Chapter 4

High Dilution Synthesis of The Cryptands from Tris-(-2-aminoethyl)amine and Their Study
4.1 Introduction

The macrocyclic supramolecular structures having more than one macrocycle included in them are termed cryptands. ‘Cryptand’ is derived from the Greek word *kruptos* meaning hidden. Cryptands have multiple binding sites through which they can include metal cations with the help of supramolecular interactions. This inclusion is like hiding of cations in the pocket(s) formed by such macrocycles. Cryptands bound with such cations are known as cryptates. Binding of these supramolecular hosts with guest cations or molecules is stronger compared to binding by analogous corands or podands and is more specific. Nowadays some simple cryptands are even commercially available. The synthesis of cryptands is much more challenging than the synthesis of podands or corands because their synthesis one step synthesis requires formation of more number of cycles at a time through multiple covalent bond formation in competition with the formation of linear macromolecules. Thus their syntheses are low yielding in general. Azacryptands are cryptands containing nitrogen binding sites as part of macrocycle. A promising starting material for synthesis of azacryptand is tris(2-aminoethylamine) which is abbreviated as TREN. It was first employed in cryptand synthesis by Lehn and co-workers to get octaazacryptand.

TREN being a trifunctional flexible molecule on reaction with bifunctional linkers has probability of giving a cryptand structure under appropriate reaction conditions. Cryptand formation requires two of the TREN molecules acting as a capping agent in a three dimensional structure by reacting with three molecules of bifunctional linkers. Majority of the linkers employed are aromatic dialdehydes. 1,3- and 1,4-dialdehydes have been employed for the synthesis of azacryptands. Some of the dialdehydes which have been employed for this purpose are pyridine-2,6-dicarbaldehyde\(^3\), pyridazine-3,6-dicarbaldehyde\(^10\)-\(^13\), pyrazole-3,5-dicarbaldehyde\(^14\), triazole-2,5-dicarbaldehyde\(^15\), acridine-2,7-dicarbaldehyde\(^16\), furan-2,5-dicarbaldehyde\(^17\),\(^18\), pyrrole-2,5-dicarbaldehyde\(^18\), isophthalaldehyde\(^19\)-\(^23\), terephthalaldehyde\(^24\)-\(^32\). The reaction of TREN with dialdehydes in 2+3 reaction results in imino functionalities present in the cryptand which can be reduced to secondary amines.
The cryptands with amide linkage can be obtained from the reaction of TREN with carboxylic acids or their derivatives such as acylhalides.

Pyridine containing octa-azacryptands were synthesized and found to be distinguishing Cu(I) and Cu(II) \(^3\) (Fig. 4.1). They have been also studied in detail for their formation and stability of various metal complexes with metal cations such as Ag\(^+\), Co\(^{2+}\), Ni\(^{2+}\), Zn\(^{2+}\), Hg\(^{2+}\) using ESI mass spectrometry.\(^4\) Pyridine and salicylaldehyde derived dialdehyde resulted in expanded cryptand which was synthesized under metal free conditions \(^5\) (Fig. 4.2).

Pyridine derived polyamide cryptands were synthesized by [2+3] condensation of TREN and 2,6-pyridinedicarbonyl dichloride in dichloromethane. It recognized anions like F\(^-\), Cl\(^-\), H\(_2\)PO\(_4\)^- and CH\(_3\)COO\(^-\) with marked preference for fluoride ions \(^6-8\) (Fig. 4.3). Unsymmetrical octamidocryptand was prepared by introducing a spacer between two pyridine-2,6-diester and reacting in stepwise manner with the prepared spacer. The resulting unsymmetrical cryptand hosted both anions and metal ions.\(^6\) Pyridazine
containing cryptand was found to give heterobinuclear cryptates with Cu\(^+\), Cu\(^{2+}\) and Co\(^{2+}\) ions\(^{10-13}\) (Fig. 4.4).

