A Review on Calixarene Fluorescent Chemosensor Agents for Various Analytes

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Abstract
Calixarenes are well-known supramolecular host molecules with versatile applications. Over the past decades, hundreds of selective and sensitive detections have been reported by employing calixarenes as the chemosensor agent. The detection and quantification of ionic species are crucial as heavy metal ions are harmful to living organisms, while monitoring anions is pivotal in environmental samples. On the other hand, detecting and quantifying biomolecules and neutral molecules are critical due to their irreplaceable role in human health. In this review, we summarized the application of calixarenes as the supramolecular chemosensor agent for detecting metal ions, anions, biomolecules, and neutral molecules through fluorescent spectroscopy. This review updates the world with the application of calixarene derivatives as fluorescent chemosensors and challenges researchers to design and develop better chemosensor agents in the future.

Keywords: chemosensor; calixarene; fluorescent; supramolecular

1. INTRODUCTION

The design and development of sensitive and selective chemosensor agents have received significant attention from researchers over several years [1]-[5]. A chemosensor agent is a chemical that can provide specific intermolecular interactions with a particular substrate or analyte, producing a detectable signal response. According to the targeted analyte, chemosensor agents can be classified into three classes, i.e., cationic, anionic, and neutral chemosensor agents [6]. Sensing of these analytes by using an optical chemosensor agent had received special attention due to its merits, such as easy sample preparation, quick response rate with high precision, and low-cost analysis [7]. Specifically, optical chemosensors are usually employed by using spectroscopic techniques such as colorimetric and fluorometric methods. Compared to the other spectroscopic techniques, colorimetric and fluorometric methods offer a simple operation with high sensitivity and can be used as a real-time analysis for a selective detection of analyte [8].

A chemosensor agent is also known as a molecular sensor or probe. Chemosensor agents can be employed in the form of a supramolecular-based compound. In this case, the non-covalent interaction between chemosensor and analyte is usually defined as the host-guest interaction [9]. Chemosensor usually contains at least two parts: the binding site (receptor) and signaling unit (detector). The receptor plays a role as the part for interacting with the analyte to induce signal change. On the other hand, the signaling unit provides a signal response change after the interaction with the analyte. The signaling unit may be composed of the chromophore (in colorimetric sensor) or fluorophore (in fluorometric sensor) [10]. The colorimetric chemosensor agent involves a sensing mechanism that leads to a naked eye color change when interacting with the analyte. Meanwhile, the fluorometric chemosensor agent works through two mechanisms, i.e., fluorescent-OFF à ON and fluorescent-ON à OFF (see Figure 1). The design and development of chemosensor agents with a suitable host-guest interaction to the specific analyte are interesting topics for several decades. Furthermore, the topic of chemosensor also includes the preparation of chemosensor agents through either organic or inorganic synthesis, optical properties, and its analytical application [11].

Chemosensor agent has been widely applied to detect and quantify cations, anions, or neutral molecules in simulated or real sample analysis. As
an example, detection and quantification of heavy metals are crucial as they are harmful to living organisms. These heavy metals are often found in polluted aquatic samples. Because of that, cation sensing gained significant attention to establish a sustainable future [12]. The detection of anions is also essential due to their important role in biological and environmental ecosystems. The presence of a certain anion in an acceptable amount can be useful in some applications but not in an excessive concentration [13]. Meanwhile, the detection of neutral molecules usually involves recognizing biomolecules such as amino acids and nucleotides [14]-[15].

Calixarene derivatives are well-known host molecules with versatile applications, including chemosensor agents [16]-[21]. Calixarenes consisted of a macrocyclic oligomer framework resulted from the condensation reaction between formaldehyde and tert-butylphenol [22]. Calixarene has a specific ring size that can be controlled by using an ion-template synthesis. The control on the ring size of calixarenes yields calix[4]arene, calix[5]arene, calix[6]arene, and calix[8]arene [23]-[24]. The conformation of the calixarene can also be controlled in various conformations such as cone, partial cone, 1,2-alternate, and 1,3-alternate [25], as shown in Figure 2. Moreover, the calixarenes can be easily modified on their upper or lower rim [26].

Calixarenes are reported to have good photoluminescence properties; thus, calixarenes have been extensively used as the chemosensor agent. Because of that, a brief review on the application of calixarenes as the fluorescent chemosensor agent is useful to give brief information about the design and development on the chemosensor field. However, the latest review article on the fluorescent chemosensor based on calixarene derivatives was published in 2013 [23]. Furthermore the application of supramolecular calixarenes as fluorescent chemosensor was not discussed in particular in the recent literature. From that report, an updated review specifically on the fluorescent chemosensor based on supramolecular calixarene derivatives has not been available yet as for today. To a certain extent, this review provides a brief update on the utilization of supramolecular-based calixarene derivatives as the fluorometric chemosensor agent for the detection of cations, anions, and neutral molecules. In the present article, we also summarized the performance of each chemosensor agent and provided a brief perspective for future research.

### 2. COLORIMETRIC AND FLUOROMETRIC DETECTIONS

Colorimetric is the simplest detection method in the chemosensor field. Colorimetric offers the naked eye investigation using a visible spectrophotometer instrument [27]. In the colorimetric method, a chemosensor should contain a chromophore group as the signaling unit. The chromophore is responsible for the color of the

![Figure 1](https://example.com/image1.png)

**Figure 1.** The general sensing mechanism of colorimetric and fluorometric chemosensor agents.
chemosensor in its free form and the specific color change after its interaction with a particular analyte. Therefore, the colorimetric method works by measuring the absorbance change after the addition of the analyte [28]. Because of that, the colorimetric method has a limitation on poor sensitivity and background interference.

