CHAPTER-II

SYNTHESIS, CHARACTERIZATION AND COMPETITIVE BINDING PROPERTY OF A FAMILY OF CALIX-CROWN HYBRID IONOPHORE
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**Chapter: II Synthesis, Characterization and Competitive Binding Property of a Family of Calix-Crown Hybrid Ionophore**

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References
2.1. Introduction

Calixarenes, which are macrocyclic oligomers, made up of phenol units linked by methylene bridge, are receiving increasing attention because of their ability to bind variety of ions.\textsuperscript{1-7} In the calixarene family, calix[4]arenes are most popular because of their rigid structures, which make them ideal candidates for the complexation with metal ions.\textsuperscript{1-16} This chemistry has become even more versatile because of the ease with which calix[4]arene can be modified depending on the requirement. These modified calixarenes provide a highly preorganized architecture for the assembling of converging binding sites.\textsuperscript{17-22} Among these calixarene derivatives, calix[4]arene-crown ethers have attracted intense interest as alkali-metal-selective extractants.\textsuperscript{23-32} The ion selectivity of this class of compounds is controlled mainly by the conformation of the calixarene platform, the size of the crown ether ring and substituents attached with the calix or crown moiety(s). Among various conformations of the calixarene, 1,3-alternate conformers have been studied extensively as complexing agent for alkali-metal ions.\textsuperscript{26-39} Other conformers have also been prepared but metal ion complexation studies are rare. Among various crown ethers, crown-5 and crown-6 containing calixarene derivatives are found more suitable for complexation with alkali-metal ions.\textsuperscript{22-32} Synthesis of a series of \textit{p}-tert-butylcalix[4]arene-crown-5/6 with various substituents in lower rim and study on their competitive complexation property with selected alkali and alkaline earth metal ions has also been reported from this laboratory.\textsuperscript{29-32}

In this Chapter, synthesis and competitive complexation property of calix[4]arene-crown-n (n = 4, 5 and 6, Fig. 2.1) with the metal ions Li\textsuperscript{+}, Na\textsuperscript{+}, K\textsuperscript{+}, Mg\textsuperscript{2+}, Ca\textsuperscript{2+} and Sr\textsuperscript{2+} has been reported. Selectivity of these ionophores towards the above mentioned metal ions has been evaluated by two-phase extraction using aqueous solution containing equimolar mixture of these ions. The concentration of metal ion in the extract (organic phase) has been estimated by ion chromatographic assay. Association constants for strongly interacting metal ions were also determined. The molecular structures of the Na\textsuperscript{+} and K\textsuperscript{+} complexes of the two ionophores were also determined by single crystal X-ray study.
2.2. Experimental section

2.2.1. Materials

The compound 2-hydroxy-5-nitrobenzyl bromide was purchased from Sigma-Aldrich and other chemicals were purchased from S.D Fine chemicals. All the solvents were of analytical grade and purified by standard procedures before use. Milli-Q (Millipore Corporation) water was used for extraction and ion chromatography. Metal picrate salts were prepared by the reaction of picric acid and metal hydroxide in aqueous media. The reagents 2-(2-chloroethoxy)ethyl, 4-methylbezene sulfonate and pentaethylene glycol ditosylate were prepared following the literature procedures. The starting materials such as p-tert-butyl calix[4]arene, dealkylated calix[4]arenes were synthesised following the literature procedure.

2.2.2. Physical measurement

Elemental analysis (C, H & N) was performed on a model Vario Micro CUBE elemental analyzer. Mass spectra were recorded on a Q-TOF Micro™ LC-MS instrument. Infrared spectra were recorded on a Perkin-Elmer spectrum GX FT-system as KBr pellets. NMR spectra were recorded on models DPX200 and Avance II 500 Bruker FT-NMR instruments. The UV/VIS spectra were recorded on a CARY 500 scan Varian spectrophotometer. The cation concentration was measured with a Dionex 500 ion chromatography. Single crystal X-ray structures were determined using a Bruker SMART1000 (CCD) diffractometer.
2.2.3. Synthesis of calix-crown hybrid ionophores (1-3)

The ionophores 1-3 were synthesized following the modified literature procedure. In a typical procedure, a mixture of calix[4]arene (3.0 g, 7.1 mmol), tri-/tetra-/penta-ethyleneglycol di-p-toluenesulfonate (7.1 mmol) and K₂CO₃ (0.98 g, 7.1 mmol) in 100 mL of acetonitrile was refluxed under nitrogen for 24 h (in case of triethyleneglycol di-p-toluenesulfonate refluxing continued for 10 days). After complete reaction (checked by TLC) the solvent was removed under reduced pressure. To the resulting crude product, 100 mL of 5% aqueous HCl and 50 mL of CH₂Cl₂ were added; the organic layer was washed with 50 mL of aqueous HCl and was dried over anhydrous MgSO₄. The solvent was evaporated using rotavapour to give brown coloured oil, which was purified by column chromatography over silica gel using ethyl acetate-hexane (1:3) as eluent to get the desired product (yield, 70-75 % ) as a white solid.

