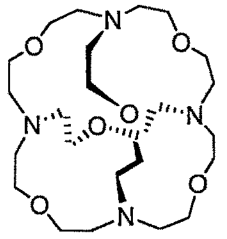
CHAPTER -5

Synthesis of an Oval-shaped Spherical Azacryptand

5. Synthesis of an Oval-shaped Spherical Azacryptand

5.1 Introduction

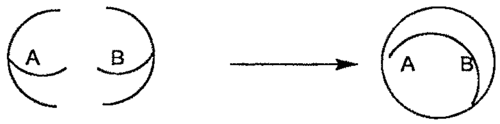
Supramolecular chemistry is the chemistry of molecules, which can form association of two or more chemical species through weaker secondary forces. As discussed earlier acyclic organic ligands known as podands have more flexibility but lower selectivity. In comparison monocyclic ligands show better selectivity. The aspects of selectivity of cations by monocyclic crown ethers was studied in detail by Pederson who synthesized over fifty cyclic polyethers of different size and observed marked selectivity of some of these compounds toward certain alkali metal ions.[1] Bicyclic host compounds have greater ability to bind with guest molecules. One of the important classes of supramolecules are the bicyclic compounds known as cryptands. Cryptands are three-dimensional host molecules which can entirely encapsulate guest molecules. Because of their spherical binding ability and cave like shape, they are named as cryptands based on Greek word *Kryptos* meaning hidden. The three dimensional cavity in cryptands is much more pre-organized for binding. Various strategies for synthesis of cryptands have been developed and presented by Lehn's group[2] though the concept was published earlier.[3] In one of the earlier preparations, a spherical host molecule **1** with symmetrically placed four nitrogens interlinked via carbon oxygen chain was reported by Graf and Lehn.[4] This is one of the



1

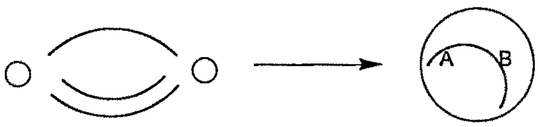
noteworthy examples of cyclic compounds containing nitrogen in monocyclic, bicyclic or multicyclic systems.[5] Nitrogen containing monocyclic systems are called aza-corands. Similarly there are a number of cryptands which contain nitrogen alongwith oxygen or sulfur as donor atoms reported so far.[6] Nitrogen based macrocyclic host molecules have unique ability to act as receptors for anions[6(a)] in addition to cationic and neutral molecules because nitrogens present in the macrocycles can act as base for cation guest and can act as donor atoms for hydrogen bonding or can have other weak forces to hold neutral molecules. Nitrogen~~d~~s present in these molecules on protonation can accommodate anionic guests. As nitrogen can easily be tri-alkylated it is possible to prepare cryptands with diagonally located nitrogens. Most of the cryptands include nitrogen as one of the donor atoms. Various techniques and approaches have been employed in the synthesis of nitrogen containing cryptands.

Application of high dilution principle, selection of appropriate solvent, selection of protecting and leaving groups if required and use of template are some of the important techniques which need to be considered while planning a experiment. Synthetic strategies for the synthesis of cryptands include tripod-tripod coupling, single capping of a tripod unit or double cappingusing bridging units or capping with a tripod unit itself **(Figure 1)**.[7]

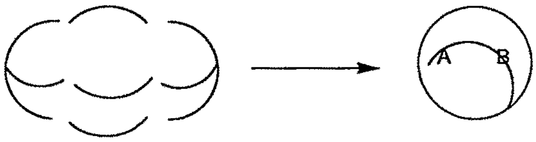


tripode coupling

single capping



double capping



tripode capping

Figure 1

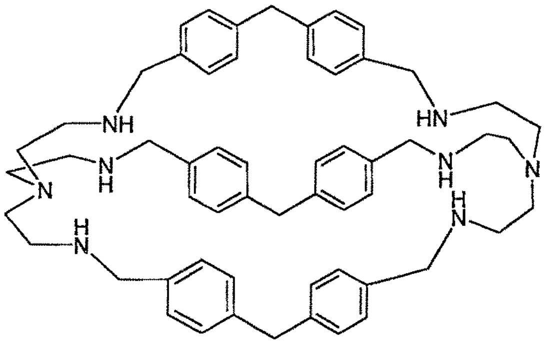
ω-Substituted tri-alkyl amines are useful in one or more synthetic approaches mentioned above. They include tris(ω-haloalkyl)amines, tris(ω-hydroxyalkyl)amines, tris(ω-mercaptoalkyl)amines and tris(ω-aminoalkyl)amines. Tris(ω-aminoalkyl)amines are versatile reagents not only for the preparation of cryptands but also for atom transfer radical polymerization as a ligand for complexing with Cu(I) salts.

