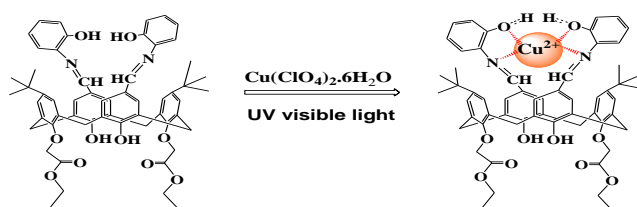# A Calix [4]Arene Based Chemosensor For Recognition Of Cu^{2+} Ion.

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Abstract: *A novel calix[4]arene based chemosensor having two schiff's base units has been designed, synthesized and characterized by NMR and ESI-MS analysis. It is found to exhibit excellent selectivity for Cu^{2+} over a wide range of alkali, alkaline earth and other transition metal ions in acetonitrile solution. Its metal binding affinity and binding constant studies revealed a 1:1 binding stocheometry of the ligand with Cu^{2+} ion.*

Keywords: *calix[4]arene, chemosensor, Cu^{2+}, recognition, schiff's base*

I.   INTRODUCTION

Calix[4]arene derivatives play an important role in the recognition of ions and molecules [1-4]. Binding ability of parent calix[4]arene can be modified to develop additional binding sites at the upper/lower rim so that functional groups get orientated to provide well-organized cavities. Among various reactions studied on calixarene functionalization, schiff's base units have recently been incorporated onto both the upper and the lower rims of calix[4]arene [5] and studied for their ability to complex transition metals in a few cases [6-8]. Though a number of calix[4]arene derivatives were subjected to metal ion complexation studies [9-11], complexes of imine linked derivatives having fluorescent and ultraviolet probes have received little attention.

In past few years, development of chemosensors for the detection of Cu2+ ion has drawn much attention because of its importance in environmental and biological systems [12]. However, the major challenge is the interference of similar divalent cations. For example, a number of Cu^{2+} fluorescent sensors have been developed in recent years [13-18]; but many of them still suffer from interference from other similar divalent metal ions (particularly Mg^{2+}, Ni^{2+}, Zn^{2+} and Cd^{2+}). There are some examples of selective recognition of Cu^{2+} ion reported in the literature [19-22]. Still design of efficient chemosensor for selective recognition of Cu^{2+} ion following simple methodology is always in great demand. We have designed and synthesized a series of novel calix[4]arene based schiff's bases, following simple experimental pathway, which behaves as an efficient chemosensor. One of them was found to show selective recognition of cu^{2+} ion. To study whether there is any interference of calix[4]arene cavity, we compared the results with a reference compound having similar network for detailed study.

II.   RESULTS AND DISCUSSION

All the reagents used in the study were purchased from Sigma-Aldrich or Merck and were chemically pure. All the solvents used were distilled and dried before use. ^{1}H NMR, ^{13}C NMR and [1]H-^{1}H cosy spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature using tetramethylsilane (TMS) at 0.00 as an internal standard. FT IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks. Melting points were determined on an electrothermal melting point apparatus obtained from M/S Toshniwal Brothers, Mumbai and were uncorrected.

II.1. Synthesis of schiff's bases 4, 5, 6 and 8

p-tert-butylcalix[4]arene **1** was synthesized by the method described by Gutsche *et. al*.[23]. It was alkylated in the presence of ethylbromoacetate, K$_2$CO$_3$ and acetonitrile according to literature [24] to yield the desired calix[4]arene ester **2**. This was further formylated by using a Duff reaction protocol [25] (as given in the following section) to give the desired calix[4]arene derivative **3**.