The trispyrazole derived cryptand and its disilver complex were obtained by [2+3] condensation of TREN and 3,5-pyrazoledicarbaldehyde in absence as well as in presence of silver(I) ions respectively. The reduced cryptand was found to form di and tetra nuclear Cu\(^{2+}\) and Zn\(^{2+}\) complexes\(^{14}\) (Fig.4.5). Similarly 1,2,4-triazole-3,5-dicarbaldehyde derived cryptands were found to give dinuclear Ag\(^+\), trinuclear Cu\(^+\), trinuclear Ni\(^{2+}\) and Cu\(^{2+}\) complexes\(^{15}\) (Fig.4.6).
A water soluble macrobicyclic cryptand was obtained from reaction of TREN with acridine-2,7-dicarbaldehyde followed by reduction and protonation with hydrochloric acid. The cryptand was used for the detection of organic anions through complexation enhanced fluorescence \(^{16}\) (Fig. 4.7).

![Acridine dicarbaldehyde derived octa-aza cryptand](image)

**Acridine dicarbaldehyde derived octa-aza cryptand**

Fig. 4.7

The reaction of TREN with isophthalaldehyde or terephthalaldehyde resulted in isomeric cryptands. Isophthalaldehyde derived cryptands and their cryptates with Cu\(^{2+}\) and Co\(^{2+}\) were studied for their binding constant determination and their ability to bind with hydroxide and carbonate ions. \(^{19,20}\) These cryptands when incorporated in sol-gel material were found to undergo reversible binuclear Cu\(^{2+}\) complex formation and same were studied for various properties including optical sensing capability of azide anion \(^{21,22}\) (Fig. 4.8). The cryptand with amide linkage was prepared by reacting TREN with isophthaloyl dichloride or isophthaloyldiester which was found to recognize fluoride ions \(^{23}\) (Fig. 4.09). Its cofacial dicobalt complex was used to recognize cyanide ion. \(^{24}\)
The octaazacryptands from TREN and terephthalaldehyde were prepared either in presence or absence of template \(^{25-32}\) (Fig. 4.10).

These cryptands have been studied in detail for their complexation and other properties. Their copper cryptates were found to recognize azide ion with linear geometry.\(^{25}\) The corresponding zinc cryptate with one of the phenyl ring replaced with anthraceny group acting as a fluorophore showed azide sensing ability due to quenching of fluorescence in its presence \(^{26}\) (Fig.4.11).
Crystal structure of the saturated azacryptate revealed a strong affinity towards water molecules and were found to incorporate water clusters depending on anion in the cryptates (Fig. 4.12). The cryptand was also found to form infinite 2D-layered water due to its cluster formation with cryptand. Vesicular microcapsules were formed when secondary nitrogen of the saturated cryptand was acylated with long chain acid chlorides. It was found that they encapsulate hydrophilic dye molecules.

Azide recognition by zinc cryptate
Fig. 4.11

Octaamino cryptand
Fig. 4.12
When 2,6-diformylphenol was used as a linker for the cryptand formation with TREN, it resulted in the cryptands with three phenolic groups which can be easily converted to phenolate ions (Fig. 4.13). They formed dinuclear lanthanide (Ln(III)) complexes.\textsuperscript{33,34} They were also studies by electron spray mass spectrometry.\textsuperscript{35} Photophysical property study of their lanthanide complexes suggested them to be good candidates for designing of nanometric light converting devices due to their ability to convert absorbed visible light into emitted NIR radiation.\textsuperscript{36} Their heterodinuclear cryptates were synthesized by using Ln(III)-Cu(II) mixed salts.\textsuperscript{37} Cd\textsuperscript{2+} and Ag\textsuperscript{+} ions could act as templates to form [2+3] thiocryptates which have higher hydrolytic sensitivity than the phenolate analogue.\textsuperscript{38}

Laterally nonsymmetric or heterodiatomic cryptands were prepared by two step synthesis. In the first step phenolic aldehyde was reacted with tris(2-chloroethylamine) or equivalent trihalide giving tripodal trialdehydes with ether linkage which were then reacted with TREN in the presence of sodiumborohydride resulting in the heterodiatomic cryptands with tetraaza binding site at one end and triether at the other \textsuperscript{39,40} (Fig. 4.14, 4.15).
Such cryptands were prepared with the aim of binding a metal cation at only one receptor site, leaving the other site available. The other binding site could accept the other guest anion depending on the first guest accommodated. This made the metal cryptate an efficient anion sensor. Transition metal ions enter the cavity with weaker counter anions. On addition of coordination anions such as Cl\(^-\), N\(_3\)-, SCN\(^-\), the metal ion comes out the cavity and binds the cryptand outside. Thus a metal ion can be translocated depending on nature of the counter anions.

