

Calix[N]Arene: A Efficient Molecular Scaffold for Development of Molecular Sensor For Metal Ion Sensing

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ABSTRACT: Heavy metal ions (HMI) are critical for numerous biological and physiological process for example metal ion like Fe^{2+} , Fe^{3+} , Cu^{2+} , Ni^{2+} and Zn^{2+} metal ions are necessary in trace amount for living system to balance various biological function. On the other hand, excess amount causes serious threat to living system like permanent damage of several organisms like kidney, bones, liver, central nervous system *etc.* In view of these toxic effect, there is requirement to develop some synthetic molecular sensor for sensing of these metal ions with high selectivity and sensitivity. In this context, molecular recognition is known as scientific tool which signifies the specific binding of guest molecule via non-covalent, electrostatics, hydrogen bonding, and π - π stacking interactions. In past decades a number of organic host molecule were reported for the same purpose such as Crown ethers, thio-crown ethers, aza-crown ethers, thio-urea, thia-diazole, bithiazole, benzimidazole, imidazole, Bodipy, calixarene, Cumarin, rhodamine, 1,8-naphthalimide, indole, and azo derivatives *etc.* In this review article, we describe calixarene based molecular sensor for cation recognition.

Key words: Heavy metal ion (HMI), cation, sensor, calixarene

I. INTRODUCTION

Metal ions and anions are ubiquitously distributed in nature and their presences in permissible limits are essential for several biological, physiological and environment process. Such as Fe^{2+} , Fe^{3+} , Co^{2+} , Mg^{2+} , Al^{3+} , Cu^{2+} , Ni^{2+} , Zn^{2+} metal ions are required in trace amount for living system to balance various biological function, such as a range of redox active ($\text{Cu}^+/\text{Cu}^{2+}$ and $\text{Fe}^{2+}/\text{Fe}^{3+}$) and redox inactive (Li^+ , Na^+ , K^+ , Mg^+ , Ca^{2+} and Zn^{2+}), however they may be pose serious threat to living system beyond permissible limits due to accumulation, resulting permanent damage of several organisms like kidney, bones, liver, central nervous system *etc.* For instance intake of excessive Cu^{2+} ions will leads Alzheimer's disease, Wilson's disease and Parkinson's disease. Likewise silver metal ions interfere with certain drugs, such as penicillamine, quinolones, tetracyclines and thyroxine, consequently disturb immunological response of body. Or higher concentration of nickel leads serious lung and kidney problems and it is also considered human carcinogen. Apart this, zinc is plentifully present metal ion in living system and play various biological functions including DNA synthesis, apoptosis, structural motifs in proteins, control of gene transcription, metallo enzyme function, as well as enzyme co-factors. But simultaneously, it is reported that zinc metal ion in free form have toxicity due to its interaction with a variety of amino acids site chains such as histidines, cysteines, which allows Zn^{2+} to bind to numerous proteins even at nano molar concentrations, resulting in enzyme inhibition or induction of protein-protein interactions. It is also reported that intentional or accidental ingestion of large amounts of zinc leads to gastrointestinal effects, such as abdominal pain, vomiting and diarrhea, or in the case of long-term intakes causes prostate cancer, sideroblastic anaemia, leucopenia, diabetes, brain diseases and most effecting is disrupt the homeostasis of other trace essential elements. Besides these essential metal ions, there are some non-biodegradable heavy metal ions such as cadmium, lead, arsenic, chromium and mercury have no any beneficial role in biological system, hence they are considered as non-essential hazardous elements even at low concentration. These non essential metal ions are considered systemic toxicants even at very low concentration because they induce multiple organ damage, even at lower levels of exposure. It is estimated that number of people are exposed to

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these toxic metal ions chronically throughout the world and suffer from various disorders such as arsenic exposure leads cardiovascular and peripheral vascular disease, developmental anomalies, neurologic and neurobehavioral disorders, diabetes, hearing loss, portal fibrosis, hematologic disorders (anemia, leukopenia and eosinophilia) and carcinoma etc. Similarly chronic cadmium exposure can cause renal dysfunction, calcium metabolism disorders, and an increased incidence of certain forms of cancer, possibly due to direct inhibition of DNA mismatch repair. At low level it also leads severe pulmonary and gastrointestinal irritation, abdominal pain, burning sensation, nausea, vomiting, salivation, muscle cramps, vertigo, shock, loss of consciousness. In addition to this acute cadmium ingestion can also cause gastrointestinal tract erosion, pulmonary, hepatic or renal injury and coma etc. Among the metal ions mercury ion is considered most toxic metal ion because it is widely distributed in environment and can be inter in human body which resulting accumulation of metal in human organ and causes lethal disease. Such as brain damage, DNA lesion, malfunctioning of nerves system, deregulation of kidneys, minimata disease and muscles problems. It is also causes disturbance in metabolic process such as amino acid, protein and enzyme etc.

