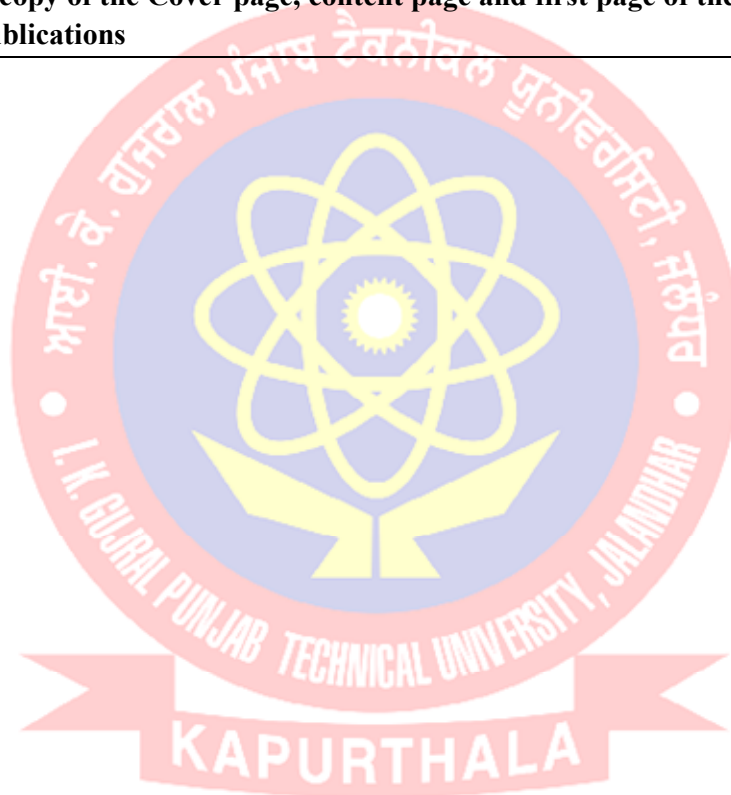


## Department: Chemical Sciences

### 3.4.6

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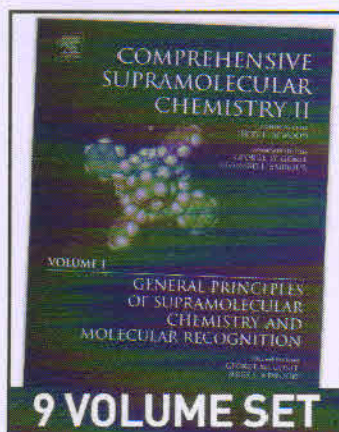


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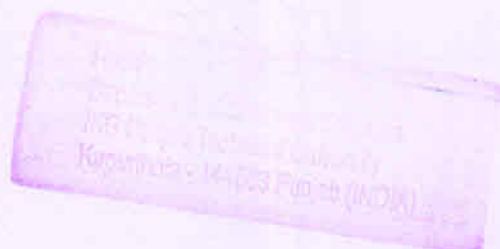
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## 8.10 Calixarene-Based Fluorescent Molecular Sensors

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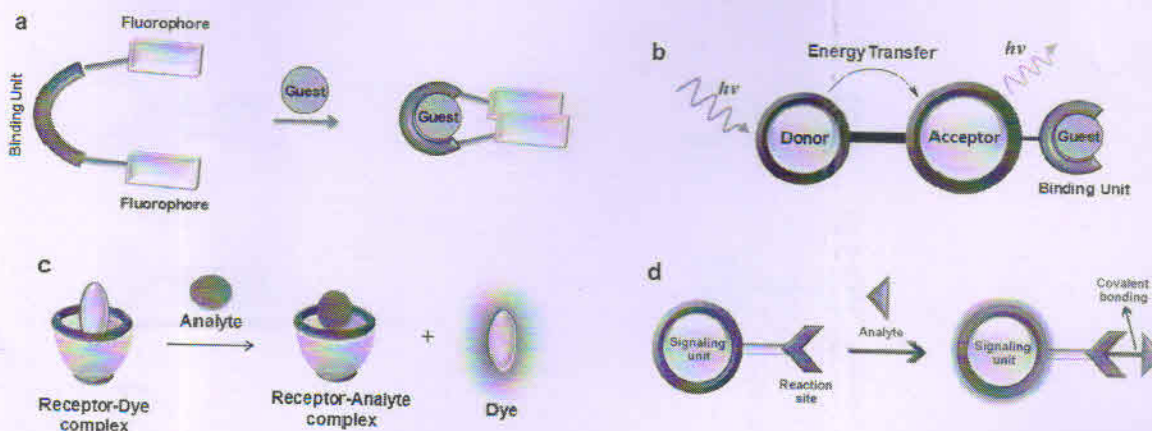
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### 8.10.1 Introduction