When a strong π-acceptor group such as 2,4-dinitrobenzene was attached to one of the secondary amines, the binding could be monitored by photoluminescence study. The free cryptand did not show any fluorescence due to photoinduced intramolecular electron transfer (PET) process but when metal ions like Cd(II) are bound to the cryptand, the PET is disturbed which results in fluorescence of metal cryptate. When stronger anions are added the fluorescence is quenched due to restoration of intramolecular PET because of translocation of metal ion outside the cavity. The thioether analogous of the cryptand with anthracene fluorophores substituting the nitrogens were shown to undergo translocation of copper ion inside the cavity reversibly which was detected by fluorescence on-off process (Fig. 4.16).
The cobalt(II) cryptate of the heterodiatopic cryptand with ether linkage exhibited efficient catalytic oxidation ability for conversion of olefins to epoxides and benzylic compounds to corresponding carbonyl compounds.\textsuperscript{44} Such kind of heterodiatopic and homodiatopic polyoxa-azacryptands were obtained in high yields by reaction of tripodal trialdehyde with TREN or ethylenediamine.\textsuperscript{45} Various tripodal trialdehydes were reacted with TREN resulting in the creation of dynamic combinatorial libraries of cryptands.\textsuperscript{46}

3,3'-Bis-salicylaldehydes separated by three carbon bridges were employed for the synthesis of dinuclear lanthanide cryptates by their reaction with TREN in the presence of lanthanide ions as template\textsuperscript{47} (Fig. 4.17). A flexible dialdehyde with ethylene-dioxy bridges connecting two benzaldehyde moieties at para positions has also been employed with TREN for the synthesis of the corresponding cryptand\textsuperscript{48} (Fig. 4.18).
Lanthanide cryptate

Fig. 4.17

M=Lanthanide ion

Larger imino cryptand from ether bridged dialdehyde linkers

Fig. 4.18
4.2 Aim and Objectives

After studying the supramolecular structures of corands by using chiral diamines we targeted the synthesis of cryptands by reacting the bis-aldehydes as linkers with the tripodal triamine namely tris(2-aminoethylamine) TREN, as its reactions with dialdehydes are well documented for the synthesis of variety of cryptands. The first bis-aldehyde employed for the synthesis of cryptand using TREN was 4,4’-methylene-bis-benzaldehyde by Lehn et. al. (Fig. 4.19)

Metal bridged bis aldehydes such as 2,2’-selenium-bis-benzaldehyde and 2,2’-tellurium-bis-benzaldehyde have also been employed with TREN for cryptand synthesis (Fig. 4.20). The octaazacryptands which can be obtained by the use of TREN are versatile hosts for a variety of guests including cations, anions and neutral molecules as expected, they have higher binding constants compared to the corands. Their Gd(III) cryptates can be used as NMR contrast agents.

A work on synthesis of cryptands by using TREN and methylene-bis-aldehyde was also initiated in our laboratory. In continuation of the work with the aim of the synthesis of
some novel cryptands we decided to employ different methylene-bis-aldehydes synthesized by us, as linkers and TREN as a tripodal capping partner.

4.3 Results and Discussion

With the expectation of the formation of cryptands by application of methylene-bis-aldehydes and ketones prepared by us (Chapter-2) by [2+3] cyclo condensation with the trifunctional TREN, we carried out the reaction under high dilution conditions. Various modifications in this reaction conditions were also studied when the reactions under high dilution conditions were unsuccessful.

Thus 5,5’-methylene-bis-(3-tert-butylsalicylaldehyde) was subjected to macrocyclization by its reaction with TREN under high dilution condition in dichloromethane. The progress of the reaction was slow as could be visualised by colour change of reaction mixture and by TLC monitoring. After the completion of reaction and evaporation of solvent the residue was subjected to column chromatography. The starting material and less polar products were removed by elution with 80:20 mixture of pet-ether:MDC. The major product was collected by eluting the column with dichloromethane : methanol in 99:1 ratio in 21% yield. The product was confirmed to be [2+3] cryptand with the help of its mass spectrum and was characterized by various spectral techniques while its purity was established with the help of HPLC (Fig. 4.21).