In accordance with toxicity data and scientific studies, the World Health Organization (WHO) had recommended permissible limits of metal ion and anions in drinking water. These are summarized in Table 1

Sr. No.	Metal ion and anions	Permissible limits (WHO)	Sr. No.	Metal ion and anions	Permissible limits (WHO)
1	F ⁻	1.5mg/l	9	Hg ²⁺	0.001mg/l
2	Cl ⁻	200mg/l	10	Cd ²⁺	0.005mg/l
3	NO ₃ ⁻	-	11	Se ²⁺	0.01mg/l
4	SO ₄ ⁻	-	12	Pb ²⁺	0.05mg/l
5	Ca ²⁺	75mg/l	13	Zn ²⁺	5.0mg/l
6	Mg ²⁺	50	14	Cr ²⁺	-
7	Co ²⁺	1.0mg/l	15	As ³⁺ , As ⁵⁺	0.01mg/l
8	Fe ²⁺ , Fe ³⁺	0.1ml/l			

Molecular recognition is a scientific tool which signifies the specific binding of guest molecule via non-covalent, electrostatics, hydrogen bonding, and π - π stacking interactions. Its origin was start with Pedersen's finding that macrocyclic polyethers (crowns) are capable for selective binding of alkali metal ions and dissolve them in organic media. Since then, the topic of ion recognition by synthetic receptors has developed tremendously and is still quite fertile. In past decades a number of organic host molecule were reported for the same purpose such as Crown ethers, thio-crown ethers, azacrownethers, thio-urea, thia-diazole, bithiazole, benzamidazole, imidazole, Bodipy, calixarene, Cumarin, rhodamine, 1,8-naphthalimide, indole, and azo derivatives etc. Some of reported molecular receptor for cation recognition is reviewed below- Calix[*n*]arenes (*n*=4-20) are phenolic [1]*n*-metacyclophanes which can be suitably obtained through acid- or base-catalyzed condensation reaction of *p*-substituted phenols with formaldehyde. They possess a distinct hydrophobic upper (or "narrow") rim and a hydrophilic lower (or "wide") rim to encompass a hollow cavity with dimensions that can be varied by varying the number of the phenolic units (*n*) present. Cone, *partial-cone*, *1, 3-alternate* and *1, 2-alternate* conformations of calix[4]arene derivatives (Figure 1) provide differential capabilities for ionic and molecular recognition. A major driving force for separation techniques is the analysis of metal ions without first requiring their physical separation. Extraction of metal ions from waste water or water bodies has been an important practical application of calixarenes. Since the first experiments on calixarene as sensing agent was reported in 1986 by Diamond *et al.* for sodium sensing, after this report various calix[*n*]arene derivatives have been explored for extraction of metal ions.

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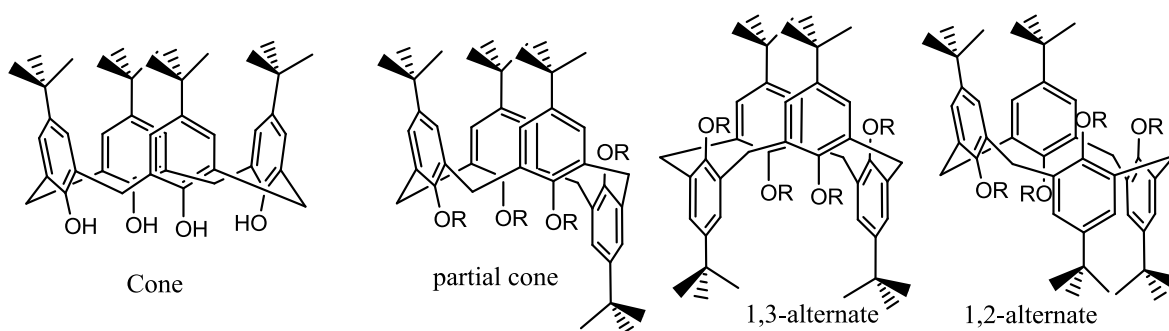