5.1.1 Application of tris(aminoalkyl)amines in supramolecular chemistry

Tris(2-aminoethyl)amine (TREN) and tris(3-aminopropyl)amine have been extensively used in the synthesis of cryptands and other macrocycles.[6,8,9] Tris(2-aminoethyl)amine (TREN) is the only member which is commercially available from this class of compounds namely tris(ω-aminoalkyl)amines. Tris(ω-aminoalkyl)amines have been also used for preparation of dendritic molecules.[10] TREN on (2+3) condensation with a variety of diformyl aromatic and heterocyclic compounds give Schiff bases in good yield.[8(a), 9(b), 11] Schiff bases are most popular among coordination chemistry and the Schiff base complexes derived with a wide spectrum of metal ions have been extensively studied with a variety of perspectives. A vast range of Schiff base containing macrocycles and macrobicycles also exist and have been of great importance in macrocycle coordination chemistry, particularly complexes of transition metal ions, from the very beginning of supramolecular chemistry. The key Schiff base condensation reaction involves simply the reaction of an amine with an aldehyde to eliminate water and give an imine. If desired, the product may be reduced (e.g. using $NaBH_4$) to give an amine or a secondary amine based macrocycle.

Schiff bases from tripodal TREN, having macrocyclic corand or cryptand structure have been employed for complexation with transition metal ions.[8(b),9(b)] Crytpand structure generated from (2+3) condensation of TREN and dialdehydes offer trigonally placed two coordinating sites with four nitrogen atoms situated at each end giving dinuclear metal complexes. Silver complexes of such type of ligands have been reported simultaneously by two groups.[8(b),12] Heterocyclic and aromatic bisaldehydes have been used for the synthesis of the ligands. Similar cryptands with heterocyclic rings have been found to form unsymmetrically placed mononuclear sodium ion complexes which have been studied using X-ray and ^{23}Na NMR.[11(e)] There are a number of reports involving synthesis and study of different transition metal ion complexes with these type of cryptands. The octa-aza cryptand based homo and hetero binuclear complexes with copper and silver ions have been studied by Nelson and co-workers.[13] Complexes using Cu (II), Co (II), Ni (II) with these compounds have also been prepared and studied in detail.[6(c),9(b),11(a)] The research on lanthanide complexes has attained special attention because of their application as contrast agents, for NMR imaging, as NMR shift reagents, as catalyst in RNA hydrolysis, as active agents in cancer therapy. f –f and f-d Lanthanide (III) Schiff base cryptands from TREN have been prepared, characterized and their EPR and their magnetic properties have been studied.[14]

4,4'-Methylenebis(benzaldehyde) was employed as a dialdehyde in the preparation of cryptand **3** using TREN by Lehn, Pascard and co-workers. The involvement of the



3

bisaromatic substrate provides more number of aromatic rings in bridging with increased π-stacking and complexing ability. This is the only report so far with these features included in cryptands using TREN. With this background, our project on preparation of new cryptands was initiated.