**Characterization data for 1**: Elemental analysis, calculated for C₃₄H₃₄O₆: C, 75.82; H, 6.36. Found: C, 75.08; H, 6.38; ES-MS, m/z: 561.91 [1+Na⁺] (calculated, 561.58), Selected IR band (KBr pellet, cm⁻¹) 3374 (OH), 1460 (C=C, aromatic), ᵃ¹H NMR (CDCl₃, 500 MHz, ppm): δ 7.42 (s, 2H, Ar-OH); 7.06 (d, 4H, J = 7.5 Hz, Ar-H); 7.03 (d, 4H, J = 7.5 Hz, Ar-H); 6.83 (t, 2H, J = 7.5 Hz, Ar-H); 6.61 (t, 2H, J = 7.5 Hz, Ar-H); 4.38 (d, 4H, J = 13.0 Hz, ArCH₂Ar); 4.24 (broad s, 4H, crown-CH₂); 4.19 (d, 4H, J = 3.0 Hz, crown-CH₂); 4.02 (s, 4H, crown-CH₂); 3.41 (d, 4H, J = 13.0 Hz, ArCH₂Ar).

**Characterization data for 2**: Elemental analysis, calculated for C₃₆H₃₈O₇: C, 74.21; H, 6.57. Found: C, 73.71; H, 6.43; ES-MS, m/z: 605.70 [100%, 2+Na⁺], 621.68 [36%, 2+K⁺] (calculated, 605.63 and 621.74, respectively), Selected IR band (KBr pellet, cm⁻¹) 3370 (OH), 1461 (C=C, aromatic), ᵃ¹H NMR (CDCl₃, 500 MHz, ppm): δ 7.74 (s, 2H, Ar-OH); 7.074 (d, 2H, J = 7.5 Hz, Ar-H); 7.05 (d, 2H, J = 7.5 Hz, Ar-H); 6.87 (d, 4H, J = 7.5 Hz, Ar-H); 6.72 (t, 4H, J = 7.5 Hz, Ar-H); 6.67 (t, 4H, J = 7.5 Hz, Ar-H); 4.43 (d, 4H, J = 13.0 Hz, ArCH₂Ar); 4.10 (s, 8H, crown-CH₂); 3.96 (t, 4H, J = 5.5 Hz, crown-CH₂); 3.86 (t, 4H, J = 5.5 Hz, crown-CH₂); 3.37 (d, 4H J = 13.0 Hz, ArCH₂Ar).

**Characterization data for 3**: Elemental analysis, calculated for C₃₈H₄₂O₈: C, 72.83; H, 6.75. Found: C, 71.70; H, 6.58; ESI-MS, m/z: 649.38 [85%, 3+Na⁺], 665.35 [100%,
3+K\(^+\}) (calculated, 649.67 and 665.78, respectively). Selected IR band (KBr pellet, cm\(^{-1}\)) 3360 \(\nu\) (OH), 1459 \(\nu\) (C=C, aromatic). \(^1\)H NMR (CDCl\(_3\), 500 MHz, ppm): \(\delta\) 7.50 (s, 2H, Ar-OH); 7.07 (d, 2H, \(J = 7.5\) Hz, Ar-H); 7.05 (d, 2H, \(J = 7.5\) Hz, Ar-H); 6.84 (d, 4H, \(J = 7.5\) Hz, Ar-H); 6.73 (t, 4H, \(J = 7.5\) Hz, Ar-H); 6.67 (t, 4H, \(J = 7.5\) Hz, Ar-H); 4.41 (d, 4H, \(J = 13.0\) Hz, ArCH\(_2\)Ar); 4.14 (t, 4H, \(J = 4.5\) Hz, crown-CH\(_2\)); 4.01 (t ,4H, \(J = 4.5\) Hz, crown-CH\(_2\)); 3.93 (t, 4H, \(J = 4.5\) Hz, crown-CH\(_2\)); 3.84 (t, 4H, \(J = 4.5\) Hz, crown-CH\(_2\)); 3.71 (s, 4H, crown-CH\(_2\)); 3.37 (d, 4H, \(J = 13.0\) Hz, ArCH\(_2\)Ar).

### 2.2.4. Procedure followed for two-phase extraction of metal ions

Selectivity of the ionophores towards Li\(^+\), Na\(^+\), K\(^+\), Mg\(^{2+}\), Ca\(^{2+}\) and Sr\(^{2+}\) was determined using equimolar mixture of the picrate salts of these ions. In a typical procedure, equal volume (10 mL) of aqueous solution of equimolar mixture of alkali metal picrate (Li\(^+\), Na\(^+\), K\(^+\), Mg\(^{2+}\), Ca\(^{2+}\) and Sr\(^{2+}\)) and CH\(_2\)Cl\(_2\) solution (10 mL) of the required ionophore (0.002 M) were mixed and vigorously shaken in a vortex mixture for 30 min and the solution was transferred to a separating funnel and allowed to stand for 4-5 h. The metal ions added with stoichiometric amount and also with 25, 50, 75 and 100 times excess compared to the concentration of ionophores. After settling down, the dichloromethane layer was separated and transferred to a crucible, the solvent was evaporated by gentle heating on a water bath, and then heated in a furnace at 550 °C for 4-5 h. The residue was dissolved in deionized water (~ 5 mL) and filtered on 0.2 μm filter paper. The relative concentrations of the cations in the filtrate were determined by ion chromatography using Ion Pac CS12 (2 mm) analytical column and 20 mM methylsulphonic acid as eluent with a flow rate of 0.25 mL/min. Quantification was made using a standard solution containing a mixture of LiCl, NaCl, KCl, MgCl\(_2\), CaCl\(_2\) and SrCl\(_2\) (10 ppm each).