Figure1. Different conformation of calixarene

For example calixarene derivative containing triphenylamine units were synthesized by S. Erdemir et al. as a colorimetric and fluorescent sensor for Hg^{+2} metal ion sensing. Free receptor (**figure 2**) shown an absorption peak in UV visible at 290nm and 358nm, when Hg^{+2} gradually added in receptor solution a new absorption peak appear at 430nm with decreasing absorption intensity at 358nm. 1:2, stoichiometry of receptor: Hg^{+2} were determined by job's plot data and association constant for Hg^{+2} ion were calculated $7.52 \times 10^4 M^{-1}$ by Benesi-Hildebrand plot.¹

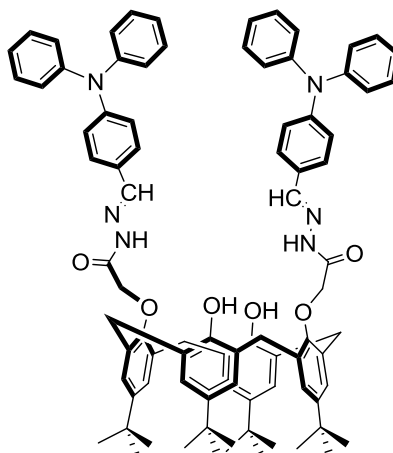


Figure 2

Similarly calix[4]arene derivative also prepared for selective detection of Cu^{+2} ion in presence of other metal ion by S. Erdemir et al. Receptor having (**figure 3**) benzothiazole group in 1,3 alternate conformation for multi analyze sensing and it established "on-off-on" type fluorescence recognition in CH_3CN/H_2O (4/1, v/v) solvent. Receptor exhibits fluorescent quenching towards Cu^{2+} ion. From the job's data, S. Erdemir and co-workers analyzed receptor recognized Cu^{+2} in 1:2 binding mode.²

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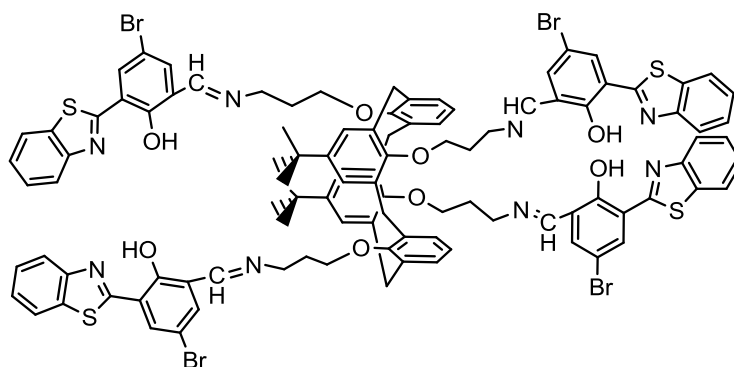


Figure 3

It is well known, calixarene have chemically stable intermolecular cavity of tunable size and excellent framework for designing different type of molecular receptor. C.Wu et al. designed a new fluorescent chemosensor (**Figure 4**), which have triazole linking on calix [n] arene platform via click reaction. Recognition behavior of synthesized derivative were carried out with fluorescent measurements in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10:1, v/v), when Zn^{+2} added in Pyrene functionalized triazole-linked hexahomotrioxacalix[3]arene solution, it is found that receptor display weak monomer emission at 380nm and 398nm but strong excimer emission around 484nm from 343nm which was due to pi-pi stacking between the neighboring pyrene units.³

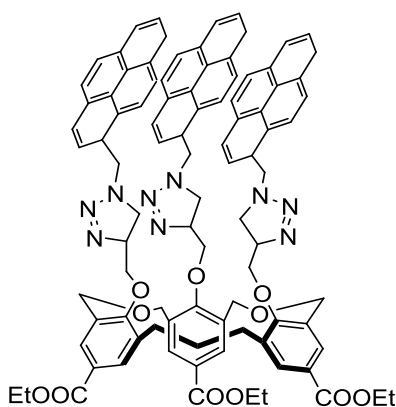


Figure 1.4

Similarly a pyrene bearing calix[4]arene derivative 25,26,27,28-tetra-hydroxy-11,23-di-(tert-butyl)-5,17-di-(1-pyrenyl)azocalix[4]arene and anthracene bearing derivative 25,26,27,28-tetra-hydroxy-11,23-di-(tert-butyl)-5,17-di-(2-antraceny)azocalix[4]arene (**figure 5**) have been reported by S. Elcin and co-workers for Cu^{+2} detection in living cell line. Both compound have complexation towards Cu^{+2} ions in presence of competitive other cations and their complexation studies were carried out by UV-visible and FTIR spectroscopy.⁴

