Chromogenic Sensors for Anionic Species Based on Indicator Displacement Approach

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Abstract: This review describes some developments on the anion sensing based on the indicator displacement. The reported systems are mainly from 2006. The simple IDAs approach, as a useful and facile technique for the creation of optical sensors, would give rise to much more attention and destined to flourish in future.

Keywords: Optical sensors, indicator displacement assays, supramolecular chemistry, molecular recognition.

I. INTRODUCTION

Anion recognition has attracted considerable attention in the supramolecular chemistry [1-4] in recent decades because of the importance of anionic species in biological system, medicine, catalysis and the environment. One of the more appealing approaches in this context involves the construction of optical sensors due to their remarkable detectability, experimental simplicity and low cost. These can be classified mainly according to the designed principles for anion sensing as receptor-spacer-reporter approach [4-6], chromoreactands approach [5, 6], and indicator displacement assays (IDAs) [5-7]. Among these, receptor-spacer-reporter approach [4, 6] is used widely in chemosensors. In this approach, the receptor (binding sites) generally links covalently with reporter (chromophore and fluorophore). Commonly, information (binding events of specific analytes) on the molecular level is amplified to a macroscopic level, namely, the production of fluorescence and/or Uv-vis absorbance. Furthermore, binding constants and stoichiometries are obtained based on changes of fluorescence and/or absorption.

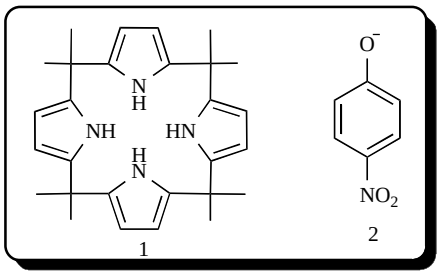
Chromoreactands approach [6] involves reversible or irreversible reactions, which are induced by specific anion. In this approach, anion displays mainly two typical modes. One is the anion reacts with the receptor. The other is the anion catalyses the chemical reaction of receptor. These result in new compound, concomitantly, with the occurrence of color changes and/or emission variations. Therefore, chromoreactands show high selectivity and high sensitivity.

For these two approaches, miscellaneous synthesis is required. This restricts their application to some extent. To circumvent this problem, IDA [7] is used in molecular recognition. This involves the competition between the indicator and the analyte for the receptor. In this approach, receptor and indicator are not covalently linked, but form (super)molecular assemblies with advantages of variation of indicator (signaling moiety) and the ratio between indicator and receptor in terms of practical problems. By choosing an appropriate indicator, the sensing ensemble can discriminate the desired analytes. However, for higher sensitivity and excellent selectivity for target analytes over other ones, displacement of indicator from the ensemble should induce distinct and measurable changes in color and/or fluorescence, and the corresponding spectrum of the system, therefore to signal the presence of analytes. Indicators commonly used in the development of displacement assays are some dyes, for example fluorescein derivatives [6], pyrocatechol violet [6], methyl red [6] etc.

The design of ensembles for optical sensing anion has been thoroughly reviewed [8, 17, 20] by Anslyn and coworkers. Therefore, the work done excellently by Anslyn groups was not considered in this paper. Herein, we focus on the recent development of chromogenic sensors based on the indicator-displaced approach, and the IDAs were divided into two categories: metal IDAs (mIDAs) and non-metal IDAs (nIDAs) according to varieties of receptors in IDAs.

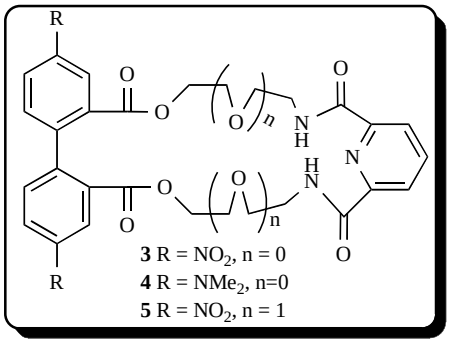
II. NON-METAL COMPLEXING INDICATOR-DISPLACEMENT ENSEMBLES

Non-metal receptors have been used comprehensively in the development of IDAs. In IDAs, receptors can offer suitable bonds with indicators by H-binding and electrostatic interaction. Upon addition of analytes, the indicator is free, and the signal including photoinduced electron transfer, electronic energy transfer, fluorescence resonance energy transfer, pH and ionic strength occurs. These depend on the geometry of the guest, its hydrophobicity, its charge and the solvent used in the system.