![TREN & methylene-bis(tert-butyl salicylaldehyde) derived hexa-imino cryptand 1](Fig. 4.21)
In its proton NMR a phenolic protons show a broad singlet at 14.45 δ, CH protons of imine linkage are observed at 7.80 δ and two meta coupled aromatic protons are observed as doublets at 7.14 δ and 6.23 δ. Protons at the methylene bridge are observed as a singlet at 3.58 δ and the protons on the ethylene bridge from TREN are observed at 3.50 δ and 2.88 δ with a poor resolution. An intense singlet is observed for protons of tert-butyl group at 1.34 δ. All these signals have expected integration values. From proton NMR the inclusion of a minute quantity of starting bis-aldehyde was also detected. Repeated crystallization or column chromatography did not help in its removal (Spectrum 4.2). ¹³C NMR shows twelve signals as expected ranging between 167 δ to 29 δ proving symmetrical structure of the cryptand (Spectrum 4.3).

The 2D NMR studies include a COSY establishing a clear correlation between various aliphatic and aromatic protons. The ethylene bridge correlation is observed as cross peaks at 3.5 δ and 3.88 δ (Spectrum 4.6). The cross peaks are observed in NOESY spectrum due to through space interactions between CH proton of imine linkage with aromatic proton at carbon ‘6’ as well as between tert-butyl group protons and aromatic proton at carbon ‘4’ (Fig. 4.22, Spectrum 4.7).

Fig. 4.22

¹H-¹H correlation in cryptand ⊥ as observed in NOESY

HSQC spectrum of the cryptand helps in clear assignment of each carbon signal due to its correlation with corresponding protons (Spectrum 4.8). HMBC of the cryptand was
helpful in confirming the assignments of various carbon and proton nuclei by interpreting the cross peaks observed. The up field signal for the aromatic proton between methylene bridge and imine linkage is observed at higher field as it is pointing inside the cavity experiencing the anisotropic shielding effect (Spectrum 4.9). In IR spectrum $\nu$(OH) is observed as weak bend at $3421 \text{ cm}^{-1}$ compared to strong broad bend due to various $\nu$CH. $\nu$C=N is observed at $1635 \text{ cm}^{-1}$. $\delta_{\text{as}}$(CH$_3$) and $\delta_{\text{a}}$(CH$_2$) are observed at $1439 \text{ cm}^{-1}$ while $\delta_{\text{a}}$(CH$_3$) is observed at $1360 \text{ cm}^{-1}$. (Spectrum 4.1) Q-TOF mass analysis of the cryptand shows mass peak at $1289.9 \text{ m/z}$ corresponding to its molecular ion which supports the proposed structure corresponding to [2+3] cycloimination (Spectrum 4.10).

One of the other bis-aldehydes which resulted in a successful synthesis of the cryptand was 5,5’-methylene-bis-(3-bromosalicylaldehyde) which was prepared by bromination of 5,5’-methylene-bis-salicylaldehyde in acetic acid. The reaction of bromo-bis-salicylaldehyde with TREN carried out under high dilution condition, gave a low isolated yield, compared to the earlier case, of 12% after column chromatography on silica gel (Fig. 4.23).

![Figure 4.23](image_url)

**TREN & methylene-bis(bromo-salicylaldehyde) derived hexa-imino cryptand**

Fig. 4.23

In proton NMR phenolic OH protons are observed at 15.49 $\delta$, CH protons of the imine linkage at 8.16 $\delta$, aromatic protons doublet at 7.91 $\delta$ and 5.50 $\delta$, methylene singlet at 3.54 $\delta$ and protons of ethylene bridge are observed at 3.76 $\delta$, 3.31 $\delta$ and 2.87 $\delta$ (Spectrum 4.13).
In IR ν(OH) is observed at 3450 cm$^{-1}$, νC=N at 1632 cm$^{-1}$ and δ$_s$(CH$_2$) at 1459. νAr-Br is observed at 1038 cm$^{-1}$. (Spectrum 4.12) Its Q-TOF mass spectrum gave mass peak at 1448.99 corresponding to M+23 (Spectrum 4.14).