International Journal of Innovative Research in Science, Engineering and Technology

(A High Impact Factor, Monthly Peer Reviewed Journal)

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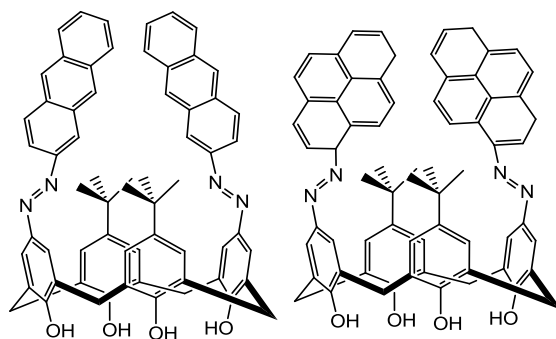


Figure 1.5

A chromogenic optical sensor based on calix[n]arene for Ag^{3+} detection have been reported by M. Echabaane et al. UV-visible studies of azo calix[4]arene(**figure 6**) in presence of Al^{3+} reveal that it have high affinity towards Al^{3+} in presence of other metal cations such as Li^+ , Cs^+ , K^+ , Sn^{2+} , Pb^{2+} , Cu^{2+} , Eu^{3+} , Er^{3+} and Al^{3+} . Job's measurement data were displayed stoichiometric ratio and the association constant as 1:1 and $1.24 \times 10^4 \text{M}^{-1}$. In UV-visible spectra a hyperchromic and bathochromic shift of 344nm with appearance of new band at 294nm is observed which is due to binding of Al^{3+} on amide and ester group at the lower rim of azocalix[4]arene which induced charge transfer and resulting change the charge density of the azocalix[4]arene.⁵

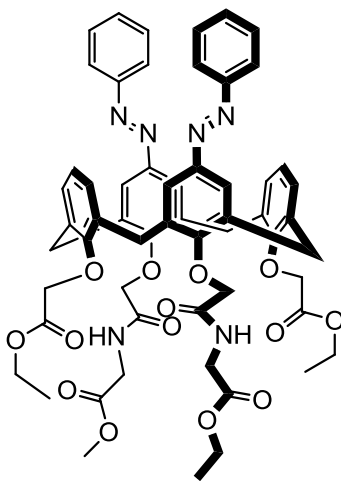


Figure 1.6

Calixarene scaffold offer unshared significant in actinides, lanthanides recognition when functionalization carried out at different positions, for example separation and preconcentration of lanthanum(III), cerium(III), thorium(IV) and uranium(VI) metal ions were carried out by V.K. Jain et al. by using calix[4]arene chelating resin 11,23-disemicarbazono-26,28-*n*-dipropoxy-25,27-dihydroxy calix[4]arene, (**figure 7**) which have good affinity towards these metal ions, similarly B. Boulet et al. have been reported a calix[4]arene derivative for plutonium and uranium detection which bearing hydroxamic acid as binding arms for target metal ion. With this receptor on varying pH (2-5) values effectively separated plutonium and uranium metal ion from samples.⁶

International Journal of Innovative Research in Science, Engineering and Technology

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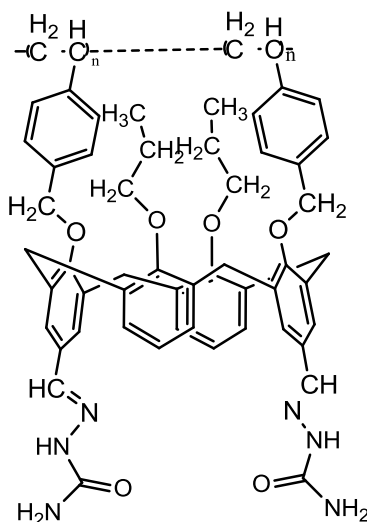