In contrast, the fluorometric method is preferable for actual application due to its higher sensitivity than the colorimetric method. The fluorometric method has been widely used to detect and quantify cations, anions, or neutral molecules. The fluorometric technique uses a chemical with a fluorophore unit, in chemosensor application [29]. The fluorometric chemosensor can interact with the analyte through several sensing mechanisms such as intramolecular charge transfer (ICT), photoinduced electron transfer (PET), chelation-induced enhanced fluorescence (CHEF), chelation quenched fluorescence (CHQF), aggregation caused quenching (ACQ), and aggregation-induced emission (AIE) [30]-[35]. Schematic examples for each sensing mechanism are depicted in Figure 3. The different phenomenon leads to a different pathway to detect a certain analyte. However, detection using the fluorometric method generally can be classified into two pathways: Fluorescence OFF and Fluorescence ON. Fluorescence OFF happened when the emission intensity of the free chemosensor agent was quenched due to the addition of a certain analyte. Meanwhile, the Fluorescence ON increases the emission intensity due to the interaction between the chemosensor agent and analyte.

3. CALIXARENE FOR CATION CHEMOSENSOR

The usage of calixarenes for the detection of metal ions have been developed in recent years. For example, Xu and coworkers utilized naphtalimide-calic[4]arene (1) for selective detection of Cu$^{2+}$ ions in MeCN:H$_2$O (9:1 v/v) solvent system. Compound 1 gave the quenching phenomenon at emission wavelength ($\lambda_{em}$) of 490 nm (excitation wavelength, $\lambda_{ex} = 435$ nm) with the presence of Cu$^{2+}$. An excellent selectivity was observed over the other metal ions such as Ag$^+$, Li$^+$, Na$^+$, K$^+$, Rb$^+$, Cs$^+$, Ca$^{2+}$, Cd$^{2+}$, Co$^{2+}$, Hg$^{2+}$, Mg$^{2+}$, Mn$^{2+}$, Ni$^{2+}$, Pb$^{2+}$, and Zn$^{2+}$, which was remarkable. The oxygen atoms of calixarene and nitrogen atoms of naphthalimide are responsible for Cu$^{2+}$ binding, generating a 1:1 complex with an association constant ($K_a$) of $2.9 \times 10^4$ M$^{-1}$ [36].

Wang and coworkers employed a pyrene-modified calix[4]arene (2) for selective detection of Na$^+$ cation in DMSO:MeCN (1:9 v/v). When the calixarene 2 was excited at 343 nm, its excimer emission signal at 477 nm was quenched, while the monomer emission signal at 375 nm was increased with the presence of Na$^+$. In contrast, the emission signal was not significantly changed by the addition of the other metal ions such as Li$^+$, K$^+$, Cs$^+$, Mg$^{2+}$, Ca$^{2+}$, Sr$^{2+}$, and Ba$^{2+}$. This excellent selectivity was caused by the presence of four carbonyls of ester functional group encapsulated the Na$^+$ ions in an ionophoric cavity. The complexation happened on the calixarene 2 lower rim, thus affecting the pyrene moieties on the upper rim. Calixarene 2 acted as a molecular tweezer with an on-off mechanism controlled with Na$^+$ ions. Initially, the pyrene moieties overlapped through $\pi-\pi$ stacking, thus
generating an excimer emission signal at 477 nm. In contrast, complexation with Na\(^+\) ions at the lower rim of calixarene 2 forced the pyrenes to stay away from each other; thus, the excimer emission signal was quenched, but the monomer emission signal was activated. The calixarene 2 formed a 1:1 complex with Na\(^+\) ions giving a \(K_a\) value of 2.2 \(\times\) 10\(^3\) M\(^{-1}\) \([37]\).

Dinda and coworkers used the nitrobenzoxadiazole appended calix[4]arene derivative (3) for selective recognition of trivalent metal ions, i.e., Cr\(^{3+}\), Fe\(^{3+}\), and Al\(^{3+}\). The detection of these trivalent metal ions occurred through a fluorescence ON as the fluorescence quantum yield of calixarene 3 was significantly enhanced after the addition of metal ions. The calixarene 3 had a low emission intensity at 550 nm (\(\lambda_{ex} = 470\) nm); however, the addition of M\(^{3+}\) increased its fluorescence intensity in a 4-fold increment of quantum yield. This phenomenon happened because of chelation enhanced fluorescence intensity between calixarene 3 and metal ions. From the spectroscopic study, the M\(^{3+}\) ions interacted with benzofurazan rings, amide oxygens, and phenoxy oxygen atoms of calixarene 3. The \(K_a\) value of this chelation was 1.0 \(\times\) 10\(^4\) M\(^{-1}\) suggesting a moderate strength complexation. The sensitivity of calixarene 3 was shown from a low limit detection (LoD) value (5 \(\mu\)M). The formed complex between calixarene 3 and M\(^{3+}\) ions was reversible by the addition of H\(_2\)PO\(_4\)\(^-\). Therefore, this chemosensor agent can be reused for the detection and quantification of these trivalent metal ions. Furthermore, a real application of calixarene 3 for the detection of M\(^{3+}\) ions was also established within MCF-7 cells \([38]\).