Calix[n]arenes ( $n=4, 6$ , and  $8$ ) are one of the synthetic molecular scaffolds, which have been widely employed in molecular recognition chemistry.<sup>1</sup> The features that make this scaffold a unique molecular system include (1) easy chemical synthesis of calix[n]arenes from reaction of *p*-tert-butylphenol and formaldehyde under basic conditions (Scheme 1A), (2) well-defined conformational preferences and hydrophobic cavities of molecular dimensions, and (3) wide possibility of chemical modifications at lower or upper rims. Therefore, calix[n]arenes can be chemically modified to work as effective host system either by adjusting their conformations or by introducing a variety of coordinating sites and signaling units. Among different types of calixarenes, special attention has been paid to calix[4]arene as it exists in four different conformations (Scheme 1B) and we can easily lock the parent scaffold in a particular conformation by chemical functionalization, which is advantageous for guest molecule coordination. For example, calix[4]arene with crown rings known as calixcrown ether has been developed where the parent scaffold is locked in 1,3-alternate conformation for the binding of alkali metal ions (Scheme 1C). Although guest coordination directly depends upon the type and number of binding sites, the calix[4]arene framework also plays an essential role, for instance, phenyl rings of calix[4]arene moiety favor cation- $\pi$  interactions.<sup>2</sup> In addition to conventional calixarenes, thiacalix[n]arenes ( $n=4, 6$ , and  $8$ ) in which sulfide bonds are introduced instead of methylene bridges (Scheme 1A) have also been utilized for the guest coordination.<sup>3</sup> The presence of bridged sulfur atoms provided thiacalix[n]arenes with more conformational flexibility and is beneficial to metal ions complexation.<sup>4–6</sup> Therefore, in recent years, a variety of fluorophores and binding sites have been incorporated within thiacalix[n]arene, particularly thiacalix[4]arene scaffold.

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**Figure 3** (A) Excimer formation, (B) energy-transfer process, (C) dye displacement, and (D) chemodosimeter-based approach.

when a fluoroionophore contains two fluorophores whose mutual distance is altered by guest inclusion. The principle of fluoroionophore based on excimer formation is given in Fig. 3A.

#### 8.10.2.4 Energy Transfer

Resonance energy transfer is a phenomenon in which a donor molecule is excited and transfers the excitation energy to an acceptor (Fig. 3B).<sup>9</sup> This energy transfer might take place either through space or through bonds. Through-space energy transfer is normally identified as Förster resonance energy transfer (FRET) and requires a spectral overlap between donor emission and acceptor absorption.

The distance between the donor and the acceptor, the spectrum overlap, and the relative orientation of the dipole moment are the factors that governs the energy-transfer efficiency, which is given by the following equation:

$$\Phi_T = \frac{1}{1 + \left(\frac{r}{R_0}\right)^6}$$

where  $r$  is donor-to-acceptor separation distance and  $R_0$  is the Förster distance of this pair of donor and acceptor, defined by

$$R_0 = 0.2108 \left[ \kappa^2 \Phi_D^0 n^{-4} \int_0^\infty I_D(\lambda) \epsilon_A(\lambda) \lambda^4 d\lambda \right]^{1/6}$$

In this equation,  $\kappa^2$  is the dipole orientation factor,  $\Phi_D^0$  is the fluorescence quantum yield of the donor,  $n$  is the refractive index of the medium,  $I_D(\lambda)$  is the normalized fluorescence spectrum of the donor,  $\epsilon(\lambda)$  represents the acceptor's molar absorption coefficient ( $\text{M}^{-1}\text{cm}^{-1}$ ), and  $\lambda$  is the wavelength (nm).

