2025
5(1), 1201

Journal of
Molecular Chemistry

Charged Cyclodextrin-based self-assembly for Biosensing applications

Shraddha V. Sonavane,[1] Sujata Bais,[2] Vidhi Sehgal,[3] Prabhat K. Singh[1,2,*]

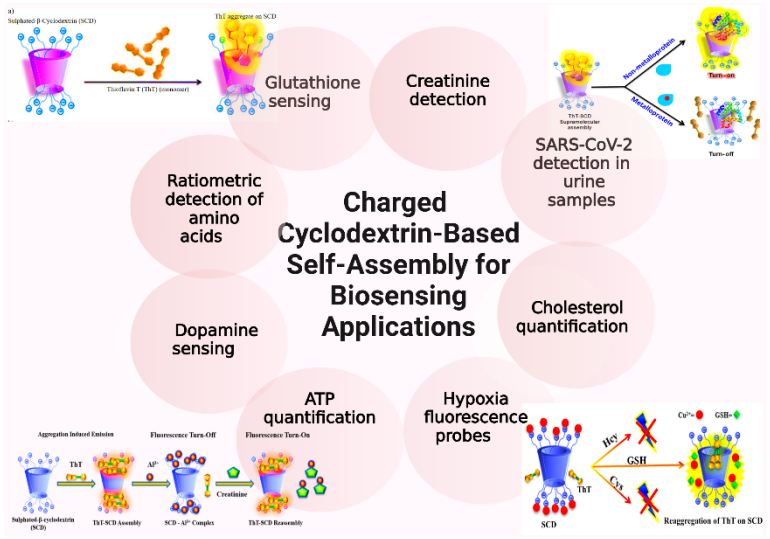
[1]*Homi Bhabha National Institute, Anushaktinagar, Mumbai-400085, India.* [2]*Radiation & Photochemistry Division, Bhabha Atomic Research Centre, Mumbai 400085, India.* [3]*Department of Biotechnology, Mithibai College of Arts, Chauhan Institute of Science & Amrutben Jivanlal College of Commerce and Economics, Vile Parle (W), 400056, India.*

Submitted on: 14-Nov-2024, Accepted and Published on: 02-Dec-2024

Review

ABSTRACT

This review explores the application of charged cyclodextrins in biosensing systems, highlighting their unique advantages over neutral cyclodextrins. Charged cyclodextrins exhibit distinctive geometrical features, self-assembly capabilities, and molecular recognition properties, which make them highly effective in biosensing at the molecular level. The primary focus of this review is on the biosensing applications of charged cyclodextrin-modified sensors for detecting biomolecules, pharmaceuticals, and environmental pollutants, with a particular emphasis on systems utilizing fluorescent sensors. The key benefits of charged cyclodextrin-based systems include enhanced sensitivity, improved selectivity, and customizable structural attributes, allowing for targeted detection in complex environments. Additionally, this review discusses future perspectives, such as the integration of charged cyclodextrins with nanoscale systems, the potential for early disease detection, environmental pollution monitoring, and the development of wearable sensing devices. As one of the most promising advancements in biosensor technology, charged cyclodextrin-based sensors have opened new pathways for analytical applications in healthcare, environmental science, and beyond, offering innovative solutions to contemporary analytical challenges.



Keywords: Charged cyclodextrins, Self-assembly, Biosensing applications, Optical Sensors

INTRODUCTION

Cyclodextrins (CDs) are remarkable supramolecular macrocyclic host molecules that have gained widespread interest in various scientific disciplines, including analytical chemistry[1,2] materials science[3,4], catalysis[5-7] and biological science.[8,9] These versatile oligosaccharides, connected through α-1,4-glycosidic bonds, exist in three primary forms— α-, β-, and γ-CDs—comprising six, seven, and eight D-glucose units, respectively.[10] The unique structure of cyclodextrins, with a hydrophilic exterior and a hydrophobic inner cavity, facilitates the formation of inclusion complexes with a wide variety of guest molecules.[11-13] This feature makes CDs highly suitable for numerous applications, especially in biomedical and biosensing technologies, where their molecular recognition and encapsulation capabilities are leveraged to improve stability, solubility, and bioavailability of guest compounds.

Researchers have expanded the molecular recognition and self-assembly capabilities of cyclodextrins by modifying their hydroxyl groups with various functional entities. These include polyethylene glycol (PEG) chains,[14] photosensitizers,[15] luminophores,[16] and polymers.[17] Recently, the development of charged cyclodextrins has opened new avenues in biomedical research due to their enhanced solubility, improved electrostatic interactions, and increased molecular recognition capabilities.[18,19] By introducing positively or negatively charged groups to the CD structure, charged cyclodextrins can interact with oppositely charged molecules, forming stable supramolecular self-assemblies through electrostatic forces.[20-22] This modification enables the creation of highly stable and functionalized nanostructures, which have shown promise for various applications, including drug delivery, gene therapy, and biosensing.[9,23,24]

*Corresponding Author: Prabhat K. Singh, Radiation & Photochemistry Division, Bhabha Atomic Research Centre, Mumbai 400085, INDIA
Tel: 91-22-25590894; Email: prabhatk@barc.gov.in; prabhatsingh988@gmail.com:

URN:NBN:sciencein.jmc.2025.1201
DOI: 10.62110/sciencein.jmc.2025.1201
Published by: ScienceIn Publishing https://pubs.thesciencein.org/jmc

The incorporation of charged cyclodextrins in biosensing applications is particularly impactful. Charged CD-based assemblies offer a versatile platform for detecting biomolecules, facilitating diagnostic procedures, and enhancing the sensitivity and selectivity of the sensors.[25-28] These supramolecular systems can be tailored for specific interactions with target analytes, making them invaluable for the development of sensors for detecting drugs, monitoring biomolecular interactions, and diagnosing diseases. The charged groups on cyclodextrins not only strengthen the host-guest interactions[29-31] but also allow for complex detection mechanisms, such as ratiometric fluorescence[28,32] and electrochemical detection,[33] which are critical for achieving high precision and reliability in biosensing. This chapter reviews the emerging applications of multicharged cyclodextrins and their self-assembled systems in biosensing. By highlighting recent advances, this review underscores the transformative potential of charged cyclodextrin-based self-assemblies in creating next-generation biosensors, with applications ranging from drug detection and biomolecule sensing to diagnostic tools for infectious diseases. Through an exploration of various biosensing approaches, including displacement assays, fluorescence detection, and molecular recognition, this chapter aims to provide a comprehensive understanding of how electrostatically driven self-assemblies can contribute to the advancement of biosensor technologies, offering new solutions to complex challenges in biomedical research and clinical practice.

1. Structure of Cyclodextrins

Cyclodextrins (CDs) are natural cyclic oligosaccharides that exist primarily in three forms: α-, β-, and γ-CDs, each containing six, seven, and eight D-glucose units, respectively. These variations result in distinct cavity sizes, allowing the CDs to encapsulate different guest molecules. First isolated and characterized by Freudenberg, Cramer, and collaborators[34], CDs are connected by α-1,4-glycosidic bonds that give rise to their unique toroidal or bucket-like shape, where each glucose unit contributes one primary hydroxyl group at the 6-position and two secondary hydroxyl groups at the 2- and 3-positions. In this arrangement, the primary hydroxyls face the narrower end of the CD cavity, whereas the secondary hydroxyls face the wider end, creating a distinctive truncated cone shape with a hydrophilic exterior and a hydrophobic interior, as shown in Figure. 1. Such a truncated conical shape, with an exterior hydrophilic and an interior hydrophobic, allows CDs to form inclusion complexes with many guest molecules.[11,13] Hence, CDs are highly versatile for a wide variety of applications in addition to biomedical applications in biosensing.

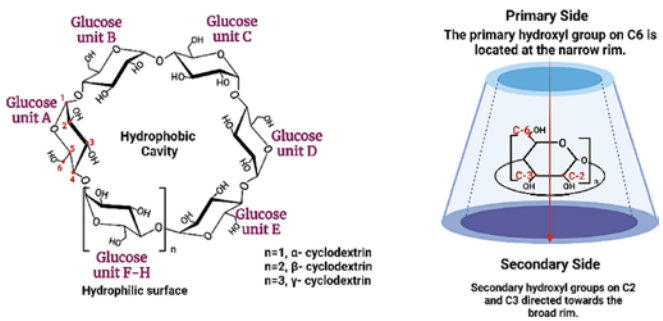


Figure 1: Structure of cyclodextrins. Reproduced with permission from Reference 35.