Zhan and coworkers used the anthraquinone-calix[4]arene (4) for selective detection of Ca\(^{2+}\) ions. The selective detection of Ca\(^{2+}\) ions was found over the other metal ions such as Ag\(^+\), Na\(^+\), K\(^+\), Li\(^+\), Cs\(^+\), Mg\(^{2+}\), Sr\(^{2+}\), Ba\(^{2+}\), Cu\(^{2+}\), Cd\(^{2+}\), Ni\(^{2+}\), Mn\(^{2+}\), Co\(^{2+}\), and Zn\(^{2+}\). The sensing method was performed in acetonitrile media, and it was found that the interaction between calixarene 4 and Ca\(^{2+}\) ions...
increased the emission intensity at 510 nm ($\lambda_{\text{ex}} = 390$ nm). The addition of Ca$^{2+}$ ions at various concentrations gradually increased its fluorescence intensity yielding a LoD value of 50 µM. The fluorescence ON phenomenon was generated from a 1:1 complexation reaction between calixarene 4 and Ca$^{2+}$ with a $K_a$ value of $1.2 \times 10^4$ M$^{-1}$. The Ca$^{2+}$ ions bind to the nitrogen atoms of triazole in calixarene 4, leading to a restriction of the PET and an increase in emission intensity [39].

Li and coworkers employed calixarene 5 for the detection of Fe$^{3+}$ and Cu$^{2+}$ ions in H$_2$O:MeOH (1:1 v/v) media. The fluorescence intensity of calixarene 5 was significantly quenched by the addition of Fe$^{3+}$ and Cu$^{2+}$ ions. Meanwhile, the addition of other metal ions such as Co$^{2+}$, Ni$^{2+}$, Zn$^{2+}$, Mn$^{2+}$, Mg$^{2+}$, and Ba$^{2+}$ did not significantly change the fluorescence intensity of calixarene 5. The calixarene 5 formed a 1:1 complex structure with either Fe$^{3+}$ or Cu$^{2+}$ ions only at a low concentration.

**Figure 4.** Chemical structures of calixarene-based chemosensor agents 1–10 for cations sensing.
Table 1. Performance of calixarene-based chemosensor agents for cation sensing.

| Calixarene | Sensing media | LoD (nM) | $K_a$ (M$^{-1}$) | Analyte | Reference |
|------------|---------------|----------|----------------|---------|-----------|
| 1          | MeCN:H$_2$O (9:1 v/v) | n/a      | $2.9 \times 10^4$ | Cu$^{2+}$ | [36]      |
| 2          | DMSO:MeCN (1:9 v/v) | n/a      | $2.2 \times 10^3$ | Na$^+$  | [37]      |
| 3          | n/a           | 5,000    | $1.0 \times 10^4$ | Cr$^{3+}$, Fe$^{3+}$, and Al$^{3+}$ | [38] |
| 4          | MeCN          | 50,000   | $1.2 \times 10^4$ | Ca$^{2+}$ | [39]      |
| 5          | H$_2$O:MeOH (1:1 v/v) | n/a      | n/a              | Fe$^{3+}$ and Cu$^{2+}$ | [40] |
| 6          | MeCN:CHCl$_3$ (1000:4 v/v) | n/a      | $1.6 \times 10^4$ | Cu$^{2+}$ | [41]      |
| 7          | H$_2$O:MeCN (1:1 v/v) | n/a      | n/a              | Hg$^{2+}$ | [42]      |
| 8          | MeOH          | 0.69     | n/a              | Zn$^{2+}$ | [43]      |
| 9          | n/a           | 490      | $3.7 \times 10^4$ | La$^{3+}$ | [44]      |
| 10         | DCM:MeCN (1:1 v/v) | 490      | n/a              | Pb$^{2+}$ | [45]      |

* n/a: not available

(less than 1 µM). At a higher concentration of the metal ions lead to the formation of a different complex stoichiometry. This phenomenon in fluorescence quenching was also highly related to the pH value of the aqueous media [40].

Chang and coworkers used the modified calix[4]arene with anthracene-isoxazolymethyl group (6) at the lower rim for the detection of Cu$^{2+}$ ions. The calixarene 6 showed two emission peaks at 511 nm (excimer) and 430 nm (monomer) with the $\lambda_{ex}$ of 375 nm. The calixarene 6 showed selectivity and sensitivity in the detection of Cu$^{2+}$ in CH$_3$CN:CHCl$_3$ (1000:4, v/v) solvent system, through coordination with isoxazole moieties. The selectivity was compared to the 14 metal ions including Ag$^+$, Li$^+$, Na$^+$, K$^+$, Mg$^{2+}$, Ca$^{2+}$, Ba$^{2+}$, Pb$^{2+}$, Hg$^{2+}$, Cd$^{2+}$, Ni$^{2+}$, Mn$^{2+}$, Zn$^{2+}$, and Cr$^{3+}$. The fluorescence emission intensity was quenched only with the addition of Cu$^{2+}$ ions, while the other cations did not significantly change the fluorescence spectra of the free ligand. The calixarene 6 formed complex with Cu$^{2+}$ with a 1:1 ratio with a $K_a$ value of $1.6 \times 10^4$ M$^{-1}$ [41].

Arena and coworkers utilized calix[4]arene bearing N-(phenyl)sulfonylcarboxamide (7) for selective detection of Hg$^{2+}$ ions in H$_2$O:MeCN (1:1 v/v) media. The presence of Hg$^{2+}$ ions quenched the fluorescence intensity of calixarene 7. The sensing mechanism occurred through the Turn-OFF fluorescence at $\lambda_{em}$ of 312 nm ($\lambda_{ex} = 273$ nm). The calixarene 7 showed high selectivity for Hg$^{2+}$ ions over the other heavy metal ions such as Pb$^{2+}$ and Cd$^{2+}$. Unfortunately, the sensitivity for Hg$^{2+}$ detection has not been evaluated yet [42].