Alkylated calix[4]arene **3** (500 mg, 0.61mM) and hexamethylenetetramine (40 equivalent) were taken in trifluoroacetic acid (50 mL). The reaction mixture was refluxed until the starting materials disappeared (completion of the reaction was monitered by TLC). On completion of reaction, the mixture was quenched with ice cold water and extracted with dichloromethane. The organic layer was washed with water and dried over Na$_2$SO$_4$. Solvent was evaporated under reduced pressure the residue was purified as mentioned to yield the desired formylated calix[4]arene **4**. The spectral data of the synthesized formylated calix[4]arene derivative **4** was found to be similar to the one reported earlier [26, 27].
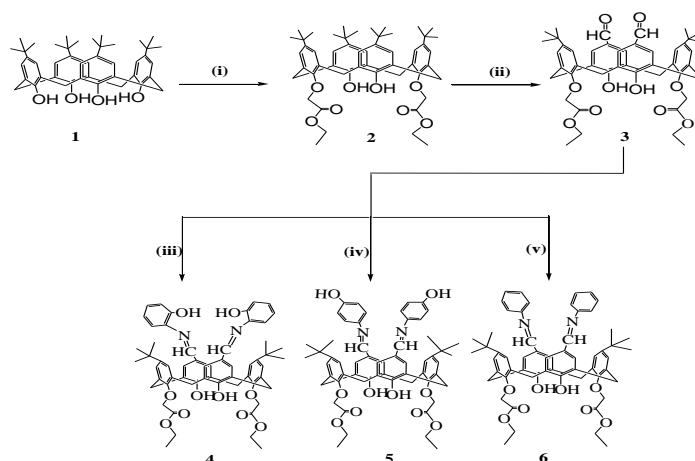
Scheme 1. Synthesis of calix-coumarin schiff's base derivative **4, 5, 6;** (i) BrCH$_2$CO(O)C$_2$H$_5$, K$_2$CO$_3$, CH$_3$CN, reflux, 48h; (ii) HMTA, TFA, reflux, 24h; (iii) *o*-hydroxy aniline, toluene, reflux,12h; (iv) *p*-hydroxy aniline, toluene, reflux,12h; (v) aniline, toluene, reflux,12h.

Following similar method, schiff's bases **5** and **6** were synthesized using *p*-hydroxy aniline/ aniline (1.1 equivalents per one formyl group) respectively in place of *o*-hydroxy aniline. Rest of the work up procedures are same as described above.

For detailed study, a reference compound of calixarene based schiff's base was also synthesized by using *p*-hydroxy benzaldehyde **7** and refluxing it with *o*-hydroxy aniline (1.1 equivalent) in toluene to give desired reference compound **8**.

The protocol adopted for the synthesis of a series of novel calix[4]arene based schiff's bases **4, 5** and **6** is depicted in **scheme 1**. The procedure for synthesis of reference compound of calix[4]arene based schiff's base 4 is depicted in **scheme 2**.
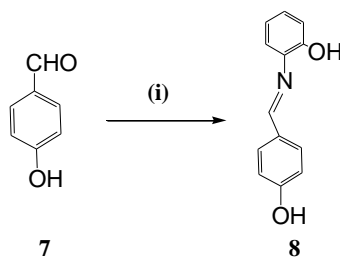
Scheme 2. Synthesis of reference compound **8**; (i) *o*-hydroxy aniline, toluene, reflux,12h.

## II.2. Charecterization of the products through NMR, FT IR and ESI-MS spectroscopy.

^{1}H NMR and ^{13}C NMR spectral analysis with combination of FT-IR and mass spectral data have proved useful to obtain the detailed structure and conformation of the synthesized compounds. For instance, compound **4,** obtained from the reaction of **3,** with *o*-hydroxy-aniline exhibited a molecular ion peak at *m/z* 948.120 (M$^+$+1) in its ESI-MS mass spectrum which indicated the substitution of *o*-hydroxy-aniline units in the molecule. The disappearance of a strong absorption bands at 1689 cm^{-1} in the FT-IR spectrum of **3** clearly suggested the absence of aldehyde functions in the molecule while the absorption bands appearing at 1623cm^{-1}, 1677cm^{-1} and 3286cm^{-1} showed CH=N, C=O and –OH functions in the molecule. ^{1}H NMR spectrum of **4** in CDCl$_3$ (fig. 1) revealed no signal at δ 9.77 that could be attributed to the aldehyde protons indicated the transformation of aldehydic functions during the reaction.
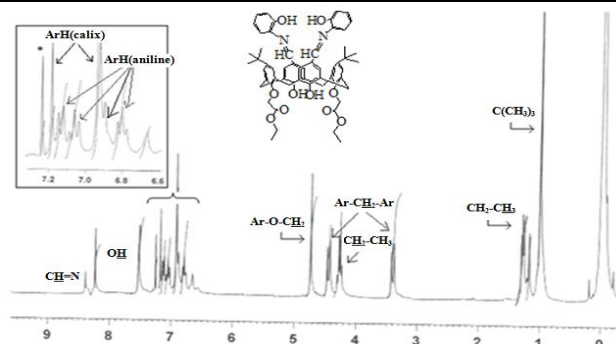
Figure 1. ^{1}H NMR spectrum of **4** in CDCl$_3$.