Cyclodextrins (CDs) have unique host-guest binding properties that enable the formation of complex molecular structures such as catenanes and polyrotaxanes. This compatibility is primarily determined by the size of the CD host cavity, which selectively binds guest molecules of a matching size. The ability to form stable inclusion complexes is a defining characteristic of CDs.[36,37] The guest molecule is held within the cavity through non-covalent interactions that may range from hydrogen bonding to van der Waals forces, hydrogen bonds, and hydrophobic interactions.[38] The main driving force for the formation of the complex is the removal of high-enthalpy polar water molecules from the apolar cavity of the CDs, which can then host hydrophobic guest molecules. The inclusion complexation process confers several benefits to trapped guests. Primarily, it increases the solubility of the normally insoluble guest molecules. The encapsulation of hydrophobic guest molecules in their cavities improves the water solubility of CDs and makes them suitable for various applications.[39] This host-guest binding ability is further strengthened by modifications to the CD structure, such as the introduction of charged functional groups. These modifications expand the utility of CDs, enabling the development of stable charged self-assemblies that improve molecular recognition, stability, and performance in biosensing applications. In the context of charged CDs, the electrostatic interaction between the charged groups on the CD and oppositely charged guest molecules creates stable, multimodal platforms that are particularly well suited for sensitive and selective detection in biosensing.[40]

1.1. Charge addition on cyclodextrins

A diverse range of cyclodextrin (CD) derivatives has been synthesized by applying chemical modifications, including amination, esterification, and etherification of the primary and secondary hydroxyl groups. These modifications fundamentally transform the properties of CDs, especially their solubility, cavity size, and stability, enabling a broader spectrum of applications than their native forms. Notably, introducing charged functional groups to CDs enhances the water solubility, electrostatic interaction capabilities, and stability of inclusion complexes, which are crucial for applications in aqueous and physiological environments. Charged cyclodextrins (CDs) represent a distinct class of modified CDs that exhibit unique electrostatic interactions with oppositely charged guest molecules, thereby facilitating the formation of stable supramolecular assemblies.[41] Among these modified CDs, charged cyclodextrins occupy a unique position. According to Ma et al.[8], the introduction of charged groups enhances the ability of CDs to form inclusion complexes by leveraging both hydrophobic and electrostatic interactions. This dual interaction mechanism is particularly beneficial for creating stable assemblies with various biomolecules such as proteins, nucleic acids, and small therapeutic molecules.

Researchers have developed various synthetic approaches to incorporate charged functional groups into CDs. For example, sulfonated CDs can be synthesized through sulfonation reactions, which introduce sulfonic acid groups onto the CD framework, resulting in highly water-soluble anionic CDs.[29] Such sulfonated CDs are commonly used in biosensing because of their ability to engage in strong electrostatic interactions with positively charged analytes, thereby enhancing both selectivity and sensitivity. Another example involves the production of polycationic CDs such as acetylated-per-azido-β-CD,[42] which serves as a precursor for assembling polycationic click clusters. These clusters are formed through click chemistry and provide an extensive platform for assembling charged nanostructures for targeted biosensing applications.

In addition, researchers have synthesized per-6-thiolated CDs,[43] which are functionalized with thiol groups to enable selective binding with specific targets such as positively charged drugs. This approach exemplifies how functional groups such as carboxyl, sulfonate, ammonium, and sulfobutylether have been strategically added to the CD structure to create negatively[28] or positively charged CDs[44] with tailored binding properties for specific biosensing needs. Scientists have effectively enhanced their application potential in biosensing by manipulating the chemical structure and charge distribution of CDs. Charged CDs not only exhibit improved stability and solubility but also provide specific recognition sites for selective molecular interactions, which are essential for diagnostic applications. This section further explores the diverse biological applications enabled by these modified cyclodextrins, emphasizing their utility in various biosensing platforms and their transformative role in diagnostics and therapeutics.

2. Self-assembly of charged cyclodextrins

Self-assembly systems based on charged cyclodextrins represent a dynamic class of materials with a significant potential for biosensing applications. These supramolecular self-assemblies utilize non-covalent interactions, including hydrogen bonding, electrostatic interactions, and π–π stacking, to form stable yet reversible structures that are highly responsive to environmental conditions, such as temperature, pH, and ionic strength.[21,41,45] This adaptability is essential for applications across various fields, including biomolecule detection, drug delivery, and diagnostic imaging.[26,40,46] Charged cyclodextrins (CDs) are particularly suited for constructing self-assembled systems owing to their structural versatility and modifiable surface properties. Modifications that introduce charged functional groups, such as sulfonates, ammonium, and carboxylates, to CDs enhance their water solubility and enable electrostatic interactions with various guest molecules.[13,31] These charged CDs can selectively interact with oppositely charged or complementary molecules, facilitating the formation of stable self-assemblies in both aqueous and biological environments. Such assemblies exhibit improved stability and enhanced functionality compared with native CDs, making them highly suitable for biosensing applications that require reliable and selective molecular recognition. In self-assembly systems based on charged CDs, non-covalent interactions drive the formation of aggregates or disassemblies in response to external stimuli. For example, surface-modified CDs can spontaneously organize into nanoscale aggregates or supramolecular structures when exposed to specific ions or molecules.[47] This aggregation/disaggregation behavior is central to biosensing, where the presence of a target analyte can trigger structural changes that translate into a measurable signal. These systems not only offer a high degree of selectivity and sensitivity but also benefit from the inherent biocompatibility and low toxicity of CDs, making them ideal for *in vivo* and *in vitro* applications.[23,46] Moreover, the ability to fine-tune the assembly properties of charged CDs allows the development of multifunctional sensing platforms. By adjusting the type and density of the charged groups, researchers can control the self-assembly behavior and optimize the system for specific applications, from detecting biomolecules and ions to serving as carriers for therapeutic agents. The versatility, adaptability, and ease of synthesis of charged CD-based self-assemblies underscore their potential as foundational technologies for biosensing and beyond.

3. Specific examples of sensing applications

3.1. Thioflavin T (ThT) and sulfated β-cyclodextrin (SCD) as sensors

Sulfated cyclodextrins (CDs) are a modified class of cyclodextrins featuring sulfate groups attached to their molecular structure. The addition of sulfate groups enhances the water solubility of the CDs and introduces negatively charged sites on their surface, enabling interactions with positively charged molecules or ions through electrostatic forces. In a detailed study, Singh and colleagues explored the fluorescence properties of H-aggregates formed by Thioflavin T (ThT), a dye for sensing amyloid fibrils, in combination with sulfated-β-cyclodextrin (SCD), a highly anionic compound. This investigation leveraged the electrostatic attraction between the SCD host and ThT guest (Fig.2).[48] Thioflavin T (ThT) is part of the molecular rotor class of molecules, which are typically weakly emissive when free in aqueous or low-viscosity solvents.[49,50] This weak emission is due to highly efficient non-radiative torsional relaxation processes that enable rapid de-excitation from the excited state.[51,52] However, these non-radiative processes are significantly reduced in high-viscosity solvents or confined environments, where rotational freedom is limited.[50,53-57] Additionally, molecular rotors like ThT exhibit reduced non-radiative relaxation and enhanced emission when they aggregate, further modulating their emissive properties. They observed that ThT exhibits stronger fluorescence in its aggregated form with SCD compared to its monomeric form in an aqueous solution, which is attributed to reduced non-radiative torsional relaxation processes.[48] Interestingly, the increased fluorescence was linked to the formation of ThT H-aggregates rather than the expected inclusion complex with SCD. SCD plays a crucial role by acting as a template for the formation of fluorescent H-aggregates of non-covalently bound ThT molecules. The suppression of non-radiative torsional relaxation in the H-aggregate form led to a notable increase in fluorescence compared with monomeric ThT.

The unique responsiveness of this system to temperature and various ionic conditions, along with its advantageous red-region emission, offers promising applications in designing stimulus-responsive systems, and supports the differential and ratiometric fluorescent detection of external additives.[26,28,32] This section discusses the potential of the ThT-SCD system to enable molecular recognition of diverse analytes within this supramolecular framework.

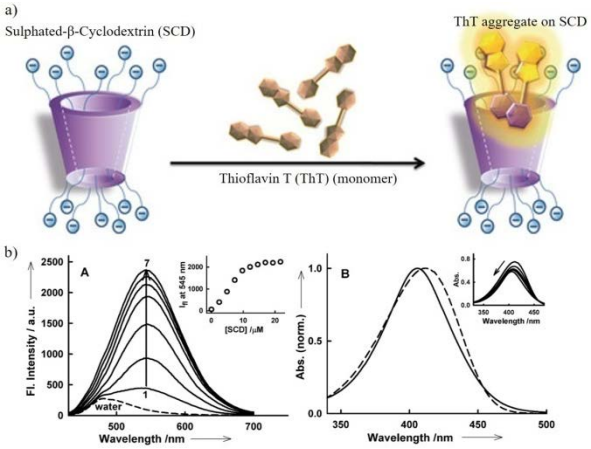


Figure 2: This figure illustrates the equilibrium between monomeric and aggregated forms of Thioflavin-T (ThT) when interacting with sulfated β-cyclodextrin (SCD). The formation of aggregates results in enhanced fluorescence, demonstrating the potential of supramolecular assembly for sensitive biomolecule detection. Reproduced with permission from Ref. 48.