1 2

Gale and his colleagues developed a competitive method based on calix[4]pyrrole for detecting halide anions in aprotic solution [8]. With the addition of calix[4]pyrrole **1**, the intense yellow color of **2** (as tetrabutylammonium salt) in CH_2Cl_2 dissipates gradually due to the formation of the complex between calix[4]pyrrole **1** and 4-nitrophenolate (coordination disturbed the charge transfer complex between oxygen and nitro unit). Upon addition of halide anions to the solution of the complex, the yellow color was retrieved because of the displacement of p-nitrophenolate anion from the calix[4]pyrrole by the stronger binding F^- and Cl^-.



3 R = NO_2, n = 0
4 R = NMe_2, n=0
5 R = NO_2, n = 1

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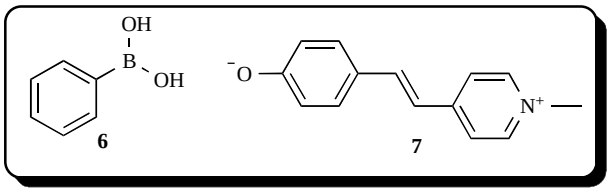
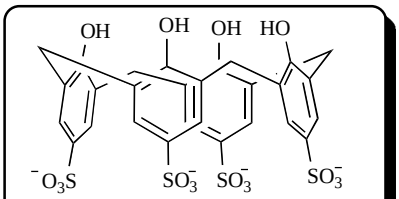
Making use of the same signaling subunit — 4-nitrophenolate, Costero and coworkers developed a new assay based on compounds **3**-**5** [9]. Upon addition of excess ligands **3**-**5** respectively, the characteristic yellow color of 4-nitrophenolate disappeared and the complex formed. Then addition of F^-, AcO^- and $H_2PO_4^-$ displaced 4-nitrophenolate from the molecular ensemble and the yellow color was reinstated. The substituents on the biphenyl moiety, cavity size and flexibility of the receptors **3**-**5** play important roles in the formation of complexes with 4-nitrophenolate. Electron deficient moieties and smaller cavity help to form stronger complexes.

Considering the excellently selective binding properties for anion [10], Machado group designed colorimetric sensor based on displacement assay of receptor **6** with indicator **7** [11]. Addition of receptor **6** to the CH_3CN solution of indicator **7** cause a color shift from violet (λ_{max}= 571 nm) to colorless (λ_{max}= 385.9 nm) due to the production of covalently linked **6**-**7** species. In presence of different anions such as F^-, Cl^-, Br^-, I^-, $H_2PO_4^-$, HSO_4^-, CH_3COO^-, and NO_3^-, only F^- and $CH_3CO_2^-$ replaced the indicator from the receptor **6** by bimolecular nucleophilic reaction, therefore, resulted in color change to original violet. Later, the group developed colorimetric sensor for F^- and HSO_4^- based on the complex of calix[4]pyrrole **1** with indicator **7** [12]. The chemosensing effect came from the displacement of the phenolate from –NH pyrrole group of calix[4]pyrrole **1**.



6 **7**

Based on the intramolecular charge transfer characteristics and the excellent hydrogen-bond acceptor, compound **9** was utilized as indicator to develop IDA with receptor **8** [13]. The ensemble of **8**:**9** displayed colorless in 1:1 DMSO/H_2O. Upon addition of F^- and H_2PO_4, the origin blue color appeared that resulted from the displacement of indicator **9**.



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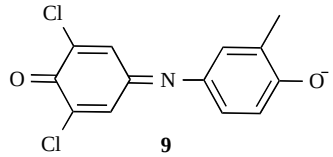