5.2 Aims and Objectives

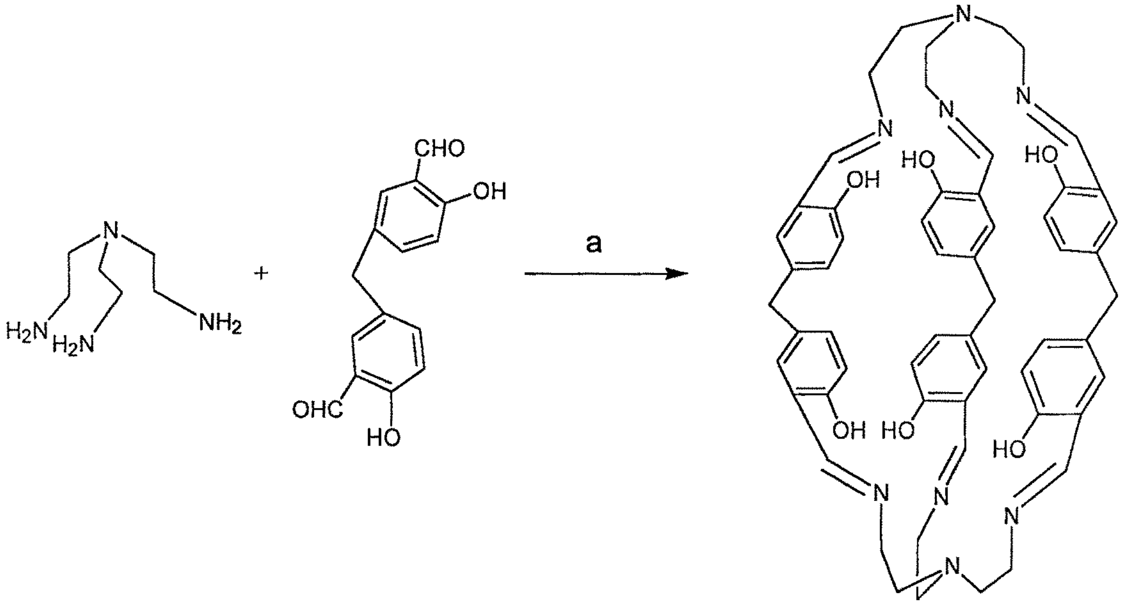
The research work with the objective of preparation of new cryptands was initiated and explored using rosolic acid as a capping agent. It resulted in preparation of various new tripodal compounds having aliphatic and aromatic pendant groups. Preparation of cryptands using TREN as a capping agent was realized to be more attractive and viable based on the work reported so far in this class of compounds. These compounds have greater binding ability due to the presence of polyaza functionality in a rigid structure. As mentioned earlier, the work on methylenebis(arylaldehydes) has not been explored.. Some binuclear Cu (II) complexes have been studied using Schiff bases from 5,5'-methylenebis (salicyldehyde) and amino alcohols.[15] We decided to probe the possibility of applying this bisaldehyde in preparation of polyaza cryptand and find out whether the hydroxyl groups in the substrate obstructs or facilitates the macrobicyclic cryptand formation. Successful synthesis of this cryptand would lead to a new host molecule with additional binding sites. There are reports[11(e),16] on synthesis of cryptands using 2,6-diformyl-4-alkylphenols with TREN giving indication that the reaction may work with the bis(phenolic) aldehydes without interference from of the phenolic groups.

5.3 Results and discussion

The phenolic dialdehyde 5,5-methylenebis(salicyldehyde) can be prepared by the reaction of salicyldehyde and formaldehyde in glacial acetic acid using H_2SO_4 as a catalyst following the reported method.[17] TREN (96%) was purchased from Aldrich Chemical co. and used as such. The preparation of cryptand involved drop-wise addition of 1.5 equivalent of 5,5'-methylenebis(salicylaldehyde) to a stirred solution of 1 equivalent of TREN in ethanol at the refluxing temperature over a period of 30 minutes. Refluxing was continued for an additional hour.

Following the above procedure the required cryptand was obtained in a low yield with the formation of polymeric material. Templates are extremely useful in the synthesis of macrocyclic molecules which otherwise pure cannot be prepared. Cesium ion (Cs^+) is one of the most effective template used in the synthesis of macrocycles. This beneficial influence of cesium ion compared to other alkali metal ions and probably any other ion employed so far is known as cesium effect. It has been observed that some reactions occur in the presence of cesium ion only.[18] In our case also the presence of cesium ions prior to the addition of phenolic aldehdye in solution showed dramatic change in favour of the cryptand which was isolated in 70% yield after crystallization. Formation of the cryptand was confirmed by using IR, PMR, CMR and mass spectroscopy alongwith elemental analysis.

Scheme 1



4 **5** **6**

Reagents and conditions: a) abs. EtOH, CsCl, Δ

Spectral Characteristics:

IR of the cryptand is very simple showing major bands for hydrogen-bonded phenolic group, O-H stretching at 3450cm^{-1}, a strong C=N stretching at 1636cm^{-1}. The band at 1490cm^{-1} contributed to C-N stretching and 1275cm^{-1} for C-O stretching with other weak bands.

PMR of the product is indicative of the C_3 symmetric cryptand with rigid structure showing the following important signals. Phenolic protons show singlet at

14ppm. Aromatic protons on carbon C-6 gives singlet while other 2 protons on the aromatic ring show coupling constant J_{ab} = 8.4hz at 7.42 ppm and 7.1 ppm. Protons attached to the methylene group between 2 aromatic rings give signal at 5.47 ppm. Methine protons of the CH=N absorns at higher field than expected probably due to the shielding effect generated by the aromatic ring current and gives a signal at 3.63 ppm. Due to the locked conformation and rigid structure of the cryptand, each proton attached to the ethyl group between two nitrogens give different chemical shift, one proton as a doublet at 3.71 ppm, 3.14 ppm (a doublet of doublet or a triplet), one at 2.86 ppm (a doublet of doublet or a triplet) and one proton as a doublet at 2.77 ppm (doublet J = 13.04 hz).