3.1.1. Ratiometric detection of lysine and arginine

The development of fluorescent sensors for detecting arginine and lysine has garnered significant attention due to their biological importance. However, existing sensors face limitations, such as low solubility in aqueous solutions, complex and time-consuming synthesis protocols, and dependence on single-wavelength measurements, making them vulnerable to small experimental fluctuations.[58] To address these challenges, Singh et al. introduced a ThT-SCD assembly based ratiometric sensor specifically for the selective detection and differentiation of arginine and lysine (Fig. 3).[32] This sensor operates through the disassembly of emissive H-aggregates of Thioflavin T (ThT) from a supramolecular self-assembly formed on the surface of the polyanionic host sulfated-β-cyclodextrin (SCD).The disassembly process shifts the equilibrium between the ThT monomers and aggregates, providing an effective ratiometric detection mechanism for arginine and lysine in aqueous solutions. Ratiometric fluorescence is a method where the intensity of light emitted at two different wavelengths is compared. This ratio helps ensure accurate detection by reducing the effect of external factors like light intensity or sensor placement. Compared to systems that rely on synthetically complex probe molecules, this sensor offers a straightforward and cost-effective approach by utilizing the accessible probe ThT. The ratiometric feature enhanced the accuracy of the quantitative measurements of these amino acids. The sensor demonstrated detection limits of approximately 40 and 50 μM for lysine and arginine, respectively. By analyzing the responses of the sensor across four wavelengths (470, 490, 520, and 550 nm), distinct recognition patterns were identified for arginine and lysine, two amino acids that are otherwise challenging to distinguish. The authors confirmed the effectiveness of the sensor not only in aqueous solutions, but also in biological media, such as serum samples. These unique recognition patterns allow for differentiation between the amino acids through principal component analysis (PCA) (Figure 3).

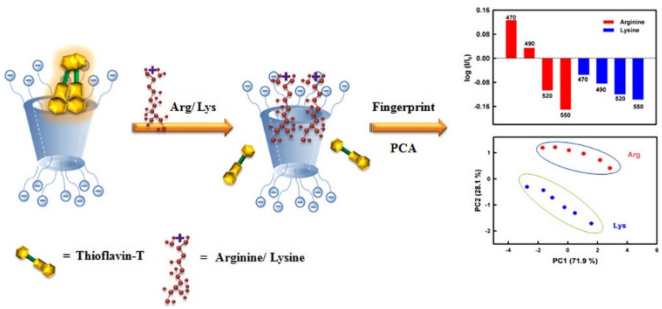


Figure 3: This figure demonstrates how the dissociation of Thioflavin-T (ThT) aggregates from the sulfated β-cyclodextrin (SCD) surface is induced by arginine and lysine. The resulting changes in fluorescence enable the identification and differentiation of these two amino acids. Principal component analysis (PCA) further highlights the distinct recognition patterns of arginine and lysine, showcasing the sensor's capability for selective and quantitative detection in aqueous solutions. Reproduced with permission from Ref. 32.

3.1.2. Detection of ATP

Singh et al. further explored the ThT-SCD supramolecular assembly for ratiometric ATP detection in an aqueous medium (Fig. 4).[28] The presence of H-aggregates of Thioflavin T (ThT) on the SCD surface was confirmed by a bathochromic shift in fluorescence emission, with the peak shifting from 490 nm (monomeric ThT) to 545 nm, along with an increase in the excited state lifetime of ThT. As noted earlier, due to torsional motion around its central C-C bond, ThT generally undergoes non-radiative processes in low-viscosity environments like water, resulting in weak fluorescence emission. The fluorescence emission of the supramolecular assembly was quenched by the Zn^{2+} ion, which electrostatically interacts with poly-anionic SCD, causing the disassembly of the ThT and SCD complex, which was also confirmed by the reduction in fluorescence lifetime. It is well known that highly negatively charged ATP shows a strong affinity for positively charged Zn^{2+} metal ions; the authors exploited this to reassemble the ThT and SCD complex after the addition of ATP, which induced the reassembly of ThT and SCD assembly by selectively binding to Zn^{2+}, which was confirmed by recovery of steady-state emission intensity. This ATP detection method, which relies on the reversible disassembly and reassembly of the ThT-SCD complex, offers a simple, label-free, selective, and sensitive optical approach that operates across multiple wavelengths.[28] The effectiveness of the sensor was also demonstrated in real blood serum samples, demonstrating its potential for practical biological applications.

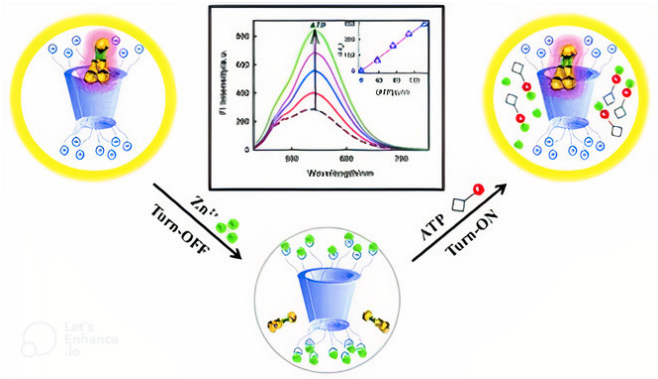


Figure 4: Schematic representation of ATP detection using the ThT-SCD assembly. The figure shows how ATP reassembles the ThT-SCD complex via selective binding to Zn^{2+} ions, leading to fluorescence recovery. This demonstrates a sensitive and selective approach for ATP detection in biological samples. Reproduced with permission from Ref. 28.

3.1.3. Glutathione sensing

The fluorescent sensing of amino acids has attracted considerable interest because of their essential roles in physiological functions. Biological thiols, such as glutathione (GSH), cysteine (Cys), and homocysteine (Hcy), are particularly important for maintaining the redox balance and play vital roles in various physiological and pathological processes.[59] GSH, in particular, has been linked to serious diseases including cancer, Alzheimer's disease, HIV infection, and liver damage. Although previous sensors have shown strong selectivity for detecting Cys over GSH and Hcy,[60] there remains a need for a simple, label-free, and cost-effective method for GSH-specific detection. Addressing this need, Singh and co-authors developed a ThT-SCD supramolecular assembly designed to detect GSH selectively over Cys and Hcy (Figure 5).[61] In this sensing method, divalent copper ions (Cu^{2+}) initially quench the fluorescence of the ThT-SCD assembly by inducing the dissociation of ThT from the SCD surface. Upon the addition of GSH, which interacts more strongly with Cu^{2+}, the copper ions are removed from the SCD, allowing the ThT-SCD assembly to reform. This sequential disassembly and reassembly process enables the sensor to function reliably as a ratiometric sensor for GSH detection in aqueous solutions. The sensor has a detection limit (LOD) of 2.4 ± 0.2 µM in aqueous solution and 13.6 ± 0.5 µM in diluted human serum, with a linear response in the concentration range of 0–250 µM. The emission signal is characterized by the ratio of the intensities at 545 nm (aggregate band) to 490 nm (monomer band), with an excitation wavelength of 410 nm.[61] Notably, this ratiometric sensor demonstrates significant selectivity for GSH over Cys, Hcy, and other amino acids, and has shown effectiveness in complex biological samples, such as serum, underscoring its potential for practical applications in clinical settings.

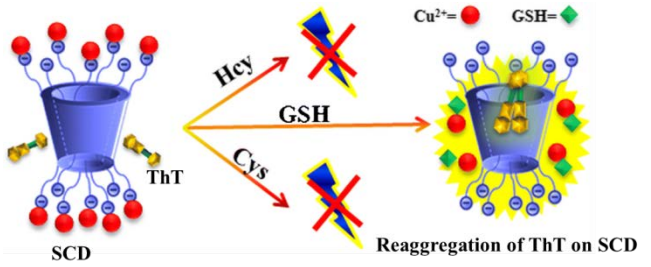


Figure 5: Diagrammatic representation of the detection scheme for glutathione (GSH) using the Thioflavin-T (ThT) and sulfated β-cyclodextrin (SCD) assembly. The mechanism involves fluorescence quenching by copper ions (Cu^{2+}), followed by fluorescence recovery upon selective binding of GSH to Cu^{2+}. Reproduced with permission from Ref. 61.

3.1.4. Detection and differentiation of Protein molecules

The development of efficient and accurate methods for distinguishing proteins has been a longstanding focus of scientific research. A key challenge remains in the development of a simple and direct approach for protein differentiation and identification. In both research and clinical fields, methods relying on specific protein-antibody interactions are valued but often result in high production costs and limited applicability due to the complexity of antibody preparation. Singh and Pettiwala[27] introduced a streamlined approach using a supramolecular assembly with a single receptor and a single transducer, based on commercially available compounds, to discriminate between metalloproteins and non-metalloproteins (Figure 6).

This supramolecular system includes a molecular motor-based bioprobe, Thioflavin T (ThT) as the guest, and multi-anionic sulfated cyclodextrin (SCD) as the host. In this setup, ThT functions as a reporter molecule, whereas SCD serves as the transducer. The authors utilized the non-covalent and dynamic interactions within this host-guest complex to modulate the photophysical properties of ThT, making it highly sensitive to minor environmental changes. This sensitivity enables the detection of proteins that exhibit distinct interactions, based on their charge and hydrophobicity. These interactions, primarily ionic and weak non-covalent bonds, produce unique fluorescence responses, allowing for a clear differentiation between metalloproteins and non-metalloproteins. For example, metalloproteins, such as ferritin (Fer) and myoglobin (Mb), quench the fluorescence of ThT aggregates at 545 nm by disrupting the SCD-ThT complex. Conversely, non-metalloproteins like trypsin, pepsin, β-lactoglobulin, lysozyme, and ovalbumin induce a hypsochromic shift in the ThT-SCD complex from 545 nm to 490 nm, indicative of ThT in its monomeric form. This shift occurs as ThT is displaced from the SCD surface, accompanied by an increase in the fluorescence intensity at 490 nm, which is the typical emission of ThT monomers. This difference in response, quenching for metalloproteins and fluorescence enhancement for non-metalloproteins, enables effective protein differentiation. Additionally, the ThT-SCD assembly demonstrates clear potential for distinguishing between metal-containing and non-

metal-containing proteins, offering a robust tool for protein analysis based on fluorescence-based sensing.