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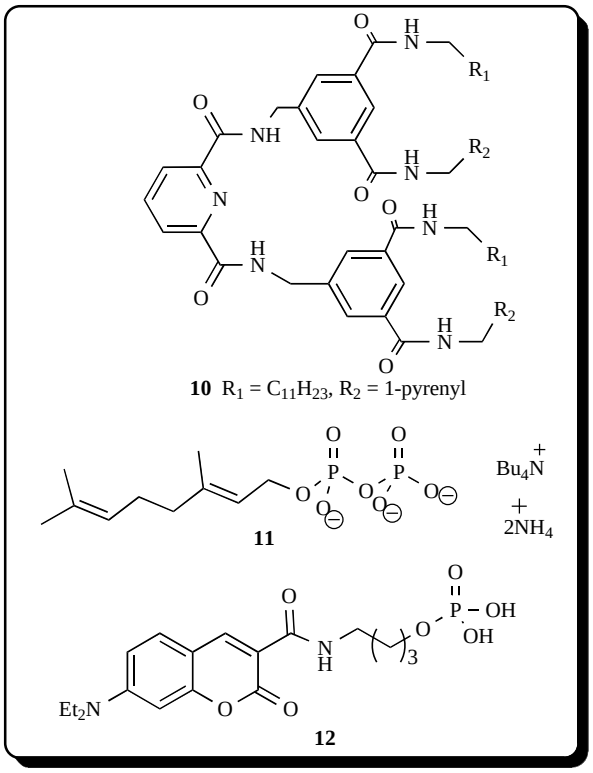
Inspired by the importance of isoprenyl pyrophosphates in the regulation of cell growth and division [14], Jim-Min and his colleagues designed hexaamide receptor **10** and studied their properties for geranyl pyrophosphate (GPP) **11** [15]. A binding constant of 3.3 $\times 10^3$ M^{-1}, which was bigger than other anions including fatty acid, was obtained by using the ^1H NMR techniques. However, the binding events did not induce appreciate fluorescence changes. Therefore, they designed a chemosensing ensemble using receptor **11** with coumain phosphate **12**. On addition of GPP, coumain phosphate **12** was displaced from the ensemble **11:12**, and the fluorescence resonance energy transfer diminished.

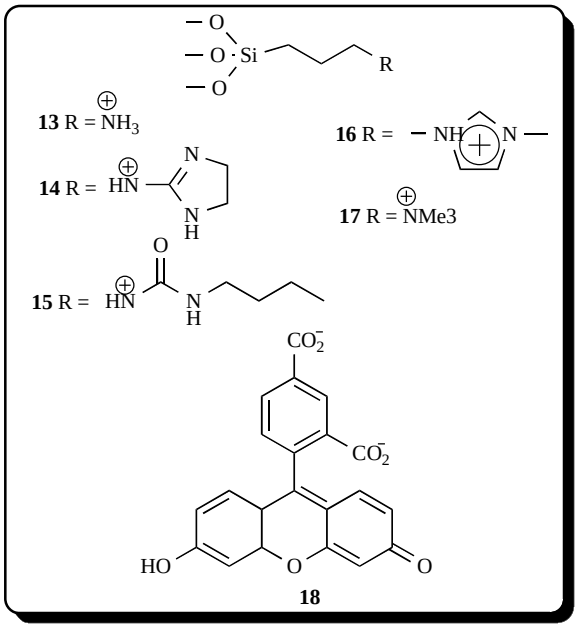


10 $R_1 = C_{11}H_{23}$, R_2 = 1-pyrenyl

11

12

Mesoporous solids, with easy-to-functionalized surface, high homogeneous porosity, inertness, thermal stability and tunable pore sizes, have received much attention in supramolecular chemistry [5, 16]. Martínez-Máñez *et al.* designed a 'solid host' [17] to bind selectively anionic species by electrostatic attractive forces (**13**-**17**) and hydrogen-bonding interactions (**13**-**16**). Dye **18** was used as the indicator in this study. Their sensing abilities for carboxylates and nucleotides were carried out in water at pH 7.5. The response to analyte was dependent on the binding pockets and the specific interaction of analyte with the binding groups in mesopores. Subsequently, a principle component analysis (PCA) was trained to recognize the patterns of absorbance at various combinations of analytes mentioned above.