Simlarly when 5,5’-methylene-bis-(3-methyl-salicylaldehyde) was reacted with TREN under high dilution conditions with slow addition of reactants in dichloromethane showed multiple spots which included a small amount of starting material and more polar impurity along with distinct spot of product on TLC. The residue obtained after removal of solvent gave 20% of the product after column chromatography on silicagel with DCM:MeOH mixture. The yellow solid product isolated on removal of solvent was found to be insoluble in most of the organic solvents. (Fig. 3.24) The unusual solubility and medicinal properties of compounds containing methyl group compared to the other substituents is well documented $^{51}$

Due to insoluble nature its characterization was a challenge except IR spectroscopy, for studying its NMR the sample was dissolved in CD$_3$COOD. Some unusual chemical shifts were observed in this solvent. The phenolic –OH is not observed due to its exchange with CD$_3$COOD which showed signal for residual proton for –COOH at 10.97 δ. CH protons of imine linkage shifted much downfield to 9.85 δ. The aromatic protons are in close proximity at 7.35 δ and 7.32 δ. The methylene bridge protons are seen as a singlet at
3.93 δ. The ethylene bridge connecting nitrogens give four distinct signals for all four protons between 3.7 to 2.9 δ. The methyl protons give singlet at 2.22 δ. Proton NMR (Spectrum 4.17) after adding D₂O resulted in shift due to –COOH group which was exchanged and residual water was seen at 6.84 δ (Spectrum 4.18).

In ¹³C NMR imine ‘C’ showed unusually downfield shift in CD₃COOD at 197.6 δ. The other ten carbons are observed between 158 to 14 δ value (Spectrum 4.19). In IR, stretching frequency of OH is observed at 3448 cm⁻¹, stretching frequency of imine linkage is observed at 1633 cm⁻¹, asymmetric bending of methyl group is observed at 1474 cm⁻¹, C-O stretching frequency is observed as a sharp bend at 1268 cm⁻¹ (Spectrum 4.12). In Q-TOF mass, the compound being [2+3] cryptand, mass peak corresponding to M⁺ is observed at 1037.6 m/z which is also a base peak. (Spectrum 4.20) Normal phase HPLC shows 99.77% purity of the cryptand (Chromatogram 4.21).

The closely related methylene-bis-aldehydes employed for synthesis of cryptand which did not result in the formation of the desired macromolecules were

1. 5,5’-methylene-bis-(3-nitro-salicylaldehyde)
2. 5,5’-methylene-bis-(2-methoxy-benzaldehyde)
3. 5,5’-methylene-bis-(2,4-dihydroxy-benzaldehyde)
4. 5,5’-methylene-bis-(4-hydroxy-3-methoxy-benzaldehyde)
5. 3,3’-methylene-bis-(4-N-dimethylamino-benzaldehyde)

The macrocyclisation with TREN was also attempted without success by using 5,5’-methylene-bis-(2-hydroxy-acetophenone) as a linker. The failure of this reaction is attributed to a low reactivity of ketone functionality. Failure in macrocyclisation in case of nitrosalicylaldehyde is due to higher reactivity of the formyl group which led the reaction towards polymerization rather than macrocyclization. The failure of other bis-aldehydes can’t be satisfactorily explained.
4.4 Conclusion

Synthesis of octazacryptands by [2+3] cyclocondensation of TREN and 5,5’-methylene-bis-aromatic aldehydes containing methyl, tert-butyl or bromo substitution along with a hydroxyl group at ortho position of aldehyde group involving the formation of six imine linkages has been achieved by using high dilution synthetic methodology. The structures of these macrobicyclic cryptands have been proposed on the basis of detailed NMR, studies and mass spectral characteristics. Attempts for the synthesis of cryptands by several other linking agents prepared by us did not result in any characterizable or desired product. Their reasons and remedies can be studied in future. The presence of ortho-hydroxy group seems to be a necessity due to its hydrogen bonding capability with formyl group. Increased activity of the formyl group due to the presence of nitro group has also proved to be a disadvantage. Attempts to obtain crystals for single crystal X-ray study are in progress.
4.5 Experimental

General Remarks

All the chemicals and reagents were purchased from Sigma-Aldrich, Merck, and Spectrochem. All solvents were distilled before use. Column chromatography was carried out using silica-gel (60-120 mesh). Thin layer chromatography was performed on pre-coated silicagel 60F_{254} (Merck) aluminium sheets.

Infrared spectra were recorded on Perkin-Elmer FT-IR 16PC spectrophotometer as KBr pellets. \(^1\)H NMR and \(^{13}\)C NMR were recorded on Bruker 200 or 400 MHz NMR spectrophotometer in CDCl\(_3\), DMSO or D\(_2\)O. ESI mass were recorded on Shimadzu LC-MS 2010-A and Waters Micromass Quattro micro T. M. API.. HPLC was carried out using Shimadzu LC-10AT and UFLC using Shimadzu LC-20AD. Melting points were measured in open capillaries and are uncorrected.
Synthesis of TREN (tris(3-aminoethyl)amine) derived cryptands

General synthesis.

