]Müller and Wenz 2007

The hydrophobic, van der Waals forces, and dipole–dipole interactions between the cyclodextrin and guest are the major driving forces of inclusion phenomena, and the stability of the inclusion complex is affected by the fitness of shape and size of the guest to the cyclodextrin cavity.

Many types of chemosensors can be constructed using cyclodextrins that recognize the shape and size of analytes. In this chapter, the molecule-sensing abilities of chromophore-appended cyclodextrins will be reviewed.

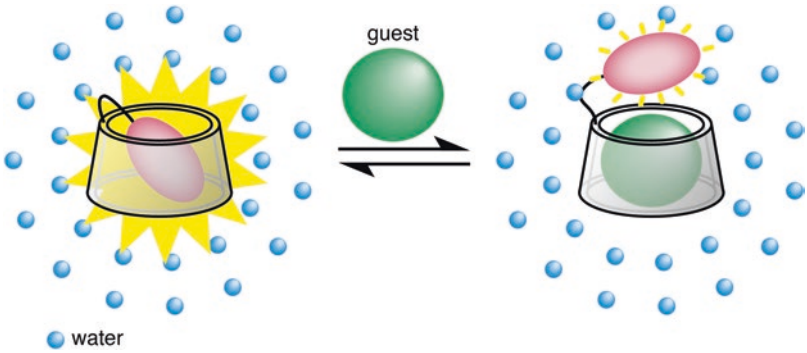


Fig. 5.2 A two-state equilibrium model for guest-induced conformational change of chromophore-appended cyclodextrins in aqueous solution; The self-inclusion state is usually the major conformation in aqueous solution (*left*). An induced-fit conformational change of the chromophore-appended cyclodextrin occurs in association with accommodation of the guest (*right*). In the case of a fluorophore, the fluorescent cyclodextrin exhibits a strong fluorescence in the self-inclusion state due to the hydrophobic environment of the cyclodextrin cavity, and exclusion of the fluorophore from the cyclodextrin cavity to the bulk water weakens its fluorescence intensity. (Adapted from Ueno et al. 1990)

5.2 Turn-Off Fluorescent Chemosensors

Ueno proposed a new system for a chemosensor to detect molecules (Ueno et al. 1990). A chromophore was connected to a cyclodextrin with a suitable spacer unit. The mechanism of this chemosensor is shown in Fig. 5.2. Although the chromophore-appended cyclodextrins can adopt some conformations in aqueous solution, the conformation equilibrium can be explained by the simplified two-state model shown in Fig. 5.2. The self-inclusion state is usually the major conformation in aqueous solution because a fluorophore unit is hydrophobic and is more stable in the central cavity of the cyclodextrin than in the bulk water. An induced-fit conformational change of the chromophore-appended cyclodextrin occurs in association with accommodation of the guest; this conformational change displaces the chromophore from inside to outside of the cyclodextrin cavity. The 'non-self-inclusion state' increases with an increase in the guest concentration. In the case of a fluorophore, the fluorescent cyclodextrin exhibits a strong fluorescence in the self-inclusion state due to the hydrophobic environment of the cyclodextrin cavity, and exclusion of the fluorophore from the cyclodextrin cavity to the bulk water weakens its fluorescence intensity. The extent of variation in fluorescence intensity depends on the affinity of the chemosensor for a guest. This chemosensor system is effective for detecting molecules.

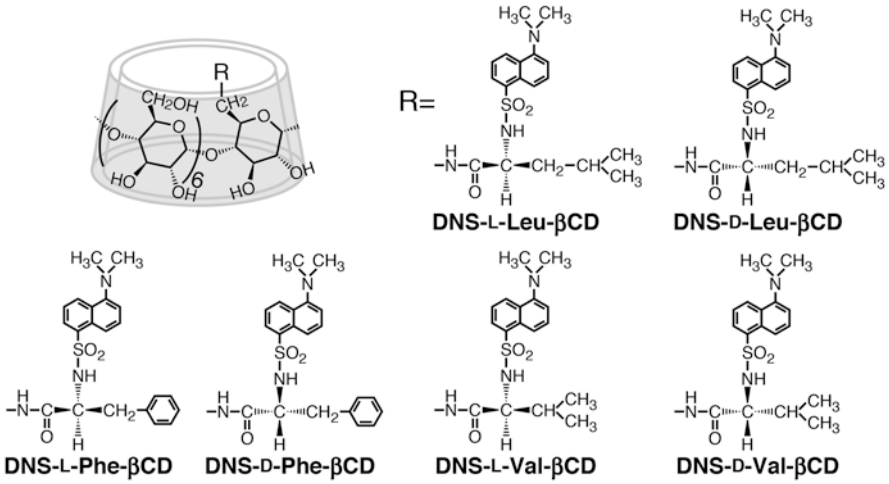


Fig. 5.3 Structures of dansyl-amino acid-cyclodextrin triad systems; *N*-dansyl-L-leucine-appended β-cyclodextrin (DNS-L-Leu-βCD), *N*-dansyl-D-leucine-appended β-cyclodextrin (DNS-D-Leu-βCD), *N*-dansyl-L-phenylalanine-appended β-cyclodextrin (DNS-L-Phe-βCD), *N*-dansyl-D-phenylalanine-appended β-cyclodextrin (DNS-D-Phe-βCD), *N*-dansyl-L-valine-appended β-cyclodextrin (DNS-L-Val-βCD), and *N*-dansyl-D-valine-appended β-cyclodextrin (DNS-D-Val-βCD)

5.2.1 Fluorophore-Amino Acid-Cyclodextrin Triad Systems for Fluorescent Chemosensors

Cyclodextrin-leucine-chromophore triad systems are examples of fluorescent cyclodextrin chemosensors (Fig. 5.3). These chemosensors contain a leucine moiety as a spacer between the cyclodextrin cavity and the dansyl moiety which acts as a fluorophore. The hydrophobic side chain of the leucine moiety is expected to increase binding affinity due to a hydrophobic cap effect. The chirality of the leucine moiety is also expected to affect the binding affinity for guests.

Ikeda et al. first investigated conformational changes of cyclodextrin chemosensors upon addition of guests via fluorescence decay and NMR techniques (Ikeda et al. 1996, 1997). While the conformational interconversion occurs too rapidly to be followed by NMR spectroscopy, analysis of the fluorescence decay of the pendant fluorophore can provide useful information with respect to conformational features because the fluorescence lifetimes of many fluorophores are of a measurable magnitude (nanoseconds) for each conformation. The dansyl moiety is sensitive to the hydrophobicity around it and has longer lifetimes when located inside the cavity as opposed to in the bulk water solution. All of the dansyl moiety fluorescence decays were analyzed by a simple double exponential function. This means that there are two kinds of observable conformational isomers which are in equilibrium. The longer and shorter lived species are the ones with the dansyl moiety inside and outside the cavity, respectively (Fig. 5.4).

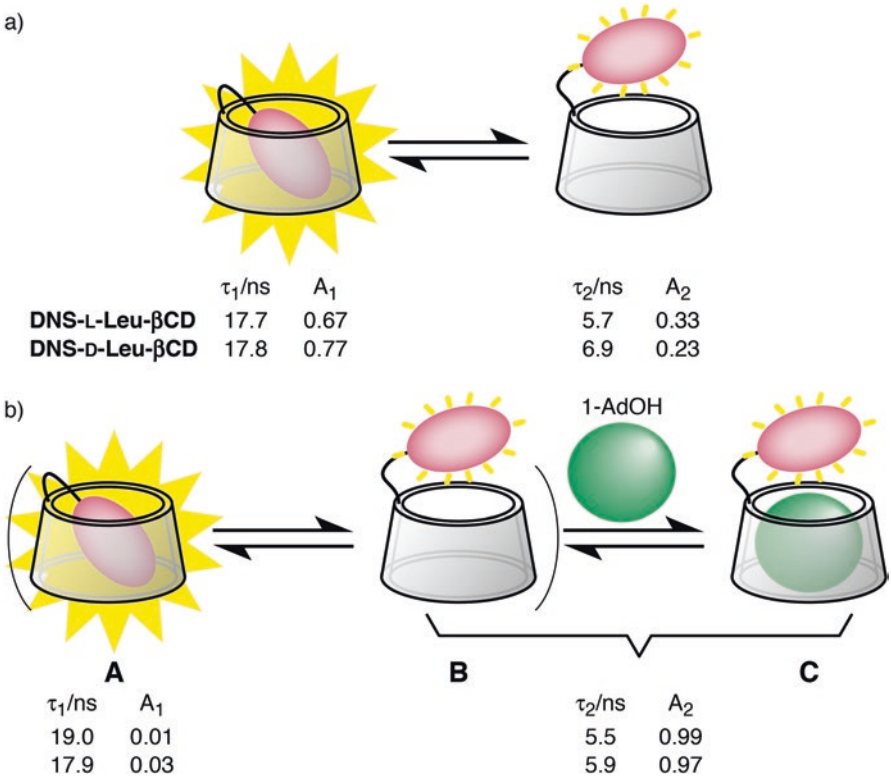


Fig. 5.4 Conformational equilibria of *N*-dansyl-L-leucine-appended β-cyclodextrin (DNS-L-Leu-βCD) and *N*-dansyl-D-leucine-appended β-cyclodextrin (DNS-D-Leu-βCD) and their guest-induced conformational changes in aqueous solution with fluorescence decay data (Adapted from Ikeda et al. 1996)

The fluorescence decay is expressed by Eq. 5.1:

$$D(\mathrm{t}) = A_1 \exp(-\mathrm{t}/\tau_1) + A_2 \exp(-\mathrm{t}/\tau_2) \tag{5.1}$$

where A_i is a pre-exponential factor contributing to the signal at zero time and τ_i is the lifetime of the *i*th component.

Alternatively, A_1/A_2 can be expressed by Eq. 5.2;

$$A_1 / A_2 = (\varepsilon_1 C_1 \Phi_1 / \tau_1) / (\varepsilon_2 C_2 \Phi_2 / \tau_2) = (\varepsilon_1 C_1 / \tau_{01}) / (\varepsilon_2 C_2 / \tau_{02}) \tag{5.2}$$

where C_i is the concentration of species i, ε_i is the molar extinction coefficient, Φ_i is the quantum efficiency, and τ_{0i} is the intrinsic fluorescence lifetime.

$$\text{If } \varepsilon_1 = \varepsilon_2 \text{ and } \tau_{01} = \tau_{02}, \tag{5.3}$$

then

$$A_1 / A_2 = C_1 / C_2 \tag{5.4}$$

A reasonable approximation of the ratio of the intrinsic lifetimes is unity because the fluorescence of the self-inclusion and non-self-inclusion states arise from the same unit (Li et al. 1975; Hashimoto and Thomas 1985; Nelson et al. 1988; Huang and Bright 1990; Dunbar and Bright 1994). Therefore, the equilibrium can be quantified from parameters obtained directly from the analysis of fluorescence decay curves. This estimation is useful for discussion of the equilibrium semi-quantitatively. However it should be noted that τ_0 of the dansyl moiety depends slightly on solvent polarity; therefore, Eq. 5.4 is only a rough approximation (Li et al. 1975).

The function ratio of two species indicates that the self-inclusion states of *N*-dansyl-L-leucine-appended β-cyclodextrin and *N*-dansyl-D-leucine-appended β-cyclodextrin are more stable than their non-self-inclusion states. The chirality of the leucine moiety also affects the stability of the self-inclusion form. The self-inclusion form of *N*-dansyl-D-leucine-appended β-cyclodextrin having the D-leucine moiety is more stable than that of *N*-dansyl-L-leucine-appended β-cyclodextrin having the L-leucine moiety.

The fractions of the shorter lifetime species of *N*-dansyl-L-leucine-appended β-cyclodextrin and *N*-dansyl-D-leucine-appended β-cyclodextrin increase upon addition of 1-adamantanol, while the fractions of the longer lifetime species of the hosts decrease (Fig. 5.4). This indicates that the induced-fit conformational change of the chromophore-appended cyclodextrin occurs in association with guest accommodation, excluding the chromophore from the inside to the outside of the cyclodextrin cavity. The fact that the fluorescence decay curves of the hosts are still double-exponential indicates that the fluorescence lifetimes of species B and C in Fig. 5.4 are similar and are not resolved by this lifetime measurement system.

Figure 5.5 shows the sensitivity parameters expressed as $\Delta I/I_0$ (where $\Delta I = I - I_0$, with I and I_0 being the fluorescence intensities in the presence and absence of the guest, respectively). Compounds *N*-dansyl-L-leucine-appended β-cyclodextrin and *N*-dansyl-D-leucine-appended β-cyclodextrin exhibit similar trends in guest dependency of the $\Delta I/I_0$ value, but the $\Delta I/I_0$ value of *N*-dansyl-L-leucine-appended β-cyclodextrin is larger than that of *N*-dansyl-D-leucine-appended β-cyclodextrin in all cases because the binding constants of *N*-dansyl-L-leucine-appended β-cyclodextrin are over twice as large as those of *N*-dansyl-D-leucine-appended β-cyclodextrin for most of the guests (Fig. 5.5).

Four steroidal compounds were detected by *N*-dansyl-L-leucine-appended β-cyclodextrin and *N*-dansyl-D-leucine-appended β-cyclodextrin with the sensitivity order cholic acid < deoxycholic acid < chenodeoxycholic acid < ursodeoxycholic acid. This order is the same as the order of their binding constants. These compounds have the same steroidal framework, and ursodeoxycholic acid and chenodeoxycholic acid are isomers with differing stereochemistry of the hydroxyl group at C-7. Deoxycholic acid is the regioisomer of ursodeoxycholic acid and chenodeoxycholic acid; it has one hydroxyl group at C-12 instead of C-7. Cholic acid has one more hydroxyl group than the other compounds.

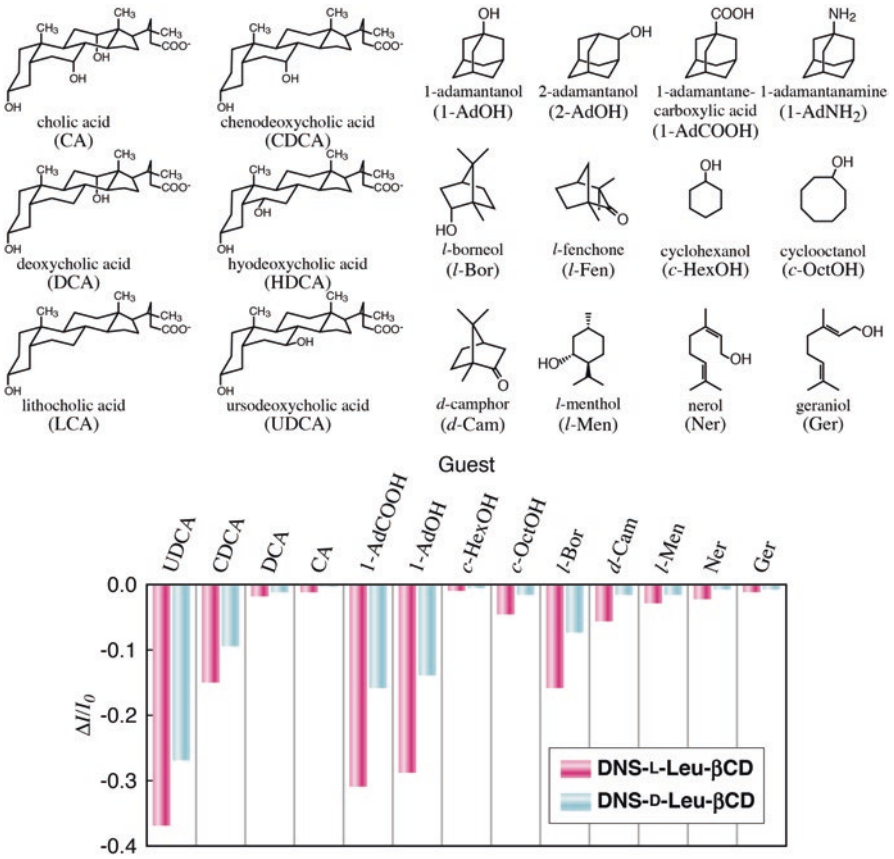


Fig. 5.5 Sensitivity parameters ($\Delta I/I_0$) of *N*-dansyl-L-leucine-appended β-cyclodextrin (DNS-L-Leu-βCD) and *N*-dansyl-D-leucine-appended β-cyclodextrin (DNS-D-Leu-βCD): [DNS-L-Leu-βCD] = [DNS-D-Leu-βCD] = 2×10^{-6} M, [guest] = 1×10^{-5} M; $\Delta I/I_0 = (I - I_0)/I_0$ (where I and I_0 are the fluorescence intensities in the presence and absence of the guest, respectively) (Adapted from Ikeda et al. 1996)

The NMR spectra of *N*-dansyl-L-leucine-appended β-cyclodextrin and *N*-dansyl-D-leucine-appended β-cyclodextrin provide information about their structures in the self-inclusion state. The dansyl moieties of *N*-dansyl-L-leucine-appended β-cyclodextrin and *N*-dansyl-D-leucine-appended β-cyclodextrin are located inside the cavity in the major conformational state. The ^{1}H NMR spectra of *N*-dansyl-L-leucine-appended β-cyclodextrin and *N*-dansyl-D-leucine-appended β-cyclodextrin were assigned using various 1D and 2D NMR techniques. Their structures were estimated from NOE data and the degree of the anisotropic ring current effect from the dansyl moiety in the ^{1}H resonances of the cyclodextrin protons (Ikeda et al. 1997). The dansyl moiety of *N*-dansyl-D-leucine-appended β-cyclodextrin is located deeper within the cavity than that of *N*-dansyl-L-leucine-appended β-cyclodextrin (Fig. 5.6). This deeper inclusion into its cavity makes *N*-dansyl-D-leucine-appended

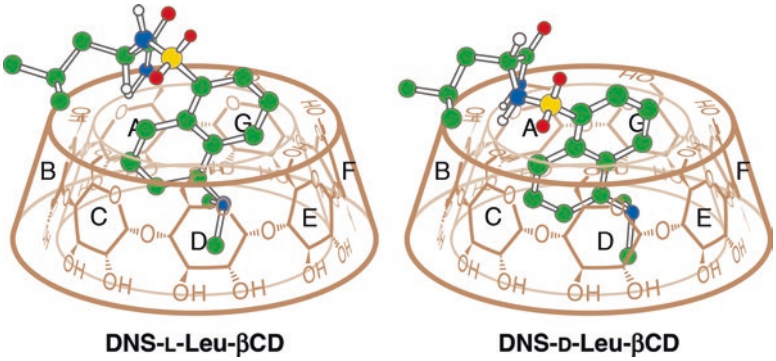


Fig. 5.6 Estimated structures of *N*-dansyl-L-leucine-appended β-cyclodextrin (DNS-L-Leu-βCD) and *N*-dansyl-D-leucine-appended β-cyclodextrin (DNS-D-Leu-βCD) (Adapted from Ikeda et al. 1996)

β-cyclodextrin the more stable self-inclusion complex, and this higher stability is also reflected in its larger fluorescence intensity and lower binding abilities.

5.2.2 *Chiral Recognition by Fluorophore-Amino Acid-Cyclodextrin Triad Systems*

There is interest in whether the influential effect of the chirality of the leucine spacer unit on the stability of the self-inclusion state is shared by other amino acid spacer units. This was investigated by preparing four kinds of fluorophore-amino acid-cyclodextrin triad systems having either phenylalanine or valine as the spacer (Fig. 5.3) (Ikeda et al. 2006a). The fluorescence intensity of *N*-dansyl-D-phenylalanine-appended β-cyclodextrin was much larger than that of *N*-dansyl-L-phenylalanine-appended β-cyclodextrin. This influence of the spacer chirality on the fluorescence intensity is similar to the *N*-dansyl-leucine-appended β-cyclodextrin. On the other hand, the fluorescence intensity of *N*-dansyl-L-valine-appended β-cyclodextrin was similar to that of *N*-dansyl-D-valine-appended β-cyclodextrin, both of which were larger than that of *N*-dansyl-L-leucine-appended β-cyclodextrin or *N*-dansyl-D-leucine-appended β-cyclodextrin. The isopropyl side chain of valine is smaller than the isobutyl side chain of leucine and scarcely inhibits the self-inclusion of the dansyl moiety into the cyclodextrin cavity, whereas the benzyl moiety of phenylalanine affects the self-inclusion depth of the dansyl moiety.

There is also interest in the ability of chemosensors having a chiral amino acid to engage in enantioselective recognition. Enantioselective chemosensors are currently of great interest to determine the enantiomeric excess of samples in drug discovery or of products in high-throughput screening of enantioselective catalysts and biocatalysts. Fig. 5.7 shows the chiral discrimination abilities of the four chemosensors for some norbornane and cyclohexane derivatives. *N*-dansyl-L-

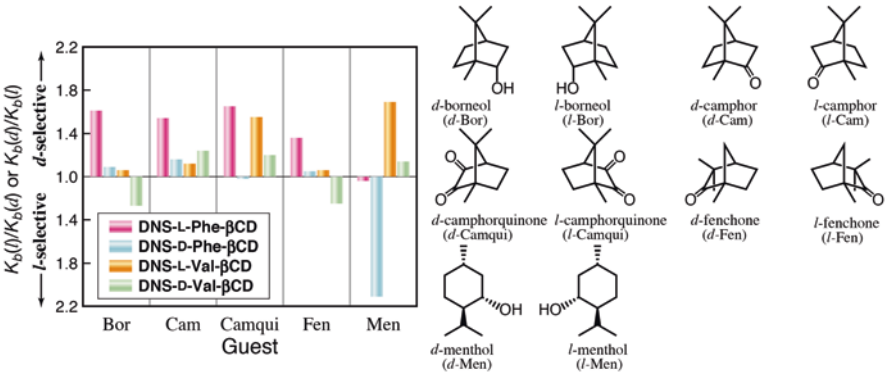
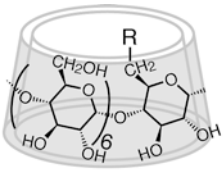


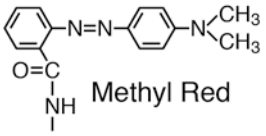
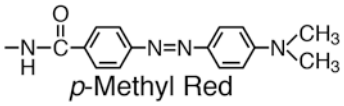
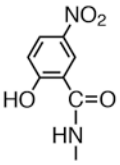
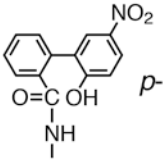
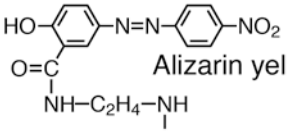
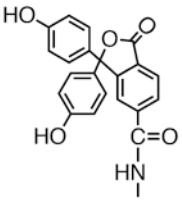
Fig. 5.7 Chiral discrimination abilities of *N*-dansyl-L-phenylalanine-appended β-cyclodextrin (DNS-L-Phe-βCD), *N*-dansyl-D-phenylalanine-appended β-cyclodextrin (DNS-D-Phe-βCD), *N*-dansyl-L-valine-appended β-cyclodextrin (DNS-L-Val-βCD), and *N*-dansyl-D-valine-appended β-cyclodextrin (DNS-D-Vale-βCD) (Adapted from Ikeda et al. 2006a)

phenylalanine-appended β-cyclodextrin exhibited good *d*-selectivity for borneol, camphor, camphorquinone, and fenchone but poor selectivity for menthol. *N*-dansyl-D-phenylalanine-appended β-cyclodextrin and *N*-dansyl-L-valine-appended β-cyclodextrin exhibited good *l*-selectivity and *d*-selectivity for menthol, respectively. Only menthol has a cyclohexane skeleton, whereas the other guests have the same norbornane framework. *N*-dansyl-L-phenylalanine-appended β-cyclodextrin exhibited high selectivity for the norbornane derivatives but does not show selectivity for the cyclohexane derivative. Each of the four chemosensors shows a different selectivity pattern for each of the norbornane derivatives having the same framework but a different functional group.

5.3 Color-Change Chemosensors

Ueno's group prepared guest responsive color-change chemosensors using dye-appended cyclodextrins (Ueno et al. 1992; Kuwabara et al. 1993, 1994, 1996, 1998, 1999; Aoyagi et al. 1997; Matsushita et al. 1997). Color-change is effective for detection by the naked eye. Methyl red-, *p*-nitrophenol-, alizarin yellow-, and phenolphthalein-appended cyclodextrins have been reported as color-change chemosensors, each acting in acidic, neutral, or alkaline solution. Fig. 5.8 shows the pH of the solution for working as a chemosensor and the color change upon addition of a guest to theses color-change chemosensors. The dye in the cyclodextrin cavity is generally protected from protonation or deprotonation. Accommodation of a guest in the cyclodextrin cavity migrates the dye from the hydrophobic cyclodextrin cavity to the bulk water. This causes protonation or deprotonation of the dye, producing the color change.



R =	without a guest	with a guest	solution pH	
 Methyl Red	yellow	red	1.6	a), c), f)
 *p*-Methyl Red	orange	red	2.4	c), f)
 *p*-Nitrophenol	yellow	colorless	5.0	h)
 *p*-Nitrophenol	yellow	colorless	6.5	b) h)
 Alizarin yellow	yellow	red	8.3	g)
 Phenolphtalein	colorless	purple	9.7	d), e)

a) Ueno 1992, b) Kuwabara 1993, c) Kuwabara1994, d) Kuwabara 1996,
e) Kuwabara 1998, f) Kuwabara1999, g) Aoyagi 1997, h) Matsushita 1997

Fig. 5.8 Structures of guest-responsive color-change chemosensors

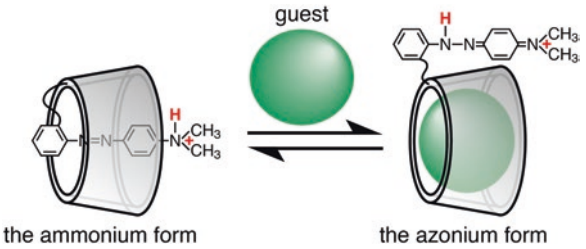


Fig. 5.9 A two-state equilibrium model for guest-induced conformational change of methyl red-appended β-cyclodextrin that causes the color change; The self-inclusion state is usually the major conformation and the ammonium form is the major form in acidic solution (left). An induced-fit conformational change of the methyl red-appended cyclodextrin occurs in association with accommodation of the guest (right). This conformational change causes the azo group to change to the azonium form, which is a tautomer of the ammonium form. This change induces the color change from yellow to red. (Adapted from Ueno et al. 1992)

For example, the azo group of methyl red-appended β-cyclodextrin is protected from protonation by the cyclodextrin cavity even in acidic solution (Fig. 5.9). Because the methyl red moiety is longer than the cyclodextrin cavity, the dimethylamino group is placed outside the cyclodextrin cavity and is easily protonated. Upon guest binding, the methyl red moiety is displaced from the cyclodextrin cavity to the acidic bulk water; the azo group changes to the azonium form, which is a tautomer of the ammonium form. This change causes the color change from yellow to red. Neutral organic molecules can be detected by these color-change chemosensors in aqueous solution. These sensing abilities for various guests are roughly parallel to the binding affinity for the guest.

5.4 Turn-On Fluorescent Chemosensors

A turn-off mechanism is greatly effective for producing a detectable change in a signal upon guest accommodation into the cyclodextrin cavity, but it has the following defects.

(1) Self-inclusion of the chromophore can inhibit accommodation of the guest. For example, the self-inclusion state of *N*-dansyl-D-leucine-appended β-cyclodextrin is twice as stable as that of *N*-dansyl-L-leucine-appended β-cyclodextrin, and the binding ability of the former for a guest is about half that of the latter.
(2) The guest selectivity of the chemosensor mainly depends on the selectivity of the cyclodextrin itself. The affinities of both β-cyclodextrin and γ-cyclodextrin for bile acid derivatives are greater than their affinities for adamantane derivatives. Therefore, the sensitivity parameter of turn-off chemosensors cannot identify whether adamantanol exists or not in a mixed solution of a bile acid and adamantanol.

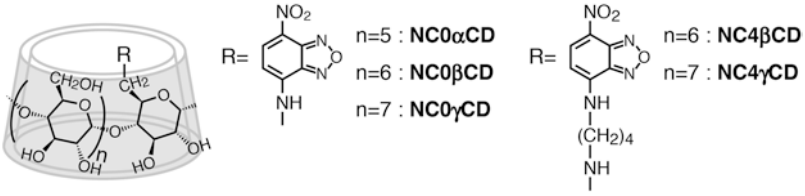


Fig. 5.10 Structures of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended cyclodextrins and (7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended cyclodextrins

(3) The detection of a guest is accompanied by a decrease in the fluorescence intensity for turn-off chemosensors, although an increase in the emission intensity caused by guest response is more effective for chemical sensing systems.

Therefore, a new fluorescent chemosensor was prepared to overcome these defects. (7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amine (NBDamine) was selected as a fluorophore for a new type of chemosensor (Ikeda et al. 2005). (7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amine displays the interesting property of fluorescing weakly in water and strongly in organic solvents, membranes, or hydrophobic environments (Uchiyama et al. 2001). One chemosensor ((7-nitrobenz-2-oxa-1,3-diazol-4-yl) aminobutylamine-appended β-cyclodextrin (NC4βCD) or (7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended γ-cyclodextrin (NC4γCD)) has a spacer similar to the turn-off cyclodextrin-based chemosensors and another chemosensor ((7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin (NC0αCD), (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin (NC0βCD), or (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin (NC0γCD)) has no spacer (Fig. 5.10).

5.4.1 Skeleton-Selective Chemosensor

The response of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended β-cyclodextrin to guests is similar to the turn-off cyclodextrin-based chemosensors but the response of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin to guests is quite different from those (Fig. 5.11). The fluorescence intensity of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin increased upon addition of 1-adamantanol (1-AdOH), indicating an increase in hydrophobicity near the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety induced by accommodation of the guest (Fig. 5.12). Figure 5.11 shows the sensitivity parameters of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin for various guests. (7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin is quite sensitive to the adamantane and borneol derivatives, which have a comparatively spherical shape that fits the β-cyclodextrin cavity. (7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin exhibits a large increase in the

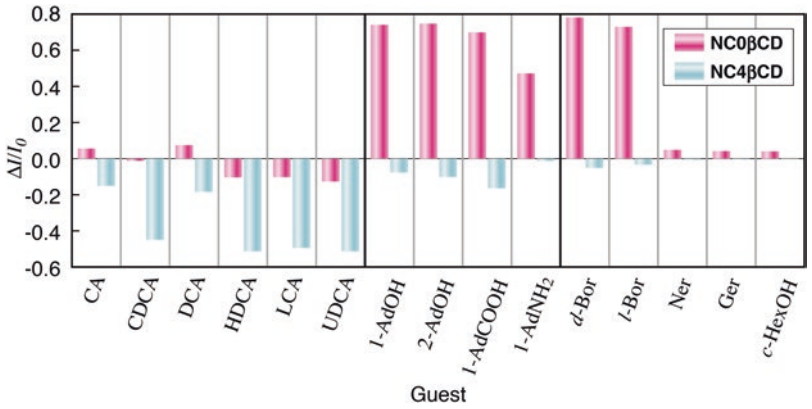


Fig. 5.11 Sensitivity parameters ($\Delta I/I_0$) of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin (NC0βCD) and (7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended β-cyclodextrin (NC4βCD): [NC0βCD] = [NC4βCD] = $5x10^{-6}$ M, [guest] = $1x10^{-5}$ M. $\Delta I/I_0 = (I - I_0)/I_0$ (where I and I_0 are the fluorescence intensities in the presence and absence of the guest, respectively) (Adapted from Ikeda et al. 2005)

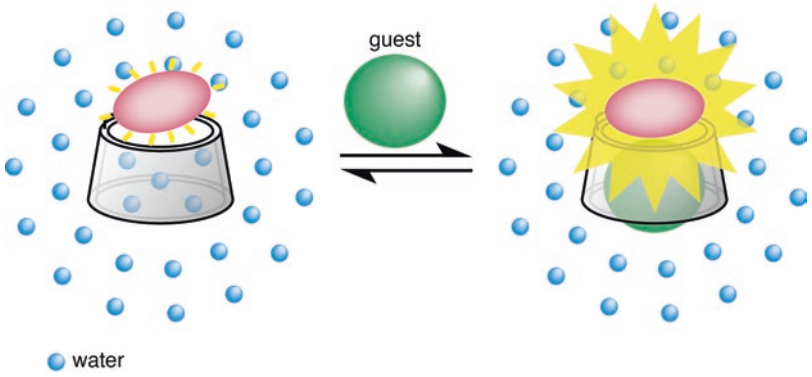


Fig. 5.12 Guest-induced conformational changes of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended cyclodextrins; Hydrophobicity near the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety increases by accommodation of the guest and its fluorescence intensity increases

fluorescence intensity in response to these guests. Notably, (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin is not sensitive to bile acids, although bile acids are strongly bound by the native β- cyclodextrin.

^{1}H NMR spectra changes upon addition of a guest suggests the fluorescence change mechanism. Upon addition of 1-adamantanol to a solution of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin in D_2O, the motion of the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety was restricted by the van der Waals interactions with 1-adamantanol. This observation indicates that the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety is still positioned at the entrance of the

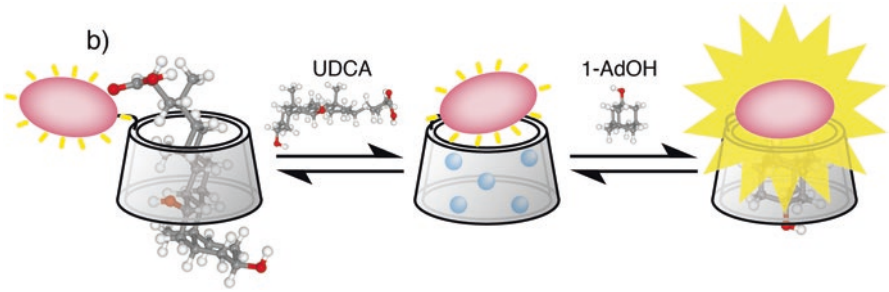


Fig. 5.13 Guest-induced conformational changes of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrins for ursodeoxycholic acid (UDCA) complex and 1-adamantanol (1-AdOH) complex; The (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety moves away from the entrance of the cyclodextrin cavity after making the inclusion complex with ursodeoxycholic acid and its fluorescence intensity does not increase. The (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety is still positioned at the entrance of the cyclodextrin cavity even when 1-adamantanol is accommodated and its fluorescence intensity increases (Adapted from Ikeda 2011)

cyclodextrin cavity, even when 1-adamantanol is accommodated. By contrast, upon addition of ursodeoxycholic acid to a solution of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin in D_2O, the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety must move away from the entrance of the cyclodextrin cavity and the motion of the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety is not restricted. These different behaviors of the (7-nitrobenz-2-oxa-1,3-diazol-4-yl) amine moiety cause the difference in the fluorescence variation observed upon addition of the guest. The ^{1}H resonances for the (7-nitrobenz-2-oxa-1,3-diazol-4-yl) amine moiety of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin alone are broader than those of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin in the presence of ursodeoxycholic acid. This suggests that the motion of the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin is restricted in the absence of the guest, because the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety interacts with the rim of the cyclodextrin cavity.

This observation can be explained by the equation in Fig. 5.13. The bile acid derivative can be accommodated inside the β-cyclodextrin cavity, but the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety moves away from the entrance of the cyclodextrin cavity after making the inclusion complex with the bile acid derivative. The (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety is still located in a hydrophilic environment in the complex with the bile acid, and its fluorescence intensity does not increase. On the other hand, the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety is still positioned at the entrance of the cyclodextrin cavity even when 1-adamantanol is accommodated.

Considering the differing guest-response patterns of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin and (7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended β-cyclodextrin, discrimination between the bile acids and adamantane derivatives at any concentration by the combined use of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin and

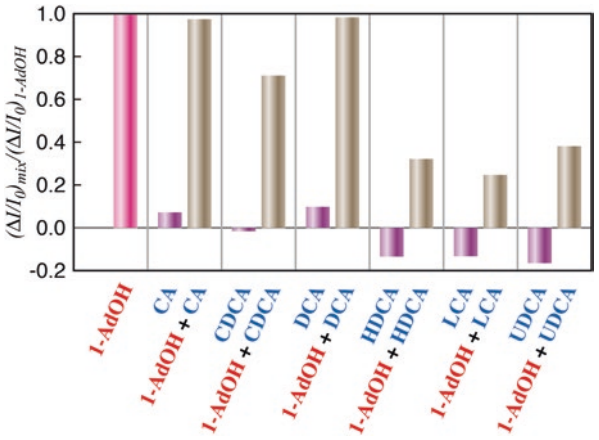


Fig. 5.14 Relative sensitivity parameters $((\Delta I/I_0)_{mix}/(\Delta I/I_0)_{1\text{-AdOH}})$ of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin (NC0βCD) ($5x10^{-6}$ M) for mixtures of guests (each at $1x10^{-5}$ M); $(\Delta I/I_0)_{1\text{-AdOH}} = (I - I_0)/I_0$ (where I and I_0 are the fluorescence intensities in the presence and absence of 1-adamantanol, respectively), $(\Delta I/I_0)_{mix} = (I - I_0)/I_0$ (where I and I_0 are the fluorescence intensities in the presence and absence of both a bile acid derivative and 1-adamantanol, respectively)). The sensitivity parameters for a bile acid derivative alone have been normalized to the sensitivity parameters for 1-adamantanol alone (Adapted from Ikeda et al. 2005)

(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended β-cyclodextrin is now a simple matter.

Notably, 1-adamantanol can be detected even in the presence of a bile acid by using (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended β-cyclodextrin (Ikeda et al. 2005). This is the first example of adamantanol being detected in the presence of a bile acid by a cyclodextrin-based chemosensor. The relative sensitivity parameters for a solution containing both a bile acid and 1-adamantanol are shown in Fig. 5.14.

5.4.2 Bile Acids-Selective Chemosensor

The sensitivity parameters of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin and (7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended γ-cyclodextrin for various guests are shown in Fig. 5.15 (Ikeda et al. 2006b). (7-Nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin is relatively sensitive to each bile acid but has no response to other guests. (7-Nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended γ-cyclodextrin is not sensitive to any of the guests. In most cases, the response of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin to the guests is an increase in the fluorescence intensity. These results suggest that the hydrophobic face of the bile acid can interact with the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety in the larger space of the entrance of the γ-cyclodextrin cavity, increasing hydrophobicity of the chromophore's

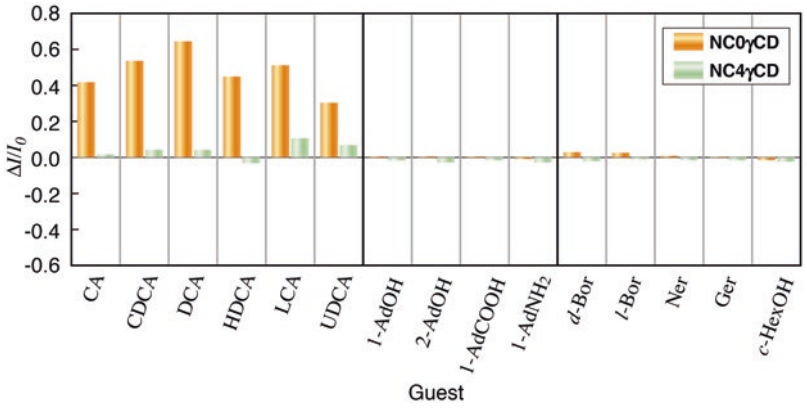


Fig. 5.15 Sensitivity parameters ($\Delta I/I_0$) of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin (NC0γCD) and (7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminobutylamine-appended γ-cyclodextrin (NC4γCD): [NC0γCD] = [NC4γCD] = 5×10^{-6} M, [guest] = 1×10^{-5} M. $\Delta I/I_0 = (I - I_0)/I_0$ (where I and I_0 are the fluorescence intensities in the presence and absence of the guest, respectively) (Adapted from Ikeda et al. 2006b)

environment. However, the γ-cyclodextrin cavity is too large for other guests, such as adamantane derivatives, to increase hydrophobicity around the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety because the water molecules cannot be completely excluded from the cavity.

The difference in the sensitivity parameters between each bile acid is not large, although the binding affinities of the native γ-cyclodextrin are different for these bile acids. The variation in the fluorescence intensity does not correlate to the binding affinity of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin. The structure of the host-guest complex has a greater influence on the fluorescence intensity than the binding affinity. The $\Delta I_{max}/I_0$ of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin for each guest differs considerably in contrast with *N*-dansyl-leucine-appended β-cyclodextrin whose $\Delta I_{max}/I_0$ is broadly similar for each guest. When a large excess of any guest is added to a solution of *N*-dansyl-leucine-appended β-cyclodextrin, the dansyl moiety is located in a similar position outside the cyclodextrin cavity and in a similar environment. The environment around the fluorophore in the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin/guest complex is different for each guest. This difference in the fluorophore environment gives rise to the observed differences in sensitivity parameters for various guests. The $\Delta I_{max}/I_0$ values of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended γ-cyclodextrin for cholic acid is three times larger than that for ursodeoxycholic acid, whereas the binding constant for cholic acid is one-third of that for ursodeoxycholic acid. Therefore, the sensitivity parameter for cholic acid is similar to that for ursodeoxycholic acid. The sensitivity parameter of the turn-on chemosensor depends on both the binding affinity for the guest and the structure of the inclusion complex; the structure of the inclusion complex strongly affects the environment around the fluorophore. In contrast, the sensitivity parameter of the turn-off chemosensors generally depends on only the binding affinity for the guest.

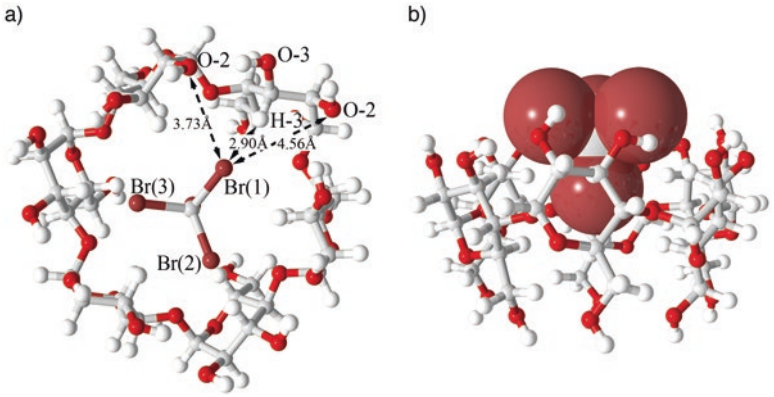


Fig. 5.16 Estimated structure of the α-cyclodextrin/CBr_4 complex (**a**) view from the secondary hydroxy side of the complex, (**b**) the side view of the complex (Adapted from Ikeda and Ueno 2009)

5.4.3 Chemosensor for Halomethanes

Although the cavity size of α-cyclodextrin is suitable for smaller guests such as halomethanes or alkanol, it is difficult to use the turn-off mechanism to construct chemosensors using α-cyclodextrin. There are few chromophores whose size and shape are suitable for the self-inclusion state in the narrow cavity of α-cyclodextrin. The chromophore in the self-inclusion state is often not excluded by guest accommodation because the binding affinity of α-cyclodextrin is not large for most guests. This disadvantage of the turn-off mechanism can be overcome by the turn-on mechanism. A fluorophore of a turn-on chemosensor is not self-included and remains at the entrance of the cyclodextrin cavity. The fluorophore does not inhibit accommodation of the guest.

Ikeda prepared a chemosensor for halomethanes using the turn-on mechanism (Ikeda and Ueno 2009). The absorption intensity of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin decreased upon addition of CCl_4 and the fluorescence intensity of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin increased upon addition of CCl_4. These phenomena indicate that the hydrophobicity around the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety increased upon addition of the guest. The ^{1}H NMR spectra of the α-cyclodextrin/halomethane complexes and MMFF94 molecular mechanics calculation of the α-cyclodextrin/halomethane complexes indicate that the (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine moiety remains at the entrance of the cyclodextrin cavity (Fig. 5.16).

The binding constants for halomethanes are quite a bit larger than those for alcohols having two or three carbons (Fig. 5.17). Although the reported binding constant of α-cyclodextrin for CCl_4 is only 40 M^{-1} (Fourmentin et al. 2007), the binding constant of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin for CCl_4 is 956 M^{-1}, over 20 times larger. The (7-nitrobenz-2-oxa-1,3-diazol-4-yl)

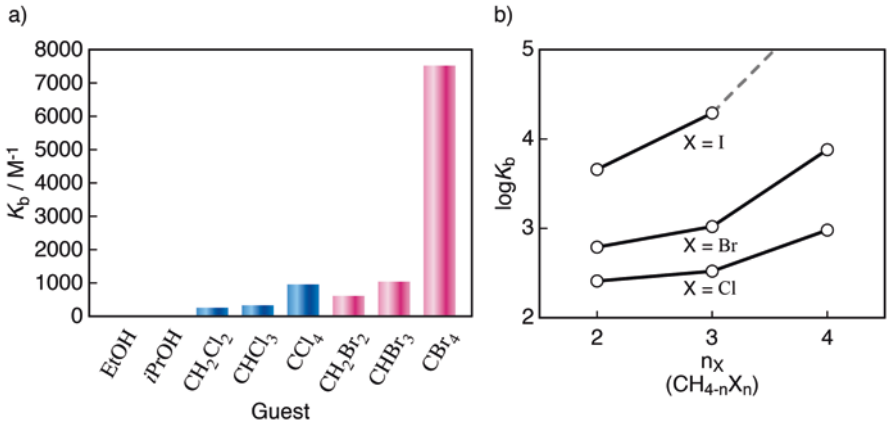


Fig. 5.17 (**a**) Binding constants (K_b) of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin (NC0αCD) for halomethanes and alcohols and (**b**) logarithms of binding constants (logK_b) of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin (NC0αCD) for halomethanes ($CH_{4-n}X_n$) vs number of halogen atoms bound to the methane (n_X). (Adapted from Ikeda and Ueno 2009)

amine moiety acts as a hydrophobic cap, increasing the hydrophobicity in the cavity. The binding constant for CBr_4 is eight-fold larger than that for CCl_4.

The cavity of α-cyclodextrin is too small to accommodate the entire CBr_4 molecule. One of the bromine atoms is accommodated in the α-cyclodextrin cavity, and the other bromine atoms remain at the entrance of the cyclodextrin cavity. This indicates that the selectivity for the halogen atom is due to a size effect. The van der Waals radii of chlorine and bromine are 1.69 and 1.83 Å, respectively, and the radius of the narrowest position in the α-cyclodextrin cavity is 2.2 Å (Müller and Wenz 2007).

The binding constants of (7-nitrobenz-2-oxa-1,3-diazol-4-yl)amine-appended α-cyclodextrin increase with increasing number of halogens. Of the brominated methane complexes, only the α-cyclodextrin/CBr_4 complex has a symmetric structure (C3 symmetry) which can cause the multisite interactions (Fig. 5.16) Alternate glucose units interact with bromine atoms to the same degree and this interaction causes the large binding constant.

5.5 Chemosensors for Anion or Cation Species

Inclusion complexes of cyclodextrin and chromophores can be used as chemosensors for anion or cation species. Binding of anion or cation species to the spacer or the rim of modified cyclodextrins induces change in fluorescence intensity or color change.

5.5.1 Chemosensor for Bicarbonate

Suzuki et al. prepared a pyrene-appended γ-cyclodextrin with a triamine spacer (Suzuki et al. 2006). This derivative formed an association dimer in aqueous solution and exhibited typical pyrene fluorescence around 370–400 nm together with strong excimer-like fluorescence centered at 475 nm. A new fluorescence band appeared around 390–460 nm upon addition of $NaHCO_3$. None of the anions (Cl^-, SO_4^{2-}, HPO_4^{2-}, AcO^-, ClO_4^-, NO_3^-) except bicarbonate (HCO_3^-) induced the new fluorescence band, and metal cations (Zn^{2+}, Na^+, or K^+) showed no ability to cause the new fluorescence band. The proposed association behavior is shown in Fig. 5.18. Binding of bicarbonate causes conformational change for the association dimer from a well-stacked conformation to an imperfectly stacked conformation, inducing the new fluorescence band. This selective fluorescence change can act as a chemosensor for bicarbonate, which is a physiologically important anion that plays a vital role in maintaining the pH of biological fluids and in signal transduction in intracellular events.

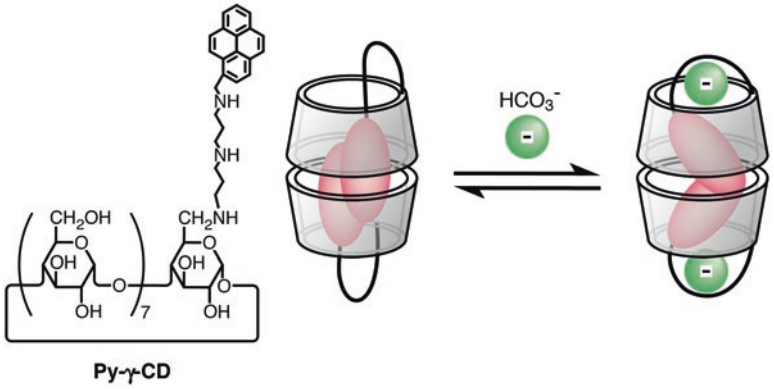


Fig. 5.18 Structure of *N*-[9-(1-pyrenyl)-4,8-diazanonyl]-6-amino-6-deoxy-γ-cyclodextrin (Py-γ-CD) as a bicarbonate sensor and its guest-induced conformational change; Binding of bicarbonate causes conformational change for the association dimer from a well-stacked conformation to an imperfectly stacked conformation, inducing the new fluorescence band. (Adapted from Suzuki et al. 2006)

5.5.2 *Chemosensors for Fe^{3+} or Ru^{3+} Cations and Phosphate or Pyrophosphate Anions*

Pitchumani et al. elucidated that the 1:1 inclusion complex of per-6-amino-β- cyclodextrin and *p*-nitrophenol can be used as a color-change chemosensor for Fe^{3+} and Ru^{3+} in water (Suresh et al. 2010). Binding of these cations causes an appreciable color change from intense yellow to colorless. They also showed that the 1:2 inclusion complex of per-6-amino-β-cyclodextrin and *p*-nitrophenol can be used as a color-change chemosensor for phosphate or pyrophosphate anions (Azath et al. 2011). Binding of these anions causes an appreciable color change from colorless to intense yellow.

5.6 Conclusion

Chromophore-appended cyclodextrins are effective for detecting molecules in water via fluorescence and absorption changes. The response pattern of cyclodextrin chemosensors for guests can be changed by varying the spacer between the cyclodextrin cavity and the chromophore. The cavity size of cyclodextrin is also an important factor for the response pattern. Many types of cyclodextrin chemosensors having different responses for guests are expected to be used for new pattern recognition systems to detect molecules.

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