### 2.2.5. Synthesis of Na\(^+\) and K\(^+\) complexes for the ionophores 2 and 3

In a typical procedure, a mixture of 0.05 mmol of the required ionophores (2/3) and Na\(^+\)/K\(^+\) picrate (0.5 mmol, ten-fold excess) was stirred in chloroform at room temperature for 24 h. The reaction mixture was then filtered to remove unreacted picrate salt and the complex was obtained by removing the solvent from the filtrate under vacuo. The yellow complex thus obtained was dissolved in a minimum amount
(ca. 3 mL) of dichloromethane (in which Na\(^+\)/K\(^+\) picrate is almost insoluble) followed by filtration to remove trace quantities of unreacted Na\(^+\)/K\(^+\) picrate. The solution was further evaporated to dryness to get yellow product. The \(^1\)H NMR spectra of the complex did not show any signal corresponding to free compound or excess picrate anion, which confirmed the complete complexation. Yield: 90–95%.

**Characterization data for 2.Na\(^+\).Pic**: Elemental analysis, calculated for C\(_{42}\)H\(_{39}\)Na\(_3\)O\(_{14}\): C, 60.58; H, 4.72; N, 5.05. Found: C, 60.26; H, 4.57; N, 4.98; ES-MS, m/z: 605.29 [100%, \(2+\text{Na}^+\)], 621.40 [47%, \(2+\text{K}^+\)] (calculated values, 605.63 and 621.74, respectively). Selected IR band (KBr pellet, cm\(^{-1}\)) 3419 \(\tilde{\nu}(\text{OH})\), 1635, 1561 (NO\(_2\) of picrate), 1460 \(\tilde{\nu}(\text{C=C, aromatic})\), \(^1\)H NMR (CDCl\(_3\), 500 MHz, ppm): δ 8.66 (s, 2H, picrate); 7.40-7.01 (m, 2H, Ar-OH, and 8H, Ar-H); 6.72-6.67 (m, 4H, Ar-H); 4.21 (br s, 4H, crown-CH\(_2\)Ar); 4.11 (br s, 4H, crown-CH\(_2\)); 3.99 (br s, 4H, crown-CH\(_2\)); 3.86 (m, 8H, crown-CH\(_2\)); 3.37 (d, 4H, J = 13.5 Hz, ArCH\(_2\)Ar).

**Characterization data for 2.K\(^+\).Pic**: Elemental analysis, calculated for C\(_{42}\)H\(_{39}\)KN\(_3\)O\(_{14}\): C, 59.43; H, 4.63; N, 4.95. Found: C, 58.76; H, 4.87; ESI-MS, m/z: 605.71 [53%, \(2+\text{Na}^+\)], 621.70 [100%, \(2+\text{K}^+\)] (calculated values, 605.63 and 621.74, respectively), Selected IR band (KBr pellet, cm\(^{-1}\)) 3431 \(\tilde{\nu}(\text{OH})\), 1635, 1559 (NO\(_2\) of picrate), 1459 \(\tilde{\nu}(\text{C=C, aromatic})\), \(^1\)H NMR (CDCl\(_3\), 500 MHz, ppm): δ 8.63 (s, 2H, picrate); 7.18-7.14 (m, 2H, Ar-OH and 4H, Ar-H); 7.04 (d, 4H, J = 6.5 Hz, Ar-H); 6.74-6.66 (m, 4H, Ar-H); 4.23 (d, 4H, J = 14.0 Hz, ArCH\(_2\)Ar); 4.16 (br s, 4H, crown-CH\(_2\)Ar); 4.11 (br s, 4H, crown-CH\(_2\)); 3.90 (s, 4H, crown-CH\(_2\)); 3.75 (s, 4H, crown-CH\(_2\)); 3.37 (d, 4H, J = 14.0 Hz, ArCH\(_2\)Ar).

**Characterization data for 3.Na\(^+\).Pic**: Elemental analysis, calculated for C\(_{44}\)H\(_{43}\)Na\(_3\)-O\(_{15}\): C, 60.27; H, 4.94; N, 4.79. Found: C, 60.49; H, 5.10; N, 4.66; ES-MS, m/z: 649.67 [100%, \(3+\text{Na}^+\)], 665.69 [80%, \(3+\text{K}^+\)] (calculated values are 649.67 and 665.78, respectively), Selected IR band (KBr pellet, cm\(^{-1}\)) 3418 \(\tilde{\nu}(\text{OH})\), 1617, 1557 (NO\(_2\) of picrate), 1465 \(\tilde{\nu}(\text{C=C, aromatic})\), \(^1\)H NMR (CDCl\(_3\), 500 MHz, ppm): δ 8.87 (s, 2H, picrate); 7.63 (s, 2H, Ar-OH); 7.06 (d, 4H, J = 7.5 Hz, Ar-H); 6.86 (d, 4H, J = 7.5 Hz, Ar-H); 6.73 (t, 2H, J = 7.5 Hz, Ar-H); 6.69 (t, 2H, J = 7.5 Hz, Ar-H); 4.31 (d, 4H, J =
13.5 Hz, ArCH₂Ar); 4.20 (br s, 4H, crown-CH₂); 3.81 (br s, 4H, crown-CH₂); 3.76 (br s, 8H, crown-CH₂); 3.47 (s, 4H, crown-CH₂); 3.39 (d, 4H, J = 13.5 Hz, ArCH₂Ar).