Figure 1.7

A two faced, highly selective fluorescent chemosensor calix[4]arene (**figure 8**) bearing naphthalimide for Cu²⁺ and F⁻ ion detection were synthesized and characterized by Z. Xu et al. Chemosensor have selective fluorescent quenching effect only with Cu²⁺ among Ag⁺, Ca²⁺, Cd²⁺, Co²⁺, Cs⁺, Cu²⁺, Hg²⁺, K⁺, Li⁺, Mg²⁺, Mn²⁺, Na⁺, Ni²⁺, Pb²⁺, Rb⁺, and Zn²⁺ metal ions. Cu²⁺ binding with chemosensor leads excitation into the naphthalimide fluorophore at 435nm and emission change of 20 folds. The association constants of chemosensor with Cu²⁺ were calculated 6.1×10⁴M⁻¹ by fluorescent titrations.⁷

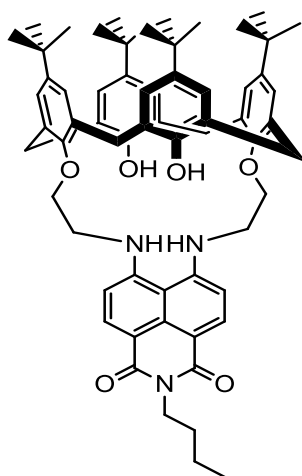


Figure 8

Similarly a calix[4]arene based fluorescent bearing rhodamin moiety receptors **9** and **10** for Hg²⁺ detection have been synthesized by M. Kumar et al. Synthesized receptors are 'Turn On' type fluorescent, which have rhodamine appended on thiocalix[4]arene, among receptors, receptor **9** have 1,3-alternate conformation which shows high selectivity towards Hg²⁺

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ions with fluorescence enhancement amongvarious metal ions cations (Hg^{2+} , Fe^{2+} , Fe^{3+} , Cu^{2+} , Ni^{2+} , Cd^{2+} , Co^{2+} , Pb^{2+} , Zn^{2+} , Ba^{2+} , Ag^+ , K^+ , Na^+ and Li^+). While adding Hg^{2+} in chemosensor **9** a new absorption band appear at 554nm with color change from colorless to pink due to opening of the spirolactam ring. Similarly receptor **10** also show a fluorescent enhancement with Hg^{2+} but it is also shows some change with Fe^{2+} and Fe^{3+} .

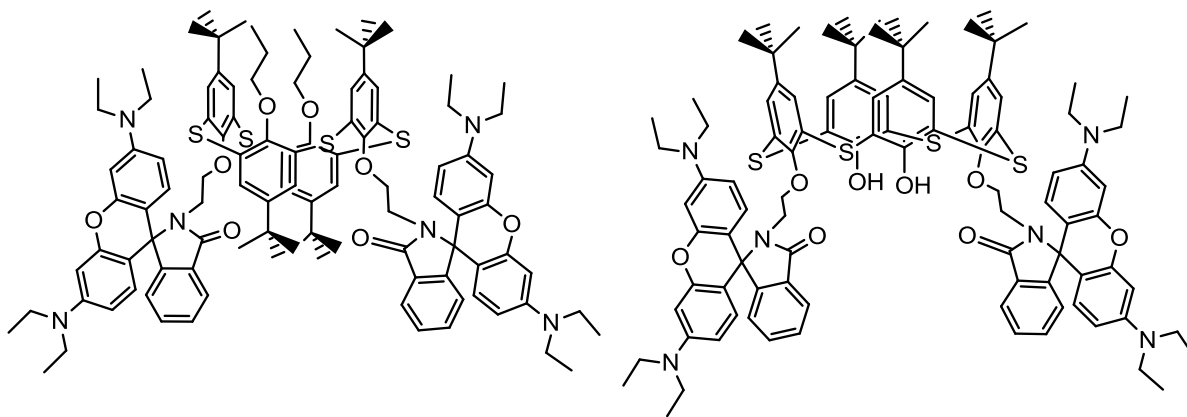


Figure 9

A calix[4]arene based sensor for sensing essential metal ion and their extraction by Pederson method have been developed by *I. Qureshi et al.* This unique *p*-morpholinomethylcalix[4]arene ionophore (**figure 10**) have sensing capability towards Cu^{2+} , Co^{2+} and Ni^{2+} metal ion. Sensor have great sensing and extraction efficiency toward Ni^{2+} , Co^{2+} and Cu^{2+} ion but for Cu^{2+} is comparatively higher. The fluorescent spectrum on treating sensor with Cu^{2+} shows a significant shift from 435nm to 490nm due to cation lone pair interaction.⁹

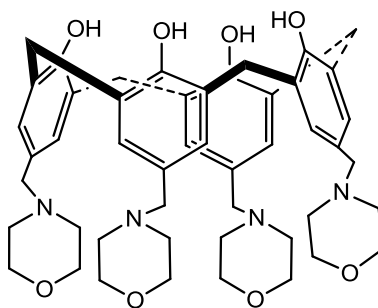


Figure 10

A calix[4]arene based bis(isatinhydrazone)calix[4]arenes (**figure 11**) for duel recognition of fluoride and silver ions have been synthesized by H.M. Chawla et al. The synthesized receptors effectively recognized fluoride and silver ions with visible color change from pale yellow to dark blue in case of fluoride and pale yellow to dark yellow in presence of silver metal ion. Selective silver metal ion sensing ability of receptor was investigated in presence of different transition metal ions (Mn^{2+} , Co^{2+} , Cu^{2+} , Fe^{2+} , Ni^{2+} , Hg^{2+} , Ag^+ , Cd^{2+} , and Zn^{2+}) there was no change in absorption spectra with these metal ions except silver. Upon adding Ag^+ in receptor THF solution a red shift observed with appearing new absorption peak at 410nm and disappearing absorption band at 373nm.⁹

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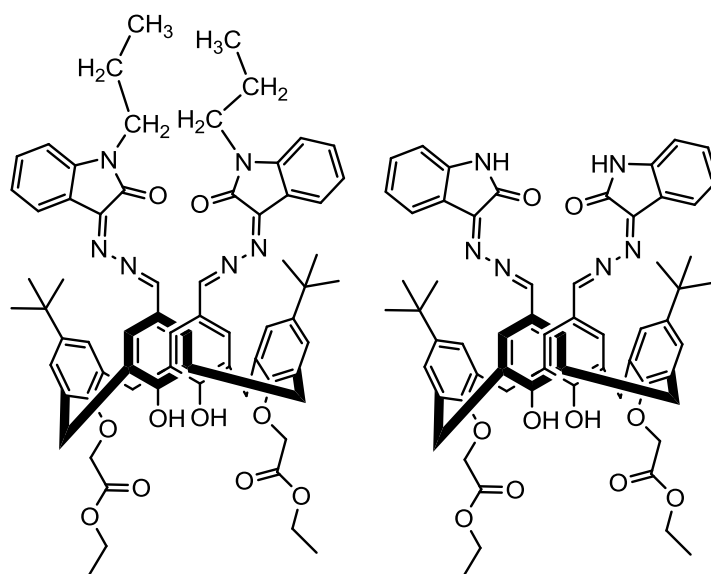


Figure 11

Similarly a calix[4]arene based diatopic receptor (**figure 12**) for simultaneous recognition of fluoride and cobalt(II) ion have been also reported by H.M. Chawla and co-workers, synthesized receptor possessing bipyridyl and hydrazone units as binding sites. The cation and anion sensing ability of receptor were examined by UV-visible studies in DMSO: CH₃CN (0.5:9.5 v/v), free receptor displayed two absorption peaks at 287nm and 388nm that was ascribed absorption maxima for bipyridyl and hydrazone moiety present in receptor. When solutions of receptor treated with perchlorate and nitrate salts of transition and alkali metal ions (Co²⁺, Cu²⁺, Ag⁺, Fe³⁺, Ni²⁺, Na⁺, K⁺) only the cobalt ion showed bathochromic shift of 21nm at 308nm while no change in the absorption peak at 388nm.¹⁰

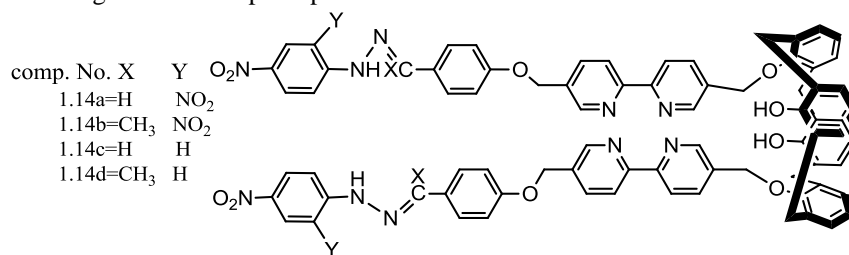


Figure 1.14

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Vol. 6, Issue 4, April 2017

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