FAB-mass of the compound was recorded at CDRI, Lucknow with m-nitrobenzyl alcohol as the matrix. The peak at 954 m/z corresponds to M+2 ion.

The polyaza cryptand possesses six hydroxy groups three each in each half of the molecule pointing towards heterocyclic cap and is the unique feature of this cryptand synthesized for the first time. The hydroxyl groups thus situated are expected to contribute greatly in binding and hold or coordinate with the guest molecule or ion at each end of the cryptand. As per the NMR spectrum, the orientation of the –OH group is symmetrical and we expect it to be pointing towards the imine nitrogen of the nearby chain forming hydrogen bonding. The synthesis of the cryptand in presence of irreversibly bound template or the presence of a guest molecule could change orientation of the hydroxyl group. The cryptand with only one hydroxyl group in the only phenyl ring acting as the linker in the cryptand is reported to form mononuclear complex for the host molecules with Tl (III) ions because all the three hydroxy groups are situated in the central plane of the molecule.[17] To find the exact orientation for prediction of the binding ability of the cryptand synthesized by us it was required to get single crystal X-ray data for the compound. For getting suitable crystals for X-ray analysis, the macrocyclic cryptand was crystallized using various solvents or solvent systems. Very good big crystals apparently of octahedral shape from both the solvent systems were obtained from pyridine-acetone as solvent-nonsolvent combination. Chloroform-petroleum ether combination resulted in small size shiny yellow crystals. The crystals obtained were found to be collapsing in to powder on filtration. In the case of crystals obtained in smaller size, crystallization solvent system was replaced by methanol as nonsolvent and submitted for X-ray analysis at CSMCRI, Bhavnagar, but collection of the diffraction data by the crystallographer has not successed so far. From their behavior, it is clear that solvent molecules are taking part in the crystal formation and the process is reversible as a result of this, on exposure to atmosphere, the reversibly bound solvent molecules leave and the crystals collapse to amorphous state. Attempts are continued for crystallization and determining the structure by single crystal X-ray analysis.

This extremely promising macrocyclic cryptand molecule has vast possibilities lying in it. The study of its binding abilities with various guest molecules and preparation of complexes are in progress.

5.4 Experimental

Reagents, Solvents and Instrumentation

Tris(2-aminoethyl)amine and Cs_2CO_3 were purchased from Sigma-Aldrich Chemical Co. Salicaldehyde and trioxane were purchased from S-d-fine Chemical. All the solvents and other chemicals were obtained from Suvidhinath Chemicals. Solvents were purified by standard methods and reagents were used without purification.

Melting points have been recorded on a Gallenkamp 350 micro melting apparatus by open capillary method and are uncorrected. Optical rotations are measured on a Jasco-Dip 370 polarimeter at 25^0C in chloroform. Infrared spectra have been recorded using Perkin-Elmer 16PC as KBr discs between 4000-600 cm^{-1}. . ^{1}H-NMR spectra are recorded on Bruker-AVX instruments at 200 MHz and 400 MHz at **Sun Pharmaceutical and Research Centre.** Elemental analysis has been carried out on Perkin-Elmer 240 C H N analyser. FAB-Mass spectra are recorded on a JEOL SX 102/DA-6000 mass spectrophotometer data system using Argon/ Xenon (6kv, 10mA) as the FAB gas at accelerating voltage 10 kv at room temperature using m-nitrobenzyl alcohol as the matrix at **CDRI Lucknow**.

Synthesis

Synthesis of 5,5'-methylenebis(salicylaldehyde) 5

To a solution of 6.9 mL (8.0 gm., 6.55 mmol) of salicylaldehyde, in glacial acetic acid (5 mL) in which trioxane (0.7gm., 2.06 mmol) was dissolved. A mixture of 0.05 mL conc. H_2SO_4 and 0.25 mL of glacial acetic acid was added slowly with stirring in N_2 atmosphere at 90-95°C. This temperature was maintained for 22h . Then the reaction mixture was then poured into ice-water (300 mL) and allowed to stand overnight. The deposited solid was filtered. The isolated solid was three times triturated with 10 ml petroleum ether and the petroleum ether was decanted (it contains tarry material). The remaining solid was recrystallized from acetone.