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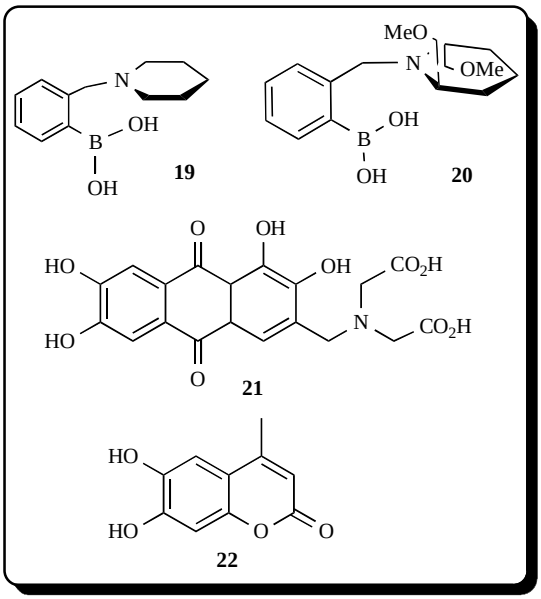
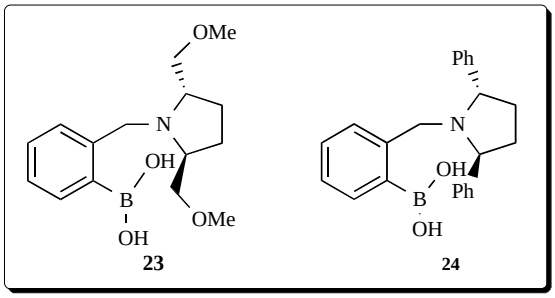
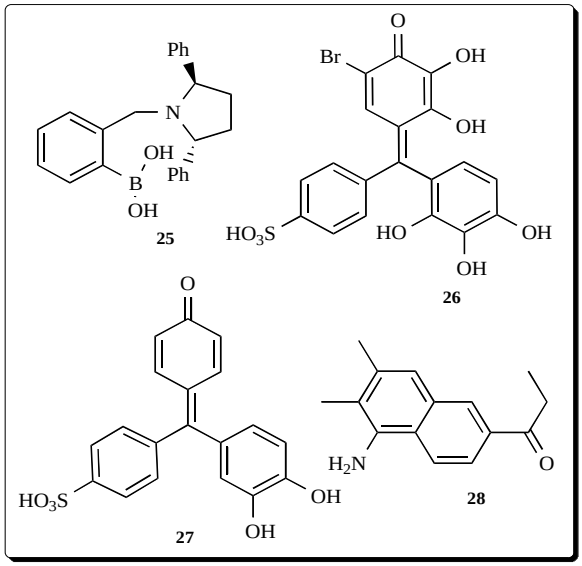
As an extension of their work [18-20], Anslyn group pioneered the development of enantioselective IDAs to determine both the concentration and the *ee* of chiral compounds, based on chiral and achiral hosts [21]. Receptors **19** and **20** [22], with one pendent boronic acid respectively, were used to analyze α-hydroxycarboxylate phenyllactate by a 'sensing ensemble' with the catechol-based indicators **21** and **22** [23]. In this study, two different approaches were developed with single spectroscopic measurement. One involved with two spectroscopic measurements. The concentration of chiral samples was determined by IDA based on achiral host **19** firstly. Then, the *ee* was obtained by a mathematical function of solution equilibrium with respect to guest concentration and *ee*-dependent optical signal, which was generated by chiral host **20**. The other dealt with single measurement, which collected absorption data at the isosbestic point and transparent region by the dual-chamber quartz cuvette. These were used to determine the concentration and *ee* of chiral samples by a mathematical process. Subsequently, an artificial neutral network (ANN) was trained to recognise *ee* of chiral sample and absorbances patterns of various combinations of guest concentration.



Considering the excellent enantioselectivity of C_2-symetric secondary amines on chiral boronic acid, the same group designed similar compounds **23** [21], **24** and **25** to distinguish the chiralities and chemical identities of subtly different analytes [24]. Diverse enantioselective sensor array was generated by using hosts **23**-**25** and pH indicator **22**, **26** and **27**. Optical changes collected from the sensor arrays were analyzed by pattern-recognition algorithms. Results indicated that these sensor arrays determined the concentration and *ee* of chiral diol samples with good enantioselective and high accuracy. Later, the Anslyn group used IDAs with indicator **28** to sense and discriminate terpens (linalool, α-terpineol, nerol, geraniol, and citronellol) in both pure solution and complex mixtures [25].