Joseph and coworkers investigated the application of calix[4]arene 8 to detect Zn$^{2+}$ ions. The calixarene 8 showed an excellent sensitivity for Zn$^{2+}$ ions with the LoD value of 0.69 nM in methanol media, which was remarkable. The emission intensity of calixarene 8 at 380–620 nm ($\lambda_{ex} = 370$ nm) was significantly increased by the presence of Zn$^{2+}$ ions. Additionally, calixarene 8 also exhibited good selectivity for the detection of Zn$^{2+}$ ions. The addition of the other metal ions such as Na$^+$, K$^+$, Mn$^{2+}$, Co$^{2+}$, Ca$^{2+}$, Mg$^{2+}$, and Cd$^{2+}$ did not significantly change the emission intensity of calixarene 8. The addition of these metal ions gave a negligible interference for Zn$^{2+}$ detection, indicating a good selectivity. The Fluorescence turn-ON phenomenon happened due to the binding of Zn$^{2+}$ to the imine and phenolic moieties of calixarene 8 blocking the PET to the salicylyl moiety [43].

Mummidivarapu and coworkers employed a calix[6]arene with triazole linked picolinamide conjugate (9) for the detection of La$^{3+}$ ions. Calixarene 9 showed a selective and sensitive detection for La$^{3+}$ ions with a LoD value of 490 nM. The sensing mechanism happened through fluorescence turn-ON on the emission intensity of 450 nm ($\lambda_{ex} = 330$ nm). The addition of the other trivalent metal ions such as Pr$^{3+}$, Nd$^{3+}$, Sm$^{3+}$, Eu$^{3+}$,
Gd\^{3+}, Dy\^{3+}, and Ho\^{3+} did not significantly increase the emission intensity. Calixarene 9 complexed with La\^{3+} ions with a $K_a$ value of $3.7 \times 10^4$ M$^{-1}$. In this case, the imino-phenolic and the pyridyl moieties play an important role in binding with La\^{3+} ions. Complex formation between calixarene 9 and La\^{3+} ions triggered the inhibition of imine isomerization and excited-state proton transfer (ESPT), leading to an increase in the fluorescence emission [44].

Kumar and coworkers applied the pyrene-appended calix[4]arenes derivative (10) for the fluorometric detection of Pb\(^{2+}\) ions in DCM:MeCN (1:1 v/v) media. Calixarene 10 exhibited excellent sensitivity and selectivity for detecting Pb\(^{2+}\) ions at $\lambda_{em}$ of 498 nm ($\lambda_{ex} = 350$ nm). By addition of Pb\(^{2+}\) ions, the fluorescence intensity increased, indicating the binding of Pb\(^{2+}\) ions.

**Figure 5.** Chemical structures of calixarene-based chemosensor agents 11–19 for anions sensing.
ions, the excimer emission intensity of calixarene 10 at 498 nm was gradually quenched, with a gradual increment of emission signal at 415 nm. This hypsochromic shifting was attributed to the deprotonation of phenolic groups of calixarene 10. The addition of other metal ions such as Ag\(^{+}\), Li\(^{+}\), Na\(^{+}\), K\(^{+}\), Zn\(^{2+}\), and Hg\(^{2+}\) (in perchlorate salts) gave no significant fluorescence change for calixarene 10. Calixarene 10 gave a LoD value for detecting Pb\(^{2+}\) as low as 490 nM as calculated from the ratiometric plot of I\(_{415}/I_{498}\). Calixarene 10 formed a 1:1 complex with Pb\(^{2+}\) ions through the imino group, causing an ICT from pyrene to the imino groups [45].

4. CALIXARENE FOR ANION CHEMOSensor

Uttam and coworkers employed a calix[4]arene conjugated with 1,3-dibenzooxadiazole (11) for the detection of fluoride anion (F\(^{-}\)) in tetrahydrofuran (THF) solvent. Calixarene 11 could selectively detect F\(^{-}\) anion over 15 other anions such as bromide (Br\(^{-}\)), chloride (Cl\(^{-}\)), iodide (I\(^{-}\)), azide (N\(_{3}^{-}\)), thiocyanate (SCN\(^{-}\)), bicarbonate (HCO\(_{3}^{-}\)), dihydrogen phosphate (H\(_{2}\)PO\(_{4}^{-}\)), carbonate (CO\(_{3}^{2-}\)), nitrite (NO\(_{2}^{-}\)), nitrate (NO\(_{3}^{-}\)), sulfate (SO\(_{4}^{2-}\)), pyrophosphate (P\(_{2}\)O\(_{7}^{5-}\)), perchlorate (ClO\(_{4}^{-}\)), and bisulfate (HSO\(_{4}^{-}\)). Calixarene 11 also exhibited a sensitive detection of F\(^{-}\) with a LoD value of 100 nM. In the detection of F\(^{-}\) ions using calixarene 11, a 1:1 complex structure was formed with a \(K_a\) value of \(1.6 \times 10^3\) M\(^{-1}\); thus, the \(\lambda_{em}\) at 520 nm (\(\lambda_{ex} = 460\) nm) was significantly quenched. From the experimental-NMR and computational-density functional theory (DFT) studies, it was found that the F\(^{-}\) ion was coordinated through extended hydrogen bonds with dibenzooxadiazole and phenoxy oxygen atoms of calixarene 11. These chelations became the reason for such excellent selectivity of F\(^{-}\) ions complexation and sensing. The chemosensor 11 offered good reusability as it can be decomplexed by the addition of Ca\(^{2+}\) ions with still good sensing capability even at 10 cycle sensing. Furthermore, a biological application for detecting F\(^{-}\) ions in the HeLa cells was also performed. The results demonstrated that calixarene 11 exhibited great application in the THF media as well as in HeLa cells [46].

Hosseinzadeh and coworkers used the ferrocene-triazole-amide functionalized calix[4]arene (12) for the detection of F\(^{-}\) in MeCN:DCM (1:1 v/v) media. Calixarene 12 showed a selective and sensitive detection of F\(^{-}\) anion compared to the other anion including acetate (AcO\(^{-}\)), Cl\(^{-}\), Br\(^{-}\), ClO\(_{4}^{-}\), NO\(_{3}^{-}\), H\(_{2}\)PO\(_{4}^{-}\), and HSO\(_{4}^{-}\). The selectivity of calixarene 12 was shown from the enhancement in fluorescence emission intensity at 418 nm (\(\lambda_{ex} = 290\) nm). In addition, the LoD value for F\(^{-}\) detection was 2.98 \(\mu\)M. The extended hydrogen bonds between F\(^{-}\) ions and amide and triazole protons of calixarene 12 corresponded to the

Table 2. Performance of calixarene-based chemosensor agents for anion sensing.

| Calixarene | Sensing media | LoD (nM) | \(K_a\) (M\(^{-1}\)) | Analyte | References |
|------------|--------------|----------|----------------|--------|------------|
| 11         | THF          | 100      | 1.6 \times 10^3 | F\(^{-}\) | [46]       |
| 12         | MeCN:CH\(_2\)Cl\(_2\) (1:1 v/v) | 2,980    | 5.35 \times 10^8 | F\(^{-}\) | [47]       |
| 13         | MeOH         | 5,000    | 1.49 \times 10^4 | \(\Gamma\) | [48]       |
| 14         | n/a          | 4,500    | 15.6 \times 10^2 | \(\Gamma\) | [49]       |
| 15         | MeCN:CHCl\(_3\) (99.6:0.4 v/v) | n/a      | n/a               | F\(^{-}\) | [50]       |
| 16         | n/a          | n/a      | n/a               | H\(_3\)PO\(_4\)^{-}, F\(^{-}\), and AcO\(^{-}\) | [51]       |
| 17         | MeCN:H\(_2\)O (7:3 v/v) | 1,260    | n/a               | CN\(^{-}\) | [52]       |
| 18         | MeCN:H\(_2\)O (8:2 v/v) | 350      | n/a               | S\(_2\)\(^{2-}\) | [53]       |
| 19         | THF:H\(_2\)O (7:3 v/v) | 164      | n/a               | \(\Gamma\) | [54]       |

* n/a: not available

\*LoD: Limit of Detection
binding site in the sensing mechanism, as revealed by the NMR titration study. The calixarene 12 and F\(^-\) ions formed a 1:2 complex structure with a \(K_a\) value of \(5.4 \times 10^8\). The complexation was formed through the hydrogen bond between F\(^-\) from both amide and triazole protons in calixarene 12 [47].

Gómez-Machuca and coworkers synthesized a calix[4]arenes with azolyl moieties (13) for the detection of I\(^-\) anion in MeOH. Calixarene 13 gave both sensitive and selective detection of I\(^-\) compared to the other anions (F\(^-\), HSO\(_4^-\), N\(_3^-\), NO\(_2^-\), NO\(_3^-\), SCN\(^-\), ClO\(_4^-\), Br\(^-\), CN\(^-\), Cl\(^-\), CH\(_3\)CO\(_2^-\), CF\(_3\)SO\(_3^-\)). The tetrabutylammonium salts were used to avoid any cationic complexation with calixarene 13. In addition, calixarene 13 gave a quenching response at \(\lambda_{em}\) of 330 nm (\(\lambda_{ex} = 225\) nm) by the addition of I\(^-\) anion yielding a LoD value of 5 µM. Calixarene 13 formed a 1:1 complex with I\(^-\) ion through hydrogen bonds with a \(K_a\) value of 1.5 \(\times 10^{-4}\) M\(^{-1}\). From the NMR titration study, the signal of N-H amide and Ar-H of benzoxazole moieties changed clearly. The N-H signal was shifted to a higher chemical shift due to an extended hydrogen bond with I\(^-\) ions. Meanwhile, the changed Ar-H benzoxazole signals occurred due to the fixed and rigid structure of benzoxazole substituents after I\(^-\) complexation reaction [48].

Memon and coworkers utilized a calix[4]arene bearing naphtyylimino moiety (14) for sensitive and selective detection of Au\(^{3+}\) cation and I\(^-\) anion. The fluorescence response in the detection of both ions occurred through a quenching phenomenon at its emission intensity at \(\lambda_{em}\) 360 nm (\(\lambda_{ex} = 330\) nm). The LoD value for the detection of Au\(^{3+}\) and I\(^-\) were 15 and 4.5 µM respectively. The quenching response was due to a 1:1 complexation reaction between calixarene 14 and either Au\(^{3+}\) or I\(^-\) which gave a \(K_a\) value of \(8 \times 10^2\) or \(16 \times 10^2\) M\(^{-1}\), respectively. The imine (C=N), amide carbonyl (C=O), and hydroxyl functional groups were important in the Au\(^{3+}\) sensing. Meanwhile, the hydroxyl and amide nitrogen atoms of calixarene 14 interacted with I\(^-\) anion through the extended hydrogen bonds [49].

Miao and coworkers applied a calix[4]arene with diaminoanthracene group (15) for the detection of AcO\(^-\) in MeCN:CHCl\(_3\) (99.6:0.4 v/v). The tetrabutylammonium salts were used to avoid any cationic complexation with calixarene 15. Calixarene 15 can selectively detect AcO\(^-\) over the other anions such as Cl\(^-\), Br\(^-\), I\(^-\), NO\(_3^-\), HSO\(_4^-\), and H\(_2\)PO\(_4^-\). The addition of AcO\(^-\) to calixarene 15 yielded a quenching of emission signal at \(\lambda_{em}\) 438 nm (\(\lambda_{ex} = 370\) nm). The quenching happened through a free PET process between calixarene 15 and AcO\(^-\) anion. Meanwhile, no spectral changes were observed by the addition of other anions. Furthermore, the detection of AcO\(^-\) occurred through hydrogen bonds between -NH and 9-H of anthracene as confirmed from the \(^1\)H-NMR titration

![Figure 6. Chemical structures of calixarene-based chemosensor agents on 20–26 for neutral molecules sensing.](image-url)
Hung and coworkers prepared a calix[4]arene owing to pyrenylacetamide functional group (16) for the detection of $\text{H}_2\text{PO}_4^−$, $\text{F}^−$, and AcO$^−$ anions. Three different binding modes were observed for these anions. Static excimer with large and small charge transfer occurred for $\text{F}^−$ and AcO$^−$ anions, respectively. Meanwhile, an increment in monomer emission of calixarene 16 happened for $\text{H}_2\text{PO}_4^−$ sensing. The dynamic excimer emission of calixarene 16 ($\lambda_{\text{em}} = 482 \text{ nm}$) was quenched by the addition of $\text{F}^−$ at a low concentration. However, in an excess concentration of $\text{F}^−$, the emission signal at 472 nm was increased significantly. This phenomenon was caused by the formation of a strong extended hydrogen bond between $\text{F}^−$ and calixarene 16 through its amide group, leading to a generation of pyrene dimers. On the other hand, $\text{H}_2\text{PO}_4^−$ sensing showed an opposite mechanism as the monomer emission at 472 nm was enhanced, but the excimer emission at 482 nm was decreased [51].

Chawla and coworkers investigated the application of calix[4]arene bearing quinoline moiety (17) for the detection of $\text{Cu}^{2+}$ and $\text{CN}^−$ ions in MeCN:HO$_2$ (7:3 v/v) media. Calixarene 17 could selectively detect $\text{Cu}^{2+}$ over the other metal ions such as $\text{Zn}^{2+}$, $\text{Pb}^{2+}$, $\text{Co}^{2+}$, $\text{Ni}^{2+}$, $\text{Na}^+$, $\text{Li}^+$, $\text{Fe}^{3+}$, $\text{Hg}^{2+}$, $\text{Cd}^{2+}$, $\text{K}^+$, $\text{Mn}^{2+}$, and $\text{Ag}^+$. The addition of $\text{Cu}^{2+}$ leads to a significant quenching at $\lambda_{\text{em}}$ of 405 nm ($\lambda_{\text{ex}} = 315 \text{ nm}$) of calixarene 17. The sensitivity of calixarene 17 for $\text{Cu}^{2+}$ detection was shown by its LoD value as low as 0.4 µM. Interestingly, the addition of $\text{Cu}^{2+}$ followed by $\text{CN}^−$ ion leads to a gradual increment of emission signal at 405 nm. It means that the calixarene 17 could also be used for the detection of $\text{CN}^−$ through the formation of $\text{Cu}^{2+}$-calixarene 17 complex. The LoD value for $\text{CN}^−$ detection was 1.26 µM. Furthermore, a selective detection for $\text{CN}^−$ was achieved over $\text{F}^−$, $\text{Cl}^−$, $\text{Br}^−$, $\Gamma$, $\text{S}^{2−}$, $\text{AcO}^−$, $\text{CO}_3^{2−}$, $\text{HSO}_4^−$, and $\text{H}_2\text{PO}_4^−$. The $\text{CN}^−$ detection was stable in a pH region of 6–8. Lower pH value protonated quinoline nitrogen atoms while higher pH value formed a hydroxide complex of $[\text{Cu(OH)}_n]^{(2-m)+}$. The selectivity of $\text{Cu}^{2+}$-calixarene 17 complex for $\text{CN}^−$ detection happened as the $\text{Cu}^{2+}$ ion itself was able to form a very stable metal complex with $\text{CN}^−$ anion. Additionally, the chelation of calixarene 17 aided in locking the $\text{CN}^−$ anion through extended hydrogen bonds with quinoline and amide nitrogen atoms, thus providing an excellent sensing site for $\text{CN}^−$ anion [52]. These results are useful for developing a dual-response chemosensor agent for the detection of cation and anion with high selectivity and sensitivity.

Ramachandran and coworkers designed calix[4]arene 18 for the detection of $\text{Cu}^{2+}$ and $\text{S}^{2−}$ ion in MeCN:H$_2$O (8:2 v/v) media. Free calixarene 18 showed a photoluminescence property at $\lambda_{\text{em}}$ of 637 nm ($\lambda_{\text{ex}} = 457 \text{ nm}$). The addition of $\text{Cu}^{2+}$ led to a gradual quenching by increasing $\text{Cu}^{2+}$ concentration. The LoD value of $\text{Cu}^{2+}$ was 4.11 µM, with a $K_a$ value of $2.3 \times 10^4 \text{ M}$. Calixarene 18 showed a high selectivity for $\text{Cu}^{2+}$ detection.
compared to the other cations such as Na⁺, Ag⁺, Fe²⁺, Hg²⁺, Mg²⁺, Mn²⁺, Ni²⁺, Pb²⁺, Zn²⁺, Ca²⁺, Co²⁺, Fe³⁺, and Al³⁺. For anion sensing, the Cu²⁺-calixarene 18 complex showed a selective detection of S²⁻ anion over the other anions (AcO⁻, CN⁻, CO₃²⁻, F⁻, HPO₄²⁻, HSO₄⁻, NO₂⁻, NO₃⁻, HO⁻, and SO₄²⁻), which was remarkable. The detection limit of S²⁻ was estimated to be 0.35 μM [53].