Yield:	2.55 gm. (48.2%).
M.P.:	141°C.

Synthesis of the cryptand 6 : [2+3] Schiff base condensation

Tris(2-aminoethyl)amine (0.146 gm., 0.149 mL, 1mmol) and CsCl (0.504 gm., 3 mmol) were dissolved in ethanol (20 mL). To this solution was added a solution of 5,5' methylene bis salicaldehyde (0.384 gm., 1.5 mmol) in 10 mL of ethanol in a dropwise manner with stirring over a period of 30 min. at 95°C. After the addition was complete, the reaction mix was allowed to reflux for 2 hours. The yellow solid separated was filtered by vaccue. Recrystalise the product with acetonitrile.

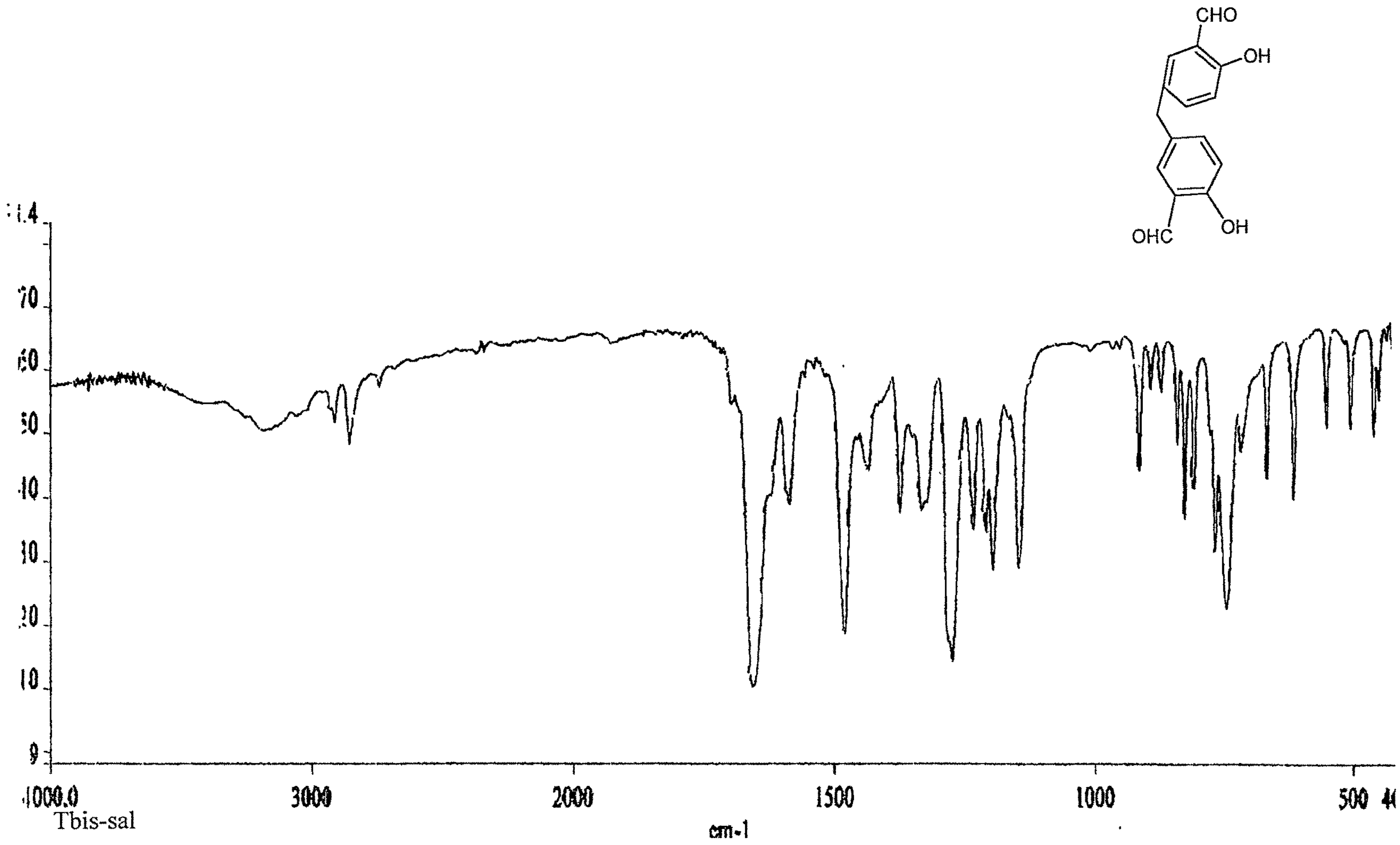
Yield:	70.0% (0.666 gm.)
M.P.:	273 °C
IR (KBr disc):	3450, 1636, 1587, 1490, 1275.
^{1}**H-NMR** (δppm):	3.63 (Ar-CH=N), 3.71, 3.14 (>N-CH_2-CH_2-N=CH-Ar), 5.47 (s, Ar-CH_2-Ar), 7.09, 7.42, 7.52 (arom. Protons), 14.0 (Ar-OH),