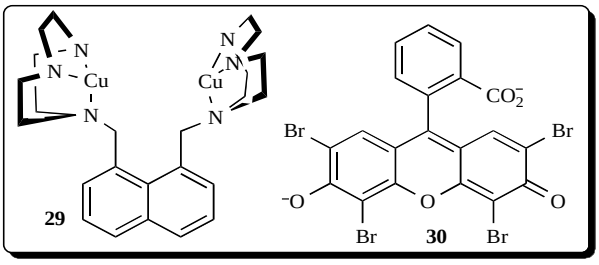




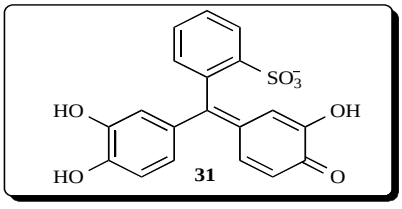
III. METAL COMPLEXING INDICATOR DISPLACEMENT ASSAYS

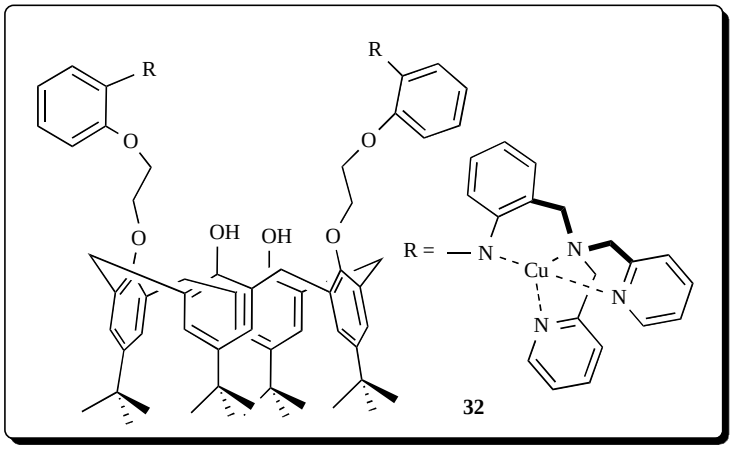
In devising chemosensing ensembles, transition metal ions were usually incorporated into ligands with substantial advantages of geometrical preferences and beneficial interaction in polar solution as water. For example, zinc(II)-dipicolylamine (Dpa) complexes were widely used in binding units in phosphate chemosensors [26-29]. Furthermore, the combination of metal complexes could be employed to engender coordination cage linking relevant indicators with suitable binding affinities. Addition of target analyte caused the displacement of indicator for optical detection of biological and environmental important substrates such as pyrophosphate, amino acids and peptides. In these receptors, Zn and Cu have been used comprehensively and effectively.

Using the Cu metal-receptor **29** [30] together with indicator **30**, Chin and Kim *et al*. achieved large fluorescence changes to oxalate in a buffered solution at pH 7.0 [31]. The dinuclear copper center in **29** displayed tight and selective link to oxalate over other dicarboxylates (malonate, succinate, glutarate), which was in agreement with the DFT calculations.



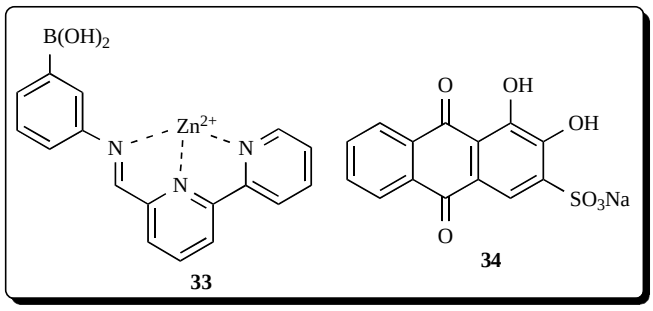
The detection of oxalate was also found in the work by Huo and coworkers [32]. The ensemble for **31** with Cu^{2+} displayed color changes from yellow to blue with the addition of $Cu(NO_3)_2$. Selectivity of ensemble on oxalate was higher than the other anions, such as F^-, Cl^-, Br^-, HPO_4^-, PO_4^{3-}, AcO^-, CO_3^{2-}, SO_4^{2-}, ClO_4^-, I^-, $P_2O_7^{4-}$. Furthermore, the ensemble was used to detect oxalate in tap water and vegetable samples.