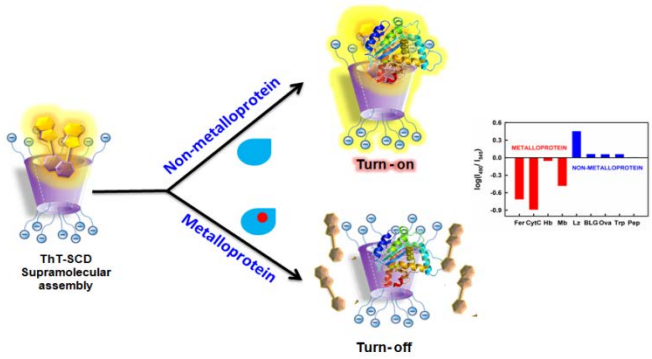


Figure 6: Schematic representation of the Thioflavin-T (ThT) and sulfated β-cyclodextrin (SCD) assembly-based sensor for detecting and differentiating metalloproteins and non-metalloproteins. Metalloproteins disrupt the ThT-SCD complex, quenching fluorescence, while non-metalloproteins displace ThT from the SCD surface, causing a fluorescence shift. These distinct photophysical responses enable accurate discrimination between the two protein classes. Reproduced with permission from Ref. 27.

3.1.5. Melamine identification

Molecular recognition by multiply charged cyclodextrins extends beyond amino acids and proteins to the detection of food adulterants. For instance, Singh et al. demonstrated that these cyclodextrins, when complexed with probe molecules, can be effectively used for the sensitive, selective, rapid, and cost-effective fluorescence-based detection of melamine, achieving a limit of detection (LOD) of 15 µM (Figure 7).[62] Melamine, a nitrogen-rich compound, is often used as an adulterant in food products. However, their consumption poses serious health risks and can lead to life-threatening conditions. This creates a pressing need for a quick and affordable method to detect melamine in food. The developed detection system includes SCD as the host and ThT as the guest. Through electrostatic interactions between SCD and ThT, ThT aggregates, with charge neutralization enhancing its fluorescence emission at 545 nm compared to that at 490 nm, which is typical for ThT monomers. For melamine detection, Ag^+ ions were introduced into the ThT-SCD assembly, quenching the ThT fluorescence by displacing it from the SCD surface. The subsequent addition of melamine to the ThT-SCD-Ag^+ system caused a significant fluorescence increase at 490 nm, indicating that ThT was now monomerically bound near SCD. This detection process was confirmed using ground-state absorption, steady-state, and time-resolved emission spectra, FTIR, and AFM measurements.[62] The system demonstrated strong selectivity over various nitrogen-containing compounds, amino acids, and salts commonly found in food, making it a reliable tool for melamine detection. The effectiveness of the sensor was validated in milk samples, setting the stage for the further development of similar sensors for food safety applications.

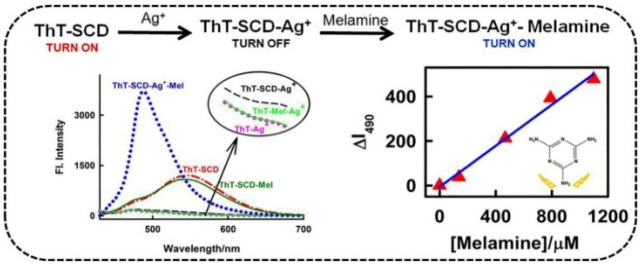


Figure 7: Schematic representation of melamine detection using the Thioflavin-T (ThT) and sulfated β-cyclodextrin (SCD) supramolecular assembly. The detection process involves fluorescence quenching of the ThT-SCD complex by silver ions (Ag^+), followed by fluorescence restoration upon melamine binding to Ag^+. Reproduced with permission from Ref. 62.

3.1.6. Fluorescence "Turn on" sensors for creatinine detection

Bais and Singh[26] introduced a ThT-SCD-based ratiometric fluorescence sensor for creatinine detection, addressing the limitations of traditional detection methods such as complex probe synthesis and sensitivity to solution conditions (Fig.8). Creatinine, a critical biomarker of kidney function, was detected using this novel system, which operates by modulating the monomer-aggregate equilibrium of Thioflavin T (ThT) on the surface of sulfated-β-cyclodextrin (SCD) through Al^{3+} ions. The sensor mechanism involves a two-step disassembly/reassembly process: Al^{3+} ions induce dissociation of ThT-SCD aggregates, quenching fluorescence, whereas creatinine rebinds Al^{3+}, restoring the ThT-SCD structure and increasing fluorescence at 545 nm. This ratiometric design enhances the reliability by using the emission ratio at 545 nm (aggregated ThT) and 490 nm (monomeric ThT), yielding a low detection limit of 0.5 µM. The sensor demonstrated a wide linear response range (0-200 µM) and effectively detected creatinine in artificial urine and diluted human serum samples, thereby demonstrating its potential for real-world applications. This approach, leveraging the accessible ThT dye, provides a straightforward and cost-effective solution for accurate creatinine monitoring, which is crucial for early diagnosis and management of kidney diseases.

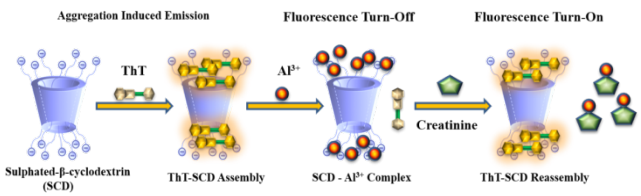


Figure 8: Schematic representation of creatinine detection using the Thioflavin-T (ThT) and sulfated β-cyclodextrin (SCD) supramolecular assembly. The detection mechanism involves the dissociation of ThT-SCD aggregates by aluminum ions (Al^{3+}), resulting in fluorescence quenching, followed by reassembly and fluorescence restoration upon creatinine binding to Al^{3+}. Reproduced with permission from reference from Ref. 26.

3.1.7. Detection of Trypsin

Kaur et al.[21] developed a highly selective and sensitive fluorescent biosensor for trypsin detection, leveraging an

aggregation-induced emission (AIE) approach combined with a supramolecular assembly of sulfated-β-cyclodextrin (S-βCD) and a tetraphenylethylene-imidazolium (TPE-IM) derivative (Fig. 9). Aggregation-induced emission (AIE) occurs when molecules that are usually non-luminescent in their isolated form emit light after they aggregate. This system addresses the challenges associated with conventional trypsin detection methods, such as high costs, sensitivity limitations, and complex processing. The biosensor operates through a "Turn-on" fluorescence mechanism that responds specifically to trypsin activity. In the presence of protamine sulfate (PrS), a natural substrate of trypsin, the TPE-IM/S-βCD complex initially forms a quenched supramolecular assembly. However, upon trypsin addition, PrS was enzymatically cleaved, disrupting the PrS-S-βCD complex and allowing the TPE-IM/S-βCD assembly to re-aggregate, restoring fluorescence at 475 nm. This fluorescence enhancement correlates with the trypsin concentration, providing a linear detection range from 0 to 10 nM and a limit of detection as low as 10 pM. This sensing platform demonstrated robustness under various environmental conditions and high selectivity for trypsin, with minimal interference from other proteins. Furthermore, it proved effective in real biological samples, achieving reliable detection in human serum, with a detection limit of 78 pM. This approach offers promising potential for diagnostic applications in monitoring trypsin-related diseases and trypsin inhibitor screening, marking a significant advancement in enzyme-responsive biosensing.

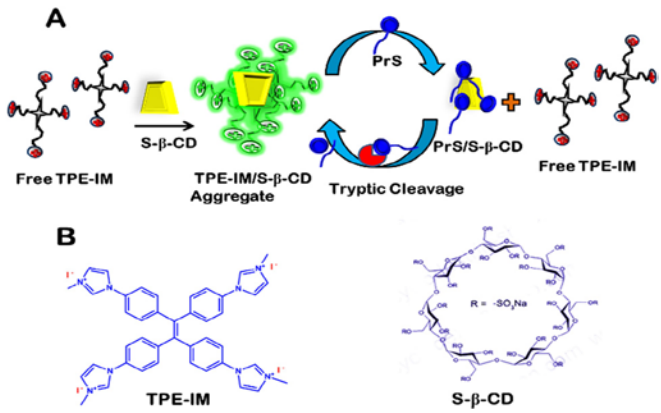


Figure 9: (A) Schematic representation of the trypsin detection mechanism using the Thioflavin-T (ThT) and sulfated β-cyclodextrin (SCD) supramolecular assembly. The fluorescence 'turn-on' mechanism is triggered by the enzymatic cleavage of protamine sulfate (PrS), disrupting the PrS-SCD complex and allowing reassembly of the TPE-IM/SCD system. (B) Chemical structures of the tetraphenylethylene-imidazolium (TPE-IM) derivative and sulfated β-cyclodextrin (S-βCD), key components of the sensor. Reproduced with permission from reference from Ref 21.

4. Detection of various other biomolecules

Charged cyclodextrins have demonstrated significant potential in sensing applications, ranging from the detection of various biomolecules to the quantification of drugs and the identification of pathogens. These highly mobile macrocyclic compounds have been useful in the fabrication of new sensing and diagnostic methods to tackle challenges in understanding complex biological systems and overcoming healthcare problems related to patient well-being.

4.1.1. Pattern-based Heparin contaminant detection

Heparin is an anticoagulant used to treat thrombosis.[63] In the early 2000s, hundreds of patients died or suffered severe injuries in the US and Germany during anticoagulation therapy, arising from the wrong administration of contaminated unfractionated heparin.[64] Oversulfated Chondroitin sulfate (OSCS) was detected as a contaminant through different methods such as HPLC, electrophoresis and spectroscopy.[65] This created a need to develop specific biosensors to detect impurities in heparin.[66] Thus, the authors of this work[67] reported the formation of a positively charged fluorescent supramer that was found to possess the ability to detect heparin-bound OSCS. Thus, in this notable study,[67] polycationic cyclodextrin units, with charges derived from amide and guanidino derivatives, were complexed with lithocholic acid to produce stable LCA-β-cyclodextrin complexes. The LCA-β-CD complex possessed a positive charge near the analyte binding site and could interact with negatively charged molecules. The cationic CD was bound to a quinolinium fluorescent reporter. This unit was exposed to heparin, containing the negatively charged anticoagulant contaminant. Research has demonstrated that quinolinium fluorophore is an effective reporter molecule that responds reliably to heparin-binding events through electrostatic interactions.[67] Thus, the main principle behind the interaction of CD with the heparin contaminant is host-guest binding, where the host is a polycationic CD and the guest is contaminated heparin. Upon electrostatic attraction of the positively charged CD and negatively charged contaminant, the fluorophore yields a detectable response, thus detecting contamination in heparin samples.

4.1.2. Dopamine detection

Dopamine is an important catecholamine neurotransmitter, and aberrant variations in its concentration levels can lead to ailments like Huntington's, Parkinson's, and schizophrenia.[68] Due to the presence of several interfering substances in biological samples, it is challenging to detect dopamine content using electrochemical techniques. These interfering substances are typically present in much larger quantities than dopamine and oxidized at comparable potentials to dopamine at most solid electrodes. This is notably true for ascorbic acid, the principal interfering component in the measurement of dopamine. Thus, in their work, Harley et al.[33] aimed to formulate a highly sensitive sensor for dopamine. This sensor system was synthesized by doping polypyrrole with anionic sulfonated β-CD. This polymer offers a high selectivity for dopamine detection in the presence of ascorbate. No ascorbate anions were detected by the developed sensor. A linear calibration curve was formed for dopamine, yielding a sensitivity of 0.886 $\mu A \mu M^{-1}$ and a detection limit of 3.2×10^{-6}. In the presence of excess ascorbic acid, the homogeneous catalytic interaction of the ascorbate anion with dopamine-o-quinone blocks dopamine regeneration. In dopamine/ascorbate combinations, a single redox wave

corresponding to dopamine oxidation was observed, resulting in a genuinely selective dopamine sensor.

4.1.3. Cholesterol detection

As a fundamental structural component, cholesterol is essential for maintaining the structural integrity and fluidity of all animal cell membranes and the synthesis of bile acid, vitamin D, and hormones.[69] Various methods have been developed for measuring cholesterol levels, including chromatography and colorimetry[70], plasma absorption spectroscopy,[71] electrochemistry,[72] and fluorescence assays.[73] However, most of these approaches require time-consuming and expensive experimental procedures, hazardous chemical reagents, or readily deactivated cholesterol oxidase. Therefore, a convenient, highly selective, stable, and environmentally friendly technique for monitoring cholesterol is required.

In their work, Li et al.[74] have synthesized colloidal gold nanoparticles enveloped with β-cyclodextrin auro-tropodium ether HCl from β-CD–AuNPs on its negatively charged assembly.[74] The NPs were made to interact with the CQDs which are positively charged and wherein fluorescence resonance energy transfer (FRET) took place as a result of electrostatic force. It has already been reported that when NPs are clamped onto CQDs by electrostatic forces, the fluorescence of the CQDs is off or quenched. Previous studies have shown that the lipophilic cavity of β-cyclodextrin facilitates host–guest interactions with cholesterol. The host-guest binding property was also observed when cholesterol was complexed with the β-CD-AuNP-CQD assembly. The cholesterol molecules effectively displaced the CQD, causing them to disperse freely in solution and recover their fluorescence properties. The LOD was determined to be 343.48 nmol L^{-1} and an excellent linear correlation between cholesterol concentration (10-210 µmol L^{-1}) and fluorescence intensity was achieved. Due to the better fluorescence quenching ability of FRET, the analytical performance (including LOD and linear range) of a turn-off fluorescent nano sensor (e.g., CQDs/β-CD@AuNPs) exceeded that of a competing host-guest recognition nano sensor (e.g., functionalized CQDs). Competitive host-guest recognition and FRET have been demonstrated to have a synergistic effect. Hence, an ultrasensitive, highly selective fluorescence turn-off-on nano sensor with a robust anti-interference capability was formulated to detect cholesterol in serum samples.

4.1.4. Hypoxia detecting fluorescence probes

Hypoxia is a crucial indicator of solid tumors caused by rapidly proliferating and expanding neoplasms, as it indicates a lack of oxygen supply and obstructed oxygen diffusion due to poorly adapted vascularization.[23] The high level of expression of various bio reductive enzymes in solid tumors results in an enhanced reductive stress microenvironment due to the low oxygen concentration.

Therefore, the development of hypoxia fluorescence probes is an expanding research area. Wang et al. introduced a biocompatible sulfated-cyclodextrin (SCD)-based turn-on fluorescence probe that responds to hypoxia.[46] The probe was constructed using an azobenzene derivative called '1' and

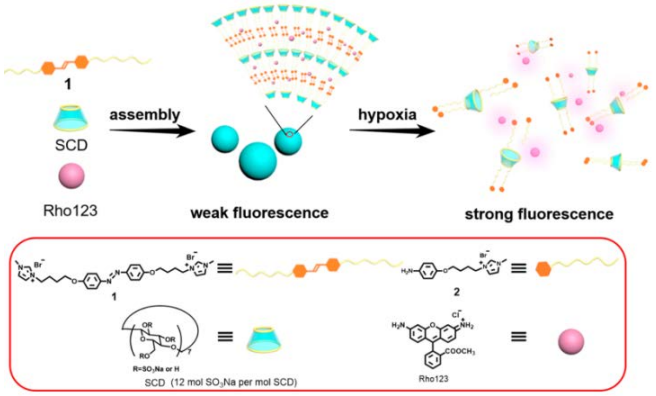


Figure 10: A noncovalent hypoxia-responsive turn-on fluorescence probe was developed using Sulfato-β-CD, a derivative of azobenzene, and a fluorochrome, rhodamine. Under hypoxic conditions, a fluorescence turn-on response was observed. Reproduced with permission from Ref. 46.

fluorochrome rhodamine 123 (Rho123).Through TEM imaging and dynamic light scattering (DLS), it was observed that the negatively multicharged SCD and positively charged '1' formed nanoparticles through electrostatic interactions. The supramolecular assembly (SCD/1) served as a carrier and fluorescence quencher for Rho123.Under hypoxic conditions, the azobenzene group of α1β was reduced by azoreductase, accompanied by the release of Rho123 and fluorescence recovery (Figure 10). Therefore, utilizing supramolecular assembly for hypoxia cell imaging gave ternary response in hypoxic circumstances.

4.1.5. Non-invasive fluorescence biofilm monitoring

Antibiotics are becoming ineffective due to the world wide spread of antibiotic-resistant bacterial strains. Gram-positive bacteria such as *Staphylococcus epidermidis* and *Staphylococcus aureus* play a significant role in nosocomial infections[75]. Isolates in hospitals can lead to significant difficulties in operations and medical implants. *S. epidermidis* is a part of the natural flora of the mucous membrane of the human skin and has been proven to cling to surfaces and create structured biofilms. Biofilms are bacterial colonies that form structured 'films' with improved resilience after tightly adhering to a surface.[76] Untreatable bacterial biofilm formation is a common cause of chronic antibiotic infection. The structure of the biofilm, along with its associated matrix, may hinder or affect the diffusion of the drug and even inhibit antibiotics by directly interacting with these drugs and increasing the number of antibiotics in the bacterial biofilm.[77] The role of charged nanocarriers in the efficiency of drug delivery to biological systems has also been studied. Recent studies have revealed that positively charged nanoparticles filled with antibiotics could further increase penetration into biofilms; however, they possess antimicrobial activity among bacteria and retention in addition to their antimicrobial activities among bacteria.[78]

The authors of this article[79] studied the ability of octakis[6-(2-aminoethylthio)-6-deoxy]- γ-CD (γCys), a positively charged single isomer cyclodextrin derivative, to improve antibiotic

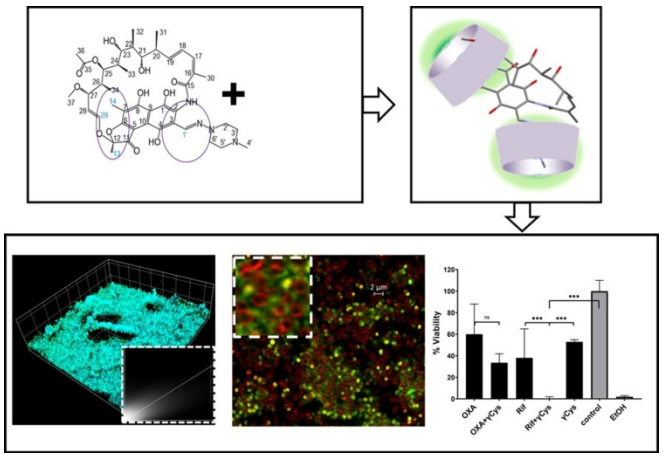


Figure 11: Multiphoton laser scanning and super-resolution fluorescence microscopy depicting the uniform distribution of positively charged cyclodextrin tagged with fluorescein on an *S. epidermis* biofilm layer. Reproduced with permission from Ref 79.

delivery to biofilms. They demonstrated that γCys tagged with fluorescein (FITC) is uniformly distributed throughout live *S. epidermidis* biofilm cultures in vitro using multiphoton laser scanning microscopy and super-resolution fluorescence microscopy. It was located extracellularly in the biofilm matrix. Biofilms were evaluated for the effectiveness of Cys/antibiotics (oxacillin and rifampicin). While the combination of Cys and oxacillin did not yield any improvement compared to oxacillin treatment alone, the Cys and rifampicin combination demonstrated a significant enhancement over rifampicin treatment alone. This combination effectively reduced the biofilm viability to baseline levels.

4.1.6. Renal-clearable molecular probes for SARS-CoV-2 diagnosis

While early and accurate detection of SARS-CoV-2 is crucial for managing the COVID-19 pandemic, current diagnostic methods are limited, as they cannot distinguish between viable and non-viable viruses or directly indicate viral replication activity.[80] Although real-time imaging of SARS-CoV-2 protease activity could address these challenges, such tools remain undeveloped. This study introduces a NIRF-activatable molecular probe, termed SARS-CyCD, designed to detect SARS-CoV-2 protease activity in live mice.[24] The probe consists of a hemocyanin fluorophore and propynyl-HP-cyclodextrin elements embedded within a protease peptide substrate, functioning as both a kidney-targeting scavenger and a NIRF signaling module. The SARS-CoV-2 main protease (Mpro) specifically cleaves the SARS-CyCD peptide substrate, releasing fluorescent fragments that activate NIRF signals. This configuration enables the sensitive detection of Mpro activity in the lungs of mice following intratracheal administration, providing a potential method for visualizing SARS-CoV-2 *in vivo* (Fig 12). Such a sensor could be instrumental in preclinical drug testing and the diagnosis of respiratory illnesses. With its distinctive properties and robust performance, this tool offers promise for enhancing our understanding of viral diseases and for improving patient care in various clinical contexts. As research in this field has progressed, further innovations in cyclodextrin-based technologies are anticipated, which could lead to new diagnostic tools and therapeutic options on a broader scale.

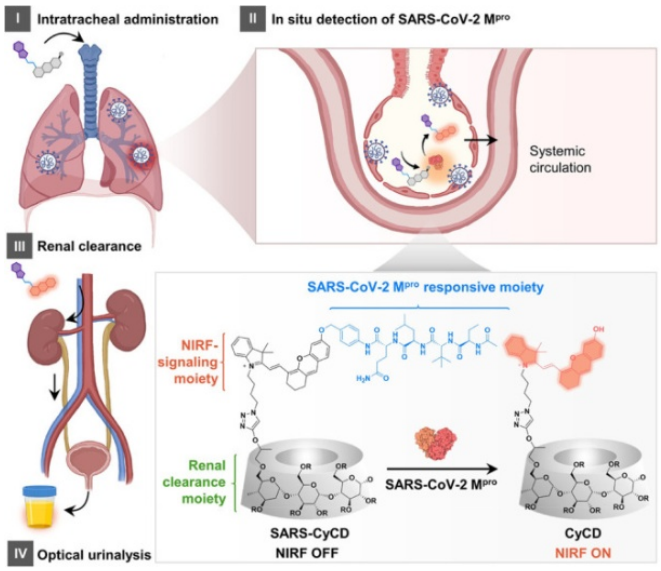


Figure 12: Graphical representation of the detection of SARS-CoV-2 using a CyCD probe. Reproduced with permission from Ref 24.

5. Advantages and Future Prospects of Charged Cyclodextrin-Based Sensors

Charged cyclodextrin-based sensors offer distinct advantages and hold tremendous potential for future applications across diverse fields. These sensors exhibit enhanced selectivity owing to the refined molecular recognition and binding properties of cyclodextrins, as well as increased sensitivity owing to the electrostatic interactions between charged CDs and their target analytes. This high selectivity and sensitivity make charged cyclodextrin-based systems exceptionally useful for specialized applications. Their adaptability allows them to detect both charged and neutral molecules, and their improved water solubility expands their functionality in biological applications. Integrating these sensors with nanomaterials could significantly increase their sensitivity, facilitating early diagnosis in biomedical applications and precise monitoring in environmental sciences in miniaturization, smart integration for data analytics, and sustainable designs to support the use of these sensors in green chemistry and environmental protection, underscoring their potential to address pressing technical and societal issues.[81]

5. 1. Enhanced sensitivity and selectivity

Charged cyclodextrin sensors exhibit exceptional sensitivity and selectivity, making them ideal for a broad array of analytical tasks. The incorporation of charged functional groups into CD structures enhances host-guest interactions, leading to improved molecular recognition and binding precision, which minimizes interference from other compounds during analysis. The electrostatic charges on these sensors amplify the sensitivity by generating a stronger response signal owing to the interaction between the charged sensor and analyte. Furthermore, the tunable

surface properties of CDs allow the customization of sensors tailored to specific analytes or classes of compounds. Current research focuses on charged cyclodextrin derivatives, refining the sensor design, and integrating these sensors into portable and high-throughput detection systems. As advancements in this field continue, charged CD sensors are expected to play a crucial role in overcoming analytical challenges, reducing detection limits, broadening analytical capabilities, and enhancing the maintenance and monitoring of complex systems.

5.2. Versatility in analyte detection

The versatility of charged cyclodextrin-based sensors allows for the detection of a wide range of analytes, offering high specificity, rapid response times, and promising miniaturization capabilities. By leveraging the structural and functional diversity of cyclodextrins, particularly those enriched with various functional groups, these sensors can effectively identify and quantify a variety of molecules, including chemicals, organic contaminants, and biological species. Compared with traditional detection methods, CD-based sensors offer greater reproducibility and stability, which is crucial for reliable performance across applications. Ongoing efforts are directed toward enhancing CD sensors, developing new cyclodextrin derivatives, and optimizing molecular assembly techniques to further boost the detection efficiency and improve analytical outcomes. This versatility, combined with scalable design options, makes position-charged cyclodextrin-based sensors valuable tools in fields ranging from environmental monitoring to pharmaceutical quality control.

5. 3. Potential for development and continued use

Charged cyclodextrin-based sensors demonstrate strong potential for future advancements in multiple disciplines. The inherent ability of CDs to undergo charge transfer and support electrostatic interactions opens new avenues for creating highly selective and responsive sensing platforms tailored for various cognitive and diagnostic applications. Future developments in this area are likely to focus on designing more distinctive and durable sensors for applications in biomedical diagnostics, environmental monitoring, and drug discovery. Innovative approaches are also being explored to enhance the binding affinity and expand the range of detectable analytes by modifying CD structures and incorporating advanced delivery methods. Additionally, integrating charged CDs with advanced materials such as nanomaterials and embedding them into microfluidic devices could lead to the creation of compact, portable sensing platforms that are ideal for point-of-care diagnostics and in-field testing. The ease with which CDs can be charged, also opens up exciting possibilities for applications in smart materials and adaptive systems, with potential impacts on drug delivery control, process analysis, and beyond. As research continues to expand, new applications are anticipated, that leverage the unique properties of charged cyclodextrin-based sensors to solve complex monitoring and diagnostic challenges across diverse scientific and technological landscapes.

Conclusion

Charged cyclodextrin-based sensors offer remarkable sensitivity, selectivity, and adaptability, making them powerful tools for biosensing applications. Their unique electrostatic interactions and tunable host-guest binding properties make them well suited for the detection and analysis of a wide range of analytes, including biomolecules, pharmaceuticals, environmental pollutants, and food contaminants. These sensors demonstrate exceptional utility in applications, such as protein differentiation, amino acid detection, biomarker identification, environmental monitoring, and food safety, making them valuable assets in medical diagnostics and health monitoring. The integration of advanced materials, such as nanomaterials and microfluidics, extends the capabilities of charged CD-based sensors and facilitates rapid, precise, and noninvasive diagnostic methods. The inherent miniaturization potential of these systems further enhances their suitability for portable point-of-care devices, promoting accessibility and efficiency in clinical and environmental settings. As research advances, further innovations are anticipated in the design of durable multifunctional devices that incorporate intelligent data analytics to support real-time monitoring and early intervention strategies. Future developments will likely expand the applications of charged cyclodextrin-based sensors, enabling breakthroughs in early disease detection, environmental monitoring, and sustainable health practice. These sensors hold substantial promise for addressing critical challenges in health and environmental protection, paving the way for innovative and impactful solutions that bridge scientific research and practical applications.

Acknowledgements

The authors duly acknowledge the support from our respective institutions and co-authors of manuscripts from our group whose work has been discussed in this review article.

References and notes

1. X. Du, Y. Wang, S. Zhang *et. al.* Microscopic Screening of Cyclodextrin Channel Blockers by DiffusiOptoPhysiology *Anal. Chem.* **2021**, 93, 14161-68.
2. L. Szente, J. Szemán. Cyclodextrins in Analytical Chemistry: Host–Guest Type Molecular Recognition. *Anal. Chem.* **2013**, 85, 8024-30.
3. A. Harada, Y. Takashima, H. Yamaguchi. Cyclodextrin-based supramolecular polymers. *Chem. Soc. Rev.* **2009**, 38, 875-82.
4. M. Votava, B.J. Ravoo. Principles and applications of cyclodextrin liquid crystals. *Chem. Soc. Rev.* **2021**, 50, 10009-24.
5. M. Guitet, P. Zhang, F. Marcelo *et. al.* NHC-Capped Cyclodextrins (ICyDs): Insulated Metal Complexes, Commutable Multicoordination Sphere, and Cavity-Dependent Catalysis. *Angew. Chem. Int. Ed.* **2013**, 52, 7213-18.
6. Y. Zhao, Y. Huang, H. Zhu *et. al.* Three-in-One: Sensing, Self-Assembly, and Cascade Catalysis of Cyclodextrin Modified Gold Nanoparticles. *J. Am. Chem. Soc.* **2016**, 138, 16645-54.
7. S.V. Bhosale, S.V. Bhosale. b-Cyclodextrin as a catalyst in organic synthesis. **2007**, 4, 231-42.
8. X. Ma, Y. Zhao. Biomedical Applications of Supramolecular Systems Based on Host–Guest Interactions. *Chem. Rev.* **2015**, 115, 7794-839.
9. J. Wankar, N.G. Kotla, S. Gera *et. al.* Recent Advances in Host–Guest Self-Assembled Cyclodextrin Carriers: Implications for Responsive Drug

Delivery and Biomedical Engineering. *Adv. Funct. Mater.* **2020**, 30, 1909049.
10. J. Szejtli. Introduction and general overview of cyclodextrin chemistry. *Chem.Rev.* **1998**, 98, 1743-54.
11. K.I. Assaf, D. Gabel, W. Zimmermann, W.M. Nau. High-affinity host–guest chemistry of large-ring cyclodextrins. *Org. Biomol. Chem.* **2016**, 14, 7702-06.
12. P.K. Singh, M. Kumbhakar, H. Pal, S. Nath. Confined ultrafast torsional dynamics of Thioflavin-T in a nanocavity. *Phys. Chem. Chem. Phys.* **2011**, 13, 8008-14.
13. P.K. Singh, A.K. Mora, S. Murudkar, S. Nath. Dynamics under confinement: torsional dynamics of Auramine O in a nanocavity. *RSC Adv* **2014**, 4, 34992-5002.
14. M. Xue, Y. Yang, X. Chi *et. al.* Development of Pseudorotaxanes and Rotaxanes: From Synthesis to Stimuli-Responsive Motions to Applications. *Chem. Rev.* **2015**, 115, 7398-501.
15. J.N. Silva, A.M.G. Silva, J.P. Tomé *et. al.* Photophysical properties of a photocytotoxic fluorinated chlorin conjugated to four β-cyclodextrins. *Photochem. Photobiol. Sci.* **2008**, 7, 834-43.
16. Y. Sugita, D. Aoki, M. Tokita, H. Otsuka. Mechanochromic cyclodextrins. *Chem. Comm.* **2022**, 58, 3067-70.
17. Y.-G. Jia, J. Jin, S. Liu *et. al.* Self-Healing Hydrogels of Low Molecular Weight Poly(vinyl alcohol) Assembled by Host–Guest Recognition. *Biomacromolecules* **2018**, 19, 626-32.
18. G. Chakraborty, J.N. Malegaonkar, S.V. Bhosale *et. al.* Host-Assisted Aggregation-Induced Emission of a Tetraphenylethylene Derivative and Its Responses toward External Stimuli. *J. Phys. Chem. B.* **2021**, 125, 11122-33.
19. Z. Liu, X. Dai, Y. Sun, Y. Liu. Organic supramolecular aggregates based on water-soluble cyclodextrins and calixarenes. *Aggregate* **2020**, 1, 31-44.
20. T.P. Shaima, H.A. Mirgane, A.H. Upadhaya *et. al.* A novel approach to supramolecular Aggregation-Induced emission using tetracationic tetraphenylethylene and sulfated β-Cyclodextrin. *J. Photochem. Photobiol. A: Chem* **2024**, 448, 115328.
21. J. Kaur, D.N. Nadimetla, S.V. Bhosale, P.K. Singh. Polyanionic Cyclodextrin-Induced Supramolecular Assembly of a Cationic Tetraphenylethylene Derivative with Aggregation-Induced Emission. *J. Phys. Chem. B.* **2022**, 126, 1147-55.
22. G. Singh, V.R. Singh, S.P. Pandey, P.K. Singh. Sulfated-β-cyclodextrin templated aggregation of a metachromatic dye, Basic Orange 21: A photophysical investigation. *Supr. Chem.* **2021**, 33, 460-74.
23. J. Han, M. Won, J.H. Kim *et. al.* Cancer stem cell-targeted bio-imaging and chemotherapeutic perspective. *Chem. Soc. Rev.* **2020**, 49, 7856-78.
24. S.S. Liew, Z. Zeng, P. Cheng *et. al.* Renal-Clearable Molecular Probe for Near-Infrared Fluorescence Imaging and Urinalysis of SARS-CoV-2. *J. Am. Chem. Soc.* **2021**, 143, 18827-31.
25. A.A. Awasthi, S.P. Pandey, P.K. Singh. Supramolecular Control on the Optical Properties of a Dye-Polyelectrolyte Assembly. *ChemPhysChem* **2021**, 22, 975-84.
26. S. Bais, P.K. Singh. Al^{3+}-Responsive Ratiometric Fluorescent Sensor for Creatinine Detection: Thioflavin-T and Sulfated-β-Cyclodextrin Synergy. *ACS Appl. Bio Mater.* **2023**, 6, 4146-57.
27. A.M. Pettiwala, P.K. Singh. A supramolecular assembly enables discrimination between metalloproteins and non-metalloproteins. *Chem Commun.* **2018**, 54, 4537-40.
28. V.R. Singh, P.K. Singh. A supramolecule based fluorescence turn-on and ratiometric sensor for ATP in aqueous solution. *J. Mater. Chem. B.* **2020**, 8, 1182-90.
29. G. Chakraborty, A.K. Ray, P.K. Singh, H. Pal. A styryl based fluorogenic probe with high affinity for a cyclodextrin derivative. *Org. Biomol. Chem.* **2019**, 17, 6895-904.
30. G. Chakraborty, A.K. Ray, P.K. Singh, H. Pal. Does the degree of substitution on the cyclodextrin hosts impact their affinity towards guest binding? *Photochem. Photobiol. Sci.* **2020**, 19, 956-65.
31. P.K. Singh, S. Murudkar, A.K. Mora, S. Nath. Ultrafast torsional dynamics of Thioflavin-T in an anionic cyclodextrin cavity. *J Photochem Photobiol A: Chem.* **2015**, 298, 40-48.
32. A.M. Pettiwala, P.K. Singh. Supramolecular dye aggregate assembly enables ratiometric detection and discrimination of lysine and arginine in aqueous solution. *ACS Omega* **2017**, 2, 8779-87.
33. C. Harley, D. Rooney, C. Breslin. The selective detection of dopamine at a polypyrrole film doped with sulfonated β-cyclodextrins. *Sens Actuators B Chem.* **2010**, 150, 498-504.
34. G. Crini. Review: A History of Cyclodextrins. *Chem. Rev.* **2014**, 114, 10940-75.
35. V. Sehgal, S.P. Pandey, P.K. Singh. Prospects of charged cyclodextrins in biomedical applications. *Carbohydr. Polym.* **2024**, 323, 121348.
36. T. Loftsson, D. Duchêne. Cyclodextrins and their pharmaceutical applications. *Int. J. Pharm.* **2007**, 329, 1-11.
37. G. Singh, S.P. Pandey, P.K. Singh. Guest Binding with Sulfated Cyclodextrins: Does the Size of Cavity Matter? *ChemPhysChem* **2023**, 24, e202200421.
38. E. Schneiderman, A.M. Stalcup. Cyclodextrins: a versatile tool in separation science. *J Chromatogr B.* **2000**, 745, 83-102.
39. G. Schmid. Cyclodextrin glycosyltransferase production: yield enhancement by overexpression of cloned genes. *Trends Biotechnol.* **1989**, 7, 244-48.
40. J. Kaur, H.A. Mirgane, V.S. Patil *et. al.* Expanding the scope of self-assembled supramolecular biosensors: a highly selective and sensitive enzyme-responsive AIE-based fluorescent biosensor for trypsin detection and inhibitor screening. *J. Mat. Chem. B* **2024**, 12, 3786-96.
41. G. Singh, P.K. Singh. Complexation of a cationic pyrene derivative with sulfobutylether substituted β-cyclodextrin: Towards a stimulus-responsive supramolecular material. *J. Mol. Liq.* **2020**, 305, 112840.
42. S. Srinivasachari, K.M. Fichter, T.M. Reineke. Polycationic β-Cyclodextrin "Click Clusters": Monodisperse and Versatile Scaffolds for Nucleic Acid Delivery. *J. Am. Chem. Soc.* **2008**, 130, 4618-27.
43. J.M. Adam, D.J. Bennett, A. Bom *et. al.* Cyclodextrin-Derived Host Molecules as Reversal Agents for the Neuromuscular Blocker Rocuronium Bromide: Synthesis and Structure−Activity Relationships. *J. Med. Chem.* **2002**, 45, 1806-16.
44. G. Chakraborty, P.K. Singh, H. Pal. A cationic cyclodextrin assisted aggregation of an anionic pyrene derivative and its stimuli responsive behavior. *J. Mol. Liq.* **2021**, 321, 114499.
45. G. Singh, P.K. Singh. Stimulus-responsive supramolecular host–guest assembly of a cationic pyrene derivative with sulfated β-cyclodextrin. *Langmuir* **2019**, 35, 14628-38.
46. H.-J. Wang, H.-Y. Zhang, C. Zhang *et. al.* Supramolecular Assembly Based on Sulfato-β-cyclodextrin for Hypoxia Cell Imaging. *ACS Appl. Polym. Mater.* **2022**, 4, 2935-40.
47. T. Gu, J. Huang, Y. Yan. New opportunities for cyclodextrins in supramolecular assembly: metal organic frameworks, crystalline self-assembly, and catalyzed assembly. *Chem. Commun.* **2023**, 59, 14759-75.
48. N.H. Mudliar, P.K. Singh. Fluorescent H-Aggregates Hosted by a Charged Cyclodextrin Cavity. *Chem. Eur. J.* **2016**, 22, 7394-98.
49. P.K. Singh, M. Kumbhakar, H. Pal, S. Nath. Ultrafast Bond Twisting Dynamics in Amyloid Fibril Sensor. *J. Phys. Chem. B* **2010**, 114, 2541-46.
50. P.K. Singh, M. Kumbhakar, H. Pal, S. Nath. Viscosity Effect on the Ultrafast Bond Twisting Dynamics in an Amyloid Fibril Sensor: Thioflavin-T. *J. Phys. Chem. B* **2010**, 114, 5920-27.
51. P.K. Singh, M. Kumbhakar, H. Pal, S. Nath. Ultrafast Torsional Dynamics of Protein Binding Dye Thioflavin-T in Nanoconfined Water Pool. *J. Phys. Chem. B* **2009**, 113, 8532-38.
52. A. Srivastava, P.K. Singh, M. Kumbhakar *et. al.* Identifying the bond responsible for the fluorescence modulation in amyloid fibril sensor. *Chem. Eu. J.* **2010**, 16, 9257.
53. S. Murudkar, A.K. Mora, P.K. Singh, S. Nath. Ultrafast Molecular Rotor: An Efficient Sensor for Premelting of Natural DNA. *Chem. Commun.* **2012**, 48, 5301-03.
54. P.K. Singh, S. Nath. Ultrafast Torsional Dynamics in Nanoconfined Water Pool: Comparison between Neutral and Charged Reverse Micelles. *J. Photochem. Photobiol., A* **2012**, 248, 42-49.

55. P.K. Singh, J. Sujana, A.K. Mora, S. Nath. Probing the DNA–Ionic Liquid Interaction Using an Ultrafast Molecular Rotor. *J. Photochem. Photobiol., A* **2012**, 246, 16-22.
56. P.K. Singh, A.K. Mora, S. Nath. Ultrafast Torsional Relaxation of Thioflavin-T in Tris(pentafluoroethyl)trifluorophosphate (FAP) Anion-Based Ionic Liquids. *J. Phys. Chem. B* **2015**, 119, 14252−60.
57. P.K. Singh, A.K. Mora, S. Nath. Ultrafast Fluorescence Spectroscopy Reveals a Dominant Weakly-emissive Population of Fibril Bound Thioflavin-T. *Chem. Commun.* **2015**, 51, 14042-45.
58. S.P. Pandey, P.K. Singh. A polyelectrolyte based ratiometric optical sensor for arginine and lysine. *Sens. Actuators B: Chem.* **2020**, 303, 127182.
59. Y. Shen, Q. Zhang, X. Qian, Y. Yang. A Practical Assay for Nitrite and Nitrosothiol as an Alternative to the Griess Assay or the 2,3-Diaminonaphthalene (DAN) Assay. *Anal. Chem.* **2014**, 87, 1274-80.
60. Z. Zhou, G. Duan, Y. Wang *et. al.* A highly sensitive fluorescent probe for selective detection of cysteine/homocysteine from glutathione and its application in living cells and tissues. *New J. Chem.* **2018**, 42, 18172-81.
61. V.R. Singh, P.K. Singh. A novel supramolecule-based fluorescence turn-on and ratiometric sensor for highly selective detection of glutathione over cystein and homocystein. *Microchim. Acta* **2020**, 187, 1-9.
62. V.R. Singh, S.P. Pandey, P.K. Singh. A unique supramolecular assembly between sulfated cyclodextrin, silver and melamine: Towards a fluorescence based dual wavelength detection approach for melamine. *J Photochem Photobiol A: Chem.* **2022**, 428, 113862.
63. B. Mulloy, J. Hogwood, E. Gray *et. al.* Pharmacology of Heparin and Related Drugs. *Pharmacol. Rev.* **2016**, 68, 76.
64. B. Blossom David, J. Kallen Alexander, R. Patel Priti *et. al.* Outbreak of Adverse Reactions Associated with Contaminated Heparin. *New Eng. J. Med.* **2009**, 359, 2674-84.
65. M. Guerrini, D. Beccati, Z. Shriver *et. al.* Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events. *Nat. Biotechnol.* **2008**, 26, 669-75.
66. C. Tami, M. Puig, J.C. Reepmeyer *et. al.* Inhibition of Taq polymerase as a method for screening heparin for oversulfated contaminants. *Biomaterials* **2008**, 29, 4808-14.
67. R.B.C. Jagt, R.F. Gómez-Biagi, M. Nitz. Pattern-Based Recognition of Heparin Contaminants by an Array of Self-Assembling Fluorescent Receptors. *Angew. Chem. Int. Ed.* **2009**, 48, 1995-97.
68. P. Phillips, G. Stuber, M. Heien *et. al.* Subsecond dopamine release promotes cocaine seeking. *Nature* **2003**, 422, 614-8.
69. J. Montero, M. Mari, A. Colell *et. al.* Cholesterol and peroxidized cardiolipin in mitochondrial membrane properties, permeabilization and cell death. *Biochim Biophys Acta.* **2010**, 1797, 1217-24.
70. N. Nirala, S. Abraham, V. Kumar *et. al.* Colorimetric detection of cholesterol based on highly efficient peroxidase mimetic activity of Graphene Quantum Dots. *Sens Actuators B Chem.* **2015**, 218, 42-50.
71. V. Raj, R. Jaime, D. Astruc, K. Sreenivasan. Detection of cholesterol by digitonin conjugated gold nanoparticles. *Biosens. Bioelectron.* **2011**, 27, 197-200.
72. K. Hojo, H. Hakamata, A. Ito *et. al.* Determination of total cholesterol in serum by high-performance liquid chromatography with electrochemical detection. *J. Chromatogr. A* **2007**, 1166, 135-41.
73. A. Mondal, N.R. Jana. Fluorescent detection of cholesterol using β-cyclodextrin functionalized graphene. *Chem Commun.* **2012**, 48, 7316-18.
74. Y. Li, J. Cai, F. Liu *et. al.* Construction of a turn off-on fluorescent nanosensor for cholesterol based on fluorescence resonance energy transfer and competitive host-guest recognition. *Talanta* **2019**, 201, 82-89.
75. M. Otto. Bacterial Biofilms, Springer, **2008**; Vol. 322, .
76. U. Römling, C. Balsalobre. Biofilm infections, their resilience to therapy and innovative treatment strategies. *J. Intern. Med.* **2012**, 272, 541-61.
77. A.D. Verderosa, M. Totsika, K.E. Fairfull-Smith. Bacterial Biofilm Eradication Agents: A Current Review. *Front. Chem.* **2019**, 7, 824.
78. Y. Gao, J. Wang, M. Chai *et. al.* Size and Charge Adaptive Clustered Nanoparticles Targeting Biofilm Microenvironment for Chronic Lung Infection Management. *ACS Nano* **2020**, 14, 5686–99.
79. H. Thomsen, M. Agnes, O. Uwangue *et. al.* Increased antibiotic efficacy and noninvasive monitoring of *Staphylococcus epidermidis* biofilms using per-cysteamine-substituted γ-cyclodextrin - A delivery effect validated by fluorescence microscopy. *Int. J. Pharm.* **2020**, 587, 119646.
80. X. Yuan, C. Yang, Q. He *et. al.* Current and Perspective Diagnostic Techniques for COVID-19. *ACS Infect. Dis.* **2020**, 6, 1998-2016.
81. N. Debabhuti, S. Mukherjee, P. Sharma, et al. Development of a portable gas sensing platform with QCM sensors for volatiles of agro products. *J. Mater. Nanosci.* **2022**, 9 (2), 115–119.