Upon complexation, the cation might affect the energy-transfer efficiency by changing the spectrum overlap or the distance between donor and acceptor groups.

#### 8.10.2.5 Fluorophore Displacement

Fluorophore displacement is another strategy in which the fluorescent indicator in an indicator-host complex is replaced by an analyte (Fig. 3C). Initially, a fluorescent indicator reversibly binds to a receptor. Afterward, that indicator is replaced by a competitive analyte and results an optical signal.<sup>10</sup> Compared with traditional approaches, the fluorescence displacement offers many advantages. Fluorescence displacement does not necessitate the covalent link between indicator and receptor and take out the difficulty of synthesis. Moreover, many different indicators might be utilized with only one receptor. Finally, this system can work very well in both organic and aqueous media.

#### 8.10.2.6 Chemodosimeter

To date, noteworthy efforts have been committed to the development of fluorescent chemodosimeters. This approach is used to selectively detect an analyte through an irreversible chemical reaction between the chemical probe and target analyte (Fig. 3D).<sup>11</sup> The host-guest interactions between chemical probe and analyte usually lead to the formation or breaking of covalent bonds instead of construction of coordination complexes. Thanks to the changes in chemical structure, chemodosimeter generally

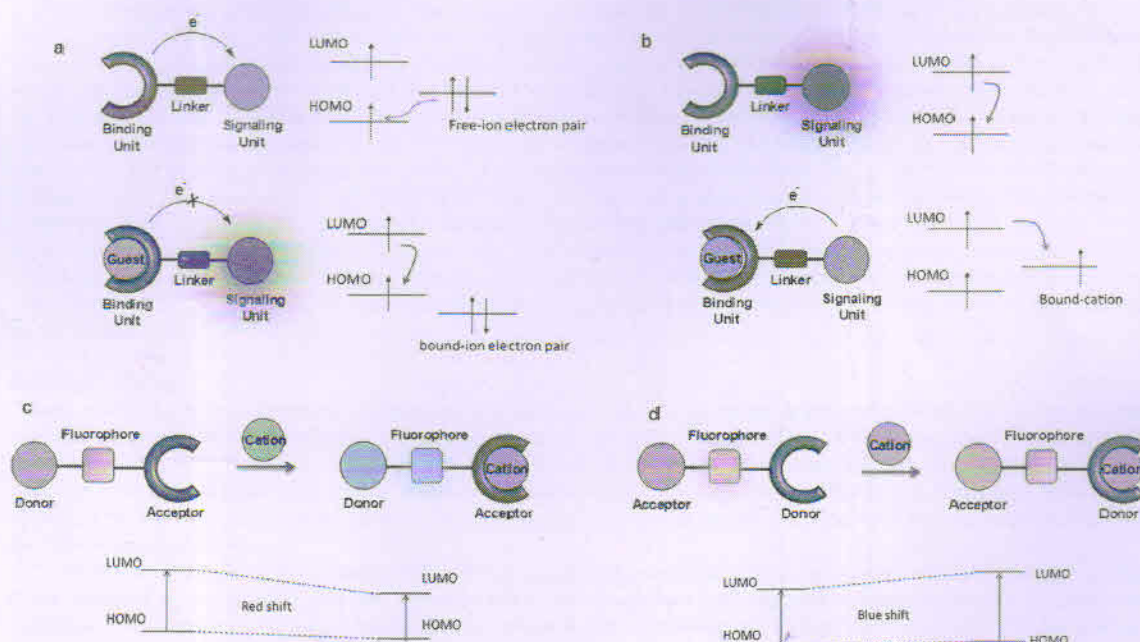


Figure 2 Photoinduced electron transfer (A, B); photoinduced charge transfer (C, D) in a fluoroionophore.

In Fig. 2A, an electron moves from the lone pair upon excitation. The formation of nonfluorescent charge-transfer species  $D^+$  induces a strong quenching. The Rehm-Weller Eq. 1 can be used to predict this effect:

$$\Delta G^0 = E_{D^+/D}^0 - E_{A/A^-}^0 - \Delta E_{00}(A) \quad (1)$$

In this equation,  $E_{D^+/D}^0$  represents ligand oxidation potential,  $E_{A/A^-}^0$  represents fluorophore reduction potential, and  $E_{00}$  represents the excitation energy.