Anal. Calcd. For $C_{57}H_{60}N_8O_6$: %C 71.84 %H 6.30 %N 11.76

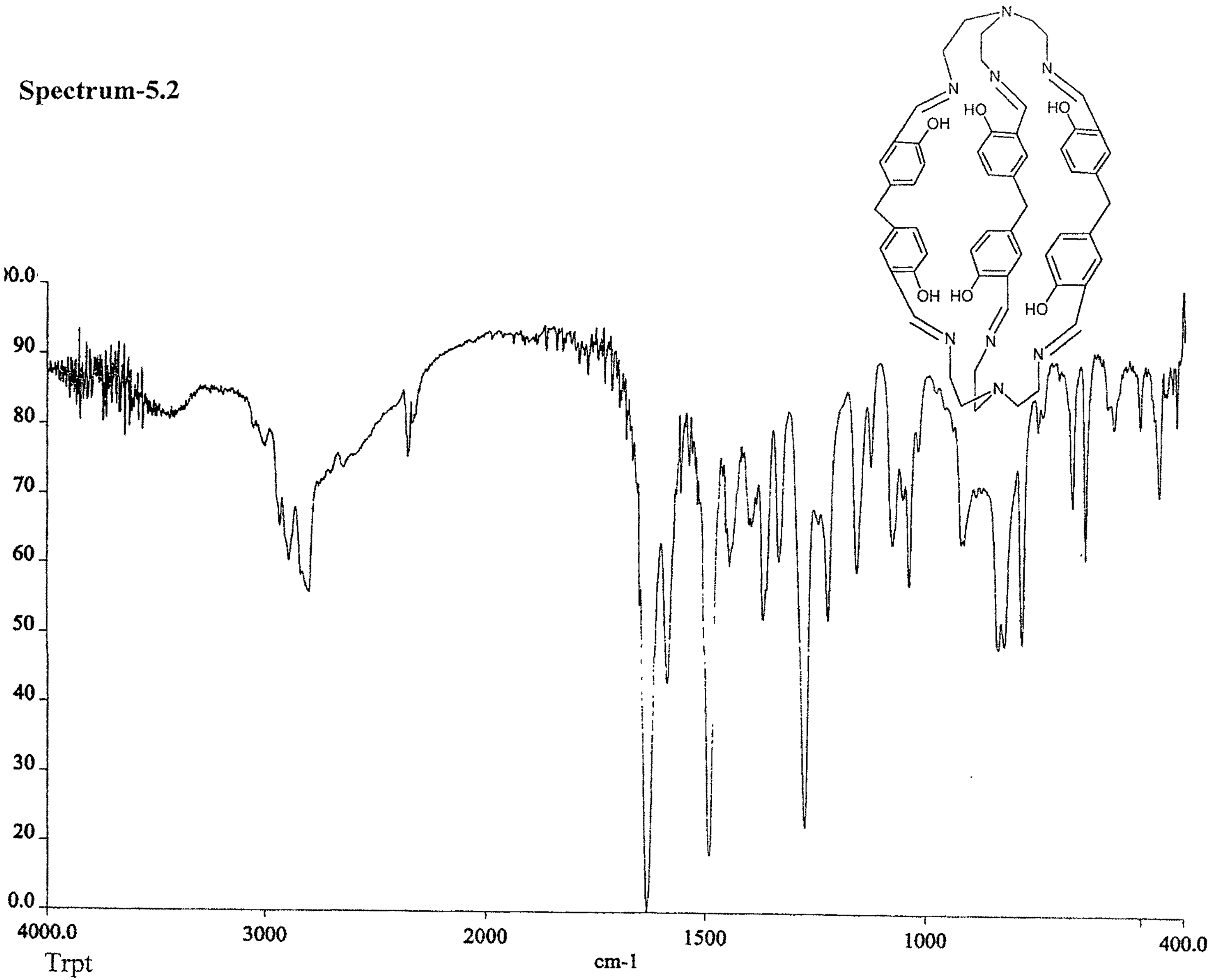
Found: %C 71.42 %H 6.36 %N 11.80

FAB Mass: 954 (M+2).