Two deuterium exchangeable singlets were observed at δ 8.38 and δ 7.53 which could be assigned to the OH protons of calix[4]arene and that of *o*-hydroxyaniline respectively. A non-D$_2$O exchangeable singlet that appeared at δ 8.40 could be assigned to the azomethine (C$\underline{H}$=N) protons of the schiff's base subunits. Detailed analysis of the proton NMR spectrum of **4** revealed the proton resonances at δ 7.16 (s) and 6.93 (s) were assigned for ArH$_{calix}$ and peaks at δ 7.14 (d), 7.06 (t), 6.89 (d) and 6.79 (t) for aromatic protons of *o*-hydroxy aniline. O-C$\underline{H}_2$ protons of the ester moiety appeared as a singlet at δ 4.74; while a quartet and a triplet at δ 4.28 (q) and 1.31 (t) could be assigned to the C$\underline{H}_2$-CH$_3$, CH$_2$-C$\underline{H}_3$ protons respectively. The methylene bridge protons of compound **4** exhibited a pair of doublet in its ^{1}H NMR spectrum which indicated a symmetrical cone conformation of **4**. The doublet at the higher chemical shift of δ 4.47 could be ascribed to the *endo* protons while that at δ 3.36 was due to the *exo* protons of the methylene bridge of calix[4]arene. This pattern of methylene bridge proton signals absolutely corroborated the symmetrical cone conformation of **4** which was further confirmed from its ^{13}C NMR spectrum that revealed a distinct carbon signal at δ 30.1 ppm for the methylene bridge carbon atoms in cone conformation [28]. The *tert*-butyl protons of calixarene appeared as a singlet at δ 1.01.

Individual assignment of this complex pattern of aromatic signals of **4** was confirmed by COSY experiments. For instance, the COSY spectrum of **4** (fig. 2) exhibited four cross correlation peaks in the aromatic region.
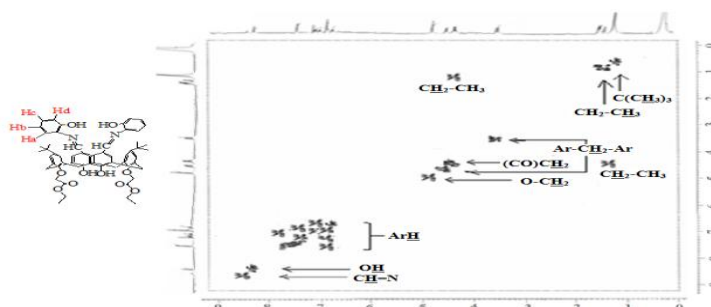

Figure 2. ^{1}H-^{1}H cosy spectrum of **4** in CDCl$_3$ at 25°C.

The coupling of the doublet and triplet at δ 7.14 and at δ 7.06 gave a cross correlation peak which indicated that these signals corresponded to the aromatic protons H$_a$ and H$_b$ of the *o*-hydroxy aniline unit present at the upper rim of the molecule. Similarly the other correlation peak that appeared for the coupling of two triplets at δ 7.06 and 6.79 for the four aromatic protons indicated that these signals correspond to the aromatic protons H$_b$ and H$_c$. A third correlation peak that appeared for the coupling of a triplet at δ 6.79 and a doublet at δ 6.89 could be assigned to the aromatic protons of the H$_c$ and H$_d$ of the *o*-hydroxy aniline unit; while the fourth cross peak could be ascribed to the coupling of the quatret at δ 4.26 and a triplet at δ 1.29 which confirmed that these signals corresponded to the C$\underline{H}_2$-CH$_3$ protons of the ester units.

Detailed spectral data for characterization of compounds **4**, **5**, **6** and **8** are listed in Table1 and Table 2.

II.3. Analysis of binding characteristics of ligand 4 by UV visible spectroscopy.

In order to evaluate binding affinities of synthesized calix[4]arene based schiff's bases **4**, **5** and **6** towards metal ions, UV-vis spectroscopic studies were conducted with transition-metal ions (Fe^{3+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Ag$^+$, Pb^{2+}, Hg^{2+}), alkali metal ions (Li$^+$, Na$^+$, K$^+$) and alkaline-earth metal ions (Mg^{2+}, Ca^{2+}, Ba^{2+}) in solution using acetonitrile as the solvent. It was observed that out of these, compound **4** was found to show significant interaction with Cu^{2+} ion (fig. 3a).
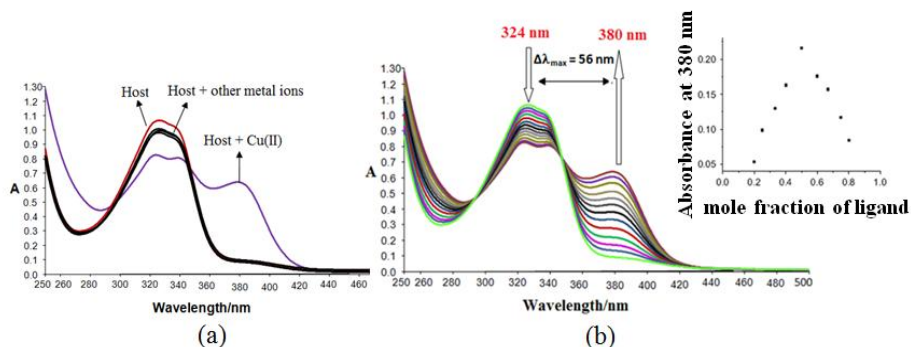
Figure 3. (a) UV-visible spectra of **4** and shifts in its □ maxupon addition of alkali, alkaline and transition metal cations; (b) UV-visible titrations of **4** (1×10^{-5}M) with 0 to 6 equiv. of Cu(ClO₄)₂.6H₂O in acetonitrile. Inset: Job's continuous variation plot indicating 1:1 complex stoichiometry between **4** and Cu²⁺.