Xie and coworkers employed the hexahomotrioxacalix[3]arene (19) for the detection of I⁻ in a THF:H₂O mixture (7:3 v/v). Calixarene 19 was found to be a selective and sensitive chemosensor agent for the detection of I⁻ ion. Calixarene 19 showed a high emission intensity at 484 nm (λₑₓ = 346 nm). The presence of I⁻ ion leads to a significant quenching at this emission intensity compared to the other anions such as F⁻, Cl⁻, Br⁻, AcO⁻, SO₃²⁻, SO₄²⁻, HSO₄⁻, NO₂⁻, NO₃⁻, and CO₃²⁻. The binding mechanism for I⁻ sensing occurred due to the hydrogen amide group of calixarene 19 to form the extended hydrogen bonds with a Kᵣ value of 2.5 × 10⁵ M⁻¹. The fluorescence titration study showed that the addition of I⁻ at higher concentration leads to a gradual decrease in emission signal at 484 nm yielding a LoD value of 164 nM. The sensitivity of I⁻ was better than using atomic absorption spectroscopy or chromatography, which was remarkable. Furthermore, the I⁻ sensing was satisfying over a broad range pH value of 2-11 [54].

5. CALIXARENE FOR NEUTRAL MOLECULE CHEMOSensor

Detection of neutral analyte is also pivotal as carnitine, nucleoside triphosphate, dopamine, tryptophan, and other biomolecules are essential in the metabolism system, and genetic expression [55]. On the other side, organic molecules such as nitroaromatic and polyaromatic hydrocarbons are also critical to be monitored due to their carcinogenic and explosive properties. Barata and coworkers used the calix[4]arene-modified carbazole polymer (20) for the sensor of the nitroaromatic explosive compounds in CHCl₃ media. Calixarene 20 showed high sensitivity towards nitroaromatic compounds such as picric acid (PA), 2,4,6-trinitrotoluene (TNT), 2,4-dinitrotoluene (DNT), and nitrobenzene (NB). The emission signal of calixarene 20 at 430 nm (λₑₓ = 360 nm) was gradually quenched by the addition of these nitroaromatic compounds at a higher concentration. Calixarene 20 exhibited the highest sensitivity for TNT detection. The sensitivity of calixarene 20 was shown from the LoD value of 3.49, 26.4, 52.7, 107 μM for PA, TNT, DNT, and NB, respectively. The PET mechanism caused the quenching phenomenon as the ligand has a conjugated electron system (electron-rich) and nitroaromatic as an electron-deficient compound [56].

Xu and coworkers employed a calix[4]arene modified bithiophene (21) for the detection of amino acids in water. Calixarene 21 gave a response for acidic amino acids, i.e., aspartic acid (Asp) and glutamic acid (Glu), through a fluorescence quenching phenomenon at λₑₘ of 566 nm (λₑₓ = 400 nm). On the other hand, calixarene 21 gave a response for basic amino acids, i.e., lysine (Lys) and arginine (Arg), through a fluorescence ON at the same λₑₘ. These responses were selective over the other amino acids. Although a quantitative detection of amino acids using calixarene 21 has not been further studied, calixarene 21 showed a moderately strong complexation with Kₑ value of 7.9 × 10¹⁴ M⁻¹, 1.4 × 10⁵ M⁻¹, 3.5 × 10⁵ M⁻¹, and 8.1 × 10⁵ M⁻¹ for Asp, Glu, Lys, and Arg, respectively [57].

Qing and coworkers investigated a calix[4]arenes bearing L-tryptophan unit (22) for the detection of amino alcohol compounds in MeCN. Calixarene 22 showed a weak emission signal at 456 nm (λₑₓ = 368 nm). The addition of phenylglycinol and phenylalaninol to the calixarene 22 significantly increased the emission signal due to π–π stacking interactions. The Kₑ value of the complex between calixarene 22 with phenylglycinol and phenylalaninol was found to be 5.6 × 10² M⁻¹ and 9.1 × 10¹ M⁻¹, respectively. However, the quantitative detection of these amino alcohol compounds has not been studied yet [58].

Zadmard and coworkers utilized a dimer of calix[4]arene (23) for the detection of NADH in an aqueous solution. NADH is an important biomolecule used in the metabolism system consisted of adenine, nicotinamide, and ribosome residues connected to a phosphate group. Calixarene 23 exhibited excellent selectivity for the detection of NADH over other biomolecules (AMP,
ADP, ATP, NAD, NADP, NADPH, uracil, cytosine, adenine, and guanine), which was remarkable. The emission signal at 325 nm ($\lambda_{ex} = 275$ nm) was significantly quenched by the addition of NADH only, yielding an LoD value of 24.5 nM. Calixarene 23 could form a 1:1 complex with a high $K_a$ value of $3.7 \times 10^5$ M$^{-1}$ [59].

Panchal and coworkers employed a bidansylated oxacalix[4]arene (24) for pendimethalin (PM) detection. This analyte is mainly found in herbicides and considered to be a toxic compound for soil and aquatic microorganisms. The emission signal of calixarene 24 at 466 nm ($\lambda_{ex} = 251$ nm) was quenched by the addition of PM. In contrast, the addition of other pesticides such as propanil, sulfofurfuran, pretilachlor, ametryn, terbuthryn, tebuconazole, clodinofop propargyl, atrazine, metalaxyl, simetryn, simazine, thiophenate methyl, and tricyclazole did not show a significant change in fluorescent emission. This result indicated an excellent selectivity of calixarene 24 for PM detection with a LoD value of 3.81 nM. Calixarene 24 could form a 1:1 complex with PM giving a $K_a$ value of $1.3 \times 10^5$ M$^{-1}$ [60].

Zeng and coworkers used a naphthol appended calix[4]arene (25) for the detection of metolcarb (MC) in MeCN media. Calixarene 25 showed high selectivity for the detection of MC over various analytes such as carbosulfan, pirimicarb, carbaryl, carbofuran, and isopropcarb. The addition of MC leads to a significant increment of the emission signal at 340 nm ($\lambda_{ex} = 265$ nm) with the LoD value of 0.1 µM. The 1:1 complex structure was generated between calixarene 25 and MC during the sensing process with a $K_a$ value of $1.2 \times 10^5$ M$^{-1}$ [61].