**Characterization data for 3.K⁺.Pic**: Elemental analysis, calculated for C₄₄H₄₃KN₃O₁₅: C, 59.18; H, 4.85; N, 4.71. Found: C, 58.89; H, 4.91; N, 4.60; ES-MS, m/z: 649.50 [30%, 3+Na⁺], 665.33 [100%, 3+K⁺] (Calcd. 649.67 and 665.78, respectively). Selected IR band (KBr pellet, cm⁻¹) 3433 ν (OH), 1615, 1533 (NO₂ of picrate), 1464 ν (C=C, aromatic). ¹H NMR (CDCl₃, 500 MHz, ppm); δ 8.84 (s, 2H, picrate); 7.19 (s, 2H, Ar-OH); 7.08 (d, 4H, J = 7.5 Hz, Ar-H); 6.81 (d, 4H, J = 7.5 Hz, Ar-H); 6.72 (t, 2H, J = 7.5 Hz, Ar-H); 6.70 (t, 2H, J = 7.5 Hz, Ar-H); 4.22 (d, 4H, J = 13.5 Hz, ArCH₂Ar); 3.90 (br s, 4H, crown-CH₂); 3.79 (br s, 4H, crown-CH₂); 3.69 (br s, 4H, crown-CH₂) 3.54 (s, 4H, crown-CH₂); 3.41 (d, 4H, J = 13.5 Hz, ArCH₂Ar).

### 2.2.6. Single crystal X-Ray study
Crystals of suitable size of the Na⁺/K⁺ complexes were selected, immersed in partone oil and then mounted on the tip of a glass fiber using epoxy resin. Intensity data for all three crystals were collected at 100 K using graphite monochromatised MoKα radiation (λ=0.71073Å) on a Bruker SMART APEX diffractometer equipped with CCD area detector. The data integration and reduction were processed with SAINT software. An empirical absorption correction was applied to the collected reflections with SADABS. The structures were solved by direct methods using SHELXTL and refined on F2 by the full-matrix least-squares technique using the SHELXL-97 package. Graphics are generated using PLATON and MERCURY 1.3. Even though data was collected under 150 K, some of the atoms in the crown moiety showed dynamic disorder and the occupancy factor and positions for the disordered atoms were determined using FAVR and PART command. In all the compounds non-hydrogen atoms were refined anisotropically till convergence is reached and the hydrogen atoms attached to the ligand moieties were stereochemically fixed. Crystallographic parameters for both the compounds are given in Table 1.

### 2.2.7. Method followed for the determination of association constant
The molar ratios of picrate to host (R) were determined by equation (1), where A is the observed absorbance in the aqueous phase, D is the dilution factor, ε is the extinction
Table 1. Crystallographic parameters for both the compounds

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<td>C₄₄H₄₄N₃NaO₁₅</td>
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<td>Yellow</td>
<td>Yellow</td>
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<td>110(2)</td>
<td>293(2)</td>
<td>110(2)</td>
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<td>P21/n</td>
<td>P21/c</td>
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<td>a(Å)</td>
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<td>14.9308</td>
<td>10.779(3)</td>
<td>10.7064(9)</td>
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<td>b(Å)</td>
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<td>25.101(3)</td>
<td>27.908(7)</td>
<td>27.437(2)</td>
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<td>c(Å)</td>
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<td>11.9078(15)</td>
<td>14.112(3)</td>
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<td>90</td>
<td>90</td>
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<tr>
<td>β(°)</td>
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<td>96.076(2)</td>
<td>98.440(5)</td>
<td>120.560(4)</td>
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<td>γ(°)</td>
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<td>90</td>
<td>90</td>
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<td>Z</td>
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<td>4</td>
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<td>V(Å³)</td>
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<td>4437.7(9)</td>
<td>4199.2(17)</td>
<td>4143.7(5)</td>
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<td>Density (Mg/m³)</td>
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<td>Reflections Collected</td>
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</table>

coefficient of the picrate salt at 380 nm in CH₃CN (ε =16900), [G⁺] the initial concentration of guest in the aqueous phase, Vₐq the volume of the aqueous phase, Vₐ₉g the volume of the organic phase, and [Hᵢ⁺] the initial concentration of the host in the CHCl₃ phase.
The molar ratio of picrate to host in organic layer ($R$) was determined in the following way. Aqueous solutions were prepared that were 0.01M in the picrate of Na$^+$ and K$^+$. In to each of two 10 mL centrifuge tubes was transferred 1 mL of the appropriate picrate solution with a syringe. 1 mL aliquots of a previously prepared chloroform solution that was 0.01 M in host were added with syringe to each tube. The two layers in each tube were mixed thoroughly using a Vortex Genie mixer for 5 min. The tubes were then placed in centrifuge for 15 min. Aliquots of 0.5 mL of the organic phase were removed from each phase with a syringe and transferred to 10 mL volumetric flask which was brought to the mark with acetonitrile. The absorbance of each sample at 380 nm was then determined and the molar ratios of picrate to host ($R$) was then calculated using eq 1. The distribution constants ($K_d$) were determined using equation 2. In a typical procedure, metal picrate solution of 0.02 M in 100 mL water was added 100 mL chloroform and the mixture was shaken in a separating funnel for 5 h. The layer of the mixture was allowed to separate for 10h, and the dichloromethane layer was transferred to a round bottom flask and the solvent was evaporated by rotary evaporator. The residue was transferred with acetonitrile to a 10 mL volumetric flask and diluted with acetonitrile upto the mark. The absorbance of organic layer was measured spectrophotometrically and the value of $K_d$ was determined using equation 2.