Gradual addition of a standard solution of Cu(ClO₄)₂.6H₂O in a UV-visible titration experiment of **4** with Cu²⁺ ions exhibited a progressive decrease in the intensity of the absorption peak at 324 nm with concurrent increase in the new absorption band centered at 380 nm in the UV-visible spectrum (fig. 3b). It exhibited a bathochromic shift ($\Delta\lambda_{max}$) of about 56 nm, with appearance of a clear isosbestic point at 348 nm, during the spectral titration, indicating the formation of a well defined **4**-Cu²⁺ complexation. These observations indicated that compound **4** has high sensitivity and selectivity for Cu²⁺.

To compare whether there is any role of calixarene network in sensing copper, a reference compound **8** was synthesized from o-hydroxy benzaldehyde and *o*-hydroxy aniline. UV-vis spectral analysis revealed no affinity of the reference compound towards sensing copper indicating that the cavity of parent calix[4]arene plays very important role in sensing copper.

Quantitative analysis of the binding characteristics of **4** with Cu²⁺ ions when determined by Job's continuous variation plots. It revealed a maximum absorbance at 0.5 mole fraction of ligand to indicate a 1:1 binding stoichiometry for the interaction between **4** and copper ions. The association constant (K_s) of **4**-Cu²⁺ complex was determined following Benesi-Hildebrand equation [29]. A plot of measured absorbance [$1/(A - A_0)$] at 380 nm versus $1/[Cu^{2+}]$ was found to exhibit a linear relationship (y = (1.73×10^{-5})x + 0.6721 and correlation coefficient, $R = 0.99639$) thereby indicating a 1:1 binding stoichiometry between the Cu²⁺ ion and **4** (fig. 4).
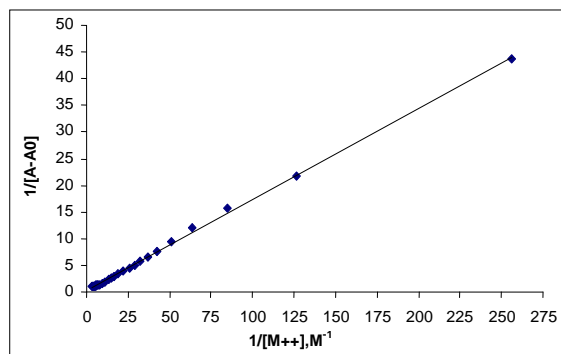
Figure 4. Benesi-Hildebrand plot of **4** (3.8×10^4 M⁻¹) with Cu(II) in acetonitrile.

The slope (m) and intercept (c) of the linear plot were found to be 1.73×10^{-5} and 0.6721 respectively. The association constant (K_s) of **4** in the presence of Cu²⁺ ion was determined from slope (m) and intercept (c) values by using the following equation.

K_s = intercept/slope = c/m

Therefore, $K_s = 0.6721/(1.73 \times 10^{-5}) = 3.8 \times 10^4$ M⁻¹

III.   CONCLUSION

A series of novel calix[4]arene based schiff's bases were designed and synthesized. The compounds were characterized using various spectroscopic techniques like NMR, FT-IR and ESI-MS spectroscopy. Detailed analysis of ¹H NMR and ¹³C NMR spectra revealed that all the compounds synthesized remain in cone conformation. In order to study their chemosensor properties, effects of different monovalent and divalent metal ions on them were studied using UV visible absorption spectroscopy in an acetonitrile solution. Out of them, compound **4** was found to show selective and efficient binding towards Cu²⁺ ion. Its metal binding affinity and binding constant studies revealed a 1:1 binding stocheometry of the ligand with Cu²⁺ ion. The reason for host

compound **4** to selectively recognize Cu^{2+} may be the "size-fit" effect of the calix[4]arene cavity in addition to π-cation-interaction strengthened by a change in dipole moment of the chromophore through possible charge transfer induced by Cu(II) binding. Studies when compared with a reference compound bearing the same functional group, other than the calix[4]arene network, it was confirmed that both the cavity of calix[4]arene along with the functional groups of the schiff's base moiety together make compound **4** an efficient chemosensor for Cu^{2+} recognition.