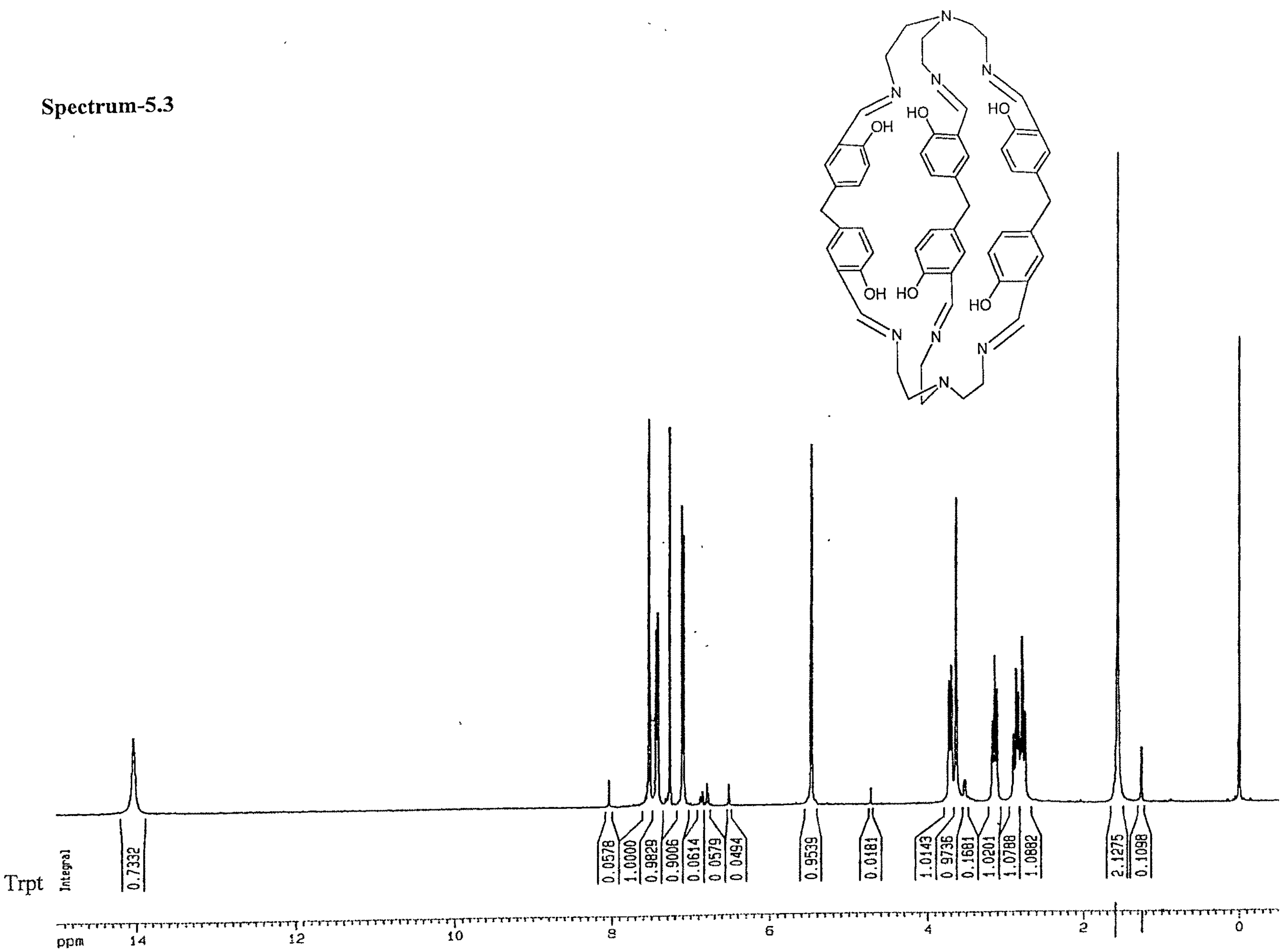
Spectrum-5.1


CHO
OH
OHC
OH
71.4
70
60
50
40
30
20
10
9
4000.0
3000
2000
1500
1000
500
40
Tbis-sal
cm-1