2.3 Results and discussion

2.3.1. Synthesis and characterization of the ionophores 1-3

The ionophores 1-3 were synthesized following the modified published procedures and the route followed for the synthesis is shown in Scheme 1.\textsuperscript{29,30,40}
These compounds were characterized on the basis of elemental analysis, mass spectrometry, IR and $^1$H NMR data, which presented in the Experimental Section. Elemental analysis and mass data are in excellent agreement with the calculated values. It may be noted that the m/z values for 1 appeared as [1+Na]$^+$, whereas for 2 and 3, it appeared as both Na$^+$ and K$^+$ salt, [2/3+Na]$^+$ and [2/3+K]$^+$, with different intensity of peaks. Association with different cations in ESI-MS depends on complexation ability of the ligand with various metal ions and the variation in peak intensity depends on the stability of the complex formed. On the basis of analytical and spectroscopic data, the molecular structures assigned for 1-3 are shown in Fig. 2.1.

### 2.3.2. Ion-binding property

Ion-binding property of 1-3 towards alkali and alkaline-earth metal ions were evaluated by two-phase extraction method using equimolar mixture of metal ions. Detail of the procedure is given in the Experimental Section and the concentration of metal ions in the extracts were determined by ion chromatographic assay. The Ion chromatograms of the solution containing equimolar mixture of Li$^+$, Na$^+$, K$^+$, Mg$^{2+}$, Ca$^{2+}$ and Sr$^{2+}$ (0.0005 M each) and that of the extract obtained from the equimolar mixture by two-phase extraction using ionophore 3 with 100 times excess of metal ions is shown in the Fig. 2.2.
Fig. 2.2. Ion chromatograms of (a) solution containing equimolar mixture of Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺ and Sr²⁺ (0.0005 M each), (b) and (c) the extract obtained from the equimolar mixture by two-phase extraction using ionophore 3 and 2 respectively.
It may be noted that the extract obtained from ionophore 1 exhibited only trace amount of a few metal ions, indicating poor complexing ability of this ionophore towards the metal ions tested. This is probably due to cavity size of crown-4, which is not large enough to allow the entry of the hydrated metal ion for complex formation. The organic extracts of 2 and 3 showed the presence of Na\(^+\), K\(^+\), Mg\(^{2+}\) and Ca\(^{2+}\), the distributions of metal ions in the extracts and the values of the observed selectivity ratios, are shown in Table 2. The plot of the mole fraction of the metal ions extracted against concentration of metal ions used in the extraction process for 2 and 3 are shown in Figs. 2.3 and 2.4. The result clearly suggests that these two ionophores prefer to bind Na\(^+\) and K\(^+\) over the other metal ions; Mg\(^{2+}\) and Ca\(^{2+}\) also form considerable amount of complexes but Li\(^+\) and Sr\(^{2+}\) do not form any complex with these ionophores. Small size and high hydration enthalpy (-520 and -1443 kJ mol\(^{-1}\) for Li\(^+\) and Sr\(^{2+}\), respectively) are likely the factors, which prevented this metal ion to form complex. For Sr\(^{2+}\), probably the large size of the hydrated metal ion also played important role to prevent its entry into the cavity of the ionophore to form complex. The other notable observation is that the selectivity ratio (K\(^+\)/Na\(^+\)) for 2 towards K\(^+\) and Na\(^+\) ions is 0.84 (Table 2), whereas the same for 3 is 1.08, indicating that the selectivity towards K\(^+\) over Na\(^+\) is significantly high for 3, which is due to better size matching for K\(^+\) with the crown-6 cavity.

### Table 2. Concentration of metal ions in the extract and selectivity ratio with respect to potassium ion

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration (%) of metal Ion in the extract(^{[a]})</th>
<th>Selectivity ratio(^{[b]})</th>
</tr>
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<tr>
<td></td>
<td>Li(^+)</td>
<td>Na(^+)</td>
</tr>
<tr>
<td>2</td>
<td>c</td>
<td>34.42</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>32.09</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Concentration (%) of metal ion in the original solution (before extract), Li\(^+\) = 3.18, Na\(^+\) = 10.4, K\(^+\) = 17.7, Mg\(^{2+}\) = 10.9, Ca\(^{2+}\) = 18.1 and Sr\(^{2+}\) = 39.5; \(^{[b]}\) the ratio is calculated by [% of K\(^+\) in the extract] [% of M\(^{2+}\) in the original solution]/[% of M\(^{2+}\) in the extract][% of K\(^+\) in the original solution]; \(^{[c]}\) trace amount.
Fig. 2.3. Bar diagram showing the fraction of metal ions extracted from equimolar solution of Li$^+$, Na$^+$, K$^+$, Mg$^{2+}$, Ca$^{2+}$ and Sr$^{2+}$ at different concentrations of metal ions using the ionophore 2 (concentration of the ionophore was 0.002 M).

Fig. 2.4. Bar diagram showing the fraction of metal ions extracted from equimolar solution of Li$^+$, Na$^+$, K$^+$, Mg$^{2+}$, Ca$^{2+}$ and Sr$^{2+}$ at different concentrations of metal ions using the ionophore 3 (concentration of the ionophore was 0.002 M).
2.3.3. Synthesis and characterization of Na$^+$ and K$^+$ complexes of 2 and 3

For structural elucidation the Na$^+$ and K$^+$ complexes of the ionophores 2 and 3 were synthesized. A detail of the procedure is given in the Experimental Section. These complexes were characterized on the basis of elemental analysis, mass spectrometry, IR and $^1$HNMR data and finally molecular structures were determined by single crystal X-ray study. It is interesting to note that the ESI-MS of all the four complexes exhibited $m/z$ values corresponding to both Na$^+$ and K$^+$ complexes, however the peak with 100% intensity corresponds to the metal ion, which used for synthesis of metal complex, i.e., for Na$^+$ complexes the 100% peak corresponds to [2/3. Na$^+$] and for K$^+$ complexes the 100% peak corresponds to [2/3.K$^+$], shown in the Figs. 2.5-2.8.

Fig.2.5. ES-MS spectrum of the Na$^+$ complex of the ionophore 2
Fig. 2.6. ES-MS spectrum of the K$^+$ complex of the ionophore 2

Fig. 2.7. ES-MS spectrum of the Na$^+$ complex of the ionophore 3
The $^1$H NMR spectrum of 1 and that in presence of metal ions were recorded in CDCl$_3$. However, the spectrum recorded in presence of metal ions did not show any significant change compared to that of 1, indicating that no considerable amount of complex is formed with the metal ions used for this study. The $^1$H NMR spectra of the ionophores 2 and 3 and that of its Na$^+$ and K$^+$ complexes (2/3.Na$^+$,pic and 2/3.K$^+$,pic) are shown in Figs. 2.9 and 2.10. It may be noted that in the $^1$H NMR spectra of the ionophore, a typical AB pattern was observed for the methylene bridge (Ar$\text{CH}_2$Ar) protons of the calix moiety, that is two widely separated doublets at $\delta$ = 3.90-4.65 and 3.12-3.36 ppm ($J$ = 12-13.8 Hz), which suggest that these ionophores exist in cone conformation in solution.$^{29,47,48}$ The low-field doublet is due to axial hydrogen atom and the high-field doublet is due to equatorial hydrogen atoms of the methylene bridge. These doublets are also observed in the Na$^+$ and K$^+$ complexes with slight change in chemical shifts, indicating that the cone conformation of the calix moiety is retained in the complexes. The chemical shifts of the signals due to crown moiety ($\delta$ = 3.71-4.15) changed significantly upon complexation with metal ion, indicating that the metal ion encapsulated in the crown cavity to form the complex. A few changes in chemical shifts are also noted in the aromatic region ($\delta$ = 6.67-7.06), which is due to overall

Fig.2.8. ES-MS spectrum of the K$^+$ complex of the ionophore 3
conformational change of the molecule because of the complexation with metal ion. A new peak appeared at \( \delta = 8.85 \) in the complexes are due to picrate counter anion. The \(^1\)HNMR spectra of 2 and 3 are, therefore, in consistent to the formation of complexes encapsulating metal ion in the calix-crown cavity.

**Fig.2.9.** \(^1\)H NMR spectra of the (a) ionophore 2, (b) complex 2.Na\(^+\)Pic\(^-\) and (c) complex 2.K\(^+\)Pic\(^-\) recorded in CDCl\(_3\).

**Fig.2.10.** \(^1\)H NMR spectra of the (a) ionophore 3, (b) complex 3.Na\(^+\)Pic\(^-\) and (c) complex 3.K\(^+\)Pic\(^-\) recorded in CDCl\(_3\).
To check purity of the complexes, powder X-ray diffraction patterns of all the four complexes were recorded and these diffractograms were compared with those obtained by simulation from single crystal X-ray data, good matching of both the patterns (Figs. 2.11 and 2.12) suggests that the molecular structures determined from single crystal X-ray analysis (described below) represent the bulk complexes.

**Fig. 2.11.** Experimental powder XRD patterns of the bulk complexes of 2.Na⁺.Pic⁻ and 2.K⁺.Pic⁻ vs. powder XRD patterns simulated from the single crystal X-ray data of the corresponding crystalline complexes.
Fig. 2.12. Experimental powder XRD patterns of the bulk complexes of 3.Na⁺.Pic and 3.K⁺.Pic vs. powder XRD patterns simulated from the single crystal X-ray data of the corresponding crystalline complexes.
2.3.4. Crystal structures of the Na\(^+\) and K\(^+\) complexes of 2 and 3

Suitable crystals for X-ray study of these complexes were grown from THF-toluene (2:3), except K\(^+\) complex of 3, which was grown from dichloromethane-toluene (1:1). Molecular structures of the Na\(^+\) and K\(^+\) complexes of 2 (2.Na\(^+\).Pic\(^-\) and 2.K\(^+\).Pic\(^-\)) and 3 (3.Na\(^+\).Pic\(^-\) and 3.K\(^+\).Pic\(^-\)) were determined from single crystal X-ray study and details of the crystallographic parameters are given in Table 1. The diagrams of the molecular structures of the complexes are shown in Figs. 2.13-2.16.

**Fig. 2.13.** Mercury diagram for the crystal structures of 2.Na\(^+\).Pic\(^-\) showing the labeling of coordinated atoms with the metal ions (hydrogen atoms are omitted for clarity).

**Fig. 2.14.** Mercury diagram for the crystal structures of 2.K\(^+\).Pic\(^-\) showing the labeling of coordinated atoms with the metal ions and the dimeric association in (hydrogen atoms are omitted for clarity).
Fig. 2.15. Mercury diagram for the crystal structures of 3.Na\(^+\).Pic\(^-\) showing the labeling of coordinated atoms with the metal ions (hydrogen atoms are omitted for clarity).

Fig. 2.16. Mercury diagram for the crystal structures of 3.K\(^+\).Pic\(^-\) showing the labeling of coordinated atoms with the metal ions (hydrogen atoms are omitted for clarity).
In all of these complexes, the metal ion is coordinated to one of the phenolic OH of the calix moiety and with oxygen atoms from picrate anion and crown moiety. The picrate anion is coordinated in a bidentate fashion using the oxygen atom of the deprotonated OH and one of the oxygen atoms of an adjacent nitro group. The Na$^+$ ion is six coordinated in 2.Na$^+$.pic and seven coordinated in 3.Na$^+$.pic, whereas K$^+$ is seven coordinated in 2.K$^+$.pic and eight coordinated in the complex, 3.K$^+$.pic. It is interesting to note that for Na$^+$, two of the oxygen atoms of the crown moiety and for K$^+$, one of the oxygen atoms of the crown ring do not participate in coordination. This is because of the size of the metal ions and this constrain, which the crown ring is expected to experience for coordination of all of the oxygen atoms to the same metal ion. The larger K$^+$ ion is better fitted in the cavity as evident from higher coordination number compared to Na$^+$ in the same crown ring. For 3, due to more flexibility of the larger crown ring (crown-6), more oxygen atoms could come closer to metal ion for coordination. It is noteworthy that the cone conformation of the calixarene moiety, found in the ionophore, is retained even after complexation with metal ion. The Na$^+$…O and K$^+$…O distances in both the complexes are found in the ranges 2.279(4) to 2.698(6) and 2.630(3) to 2.938(4) Å, respectively. In all of these complexes, there are several intra- and intermolecular O-H…O and C-H…O interactions, in which picrate anion is also involved. In an attempt to understand the interaction between the 2.Na$^+$.pic with lattice host p-xylene and 2.K$^+$.pic with lattice host toluene, packing and hydrogen bonding interaction has been analyzed in detail and the data are presented in Table 3. Packing diagrams with hydrogen bonding between 2.Na$^+$.Pic$^-$ and p-xylene viewed down b-axis and the interaction between 2. K$^+$.Pic$^-$ and toluene viewed down c-axis are given in Figs. 2.17 and 2.18, respectively. In the case of 2.K$^+$.Pic$^-$, the dimeric complex is involved in inter and intramolecular C-H…O and O-H…O H-bonding generating a corrugated layer along ab plane. Lattice toluene guest molecules are located in the clefts of the corrugated layer and anchored by C-H…π interaction between the phenyl hydrogen H9 of the calix ring with the centroid of the toluene guest with C1g…H9 distance 3.21 Å. For the Na$^+$.pic complex, host moiety is oriented diagonal to ac-plane involving inter and intra molecular C-H…O and O-H…O interactions. Lattice p-Xylene guest molecules are positioned between the diagonally oriented Na$^+$.pic host and anchored by C-H…O interaction. Thus, the methyl hydrogen H43A and phenyl hydrogen H46 of the symmetrically disposed host is involved in a bifurcated C-H…O
interaction with the nitro oxygen O13 of the picrate from the diagonally oriented Na⁺.pic host layers (C43-H43A...O13: H43A ..O13 = 2.40; C43...O(13) = 3.233(13); <C43-H43A...O13 = 145 and C46-H46....O13: H46....O13 = 2.59; C46...O13 = 3.310(10); C46-H46...O13 = 134). Details of the hydrogen bonding interaction for both the complexes with symmetry code are given in Table 3.

**Table 3.** Hydrogen bonding parameters for 2.Na⁺.pic and 2.K⁺.pic

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(H...A) (Å)</th>
<th>d(D...A) (Å)</th>
<th>∠D-H...A (°)</th>
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</thead>
<tbody>
<tr>
<td>2.Na⁺.pic</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>O(1)-H(1)....O(6)¹</td>
<td>2.01</td>
<td>2.789(5)</td>
<td>157</td>
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<tr>
<td>O(7)-H(7C)....O(2)¹</td>
<td>1.93(6)</td>
<td>2.715(5)</td>
<td>167(6)</td>
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<tr>
<td>C(7)-H(7A)....O(10)²</td>
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<td>3.513(6)</td>
<td>174</td>
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<tr>
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<td>3.362(7)</td>
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<tr>
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<td>3.373(7)</td>
<td>149</td>
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<tr>
<td>C(43)-H(43A)...O(13)³</td>
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<td>3.233(13)</td>
<td>145</td>
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<tr>
<td>C(46) -H(46)....O(13)⁶</td>
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<td>3.310(10)</td>
<td>134</td>
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<td>Symmetry code : 1. x,y,z 2. 1-x,1-y,1-z;  3. -1+x,y,z; 4. x,-1+y,z; 5. -1+x,y,1+z; 6. 2-x,-y,1-z</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(H...A) (Å)</th>
<th>d(D...A) (Å)</th>
<th>∠D-H...A (°)</th>
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</thead>
<tbody>
<tr>
<td>2.K⁺.pic</td>
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<tr>
<td>O(1)-H(1)....O(6)¹</td>
<td>2.10</td>
<td>2.814(3)</td>
<td>145</td>
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<tr>
<td>C(14) --H(14B) ..O(9)¹</td>
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<td>3.379(5)</td>
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</tr>
<tr>
<td>C(33)-H(33B) ..O(3)²</td>
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<td>3.365(5)</td>
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</tr>
<tr>
<td>C(35) --H(35A) ..O(8)¹</td>
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<td>3.398(4)</td>
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</tr>
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<td>C(35) --H(35A) ..O(14)¹</td>
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<td>3.277(5)</td>
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</tbody>
</table>
Fig. 2.17. Packing diagram viewed down b-axis depicting the diagonal orientation of the host complex 2.Na\(^+\).Pic\(^-\) and the C-H...O interaction (blue dotted line) between the guest \(p\)-xylene with the oxygen from the coordinated picrate anion.

Fig. 2.18. Packing diagram viewed down c-axis depicting the corrugated arrangement of the 2.K\(^+\).Pic\(^-\) dimers and the C-H...\(\pi\) (blue dotted line) interaction between the guest molecule and toluene with the phenyl hydrogen of the calix moiety.
2.3.5. Association constant for complex formation

The association constants \((K_a)\) for 2 and 3 with Na\(^+\) and K\(^+\) were determined by two phase extraction method following the published procedure, as described in the Experimental Section.\(^{29,49,50,51}\) The association constants were determined using equation (3), where \(K_a\) is the association constant, \(K_d\) is the distribution constant, \(R\) is the molar ratio of picrate to host in the organic layer, \([G_i]_{H_2O}\) is the initial concentration of the guest (metal ion/picrate), \([H_i]_{CHCl_3}\) is the initial concentration of the host (ionophore) in chloroform, \(V_{CHCl_3}\) is the volume of the organic layer (chloroform) and \(V_{H_2O}\) the volume of the aqueous layer. The association constants thus determined are given in Table 4.

\[
K_a = \frac{R}{(1 - R)K_d \left\{ \left[ \frac{[G_i]_{H_2O}}{[H_i]_{CHCl_3}} \right] \left[ \frac{V_{CHCl_3}}{V_{H_2O}} \right] \right\}^2}
\]  

(3)

Table 4. Molar ratio of picrate to host in organic layer \((R)\) and association constants \((K_a)\) for 2 and 3 with Na\(^+\) and K\(^+\)

<table>
<thead>
<tr>
<th>Ionophore</th>
<th>(R)</th>
<th>(K_a)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Na(^+)</td>
<td>K(^+)</td>
</tr>
<tr>
<td>2</td>
<td>0.19</td>
<td>0.34</td>
</tr>
<tr>
<td>3</td>
<td>0.14</td>
<td>0.37</td>
</tr>
</tbody>
</table>

The data show that the association constant for K\(^+\) is significantly higher compared to that of Na\(^+\), which is due to strong complexing ability of the larger K\(^+\) because of the better size-matching fitting of the metal ion with the crown cavity, as evident from the crystal structures. For Na\(^+\), two of the oxygen atoms of the crown moiety are not involved in making interaction with metal ion, whereas for K\(^+\) only one oxygen atom is left out for making coordination for both the ionophores. It is also interesting to note that between two ionophores, Na\(^+\) shows higher binding constant with crown-5
(2.Na⁺.Pic⁺) compared to that of crown-6 (3.Na⁺.Pic⁺), whereas K⁺ exhibits reverse order. This suggests that Na⁺ being smaller fits better with the smaller cavity size of the crown-5 of ionophore 2 to make strong interaction and the larger K⁺ ion matched well with the cavity size of the crown-6 of 3 and forms strong complex. The data is in consistent to the observation noted in the crystal structures of the complexes.

2.4. Conclusions

In summary, a number of calix[4]arene crown ethers with hybrid calix-crown cavity of different size as ionophore have been synthesized in cone conformation to evaluate their performance as complexing agent towards Li⁺, Na⁺, K⁺, Ca²⁺, Mg²⁺ and Sr²⁺. Competitive complexation study in aqueous media with the mixture of cations taken shows preferential binding of K⁺ and Na⁺ for the ionophores containing crown-5 and crown-6 as ion-binding cavity and the latter shows significantly higher selectivity towards K⁺. Ca²⁺ and Mg²⁺ also form complexes with 2 and 3 but with very poor selectivity, especially for 3. Li⁺ and Sr²⁺ do not exhibit any complex formation with these ionophores. No metal ion used in this study shows complexation with the ionophore 1. Association constants for 2 and 3 have been determined with Na⁺ and K⁺ and the values are significantly higher for K⁺. Molecular structures of the Na⁺ and K⁺ complexes have been determined by single crystal X-ray study. This study reveals that the size-matching factor plays the predominant role in ion-selectivity.
References

42. SADABS, Empirical Absorption Correction Program; University of Göttingen: Göttingen, Germany, 1997.