Dichloromethane 2000ml was placed in 5L three necked round bottom flask equipped with two addition funnels and nitrogen balloon. Nitrogen gas was purged for 30 minutes. Solution of 5,5’ methylene-bis-aldehydes (0.003mol, 1eq) in 1000ml dichloromethane and TREN (tris(3-aminoethyl)amine)(0.002mol, 0.66eq) in 1000ml dichloromethane was added drop wise from addition funnels over 12 hrs to the magnetically stirred dichloromethane under N₂ atmosphere. Yellow colour was developed. Stirring was continued for further twelve hours. Solvent was removed on rotary evaporator till 50 ml solution left, which was got adsorbed on silica-gel for column chromatography. TLC showed very small amount of starting material, nonpolar product spot and many polar impurities. Starting material was eluted in MDC and single spot yellow product was separated using MDC : Methanol system (gradient).
Cryptand from TREN and 5,5’-methylene-bis-(3-tert-butyl-salicylaldehyde) 1.

5,5’-Methylene-bis-(3-tert-butyl-salicylaldehyde) (1g, 0.003mol) and TREN (tris(3-aminoethyl)amine) (0.26g, 0.002mol) reacted in 4000ml MDC to yield the compound 1.

Yield: 0.371g (21%)

M.P. = 245 °C (decomposed).

$^1$H NMR: (CDCl$_3$) δ 14.44 (s, 1H), 7.80 (s, 1H), 7.15 (d, $J = 1.6$ Hz, 1H), 6.23 (d, $J = 1.6$ Hz, 1H), 3.58 (s, 1H), 3.51 (d, $J = 4$ Hz, 2H), 2.87 (d, $J = 4$ Hz, 2H), 1.34 (s, 1H).

$^{13}$C NMR: (CDCl$_3$) δ 166.8, 159.0, 137.2, 130.3, 129.7, 128.5, 118.4, 57.6, 57.2, 39.4, 34.9, 29.3

Mass: 1289.9 (M$^+$)

HPLC Purity: 99.47%

IR (KBr disc, cm$^{-1}$): 3421 (phenol, $\nu$(O-H)), 2955 (methylene, $\nu_{as}$(C-H)), 1635 (imine, $\nu$(C=N)), 1596 (aromatic ring, $\nu$(C=C)), 1439 ($\delta$(CH$_2$)), 1360, 1266, 1210 (aromatic, $\nu$(C-N)), 1158, 1026 (aliphatic, $\nu$(C-N)), 929, 885, 852, 800, 772, 692, 670, 588, 572 (out of plane, $\delta$(C-H))
Cryptand from TREN and 5,5'-methylene-bis-(3-bromo-salicylaldehyde) 2

5,5'-Methylene-bis-(3-bromo-salicylaldehyde) (1g, 0.002mol) and TREN (tris(3-aminoethyl)amine) (0.26g, 0.002mol) were reacted in 4000ml MDC to yield the compound $\textbf{2}$. 

Yield: 135mg (12%)

M.P. = 230$^\circ$C (decomposed).

$^1$H NMR: (CDCl$_3$) $\delta$ 15.49 (s, 1H), 7.92 (d, $J = 1.6$ Hz, 1H), 7.49 (s, 1H), 5.51 (d, $J = 2.0$ Hz, 1H), 3.76 (d, $J = 8.4$ Hz, 1H), 3.54 (s, 1H), 3.31 (d, $J = 8.4$ Hz, 1H), 2.87 (s, 2H).

Mass: 1448.9 (M+23)

HPLC Purity: 93.74%

IR (KBr disc, cm$^{-1}$) : 3400 (phenol, $\nu$(O-H)), 2899 (methylene, $\nu_{as}$(C-H)), 2842 (methylene, $\nu_s$(C-H)), 1632 (imine, $\nu$(C=N)), 1576 (aromatic ring, $\nu$(C=C)), 1459 ($\delta_s$(CH$_2$)), 1368, 1278, 1235 (aromatic, $\nu$(C-N)), 1139, 1038 (aliphatic, $\nu$(C-N)), 977, 888, 843, 806, 743, 668 (out of plane, $\delta$(C-H)).
Cryptand from TREN and 5,5’-methylene-bis-(3-methyl-salicylaldehyde) 3

5,5’-Methylene-bis-(3-methyl-salicylaldehyde) (1g, 0.004mol) and TREN (tris(3-aminoethyl)amine) (0.34g, 0.002mol) were reacted in 4000ml MDC to yield the compound 3.