Yu and coworkers used the tetrahydroxy calix[4]arene (26) modified metal-organic framework for the detection of glyphosate in MeOH:PrOH (1:1 v/v) solvent system. The glyphosate was used for the representative organophosphate pesticide which often used in the agricultural field. The accumulation of glyphosate in water and crops is harmful due to its toxic effect. Therefore, the detection of this compound is critical to be established. Calixarene 26 yielded a high selectivity toward glyphosate compared to the other interfering analytes such as phenylphosphonic acid, (aminomethyl)phosphonic acid, formic acid, acetic acid, benzoic acid, oxalic acid, and phosphate ions. In addition, the presence of inorganic ions such as $\text{K}^+$, $\text{Na}^+$, $\text{Zn}^{2+}$, $\text{Ba}^{2+}$, $\text{Sr}^{2+}$, $\text{Mg}^{2+}$, $\text{Co}^{3+}$, $\text{Ca}^{2+}$, $\text{Cl}^-$, $\text{Br}^-$, $\Gamma$, $\text{SO}_4^{2-}$, and $\text{NO}_3^-$ did not interfere the glyphosphate sensing using calixarene 26, which was remarkable. The emission signal at 329 nm ($\lambda_{ex} = 281$ nm) was significantly enhanced by the addition of glyphosate to give an LoD value of 2.25 µM [62].

6. PERSPECTIVE

So far, the development of supramolecular calixarenes as the fluorescent chemosensor agent exhibits a high selectivity and sensitivity for a certain analyte. Calixarene serves as an ideal framework for either ion or molecule discrimination. Furthermore, a proper modification on either at the upper or lower rim can provide a desired binding site for the particular analyte. The modification depends on the targeted analyte to be detected, which may be cation, anion, or neutral molecule. The different nature of these analytes will influence their interaction with the chemosensor agent.

In general, the mechanism for cation detection usually involves the complexion through electrostatic and/or ion-dipole interactions. However, the different types of cation required different binding sites in the chemosensor agent indeed. For example, the detection of $\text{Cu}^{2+}$ is preferable by using the –NH (amino) and oxygen atoms as -OH phenolic and ether moieties. These moieties provide a good binding site for $\text{Cu}^{2+}$ ions. The detection of $\text{Na}^+$ is preferable by using a functional group containing oxygen from ether, ester, and carbonyl moieties. To detect trivalent cations ($\text{Cr}^{3+}$, $\text{Fe}^{3+}$, and $\text{Al}^{3+}$), the presence of –OH phenolic, ether, ester, and carbonyl groups shall be considered. For $\text{Ca}^{2+}$ and $\text{La}^{3+}$, a good detection could be achieved by using a specific triazole group. For $\text{Hg}^{2+}$ heavy metal detection, it is advisable that sulfonamide-based calixarene is employed as the receptor. The presence of imine groups at calixarene was found to be important for $\text{Zn}^{2+}$ and $\text{Pb}^{2+}$ ions detection.

On the other side, the sensing mechanism of anion mainly happened through either extended...
hydrogen bond or ion-dipole interactions. Since the anion is an electron-rich species, the binding site used in the sensing for certain anions should be positive or partially positive in charge. Therefore, the easily protonated functional groups shall be used as the binding site for the anion. For example, the detection of F⁻ required the presence of -OH phenolic, amine, and amide. Besides these functional groups, the presence of the C=N (imine) group is important for the detection of I⁻. For the detection of AcO⁻ and H₂PO₄⁻, the presence of amide and OH phenolic groups is important. Another mechanism for anion sensing is through the displacement mechanism involving the formation of ligand-metal complex, which then decomplexed by the presence of anion as the analyte. In this case, the anion should form a stronger interaction with the cation. For example, CN⁻ and S²⁻ strongly interact with Cu²⁺ ions demonstrating that a Cu²⁺-ligand complex is promising for detecting these anions.

In the detection of the neutral molecules, the mechanism usually involving the hydrogen bond, π-π stacking, and electrostatic interactions. For example, the detection of nitroaromatic compounds can be achieved by using carbazole moiety as it provides the electrostatic, CH-π, and π-π interactions with nitroaromatic compounds. Cyanacrylic acid moiety could provide a good hydrogen bond interaction with amino acid compounds. Amide group is good for providing a suitable electrostatic interaction for a heterocyclic biomolecule such as NADH. For the application in agricultural scope, the dansyl chloride, naphthol, and pyridyl moieties could provide a strong π-π stacking interaction with these analytes.

7. CONCLUSIONS

The design and development of sensitive and selective chemosensor agents have received significant attention from researchers over the past several years. Chemosensor agent has been widely applied to detect and quantify cation, anion, or neutral molecules in simulated or real sample analysis. Employing an optical chemosensor agent through fluorescence spectroscopy has received special attention due to its merits: easy sample preparation, quick response rate with high precision, and low-cost analysis. Calixarenes have good photoluminescence properties with excellent selectivity and sensitivity, thus calixarenes have been extensively used as the chemosensor agent. A proper modification on either at the upper or lower rim can provide a desired binding site for the particular analyte. In general, the mechanism for cation detection usually involving the complexation through electrostatic and/or covalent interactions. On the other hand, the sensing mechanism of anion mainly happened through either hydrogen bonds or dipole-dipole interactions between the anion as an electron-rich species with the positively charged binding site of calixarenes. Meanwhile, the sensing mechanism of biomolecules and neutral analytes usually involving the hydrogen bond, π-π stacking, and electrostatic interactions. These results may provide a useful insight into the design and development of chemosensor agents based on calixarene derivatives.

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