Table I: (Characterization of Compounds 4, 5, 6 and 8)

Comp. No.	Yield %	m.p.^{o}C	M. Formula (m.wt)	MS (m/z)
4	56 %	236-238	$C_{58}H_{62}N_2O_{10}$ (947.1203)	948.121 (M$^+$+1)
5	64 %	220-222	$C_{58}H_{62}N_2O_{10}$ (947.1203)	948.447 (M$^+$+1)
6	60 %	>250	$C_{58}H_{62}N_2O_8$ (915.1215)	939.454 (M$^+$+1+ Na)
8	45 %	180-182	$C_{13}H_{11}NO_2$ (213.2319)	214.082 (M$^+$+1)

Table II: IR and ^{1}H-NMR Spectral Data of Compounds (4, 5, 6 and 8).

Compound No.	IR (KBr, υ_{max}/cm^{-1})	^{1}H NMR (300 MHz, CDCl$_3$, δ in ppm)
4	3286(OH), 1677(C=O), 1623(C=N).	8.40 (s, 2H, C**H**=N), 8.38 (s, 2H, O**H**), 7.53(s, 2H, O**H**), 7.16(s, 4H, Ar**H**$_{calix}$), 7.14 (d, 2H, J=7.8 Hz, Ar**H**$_{aniline}$), 7.06 (t, 2H, J=13.5 Hz, Ar**H**$_{aniline}$), 6.93(s, 4H, Ar**H**$_{calix}$), 6.89 (d, 2H, J=9.8 Hz, Ar**H**$_{aniline}$), 6.79 (t, 2H, J=12.3 Hz, Ar**H**$_{aniline}$), 4.74 (s, 4H, ArOC**H**$_2$), 4.47 (d, 4H, J=16.5 Hz, ArC**H**$_2$Ar), 4.28 (q, 4H, J=7.2 Hz, C**H**$_2$CH$_3$), 3.36 (d, 4H, J=16.5 Hz, ArC**H**$_2$Ar), 1.31(t, 6H,J=18.3 Hz, CH$_2$-C**H**$_3$), 1.01(s, 18H, C(C**H**$_3$)$_3$).
5	3286(OH), 1677(C=O), 1623(C=N).	8.35 (s, 2H, C**H**=N), 8.37 (s, 4H, OH), 7.56-7.47(m, 10H, 8 x Ar**H**, 2 x OH), 6.77-6.72(m, 8H, Ar**H**), 4.60 (s, 4H, ArOC**H**$_2$), 4.34 (d, 4H, J=6.8 Hz, ArC**H**$_2$Ar), 4.21(q, 4H, J=7.6 Hz, C**H**$_2$CH$_3$), 3.32 (d, 4H, J=6.8 Hz, ArC**H**$_2$Ar), 1.21(t, 6H, J=11.2 Hz, CH$_2$-C**H**$_3$), 0.88(s, 18H, C(C**H**$_3$)$_3$).
6	3288(OH), 1670(C=O), 1610(C=N).	8.51(s, 2H, C**H**=N), 7.67 (s, 2H, O**H**), 7.62 (s, 2H, O**H**), 7.26 (s, 4H, Ar**H**calix), 7.21-7.14 (m, 4H, Ar**H**$_{aniline}$), 6.92 (s, 4H, Ar**H**calix), 6.82-6.65 (m, 4H, Ar**H**$_{aniline}$), 4.79 (s, 4H, ArOC**H**$_2$), 4.50 (d, 4H, J= 7.3Hz, ArC**H**$_2$Ar), 4.34 (q, 4H, J= 12.6Hz, C**H**$_2$CH$_3$), 3.47 (d, 4H, J=7.3 Hz, ArC**H**$_2$Ar), 1.39(t,6H, CH$_2$-C**H**$_3$), 1.03(s, 18H, C(C**H**$_3$)$_3$)
8	3200(OH), 1622(C=N)	8.54 (s, 1H, C**H**=N), 7.77(s, 1H, O**H**), 7.72(s, 1H, O**H**), 7.11(d, 2H, J=7.6 Hz, Ar**H**), 6.92-6.71 (m, 6H, Ar**H**)

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