Yield: 0.230 g (19% yield)

M.P.= 232 °C (decomposed).

$^1$H NMR: (CD$_3$COOD) δ 9.85 (s, 1H), 7.33 (s, 1H), 7.35 (s, 1H), 3.93 (s, 1H), 3.69 (t, $J = 5.6$ Hz, 1H), 3.54 (t, $J = 5.6$ Hz, 1H), 3.30 (d, $J = 5.6$ Hz, 1H), 2.90 (t, $J = 5.2$ Hz, 1H), 2.22 (s, 3H).

$^{13}$C NMR: (CDCl$_3$) δ 197.6, 158.1, 138.4, 132.2, 131.1, 126.8, 119.8, 53.6, 39.0, 34.6, 14.0

Mass: 1037.6 (M$^+$)

HPLC Purity: 99.77%

IR (KBr disc, cm$^{-1}$) : 3448 (phenol, $\nu$(O-H)), 2915 (methylene, $\nu_{as}$(C-H)), 2843 (methylene, $\nu_s$(C-H)), 1633(imine, $\nu$(C=N)), 1438 ($\delta$(CH$_2$)), 1383, 1268 (aromatic, $\nu$(C-N)), 1164, 1075,1029 (aliphatic, $\nu$(C-N)), 927, 867, 791,752, 701, 673 (out of plane, $\delta$(C-H)).
4.6 Spectra

Spectrum 4.1

IR

Spectrum 4.2

$^1$H NMR
Spectrum 4.7

NOESY

Spectrum 4.8

HSQC
Mobile phase: MDC, Stationary phase: Silica column

<table>
<thead>
<tr>
<th>Peak</th>
<th>Name</th>
<th>Ret. Time</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EXPT C-244(Cryptand from TREN and 5,5’methylene –bis-3-tertbutyl salicylaldehyde)</td>
<td>3.006</td>
<td>99.4670</td>
</tr>
<tr>
<td>2</td>
<td>imp 1</td>
<td>3.261</td>
<td>0.4345</td>
</tr>
<tr>
<td>3</td>
<td>imp 2</td>
<td>3.534</td>
<td>0.0985</td>
</tr>
</tbody>
</table>

Spectrum 4.12

IR
Mobile phase: MDC:MeOH :: 98:2 (v/v). Stationary phase : Silica column

<table>
<thead>
<tr>
<th>Peak</th>
<th>Name</th>
<th>Ret. Time</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>imp 1</td>
<td>14.739</td>
<td>3.4113</td>
</tr>
<tr>
<td>2</td>
<td>EXPT C-185(Cryptand from TREN and 5,5’methylene –bis-3-bromosalicylaldehyde )</td>
<td>16.165</td>
<td>93.7434</td>
</tr>
<tr>
<td>3.</td>
<td>imp 2</td>
<td>16.381</td>
<td>0.2749</td>
</tr>
<tr>
<td>4.</td>
<td>imp 3</td>
<td>17.137</td>
<td>2.5704</td>
</tr>
</tbody>
</table>
Spectrum 4.17

$^1$HNMR

Spectrum 4.18

$^1$HNMR (D$_2$O exchange)
Spectrum 4.19

\[ ^{13}C\text{NMR} \]

Spectrum 4.20

Mass
HPLC

Mobile phase: MDC:MeOH :: 98:2 (v/v), Stationary phase : Silica column

<table>
<thead>
<tr>
<th>Peak</th>
<th>Name</th>
<th>Ret. Time</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EXPT C-231(Cryptand from TREN and 5,5’methylene –bis-3-methylsalicylaldehyde )</td>
<td>3.475</td>
<td>0.2219</td>
</tr>
<tr>
<td>2</td>
<td>imp 1</td>
<td>4.675</td>
<td>99.7721</td>
</tr>
<tr>
<td>3</td>
<td>imp 2</td>
<td>15.146</td>
<td>0.0060</td>
</tr>
</tbody>
</table>
4.7 References:


