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Cyclodextrin-Based Sensors for the Recognition of Small Molecules

Ishfaq Ahmad Rather, Ahmad Hasan and Rashid Ali

Abstract

Owing to the selective recognition ability, exceptional biocompatibility, water solubility, non-toxicity, economically inexpensive, commercial availability, and easy functionalization, cyclodextrins (CDs) act as the main building blocks for the creation of beautifully simple yet much effective supramolecular architectures of fundamental interest. Over the past few decades, CDs have engrossed a noteworthy interest in the scientific community because of their usage in the development of chemical sensors *via* molecular recognition phenomenon. Bearing the delightful sensing capability of CDs in mind, herewith, we envisioned to disclose the recent developments in the sensing of diverse biologically significant small molecules by CDs through colorimetric, fluorescence, electrochemical, and potentiometric response. Sensing events and corresponding distinguishing optical features in cyclodextrin-based monomers, dimers, clusters, and nano-assemblies have been elaborated in detail. The authors are of the opinion that this chapter will offer new dimensions to supramolecular sensors in general and CDs-based sensors in particular.

Keywords: cyclodextrins, host-guest interaction, molecular recognition, small molecules, colorimetric and electrochemical sensors

1. Introduction

Basically, the host-guest non-covalent interaction is the major subtopic of supramolecular chemistry, which succors us to realize the recognition of guest entities, particularly through non-covalent supramolecular interactions [1, 2]. In recent years, the supramolecular host molecules, such as cyclophanes, crown ethers, cryptands, calix[n]arenes, calix[n]pyrroles, cucurbiturils, and cyclodextrins, have drawn an enormous interest of the scientific community worldwide because of their exceptional signatures, particularly molecular recognition and sense of specific analytes, and still much new chemistry with these old macrocycles is to be explored [3–7]. Among the above-mentioned host architectures, the naturally occurring cyclodextrins (CDs) are regarded as most essential by virtue of their selective recognition capability, exceptional biocompatibility, water solubility, non-toxicity, economically inexpensiveness, commercial availability, and easy-functionalization [8]. With the aid of host-guest chemistry, the CDs have found a range of applications in various fields of science and technology *viz.* supramolecular self-assemblies, material sciences, pharmaceutical

chemistry, biochemistry, polymer chemistry, electronics, catalysis, and nanotechnology, besides biotechnological and chemical industries [9–11]. Remarkably, CDs have also been employed as the bricks in building frequent supramolecular structures of particular interest, such as polyrotaxanes, rotaxanes, catenanes, and supramolecular polymeric materials [12].

The CDs are cyclic oligosaccharides-based seminatural products, mostly comprising of 6–8 units (α -, β -, & γ -cyclodextrins) of glucose connected through α -1,4-glycosidic linkages to generate the torus-shaped molecules portrayed by a hydrophilic surface and hydrophobic central cavity (**Figure 1**) [8]. Notably, CDs having glucose units less than six are too much strained for existence, while the CDs containing more than eight glucose units are readily soluble and very difficult to isolate. With an increase in the number of glucopyranose units from six to eight, the inner cavity diameter also increases from 0.44 to 0.83 nm. In particular, the inner cavity diameter of 0.44 nm in α -CD is suitable to capture benzene molecule, whereby β -CD (0.62 nm) holds an appropriate cavity to encapsulate the naphthalene molecule, and importantly, the γ -CD (0.83 nm), can easily occupy the larger guest molecules *viz.* fullerene [13, 14]. The shape of these CDs resembles like a bucket and hence offers a narrow and large entrance on opposite sides. Typically, it has been revealed that there exist primary OH-moieties on the side of narrow cavities and they have got recognition as a primary face. On the front, secondary OH moieties are present on the side of a large cavity and are generally dubbed as the secondary face. It is by virtue of these primary and secondary OH groups that these CDs are selective toward the inclusion of guest entities of particular importance. As a matter of the fact, both primary and secondary OH groups arrange themselves on the outer side of two recognized faces, and the whole inside cavity of these CDs becomes a hydrophobic microenvironment. The hydrophobicity of the inner cavity in turn is responsible for the inclusion of typically hydrophobic guests in aqueous media [8]. Importantly, over the passage of time, selective methods for ease functionalization of CD-scaffold are being proposed

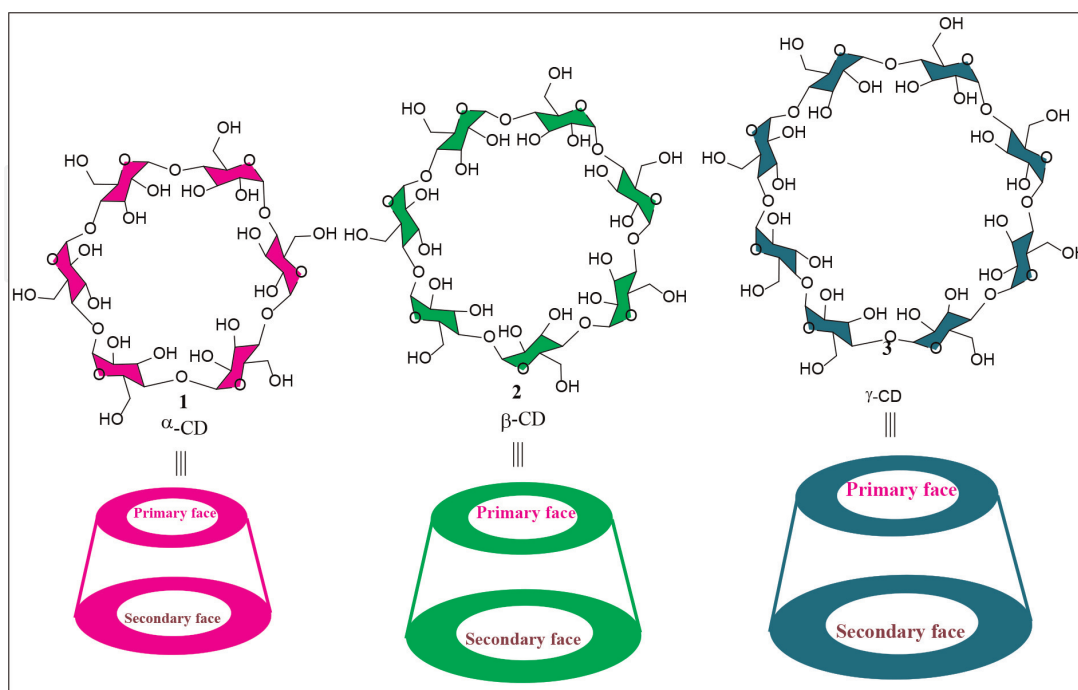


Figure 1. Chemical structures and the 3D-pictorial representation of different CDs.

constantly in order to enhance the recognition properties of CD-based supramolecular hosts toward analytes [15].

As can be straightforwardly inspected from the scientific publications appearing in the literature, the domain of chemical sensors in general and CD-based sensors in particular are rapidly progressing and strengthening their roots in various aspects of our day-to-day life besides bringing a revolution in diverse arena of science and technology [16]. Keeping these facts in mind and also to expose the importance of sensory materials based on CDs; in this meticulous review chapter, we indented to highlight the recent developments in addition to the conceptual background of CD-based chemical sensors. Hopefully, the readers will enjoy this draft and will for sure be further to explore these old yet new types of macromolecular platforms to an advanced level.

2. Chromophore-appended cyclodextrins as classical chemical sensors

Among a variety of chemical sensors, the optical chemosensors are truly interesting and advantageous [17]. This can be ascribed to the fact that optical variations *viz.* color, absorption, and/or emission developing after the recognition of the targeted guest analyte by a typical host molecule are most of the time directly visible through naked eye. In these optical chemosensors, chromophores are attached with basic sensing scaffolds in order to utilize their optical variation, impending for the determination of successful recognition/sensing event [18].

Keeping in consideration, the fact that microenvironment of the utilized chromophores offer changes in color as well as fluorescence pattern, and to get optimum output, researchers globally have functionalized the CDs with a variety of dyes besides the fluorescent moieties [19, 20]. Using chromophore-appended CDs, the detection of a range of hydrophobic guest molecules inside the hydrophobic cavities has extensively been studied in recent years. However, a plethora of chromophore-appended CDs have been constructed and their sensing activities have also been accomplished by several research groups worldwide. But, the pioneering work in this field has been revealed by Ueno and teammates; they reported many CD-based fluorescent chemical sensors through the installation of diverse fluorophores (dansyl, pyrene, anthracene, *etc.*) in CDs *via* flexible linker [21, 22]. By means of this rigid spacer, no self-inclusion complex formation has been noticed. This in turn exposes the fluorophore to a hydrophilic environment and leads to the fluorescence quenching of the CDs. Consequently, the addition of hydrophobic guest leads to its inclusion in the hydrophobic cavity of CDs, thereby bringing the appended fluorophore to a more hydrophobic environment in comparison with the free state of CD-fluorophore conjugates. Hence, enhancement in the fluorescence leads to the “turn-on” fluorescence response (**Figure 2b**) [21].

On the other hand, the same group has also constructed various colorimetric indicator dyes (*viz.* phenolphthalein, methyl red, *p*-nitrophenol, alizarin yellow) appended CD-based chemosensors, wherein the dye moiety is included in the hydrophobic cavity of CDs and generates the self-inclusion complex well isolated from the exterior aqueous hydrophilic media [23–25]. In this self-inclusion complex state, the color changes of the appended dye moiety through protonation/deprotonation-assisted pH variation are suppressed (**Figure 3**). The consequent addition of competitive hydrophobic guest molecule leads to the segregation of appended dye moiety from the interior of CD hydrophobic cavity to the exterior hydrophilic environment.

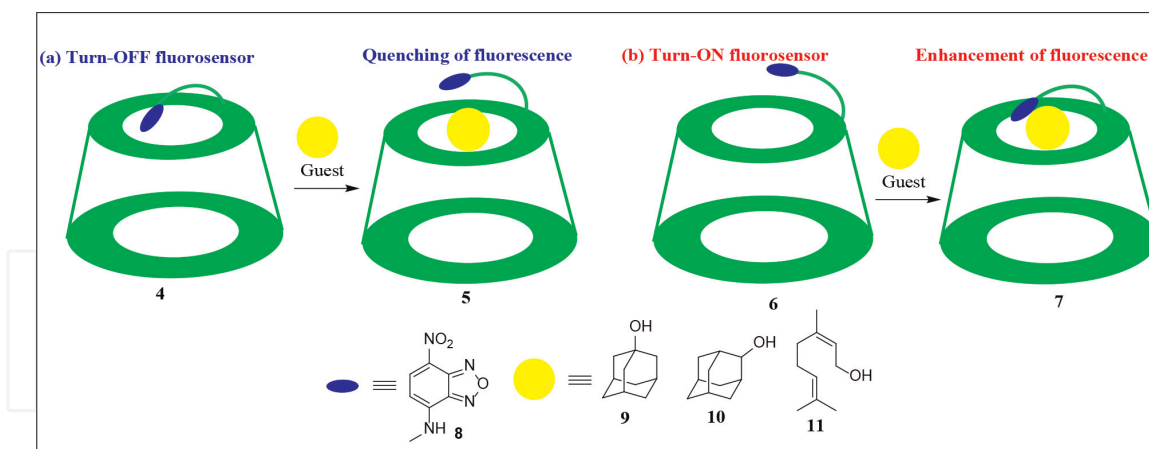


Figure 2.
Pictorial representation of the turn-off (a) and turn-on (b) fluorescent CD-based chemical sensors developed by Ueno and co-workers.

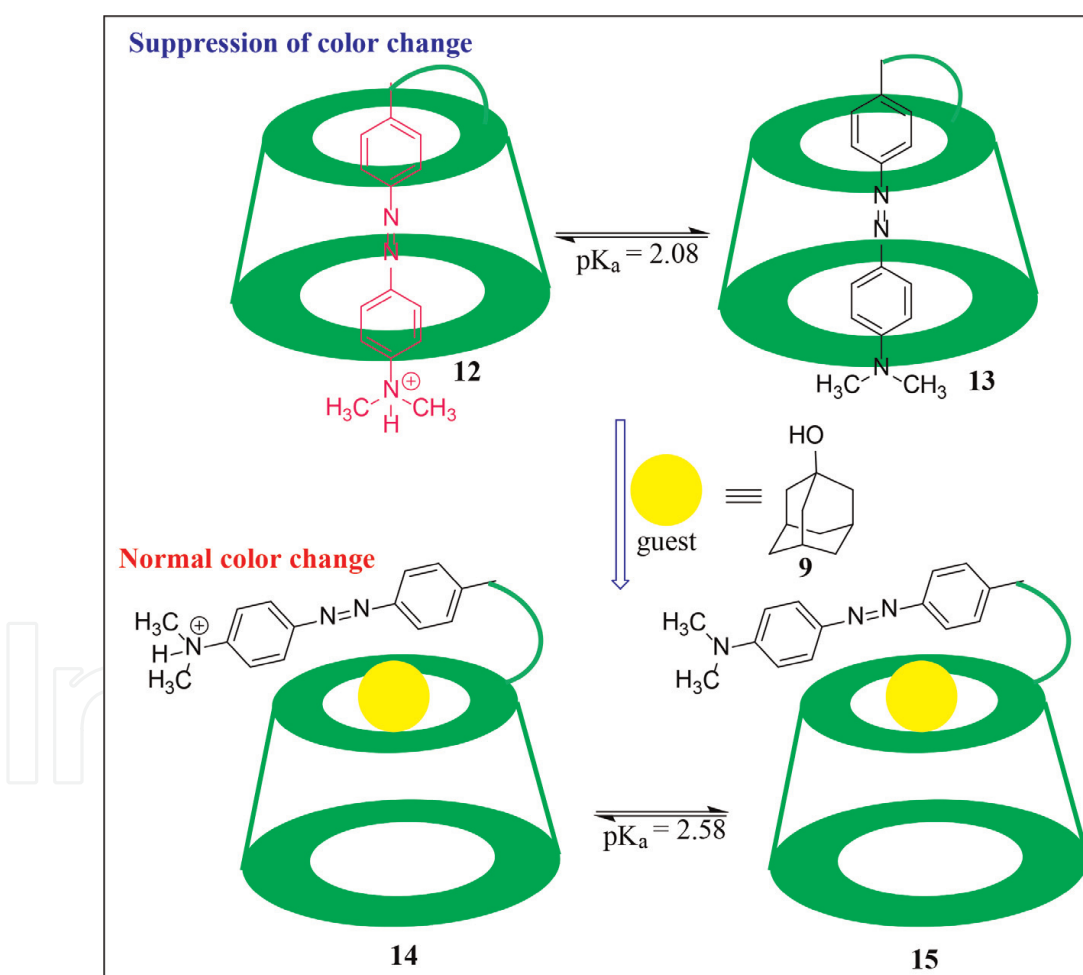


Figure 3.
Schematic representation of the p-methyl red appended CD chemical sensor.

In this manner, the appended dye moiety displays normal color variations upon changing the pH through the protonation or deprotonation tactic (**Figure 3**) [26, 27].

Sulfur dioxide is widely used as a preservative and antioxidant in the food and beverage industries. Thus, constructing sulfur dioxide sensors is of utmost significance in food and analytical chemistry. In this regard, Levine and co-workers have

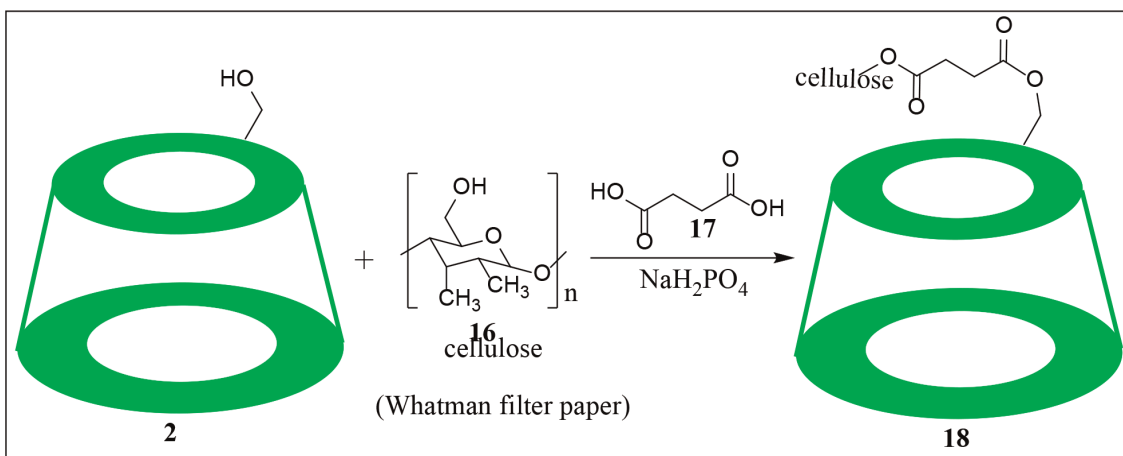


Figure 4.
 Schematic depiction of chemical reaction involved in the attachment of β -CD (2) with Whatman filter paper.

modified the Whatman filter paper with β -CD (2) and manganese in order to develop a colorimetric sensor for sulfur dioxide in an aqueous solution (**Figure 4**) [28]. It has been revealed that the developed sensor is sensitive (limit of detection up to 33 ppm), practical, and broadly applicable in the rapid detection of sulfur dioxide *via* naked eye color change. Besides, the redox reaction of the manganese has been found responsible for the perceived naked eye color variations and other UV-Vis spectral variations. For practical applications, these studies pave the way toward the construction of CD-based novel sulfur dioxide sensors for their employment in beverage and food industries.

3. Metallocyclodextrin-based chemical sensors

The metallocyclodextrin-based CDs have been developed by various research groups and utilized in the field of chemical sensors [29, 30]. To this line, ligands consisting of the metal binding sites, for example, crown ether, diethylenetriamine-pentaacetate (DTPA), and ethylenediaminetetraacetate (EDTA), have successfully been reported. Noticeably, among the various metal ions, lanthanide metal ions (Eu^{2+} & Tb^{2+}) are primarily used in the fabrication of metallocyclodextrin-based chemical sensors by virtue of the fact that they exhibit strong fluorescence and also showed the longer lifetimes [31]. Out of various sensing mechanisms, absorption energy transfer emission (AETE) has been found responsible for the sensing of metallocyclodextrins. This sensing mechanism preliminary involves the excitation of light harvesting guest molecule *via* absorption of photon energy followed by the transfer of energy to a photoactive metal ion ($\text{Eu}^{2+}/\text{Tb}^{2+}$) and subsequent emission from these metal ions. It has been revealed that the complexes of Eu^{2+} and Tb^{2+} ions with the appended CDs *viz.* crown ether-CD (19) and DTPA-CD (20) conjugate display slight fluorescence in aqueous solution due to dearth of aromatic hydrocarbons acting as light-harvesting groups (**Figure 5**) [32]. However, the addition of aromatic guest/light-harvesting molecules, such as benzene, toluene, and biphenyl, leads to the inclusion of these molecules into the inner hydrophobic cavity of metallocyclodextrins, thereby displaying fluorescence enhancement *via* AETE, and, hence, offers a unique approach to develop the turn-on fluorescent chemical sensors (**Figure 5**). On the other hand, Reinhoudt and teammates have constructed β -CD dimer (22) in which two β -CD units

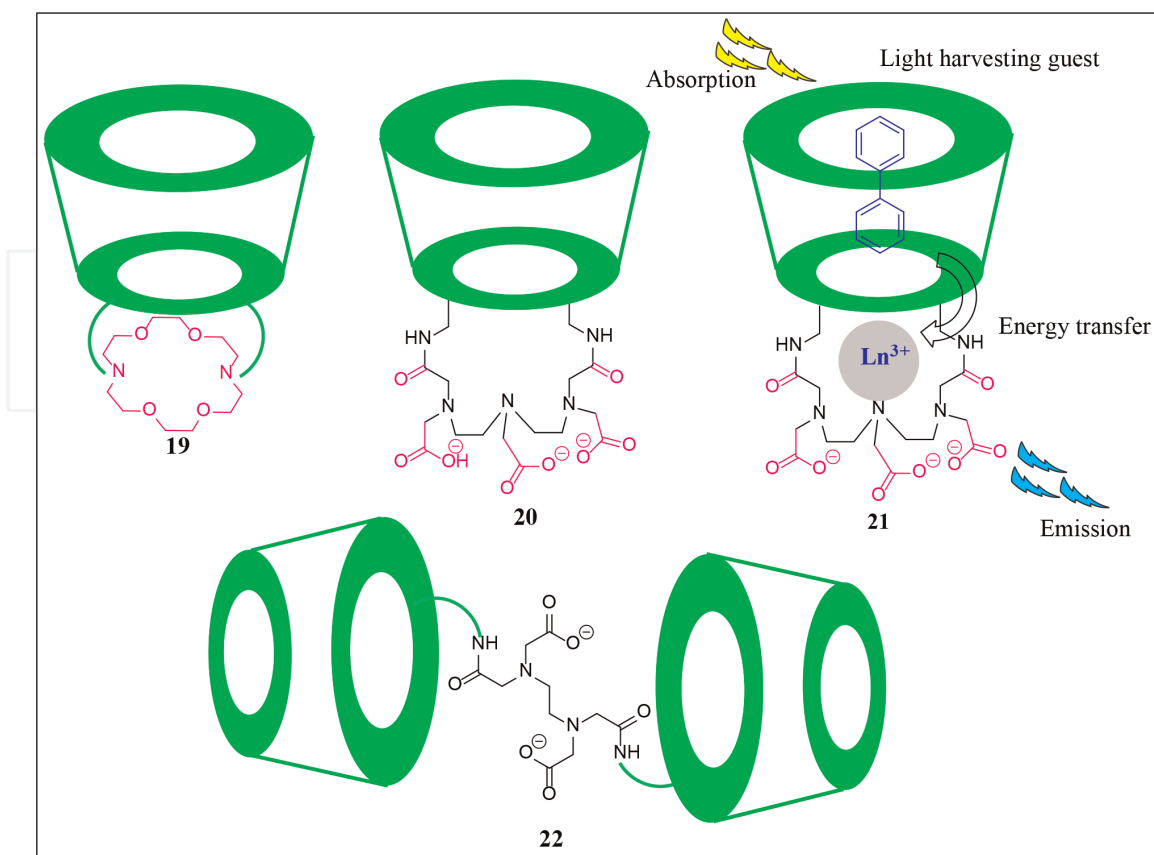


Figure 5.

Diagrammatic illustration of crown ether appended CD (**19**), DTPA appended CD (**20**), and EDTA linked β -CD dimer (**22**). Moreover, the mechanistic overview of AETE sensing phenomenon involving light harvesting guest molecules is also shown.

are linked through EDTA (**Figure 5**) [33]. From the experimental studies, it has been noticed that the complex formation occurs between **22** and lanthanide metal ions, which upon the addition of biphenyl-linked adamantane dimer results in the inclusion of adamantyl ends in the hydrophobic cavities of β -CD dimer (**22**). Consequently, AETE has been noticed from the biphenyl group of adamantane dimer to the lanthanide metal ion complexed with β -CD dimer (**22**). In this way, the overall lanthanide metallocyclodextrin-based assembly functions like a turn-on fluorescent chemical sensor. Additionally, polypyridine, as well as hepta bipyridine, appended CDs forms the complexes with lanthanide metal ions and acts as the chemical sensors toward targeted guest molecules *via* AETE sensing phenomenon [34, 35].

Liu *et al.* have studied the transition metal cation ligand-appended CDs as fluorescent chemical sensors [36]. They have synthesized β -CD dimer (**23**) in which two β -CD units are joined through the biquinolino subunits (**Figure 6**), and by virtue of this group, β -CD dimer (**23**) forms a complex with Cu(II) transition metal ion. Upon the resulting addition of steroid guest molecule, a 1:1 sandwich-type inclusion complex was formed, displaying the enhancement in fluorescence and hence acting as an efficient fluorescent chemical sensor. Moreover, the same group has also synthesized quinoline functionalized β -CD-based selective fluorescent sensor (**24**) for Zn(II) ion, among several other interfering metal ions, such as Ca(II) and Mg(II) (**Figure 6**). For real-world uses, the sensor (**24**) might prove highly valuable as an imaging agent for Zn(II) in living cells or tissues [37]. In a separate report, Yang *et al.* have established a selective and sensitive β -CD-based fluorescent sensor (**25**) for the recognition of Zn

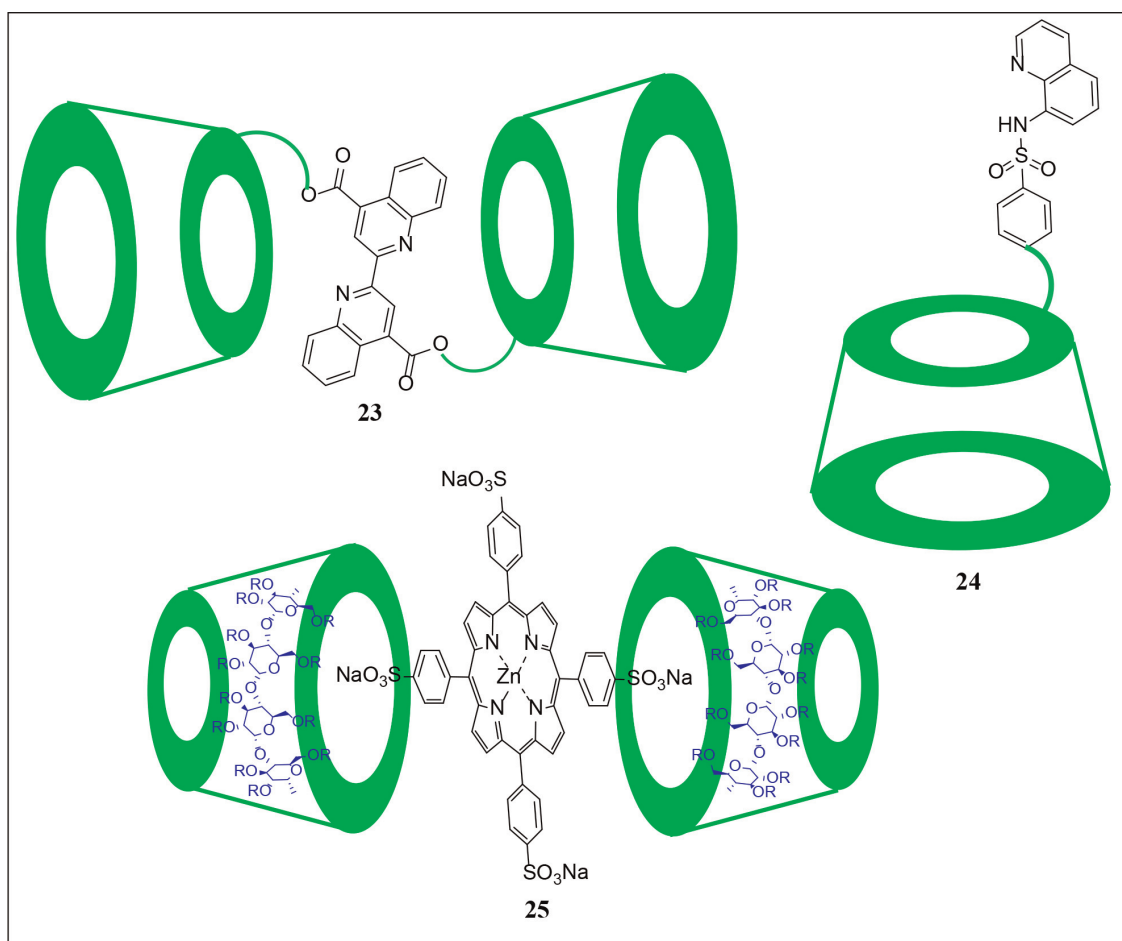


Figure 6. General structures of β -CD dimer (**23**) connected by the biquinolino group, quinoline functionalized β -CD sensor (**24**) for Zn(II) ion and alkylated β -CD/tetraphenylporphyrin-based 2:1 host-guest complex (**25**).

(II) ion (**Figure 6**). The developed fluorescent sensor (**25**) is composed of alkylated β -CD and tetraphenylporphyrin units in the stoichiometric ratio of 2:1. In this case, fluorescent enhancement has been revealed upon the selective complexation of Zn(II) with *meso*-tetraphenylporphyrin among various other interfering metal ions in aqueous medium [38].

4. Cyclodextrin-based supramolecular systems as chemical sensors

Design and construction of the supramolecular architectures utilizing CD units as the key building blocks have attracted an increasing curiosity in the development of chemical sensors [39, 40]. In comparison with CD monomers, the covalently coupled CD-dimers and CD-trimers possess bigger hydrophobic cavities to accommodate the large guest molecules, which make them ideal candidates for chemical sensing. In this context, Ueno and co-workers have reported the β -CD dimer fluorescent sensor (**26**) in which the two β -CD moieties are linked through a primary face *via* dansyl group and used it to recognize steroids (**Figure 7**) [41]. The fluorescence quenching in the dansyl moiety has been observed upon the inclusion of steroid guest molecules in the hydrophobic cavities of **26**. This is due to the fact that steroid inclusion into hydrophobic cavity brings about the exclusion of dansyl moiety from hydrophobic space to aqueous hydrophilic media. In another event, Reinhoudt's group constructed β -CD

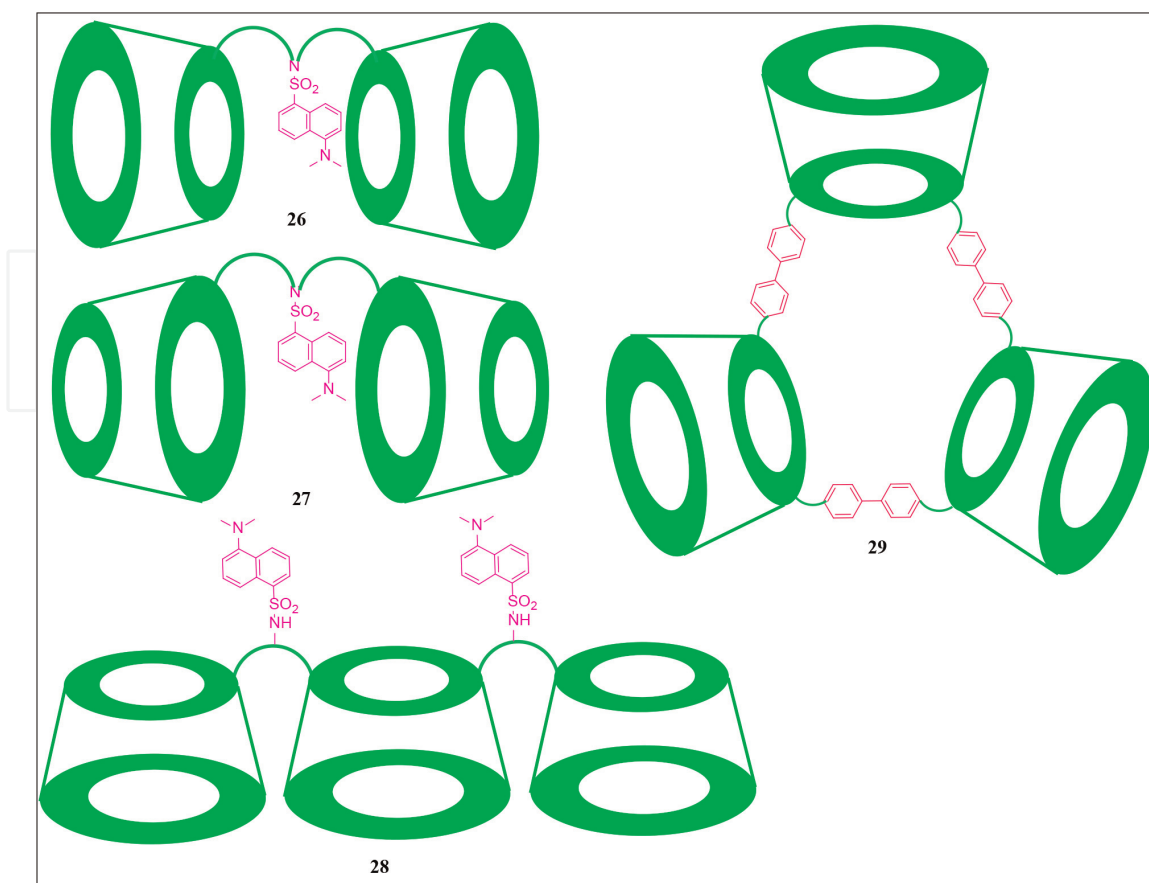


Figure 7.

Pictorial representation of the fluorescent β -CD-based dimers (26 and 27) and trimers (28 and 29).

dimer-based fluorescent sensor (27), in which the two β -CD subunits are linked through secondary face *via* a dansyl moiety (Figure 7) and also revealed different host-guest geometries in comparison with 26 [42]. On the other hand, Kikuchi *et al.* reported the β -CD linear trimer-based fluorescent sensor (28) consisting of two dansyl moieties as linkers between three β -CDs, which in turn signifies the sensing event through host-guest chemistry with bile acids *viz.* cholic acid, lithocholic acid, and deoxycholic acid (Figure 7) [43]. On the other hand, Sasaki *et al.* have fabricated permethylated β -CD-based fluorescent cyclic trimer (29) in which β -CD units are bridged through biphenyl moieties (Figure 7). From the experimental studies, it was revealed that 29 strongly captures an anthracene derivative possessing two alkyl chains and signifies the binding event *via* fluorescence modulations [44].

Interestingly, sensing conjugates of CDs with macrocyclic hosts employing cooperative molecular recognition phenomenon have also been fabricated by various researchers across the world. In this context, Hayashita and teammates have developed a highly selective hybrid molecular conjugate (30) between γ -CD and pyrene crown ether [45, 46]. It has been noticed that in the presence of K^+ ion, the emission of pyrene monomer disappears, resulting in excimer emission due to the formation of a 2:1 host-guest sandwiched complex between crown ether and K^+ ion (Figure 8a). While, Tong *et al.* have fabricated a conjugate sugar sensing system (32) between β -CD and pyrene attached boronic acid fluorophore (Figure 8b) [47]. Fluorescence enhancement has been noticed upon the sensing of sugar moiety by conjugate system (32) as can be inferred from Figure 8b. On the other hand, Kaneda *et al.* have constructed a sensing molecular conjugate (35) between methylated α -CD and crown

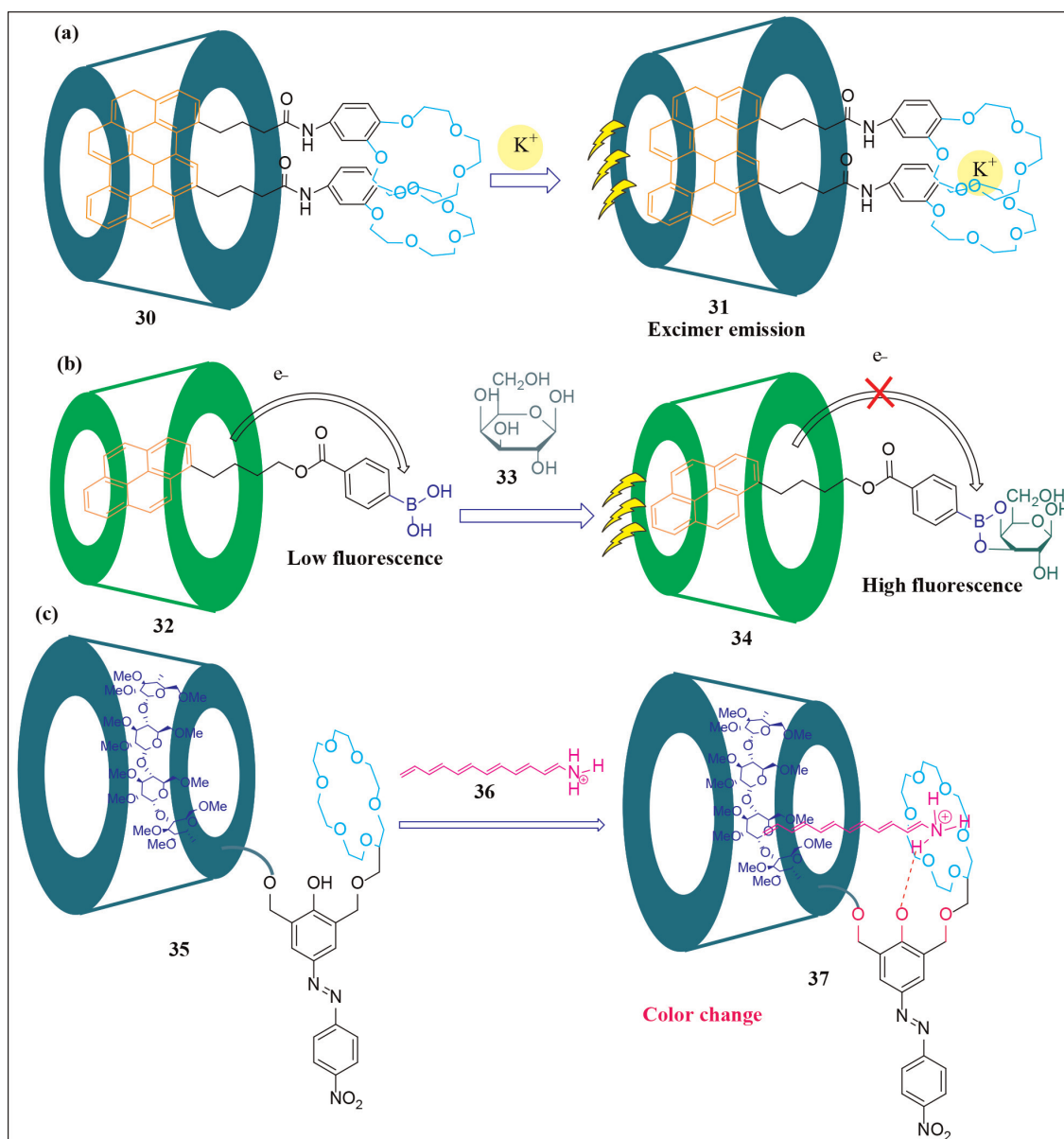


Figure 8. Schematic representations of CD-based molecular sensing conjugates (a) molecular conjugate (30) of γ -CD with pyrene crown ether, (b) molecular conjugate (32) of β -CD with pyrene-functionalized boronic acid, and (c) molecular conjugate (35) of methylated α -CD with crown ether-functionalized azo-phenyl dye.

ether functionalized azo-phenyl dye (**Figure 8c**) [48, 49]. Interestingly in aqueous media, a prominent color change was noticed upon the addition of 1° or 2° alkylamines to the conjugate sensing system (35). However, in aqueous solution, no such color changes were observed upon the addition of 3° alkylamine to 35. The reason for color change is ascribed to the fact that 1° or 2° alkylamines are strongly bonded to crown ether moiety of 35 and their lipophilic alkyl tails construct a strong complex with the CD framework (**Figure 8c**).

The research group of Anderson has used γ -CD and [2]rotaxane (possessing stilbene axle and terphenylenedicarboxylic acid stoppers) for the preparation of a unique chemosensor 38 (**Figure 9**) [50]. It has been revealed that the stilbene axle of [2]rotaxane offers hydrophobic floor to γ -CD cavity and hence leads to an increase in its affinity to 1000-fold for appropriate guests (39) in comparison with simple γ -CD (3).

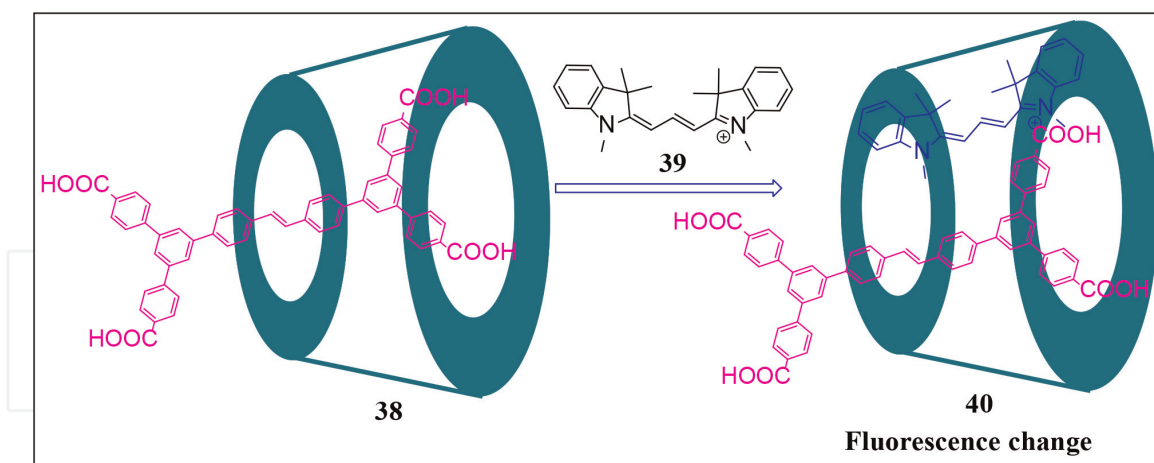


Figure 9. Schematic illustration of γ -CD and [2] rotaxane-based chemosensor (**38**) depicting sensing of a guest molecule (**39**) via fluorescence change.

Moreover, stilbene axle of [2]rotaxane also acts as a fluorophore—signifies the sensing event through fluorescence change between chemosensor **38** and suitable guest molecule **39** (**Figure 9**).

5. Cyclodextrin-based electrochemical sensors

Owing to the chief and portable instrumentation, rapid analysis, and high selectivity, as well as sensitivity, in recent years, electrochemical sensing has engrossed a significant courtesy in the recognition of biomolecules and environmentally hazardous pollutants [51–53]. Cyclodextrin-based functional materials have proven to be highly useful in the domain of electrochemical sensing in past decade [54, 55]. These functional materials mainly include CD-based carbon nanomaterials: carbon nanotubes (CNTs), graphene, and conducting polymers. Nowadays, developing the CD-based conducting polymers for the purpose of electrochemical sensing is considered a hot subject of research interest [56]. This is due to the fact that CD-based conducting polymers pasted on electrodes *via* electrooxidation process of monomers offer high stability, good catalytic ability, and electronic features [57]. To this regard, Bouchta *et al.* have fabricated gold electrode with poly(3-methylthiophene)-based γ -CD through electropolymerization process for the electrochemical determination of dopamine, chlorpromazine, 3,4-dihydroxyphenyl alanine, etc. [58]. On the other hand, Luong and co-workers have doped a diamond electrode with boron and sulfobutylether functionalized β -CD along with a composite film of polypyrrole and poly (*N*-acetyltyramine) for the selective electrochemical determination of neurotransmitter dopamine among other interfering analytes, such as ascorbic acid and uric acid [59].

In the context of CD-based carbon nanomaterials, Huang's research group has modified glassy carbon electrode (GCE) by single-walled CNT (SWCNT) and pyrene functionalized β -CD (**42**) in order to determine the 3,3',4,4'-tetrachlorobiphenyl (**41**) *via* electrochemical impedance method (**Figure 10**). It was noticed by the authors that the pyrene moiety aids in attaching the **42** onto the SWCNT (**43**) sidewall through π - π -stacking interactions, and the guest molecule **41** gets encapsulated by the hydrophobic cavity of **42** [60]. Furthermore, they also reported the electrochemical sensing

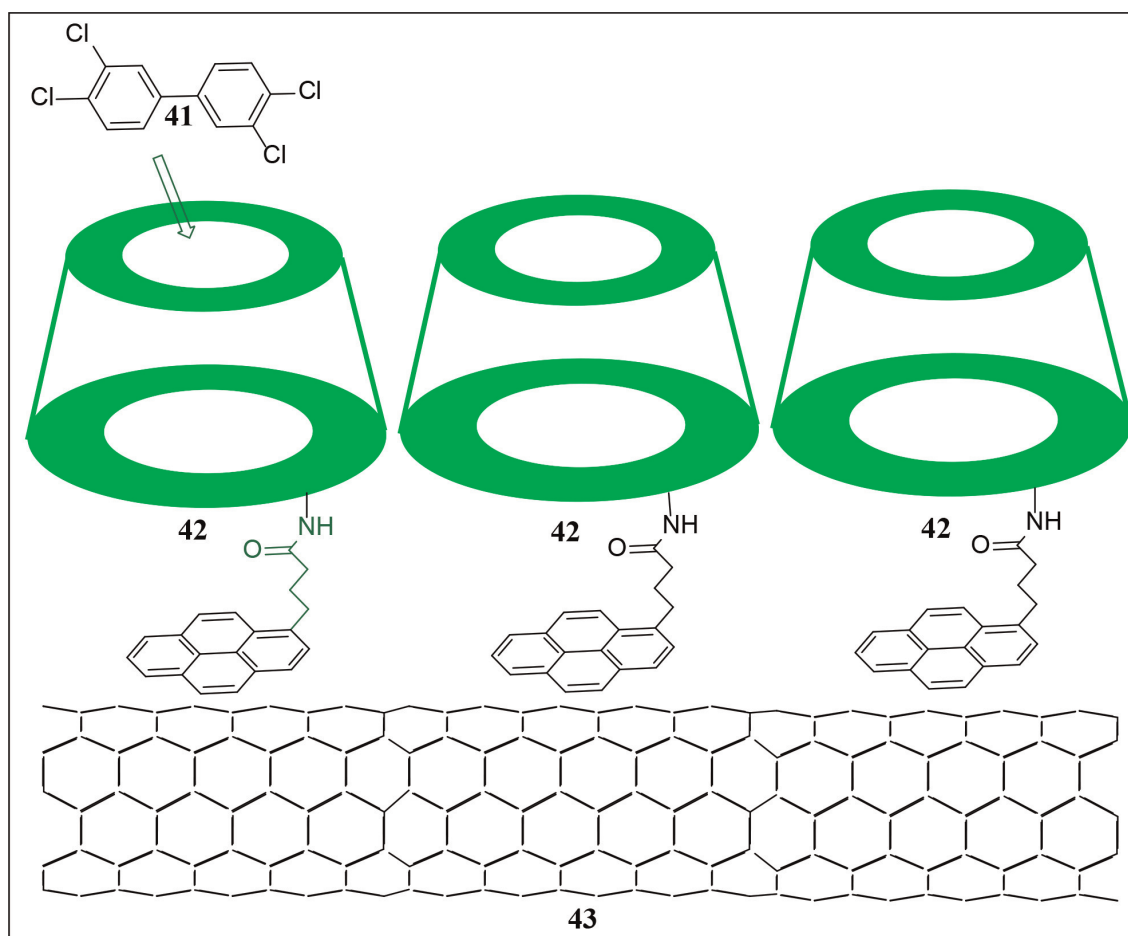


Figure 10.
 Schematic illustration of π - π -stacking adsorption of pyrene functionalized β -CD (**42**) onto the side wall of SWCNT (**43**) along with the structure of 3,3',4,4'-tetrachlorobiphenyl (**41**) guest molecule.

of *p*-nitrophenol using same SWCNT (**43**)-based pyrene functionalized β -CD nanohybrids. The nanohybrid traps *p*-nitrophenol in the hydrophobic cavity of **42** with high selectivity and sensitivity with a detection limit of 0.00086 μ M [61].

Recognition of chiral enantiomers *via* CD-based electrochemical sensors is of immense importance in the medical and pharmaceutical sciences [62]. Yang and co-workers have recently modified the surface of GCE by hydroxypropyl β -CD grafted cellulose, multi-walled CNTs (MWCNTs), and copper ions in order to develop a sensitive electrochemical sensor for the recognition of chiral enantiomers of tryptophan (*D*-Trp/*L*-Trp) [63]. It has been perceived that the fabricated electrochemical sensor has higher affinity toward *L*-Trp in comparison with the *D*-Trp (**Figure 11**). Additionally, the developed electrochemical sensor has been successfully utilized to monitor the quantity of *D*-Trp in racemic mixture. These studies thus pave the way toward the development of realistic chiral platforms for the recognition of diverse chiral molecules. On the other hand, a β -CD-based sensitive electrochemical sensor for the recognition of endocrine disrupting agent known as bisphenol A, in an aqueous solution, has been reported through the pasting of MWCNTs (**46**) and graphene oxide (**48**) on screen-printed carbon electrode (SPE) (**Figure 12**) [64]. This versatile system follows a diffusion-controlled mechanism in the sensitive electrochemical sensing of bisphenol A in drinking water with a detection limit of up to 6 nM. These studies thus offer a promising role in the determination of water quality *via* bisphenol A monitoring.

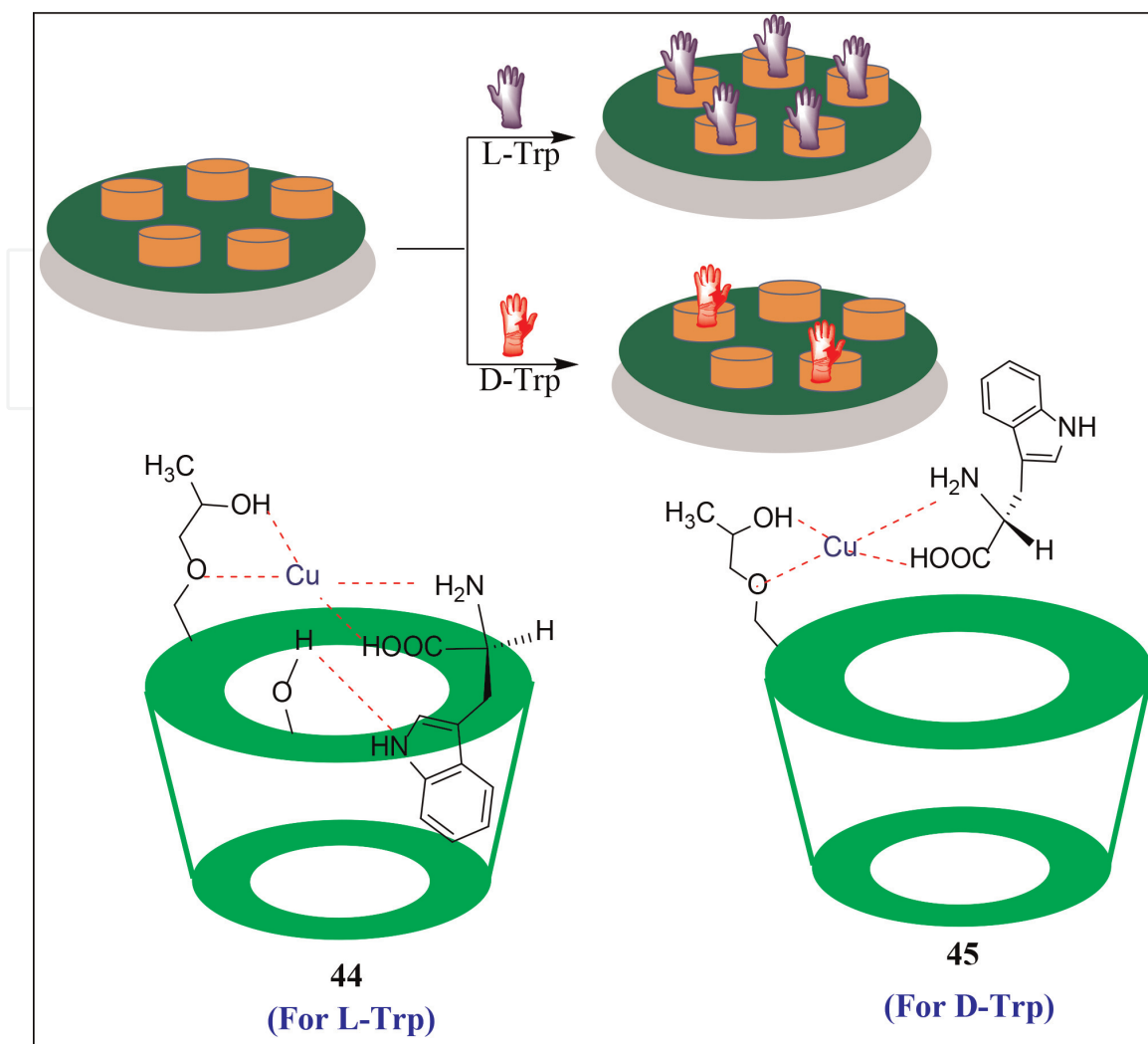


Figure 11.
Schematic illustration of electrochemical recognition of the chiral enantiomers of tryptophan (Trp) via hydroxypropyl β-CD-based electrochemical sensor.

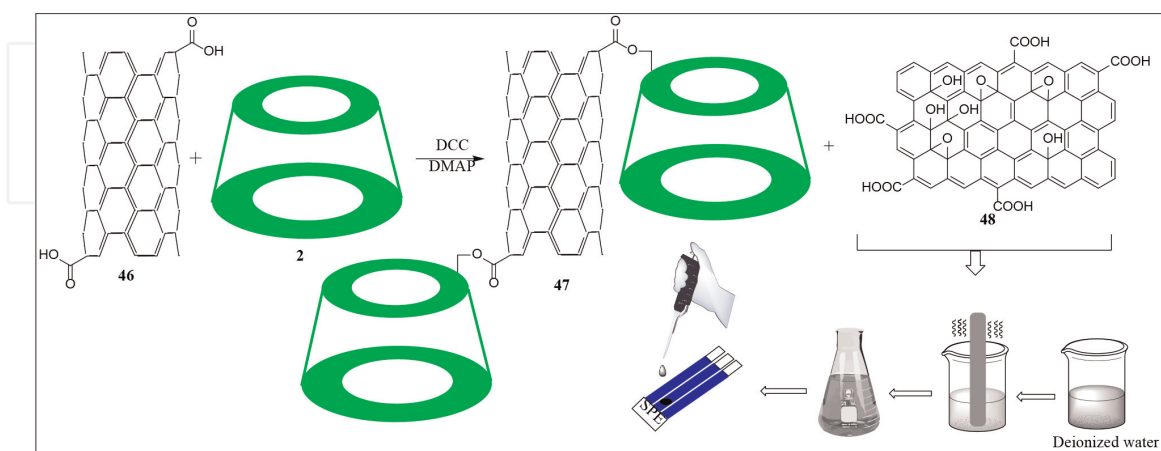


Figure 12.
Schematic illustration for the development of bisphenol A electrochemical sensor via modification of SPE with β-CD and graphene oxide-functionalized MWCNTs.

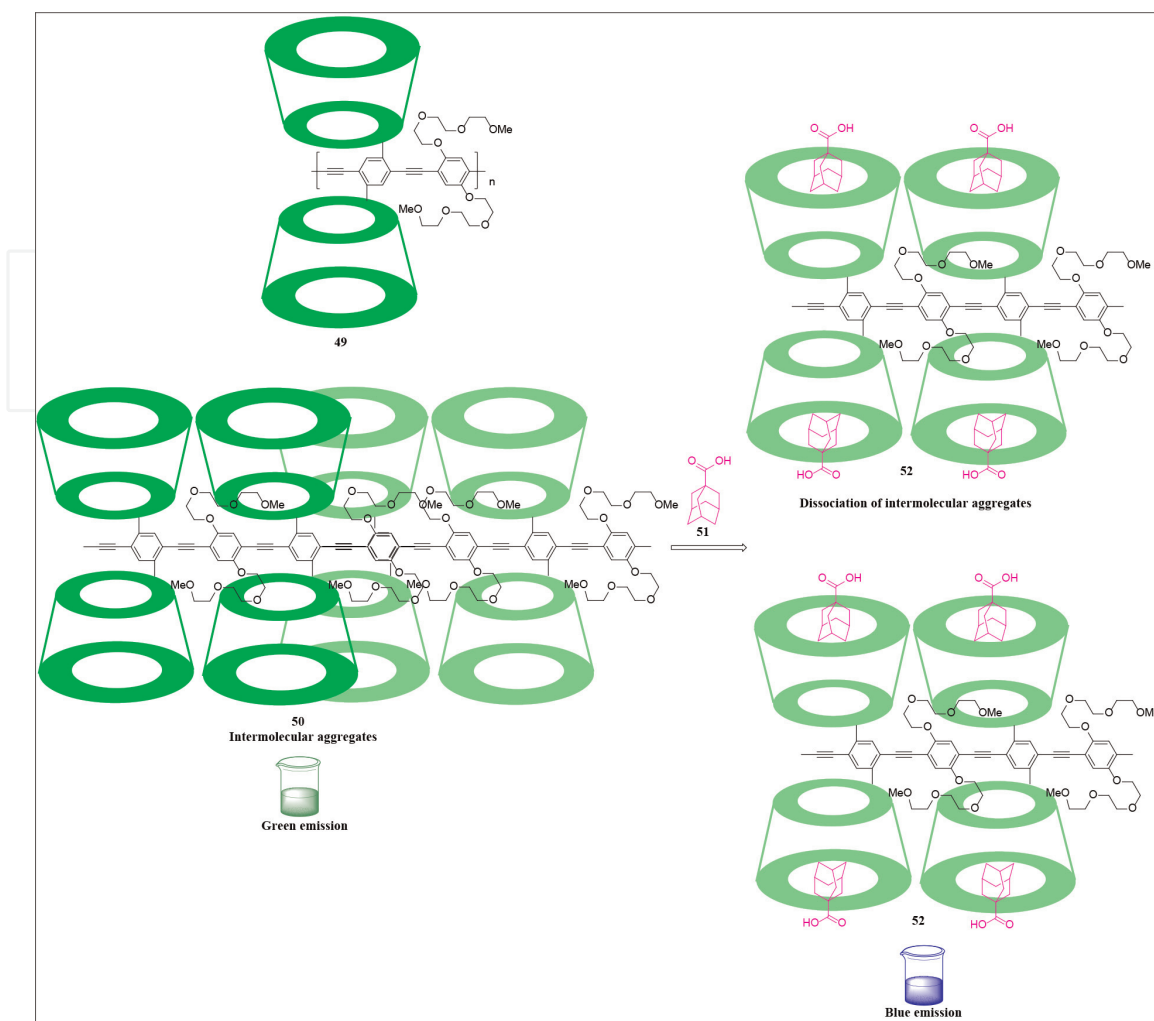
Over the past several years, diverse CD-based potentiometric sensors working through electrochemical means have fruitfully been developed, which find significant applications in medicine, agriculture, environmental monitoring, pharmaceutical

sciences, and industries [65, 66]. In this context, Lenik and teammates have developed functionalized β -CDs-based potentiometric sensors for the determination of useful pharmaceutical drugs known as naproxen and ketoprofen. It has been observed that the guest naproxen molecule is partially or completely encapsulated within the cavity of host functionalized β -CD [67, 68]. On the other hand, Amorim *et al.* have also used functionalized β -CDs in the fabrication of potentiometric sensors for psychiatric drug molecules *viz.* diazepam and midazolam [69]. On the other hand, Khaled's research group has fabricated carbon paste electrodes with β -CD based polyvinyl chloride in order to determine diverse acetylcholine derivatives *viz.* butrylcholine, acetylthiocholine, and acetylcholine [70].

6. Cyclodextrin-based polymers as chemical sensors

Due to widespread applicability of π -conjugated polymers in electroluminescence, light-emitting diodes (LEDs), electrical conductivity, and chemical sensors, researchers are curious worldwide to explore fine-tuning of their electrical and optical properties by virtue of stimuli, such as pH, metal ion, and redox reactions [71]. In this context, Harada's research group has constructed β -CD functionalized poly(phenylene ethynylene)-based π -conjugated fluorescent polymer (**49**), which is water soluble and displays blue fluorescence in DMF and green fluorescence in aqueous solutions (**Figure 13**) [72]. Upon the addition of a competitive guest molecule known as 1-adamantanecarboxylic acid (**51**) to **49**-based intermolecular aggregates (**50**), fluorescence color variation from green to blue was observed by the authors (**Figure 13**). This can be ascribed to the fact that 1-adamantanecarboxylic acid (**51**) complexation with β -CD units of **49** results in the dissociation of various intermolecular π -stacking interactions of polymeric backbone. In fact, the repulsive interactions between the anionic counterparts of 1-adamantanecarboxylic acid (**51**) hinder the polymeric chains to come into the aggregation. By adding electron-accepting adamantane-functionalized viologen derivative (**53**) to the π -conjugated fluorescent polymer (**49**), large fluorescence quenching was seen due to the formation of inclusion complex between β -CD moiety of polymer (**49**) and adamantane group of viologen derivative (**53**). Further, the host-guest interaction, assisted in upholding viologens on the polymeric side chain, results in an adept electron transfer between polymeric backbone to viologen unit of **54** (**Figure 14**).

As coumarin and pyrene scaffolds are of great importance, owing to their vital role in biological systems and sensing arena as well [73]. In this regard, Ueno's group has synthesized β -CD-peptide hybrid polymeric conjugate (**55**), having pyrene as a donor moiety and coumarin as an acceptor one (**Figure 15**) [74, 75]. The coumarin moiety is encapsulated within the hydrophobic cavity of β -CD and thus offers strong fluorescence to the hybrid polymeric conjugate (**55**) *via* fluorescence resonance energy transfer (FRET) from donor pyrene unit to acceptor coumarin unit ("FRET-ON" response). It has been remarked that the addition of competitive guest molecule, namely hydoxycholic acid (**56**), leads to the decrease in fluorescence by virtue of the exclusion of coumarin moiety from inside of the β -CD hydrophobic cavity to outside. This, in turn, leads to the association between coumarin and pyrene units and offers the "FRET-OFF" response (**Figure 15**) [74]. Inouye and Fujimoto have developed methylated β -CD-DNA hybrid polymeric conjugate (**58**) sensor for porphyrin derivatives (**Figure 16**) [76]. They observed that **58** captures

**Figure 13.**

Schematic illustration of fluorescence color variation from green to blue upon addition of 1-adamantanecarboxylic acid (51) to the intermolecular aggregates (50).

meso-tetraphenylporphyrin sulfonate (59) in a 2:1 stoichiometric ratio. This, in turn, induces the formation of DNA duplex structure and results in excimer emission (Figure 16).

On the other hand, quite recently, Badiei and co-workers have established a β -CD-based cross-linked polymer, the CD-nanosponge (62) with pyromellitic anhydride (61) cross-linker for the selective and sensitive detection of diclofenac among various other interfering analytes, such as ibuprofen, morphine, amphetamine, and codeine (Figure 17) [77]. For diclofenac, they have observed a detection limit of 0.92 μM and linear range of 1–33 μM . Interestingly for real-world applications, the established β -CD-based fluorescence probe has the utility to determine the concentration of diclofenac in commercially accessible pharmaceutical tablets.

7. Cyclodextrin-nanocarbon hybrids as chemical sensors

Over the past several decades, carbon nanomaterials for instance carbon nanotubes, fullerene and nanodiamonds, and other polyaromatic hydrocarbons because their unique electrical, structural, and mechanical properties have riveted a significant interest of the researchers across the globe to meet the challenge of

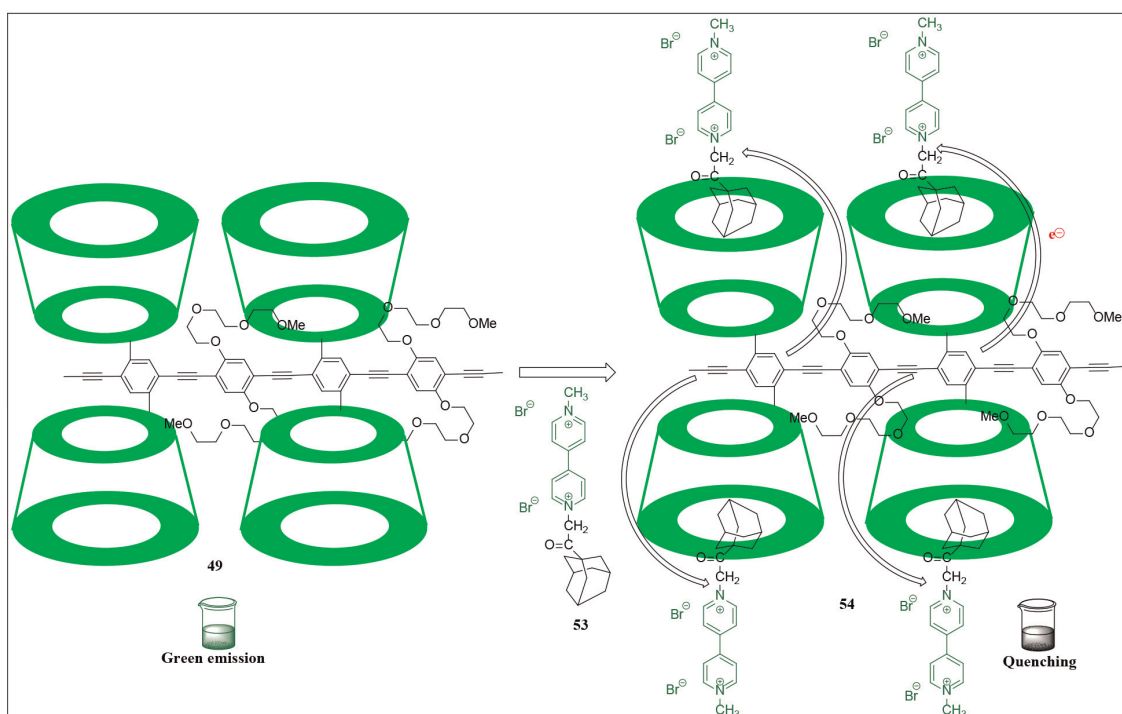


Figure 14. Schematic depiction of fluorescence quenching upon the addition of adamantane functionalized viologen derivative (53) to π -conjugated fluorescent polymer (49).

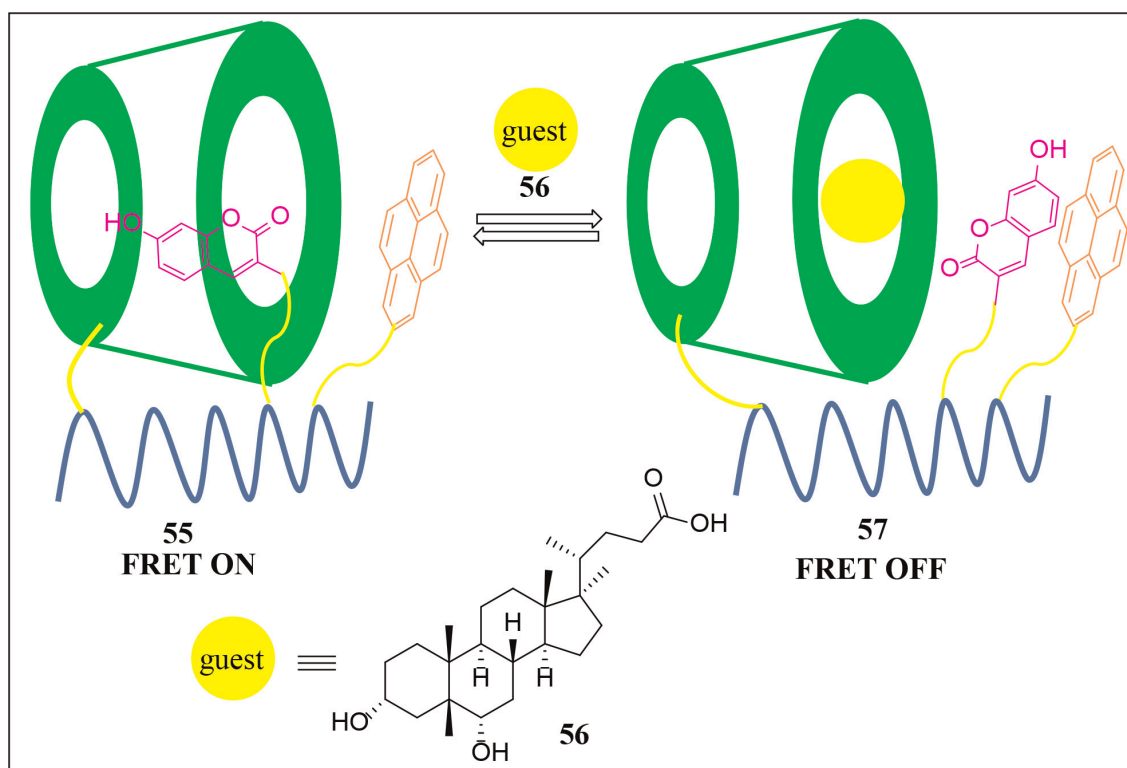
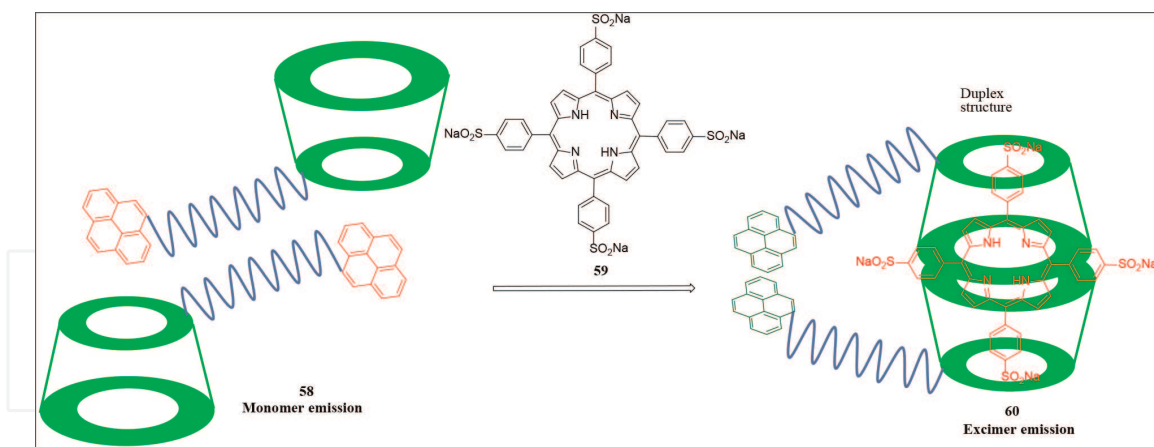
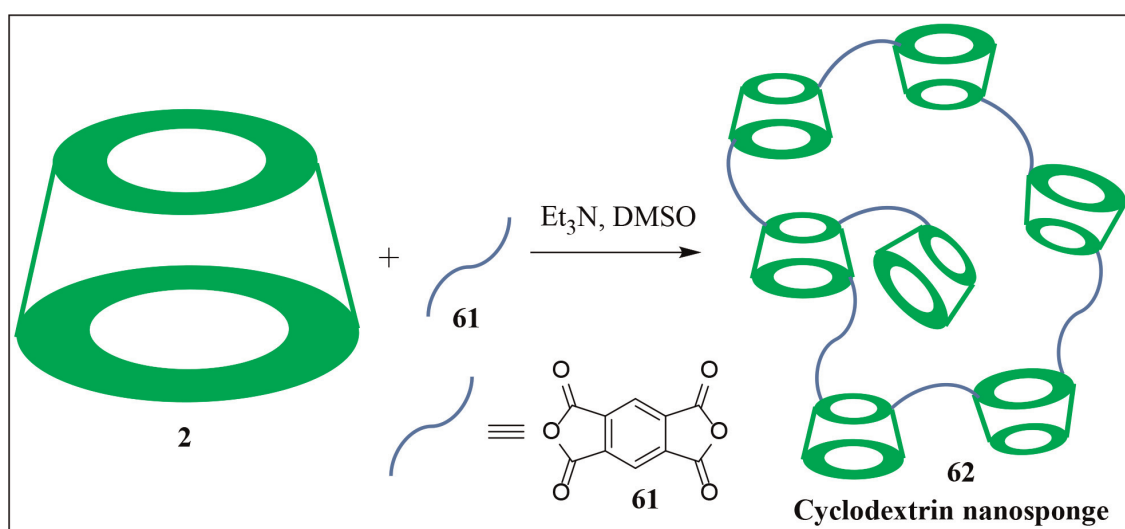


Figure 15. Schematic representation of hydoexycholeic acid (56) assisted structural variation of β -CD-peptide hybrid polymeric conjugate (55).

constructing the CD-based sensors through hybridization with carbon nanomaterials [78–81]. In this context, Fujita and Yuan *et al.* have reported a β -CD-fullerene hybrid conjugate (63), which has the ability to quench the fluorescence of rhodamine B (64),

**Figure 16.**

Schematic representation of guest (59) assisted structural variation of methylated β -CD-DNA hybrid fluorescent polymeric conjugate (58).

**Figure 17.**

Schematic illustration of β -CD based cross-linked polymer (62) with pyromellitic anhydride (61) acting as cross-linker.

after its capture in the hydrophobic cavity of β -CD (**Figure 18**) [82]. On the other hand, Harada and co-workers have constructed pyrene-functionalized β -CD-SWCNT hybrid conjugate (67) and utilized it in the development of stimuli-responsive supra-molecular hydrogel (**Figure 19**). It has been observed that the addition of sodium adamantane carboxylate as a competitive guest leads toward the conversion of a gel to sol [83]. Remarkably, the Stoddart's group has decorated pyrene-functionalized β -CDs on SWCNT hybridized with field-effect transistors (FETs) in order to sense typical organic guest molecules *viz.* 1-adamantanol, sodium cholate, 1-adamantane carboxylic acid. It was observed that the FET characteristics of these hybrid nano-conjugates are highly sensitive and dependent on the association constants between β -CDs and competitive organic guest molecules [84].

8. Cyclodextrin-nanoparticle hybrids as chemical sensors

In recent years, scientific community has exploited the unique property of gold nanoparticle aggregation in the design and construction of various optical sensory

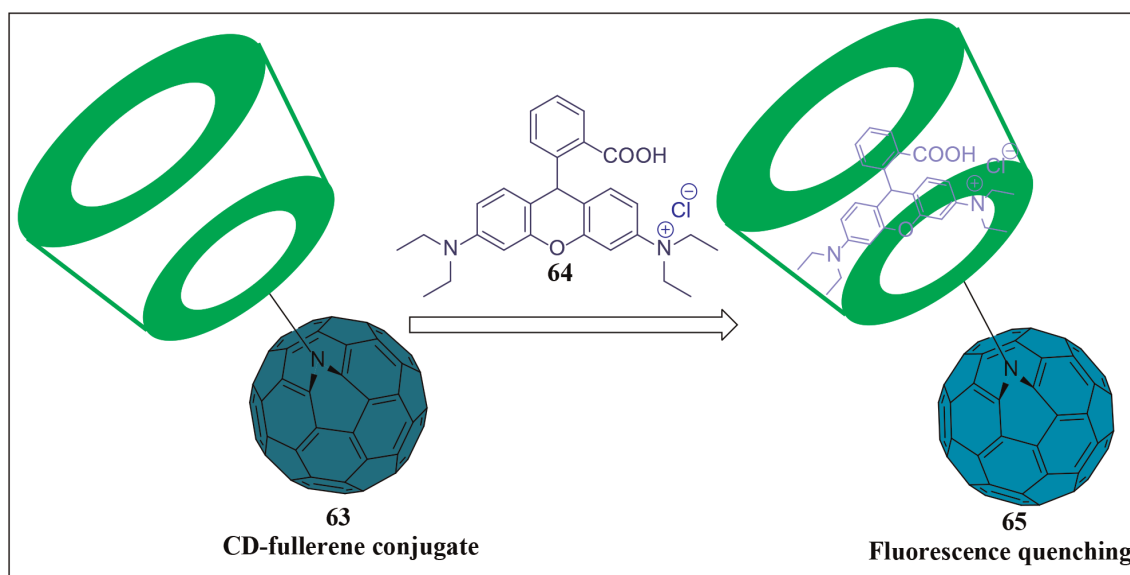


Figure 18.
 Schematic illustration of fluorescence quenching of rhodamine B (64) via the β -CD-fullerene hybrid conjugate (63).

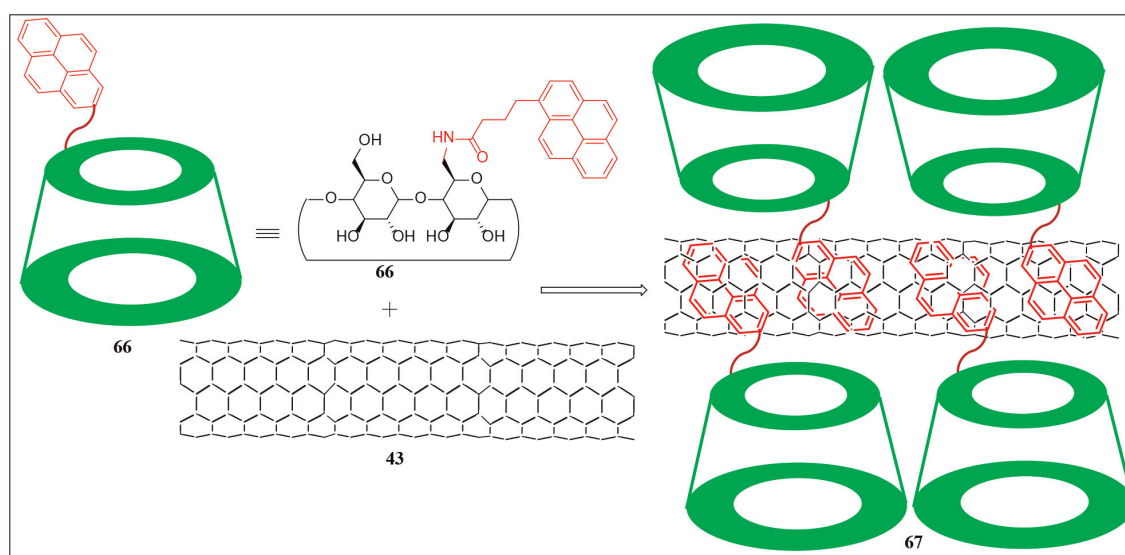
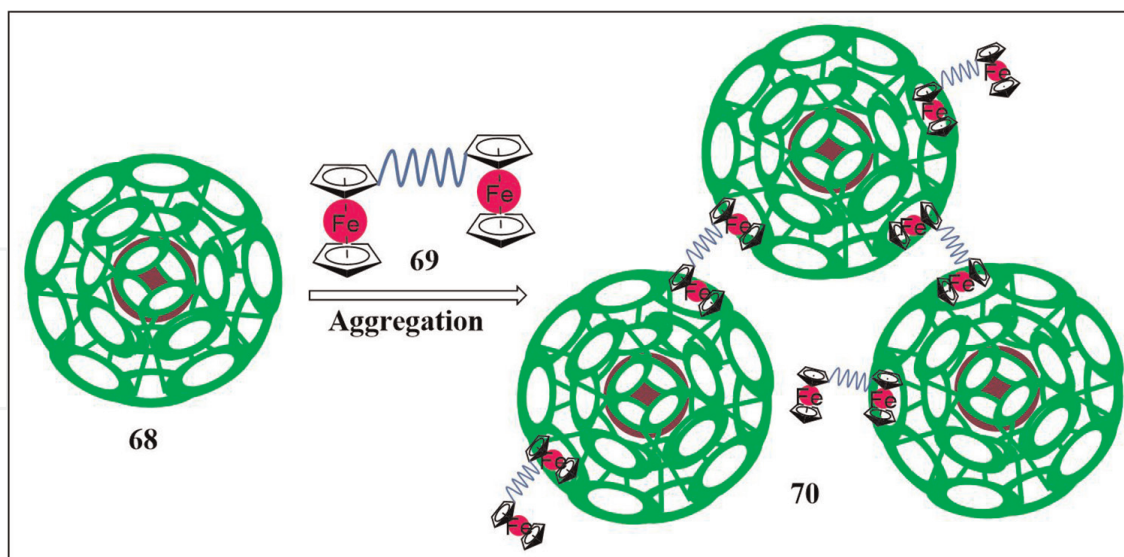
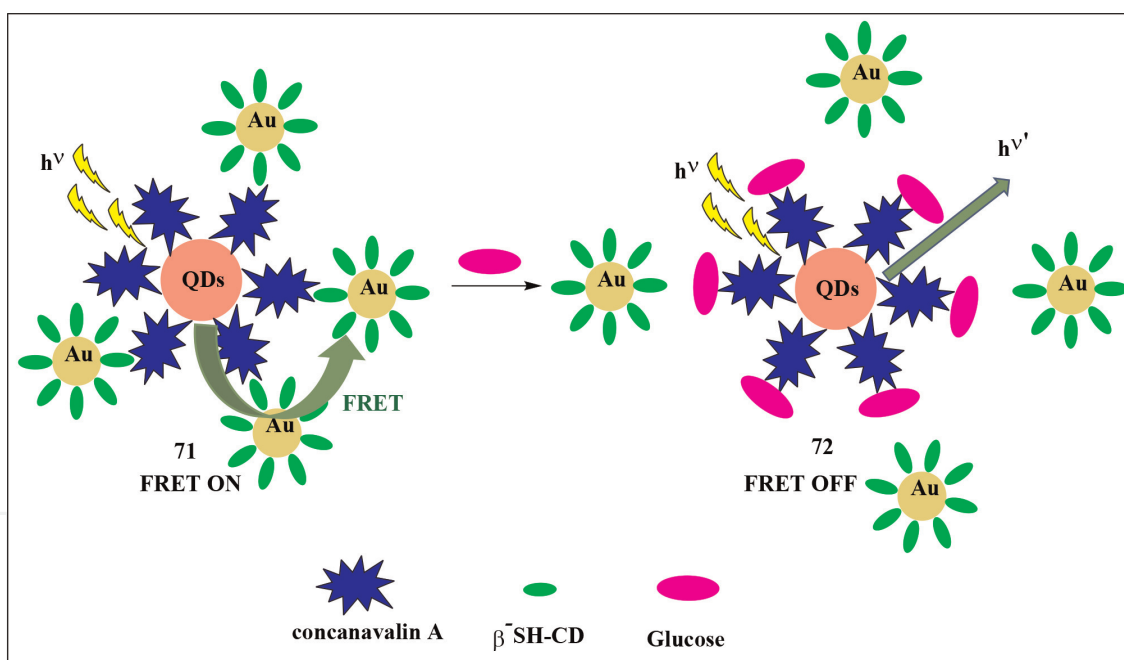


Figure 19.
 Schematic depiction of the formation of pyrene functionalized β -CD-SWCNT hybrid conjugate (67).

devices where the sensing mechanism is perceived through color variation from red to purple/blue. In this regard, Kaifer and teammates have constructed β -CD functionalized gold nanoparticles (68) and noticed that the addition of ferrocene dimer (69) as a competitive guest to colloidal solutions of 68 primarily results in a red shift followed by the precipitation of a red solid (Figure 20) [85, 86]. These observations were not perceived in case of addition of ferrocene in methanol. This indicates that the ferrocene dimer operates as a linker between diverse gold nanoparticles, and hence helps in their aggregation. This aggregation in turn offers a color change, which signifies the sensing event with typical guest molecules. The same group also utilized the γ -CD in combination with gold nanoparticles for the sensing of well-known carbon nanomaterial known as fullerene (C₆₀) through aggregation phenomenon [87]. In another event, Tang *et al.* constructed a highly selective as well as sensitive glucose

**Figure 20.**

Schematic view of β -CD functionalized gold nanoparticles (68) aggregation upon addition of ferrocene dimer (69).

**Figure 21.**

Schematic illustration of FRET on/off mechanism operating in nanobiosensor (71) constructed from concanavalin A fabricated CdTe (QDs) and thiolated β -CD functionalized AuNps.

nanobiosensor (71) in serum, which operates through FRET between concanavalin A fabricated CdTe quantum dots (QDs; energy donors) and thiolated β -CD functionalized gold nanoparticles (AuNps) acting as energy acceptors (**Figure 21**) [88]. Quite recently, Bindu and co-workers have functionalized gold nanoparticles by the β -CD in order to detect heavy metal ions in aquatic realm. Captivatingly, the sensitivity of the developed β -CD-gold nanoparticle hybrid conjugate toward copper was found to be 1.788 mM [89]. Elgamouz and teammates have functionalized silver nanoparticles by β -CD to develop a nanoprobe having the ability to encapsulate creatinine through the colorimetric response. The established β -CD-silver

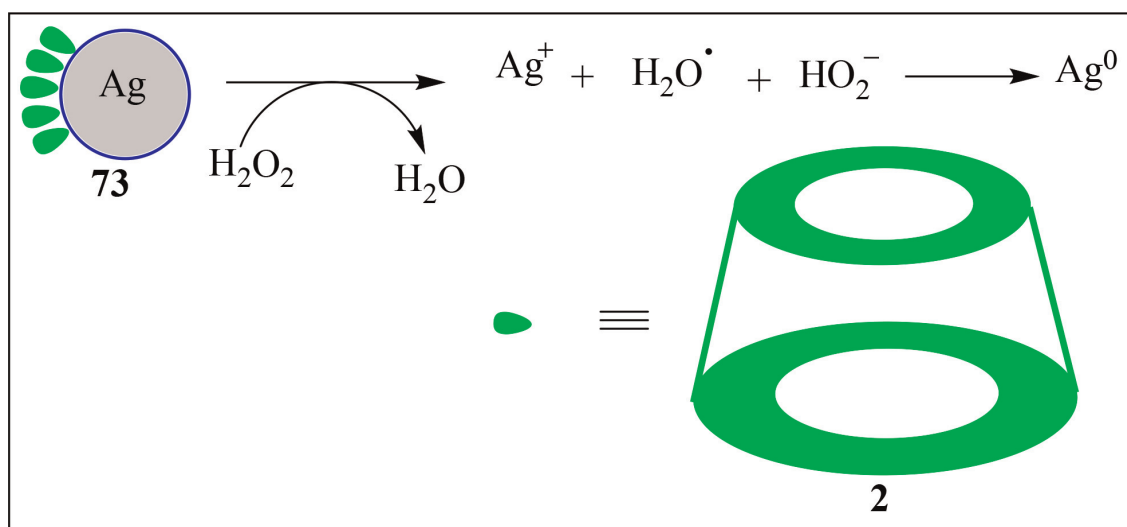


Figure 22.
 Schematic representation of the detection of H_2O_2 via β -CD-AgNP-based nano colorimetric probe (73).

nanoparticle (AgNP)-based nano-colorimetric probe (73) has successfully been applied in the detection of reactive oxygen species *viz.* H_2O_2 in human urine samples by these authors (Figure 22) [90].

9. Conclusions and outlook

In summary, this chapter discusses the conceptual background as well as evolutionary developments of chemical sensing in cyclodextrin-based monomers, dimers, clusters, and nano-assemblies with a detection limit up to $\mu\text{M}/\text{nM}$ level. The sensing event of various guest molecules *via* optical and electrochemical signatures on CD-based sensors endows them characteristics and features, which have been elaborated. In fact, the domain of CD-based chemical sensors has established its firm ground in supramolecular chemistry, biochemistry, polymer chemistry, pharmaceutical chemistry, and nanotechnology. Utilizing the fundamental principles and concepts of chemistry in combination with CD-based chemistry, diverse novel chemical sensors having high sensitivity, high functionality, and wide versatility have been constructed for analytes of typical interest. The authors are of the view that this chapter will offer new dimensions to CD-based chemical sensors and may guide the readers to develop a better understanding of cyclodextrins.

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Conflicts of interest

The authors declare no conflicts of interest.

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