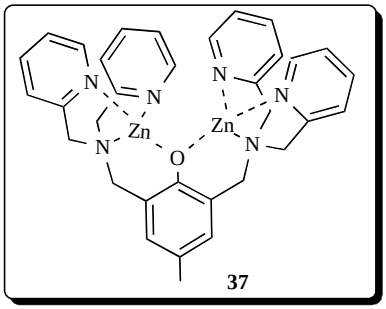
Using p-t-butylcalix[4]arene, receptor **32** was prepared [33]. By rationally designing the Cu-Cu distance and the side arms attached to calix[4]arene to tune the size and shape of recognition cavity of calix[4]arene, the ensemble of **32**:**31** was used for detection of pyrophosphate ($P_2O_7^{4-}$, PPi), the product of ATP hydrolysis and involved in DNA polymerization in biological reactions. The association constant was found to be $5.2 \times 10^5 M^{-1}$ that was larger than one between **32** and **31**. This indicated the occurrence of indicator displacement.

As an extension of their work [34], Glass *et al.* combined the boronic acid and a zinc complex into receptor **33** [35]. The simple two recognition sites' receptor was used to recognize the phosphosugar. After the addition of ribose-5-phosphate to the sensing ensemble of receptor **33** with fluorescence dye **34**, obvious fluorescent changes (decrease at the 554 nm and at the 619 nm, respectively) were observed. However, the addition of simple sugars (fructose and ribose) resulted in a decrease at the 554 nm only. These resulted from the displacement of indicator at different binding agents of receptor **33**.



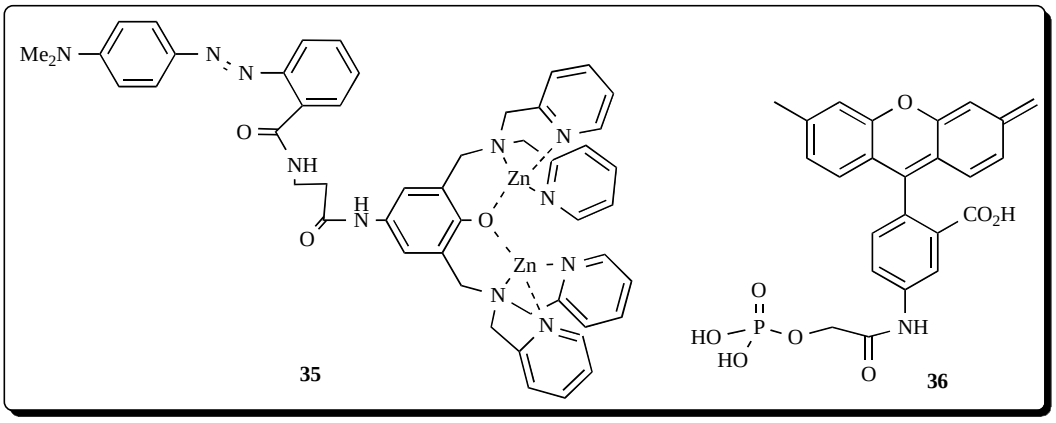
The detection of PPi was also found in Hong's studies [26, 36]. Hong *et al.* has shown that receptor **35**, with two zinc centers, has high affinity for PPi ($1 \times 10^8 M^{-1}$) in aqueous solution by quencher-fluorophore ensemble with indicator **36** [36]. The selectivity trend of **35**:**36** was PPi > ATP > ADP > AMP>AcO^- ~ F^-.

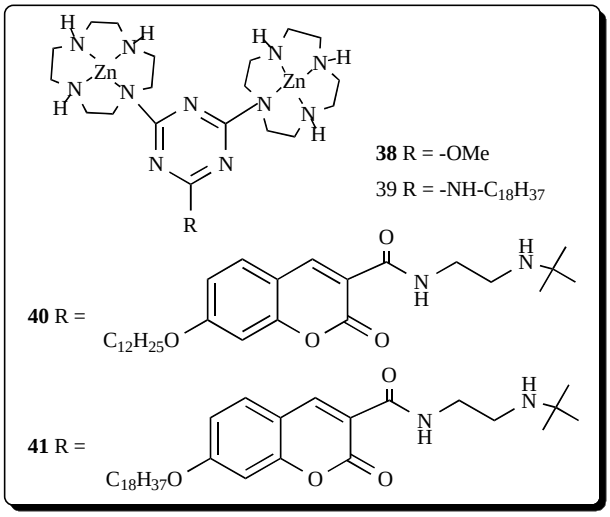
Another example to sense PPi was colorimetric chemosensing system **37** [37] designed by Smith *et al.* [38]. In this study, selective indicator displacement assays were discovered by using bromo pyrogallol red, mordant blue 9 and zincon as displaceable indicators. In these assays, differentiation of analytes relied mainly on the relative association constants of indicator and target analytes.



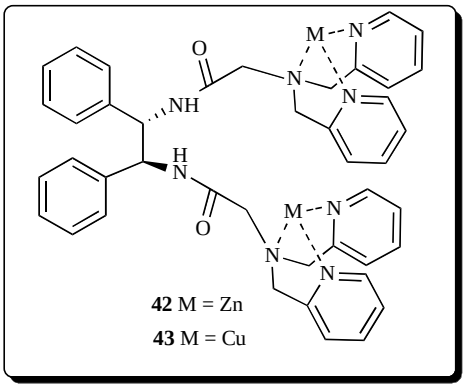
Köng group showed that polyamines **38**-**41** can be successfully used to detect phosphate anions such as uridine-5-triphosphate (UTP) or PPi by IDAs with indicator **31** [39]. Interestingly, receptors **40** and **41** displayed no response to phosphate anions in homogeneous aqueous solution, while these receptors displayed luminescent response to α-S1-Casein after embedding into vesicular membranes. Membrane-embedding of artificial receptor may present a novel type of molecular recognition.

The chiral dinuclear complexes **42** and **43** were designed and synthesized for the recognition of biologically relevant phosphate anions in aqueous solution [40]. To monitor the binding, pyrocatechol violet **31** was used as an indicator. With the addition

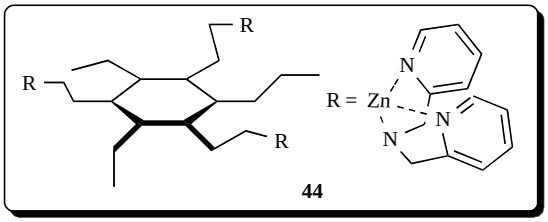




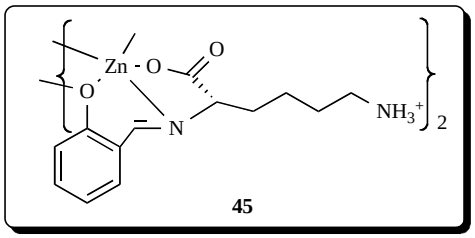
of receptors **42** and **43**, the color of the solution changed from bright yellow to dark blue. Upon addition of the PPi, the color of the sensing ensemble returned to bright yellow, which indicated the occurrence of displacement of **31**. Subsequently, CD spectra confirmed further the binding results.



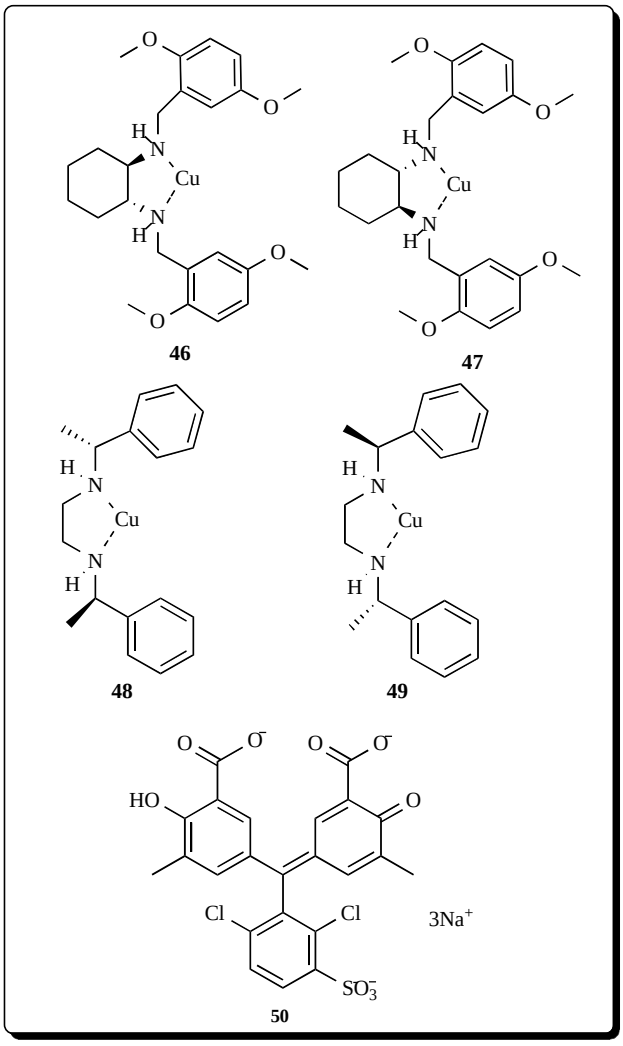
myo-Inositol 1,4,5-tris(phosphate) (IP_3), as an important signaling molecule involved in intracellular signal transduction, has received much attention in the area of chemosensors [41, 42]. Ahn *et al.* designed the benzene-based tripodal compound **44** [43], which contained no chromo- or fluoro-genic moiety, to bind IP_3. In addition, eosin Y was chosen for chemical sensing study with receptor **44**. Upon addition of IP_3, eosin Y was displaced from the assay and large fluorescence changes were achieved.



The fluorescent dinuclear zinc complex **45** containing a natural amino acid, was prepared for sensing biologically relevant phosphate anions (AMP, cAMP, ADP, PPi, ATP) by Churchill *et al.* [44]. It exhibited intense blue fluorescence (λ_{ex} = 352 nm, λ_{em} = 453nm, Φ_F = 0.17). After the addition of PPi, fluorescence quenching occurred due to the weakening of Zn-N and Zn-O bonds and subsequently, reinstatement of the C=N isomerization. The sensing ensemble for these phosphate anions included the receptor **45** and pyrocatechol violet **31**. The IDAs titration results suggested that the binding tendency was as follows: PPi≥ ATP > ADP.

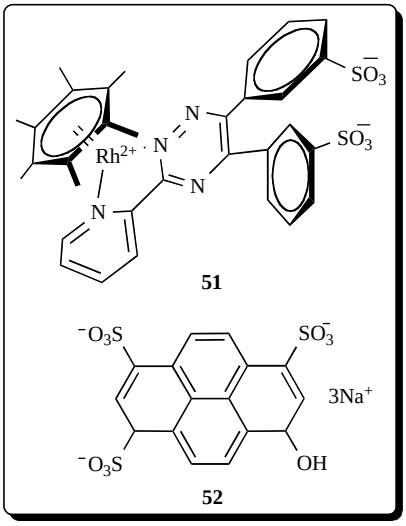


Sensing of certain enantiomeric amino acid was achieved using the receptors **46**-**49** by competitive assays with indicator **31** [45, 46]. Receptors **46**-**49** and chrome azurol **50** formed chemosensing ensembles, respectively, that allowed enantioselective discrimination of α-amino acids, with obvious color changes, in aqueous medium buffered to pH 7.5 [47]. Chelation of indicator **50** to the Cu^{II} metal center resulted in color varieties from yellow to intense blue, with corresponding absorbance shift from 429nm to 602nm. Upon addition of α-amino acids, displacement of the indicator from the chemosening ensemble led to a decrease in the absorbance measured at 602 nm and an increase in 429 nm, that could be analyzed quantitatively. Furthermore, the decrease in absorbance at 602 nm was different for two enantiomers of a given amino acid, allowing enantioselective discrimination. Receptor **46** was found generally to bind more strongly with L-α-amino acids. However, in the case of aspartate, asparagines and histidine, the D-enantiomer was preferred by receptor **46**, possibly due to the different coordination mode for these amino acids, involving binding motifs present in their side chains. Then analysis of



enantiomeric excess for true test samples displayed an overall average error of ± 10.2% by receptor **46** and ± 13.6% by receptor **49**, respectively. Subsequently, these IDAs were used in a high throughput and *ee* achieved with ANN determination with small errors [48].

Attempts to use other metals beside Zn and Cu in IDA have been explored as well. Severin and coworkers continued their work on the design of rhodium-based receptor [49]. The chemosensing ensemble **51**:**52** displayed fluorimetric detection of chloride in presence of micelles of $CTAHSO_4$ by IDAs [50].



CONCLUSION

This review gives account of the recent development in IDAs. The simple IDA approach is a useful and facile technique for the creation of optical sensors to detect biologically important anions. Furthermore, based on IDAs, the pattern recognition approach, PCA and ANN were used to sense target analytes. This work was inspired by nature's use of 'differential receptors' in mammalian tongue and nose for the senses of taste and smell. Composite fingerprints provide unique diagnostic patterns for the individual targets or mixed ones. However, IDAs with high selectivity and sensitivity need more investigation and development for practical applications. IDAs would give rise to much more attention and would destine to flourish in future.

ACKNOWLEDGEMENT

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