The complexation of a guest with ligand is an example of reverse PET-based fluoroionophore, explained in Fig. 2B. The system is fluorescent without any guest; however, guest binding initiates an electron transfer from the fluorophore to guest. Electrochemical potentials of both fluorophore and guest can be employed to predict the occurrence of this effect by using Eq. 2:

$$\Delta G^0 = E_{D^+/D}^0 - E_{A/A^-}^0 - \Delta E_{00}(D) \quad (2)$$

In this equation,  $E_{D^+/D}^0$  represents fluorophore oxidation potential,  $E_{A/A^-}^0$  represents cation reduction potential, and  $E_{00}(D)$  represents the excitation energy.

### 8.10.2.2 PCT

There is an intramolecular charge transfer (ICT) upon excitation when a chemical system contains an electron-donating group conjugated to an electron-withdrawing group. Therefore, the photophysical properties of this push-pull system can be controlled by the addition of an external guest molecule (cation, anion, or neutral molecule). For example, the interaction of a cation with the electron-acceptor group enhances its electron-withdrawing power and stabilizes the excited state (Fig. 2C). As a result, the absorption and emission spectra are redshifted. Conversely, when electron-donating group interacts with a cation, it reduces its electron-donating power and destabilizes the excited state and causes expected blueshift in both absorption and emission (Fig. 2D). Nonetheless, the observed blueshift in emission is smaller as compared with absorption due to a photodisruption of the interaction between cation- and electron-donating group.

### 8.10.2.3 Excimer Formation or Disappearance

A number of fluorophores like anthracene and pyrene can form excimer (dimer in the excited state). During its lifetime in the excited state, a molecule can come close to another, and thus, an excimer fluorescence band can be observed together with the monomer fluorescence band. The recognition of a guest molecule can be examined by the ratio of monomer/excimer fluorescence intensity



Yam and coworkers developed calixarene-based bisalkynyl-bridged Au<sup>I</sup> isonitrile complexes **3a** and **3b** for the recognition of K<sup>+</sup> and Cs<sup>+</sup>, respectively. The crown-5 of **3a** favors the coordination with K<sup>+</sup> ion, while the crown-6 of **3b** is better for larger Cs<sup>+</sup> ion. In CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN (1:1, v/v), addition of ions resulted in an appearance of new low-energy bands at 350 nm in absorption and at 600 nm in emission for the two receptors. The method of continuous variation indicated a 1:1 stoichiometry for both K<sup>+</sup> and Cs<sup>+</sup> ions with **3a** and **3b**, respectively. This behavior was ascribed to the formation of Au...Au interaction upon the binding of cations in a sandwich binding mode with the biscrown units. Chemosensors **4** and **5** having the same complexing unit calix[4]arene bisazacrown and bearing merocyanine dye (DCM) or *p*-dimethylaminobenzonitrile (DMABN) as fluorophore have been reported by Valeur, Plaza, and coworkers.<sup>16,17</sup> The addition of K<sup>+</sup> ions to **4** and **5** in acetonitrile resulted in a large blueshift in absorption but a slight blueshift in fluorescence. The reason for the large hypsochromic shift in absorption was ascribed to the coordination of K<sup>+</sup> ion in the azacrown ring, reducing the PCT process from the nitrogen atom to the dicyanomethylene group. A photoinduced disruption of the interaction between the bound cation and the nitrogen atom of the crown is responsible for the small shift in emission. In the case of two different photoactive centers in chemosensor **5**, the binding of K<sup>+</sup> on the DCM site was shown to be stronger than on the DMABN site.

#### 8.10.3.1.2 Cesium

Cesium has a variety of commercial applications including petroleum exploration, solar energy to electric energy conversion, medicine therapies, or nuclear industries. However, it has also been linked to adverse effects on the environment and human health. The toxicity of cesium is related to the fact that it can substitute potassium in muscles and red cells. Radioactive cesium is responsible for serious health effects such as cancer and neurological or fetal problems. Therefore, selective and rapid detection of cesium has always been a great motivation for investigation. Different examples of optical Cs<sup>+</sup> chemosensors are described in the following paragraphs.

1,3-Alternate calix[4]arene-bis(crown-6 ether) complexing unit was shown to exhibit remarkable selectivity toward Cs<sup>+</sup>, thanks to the presence of the crown-6 ring and aromatic system of 1,3-alternate conformation favoring the cation- $\pi$  interactions.<sup>18</sup> Dabestani et al. developed calixarene-anthracene derivatives **6** and **7** for the selective detection of cesium.<sup>19</sup> The fluorescence of the free ligands **6** and **7** is weak due to the PET from the oxygen atoms of the benzocrown to the cyanoanthracene fluorophore. In CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1, v/v), the complexation with Cs<sup>+</sup> ions leads to an enhancement of fluorescence, which was attributed to the suppression of PET effect upon interaction of Cs<sup>+</sup> ion with the benzocrown. A 1:1 stoichiometry and binding constants of  $4 \times 10^6$  and  $1.2 \times 10^7$  M<sup>-1</sup> were found for **6a** and **6b**, respectively. Derivative **7** exhibited a better affinity for cesium compared with chemosensors **6a** and **6b**. Two stoichiometries 1:1 and 2:1 were observed for **7** because of the presence of two complexing units. An anticooperative effect was found with a  $K_{21}/K_{11}$  binding constant ratio smaller than 0.25 and expected if the two binding sites were independent and equivalent. This effect can be explained by an electrostatic repulsion between the two bound cations in 2:1 complex. Similar PET process was also reported in chemosensor **8** bearing an azacrown-6 as complexing unit.<sup>20</sup> Chemosensor **9** based on calixcrown ether linked with a dansyl fluorophore has been used for the sensing of Cs<sup>+</sup> and Tl<sup>+</sup> in H<sub>2</sub>O-CH<sub>3</sub>CN (1:1, v/v).<sup>21</sup>

Leray and coworkers reported fluorescent chemosensors **10**–**14** where coumarine and BODIPY were used as fluorophores along with calix[4]bis(crown-6 ether) on the 1,3-alternate conformation as coordination site for Cs<sup>+</sup>. In acetonitrile or ethanol, **10** and **11** exhibited strong fluorescence emission band at 410 nm, resulting from an ICT from the oxygen atoms of the crown to the lactone carbonyl group of the coumarine.<sup>22</sup> The addition of either K<sup>+</sup> or Cs<sup>+</sup> ions to the solution of **10** and **11** gave fluorescence quenching and a slight hypsochromic shift of fluorescence spectra. The fluorescence changes are ascribed to the reduction of ICT processes that occur between the oxygen atoms of coordinated crown and the lactone carbonyl of the coumarine. Titration experiments in ethanol proved 1:1 and 2:1 stoichiometries with association constants of  $\log K_{11} = 6.68$  and  $\log K_{21} = 3.81$ , respectively. The chemosensors showed stronger binding affinity toward Cs<sup>+</sup> as compared with K<sup>+</sup> since the Cs<sup>+</sup> is better fitting to the cavity size of crown-6 ring.

In order to develop cesium fluorescent sensor for practical applications, water-soluble chemosensor **12**<sup>23</sup> was obtained by introducing sulfonate groups onto calixarene **11**. Chemosensor **12** displayed a strong emission band at 420 nm with a high fluorescence quantum yield in MES-NaOH buffer at pH 7. The addition of Cs<sup>+</sup> ions to the solution of **12** resulted in a bathochromic shift of 10 nm in absorption and a remarkable enhancement of fluorescence. Indeed, the different responses of **12** as compared with **10** and **11** are attributed to the presence of sulfonate groups, which are in the close interaction with coordinated cesium ion through electronic interactions. This interaction increases the overall negative charge in the vicinity of crown oxygen atoms, which enhances their donating character and the efficiency of ICT process. The binding constants  $\log K_{11}$  and  $\log K_{21}$  of 7-Cs<sup>+</sup> complexes were 4.1 and 3.8, respectively. Chemosensor **12** presents an excellent selectivity toward Cs<sup>+</sup> in the presence of various interfering cations. Novel calixarenes **13** and **14** have recently been developed in the same research group by incorporating BODIPY fluorophore in order to obtain visible excited sensors for the Cs<sup>+</sup> and K<sup>+</sup> ions.<sup>24</sup> In the case of chemosensor **13**, only a small redshift was observed in both absorption and emission spectra by adding Cs<sup>+</sup> or K<sup>+</sup> ions. Conversely, in sensor **14**, the addition of these ions resulted in a significant hypsochromic shift of absorption and fluorescence spectra, accompanied by an enhancement of fluorescence emission. The reason to this difference was ascribed to the position of calixcrown complexing unit to the BODIPY core. In chemosensor **13**, the complexing unit was substituted in the *meso*-position, which interrupts the conjugation between oxygen atoms of the crown ring and the fluorophore, resulting in a small spectral variation in **13**. In contrast, a better conjugation between the fluorophore and the complexing unit of **14** linked to  $\alpha$  position to the BODIPY core is responsible for significant variations in absorption and emission spectra. These ligands exhibit a relatively high binding constant for Cs<sup>+</sup> ( $\log K_{11}$  was 5.87 and 6.09 for **13** and **14**, respectively) as compared with K<sup>+</sup>.



Kim et al. reported chemosensor 15 based on the *partial cone* conformation of calix[4]arene for the detection of either  $\text{Cs}^+$  or  $\text{F}^-$  ions.<sup>25</sup> Upon excitation at 245 nm, 15 in acetonitrile displayed an emission band at 420 nm corresponding to fluorescence resonance energy transfer (FRET) from naphthalene donor to coumarine acceptor moieties (Fig. 5). However, the efficiency of FRET was weak due to a PET process from oxygen atoms of the crown to naphthalene moiety. The coordination with  $\text{Cs}^+$  ions inhibits this PET process, leading to an increase of the FRET efficiency and enhancing the emission of coumarine fluorophore. 15 exhibits a high selectivity for  $\text{Cs}^+$  ion in the presence of various interfering cations. The addition of  $\text{F}^-$  resulted in a bathochromic shift of coumarine moiety to 535 nm attributed to a more efficient PCT process upon interaction of amide proton with  $\text{F}^-$  ions. In addition, an inhibition of FRET process was observed, leading to an enhancement of naphthalene emission at 342 nm.

#### 8.10.3.1.3 Aluminum

Aluminum is a major metal of the Earth and is the second most widely used metal after iron. However, exposure to high levels of aluminum can be linked to serious problems of the nervous system and bone. Thus, the development of systems for the detection of aluminum is important. Leray and coworkers synthesized water-soluble chemosensor 16<sup>26</sup> for  $\text{Al}^{3+}$  ions (Fig. 6) where dansyl unit fused with azacrown-5 was attached to a tetrasulfonated calix[4]arene in 1,3-*alternate* conformation. In a buffer solution at pH 6, the presence of  $\text{Al}^{3+}$  resulted in a significant blueshift in emission and a fluorescence enhancement of threefold. These changes were attributed to an aggregation-induced emission enhancement effect due to the formation of aggregates between 16 and  $\text{Al}(\text{OH})_3$  leading to a change in the microenvironmental polarity of the ICT dansyl fluorophore. 16 exhibits a high selectivity for  $\text{Al}^{3+}$  in the presence of large excess of various metal ions with a low limit of detection (1.8  $\mu\text{M}$ ).

Chemosensor 17 based on a Schiff base calixarene with 2-hydroxynaphthalene moiety as fluorophore was reported by Menon and coworkers for the detection of either  $\text{Al}^{3+}$  or  $\text{F}^-$  ions.<sup>27</sup> Free ligand 17 exhibited a weak fluorescence emission due to a PET process between the 2-hydroxynaphthalene and the imine group. The fluorescence intensity was enhanced upon the addition of  $\text{Al}^{3+}$  ions to a solution of 17 in  $\text{THF}/\text{H}_2\text{O}$  (1:1, v/v), whereas no significant change was observed in the presence of other metals. This fluorescence enhancement was ascribed to the interaction of the imine groups with  $\text{Al}^{3+}$  ions, which leads to the suppression of

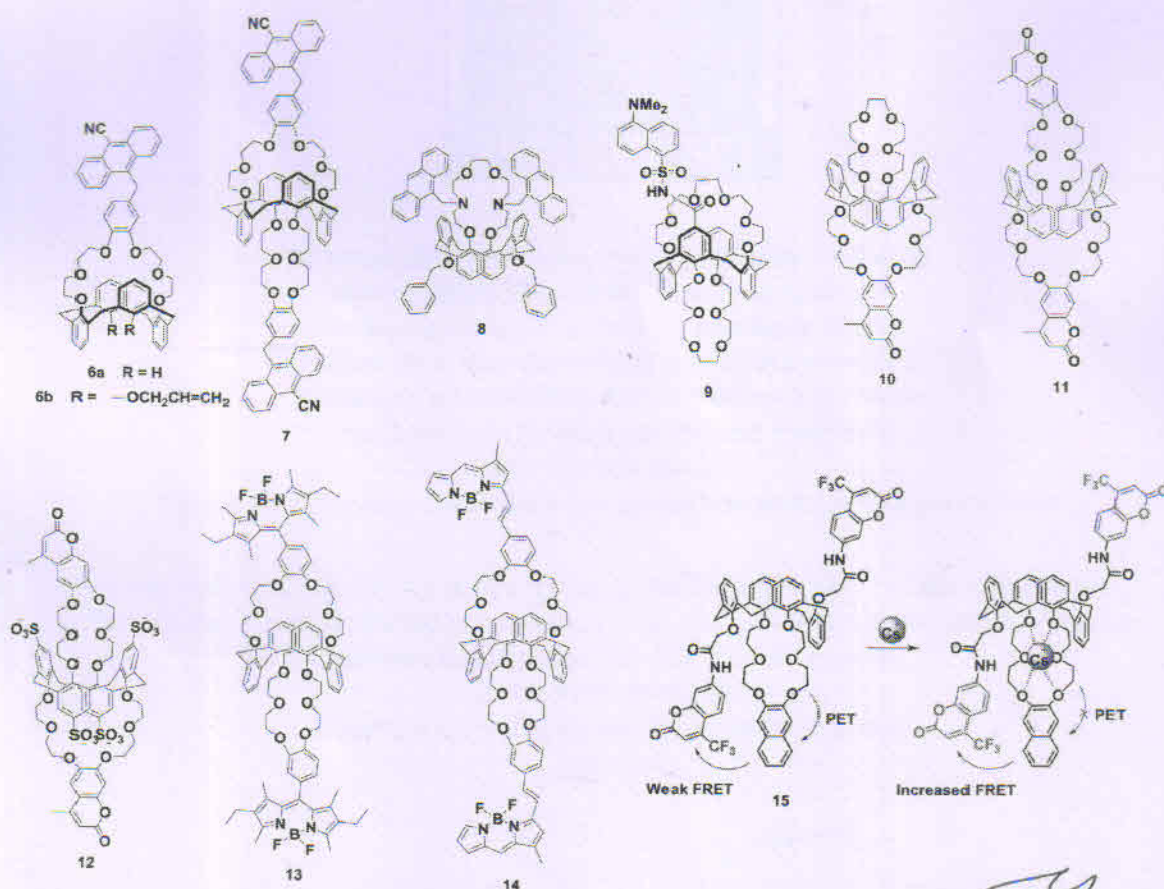


Figure 5 Structure of compounds 6–14 and  $\text{Cs}^+$ -induced FRET in 15.

## Web-link of research papers

### 3.4.6 Number of books and chapters in edited volumes published per teacher during the last five years (15)

#### 3.4.6.1: Total number of books and chapters in edited volumes / books published, and papers in national/international conference-proceedings year wise during the last five year

Sl. No.	Name of the teacher	Title of the book/chapters published	Title of the paper	Title of the proceedings of the conference	Name of the conference	National / International	Year of publication	ISBN/ISSN number of the proceeding	Affiliating Institute at the time of publication	Name of the publisher	URL
1	Dr. Roopa	Calixarene-Based Fluorescent Molecular Sensors	Comprehensive Supramolecular Chemistry II		Book chapter	International	2017	9.78013E+12	ENS Cachan, University paris Sacley	Oxford: Elsevier	<a href="https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/ejic.200900386">https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/ejic.200900386</a>