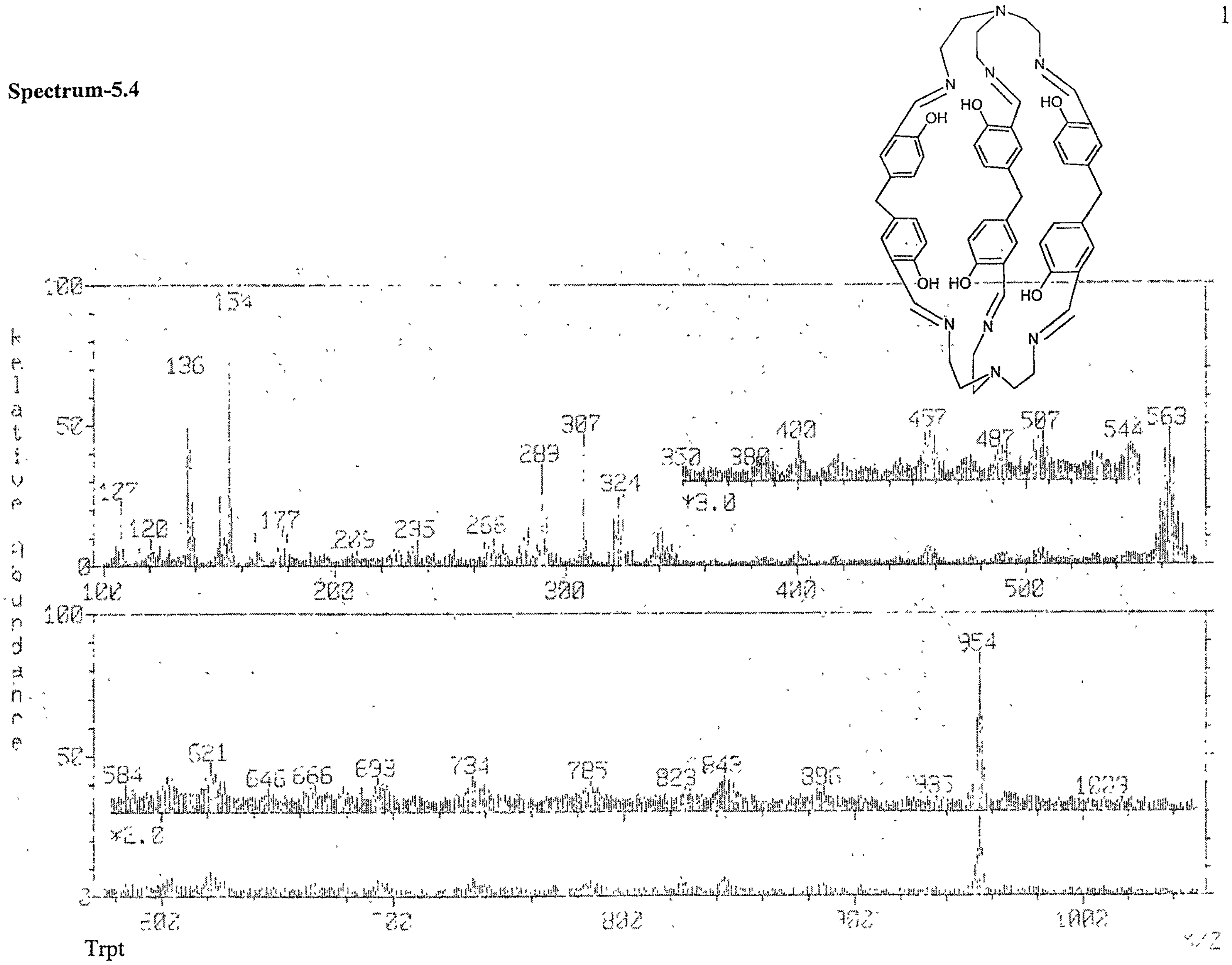
Spectrum-5.2


N
N
N
N
HO
HO
OH
OH
HO
HO
N
N
N
N
0.0
90
80
70
60
50
40
30
20
0.0
4000.0
3000
2000
1500
1000
400.0
Trpt
cm-1

Spectrum-5.3


N
N
N
N
N
N
N
N
HO
OH
HO
HO
OH
HO
HO
HO
Trpt
Integral
0.7332
0.0578
1.0000
0.9829
0.9006
0.0614
0.0579
0.0494
0.9539
0.0181
1.0143
0.9736
0.1681
1.0201
1.0788
1.0882
2.1275
0.1098
ppm
14
12
10
8
6
4
2
0

Spectrum-5.4



Trpt

5.5 Refrerences

---

1. Pederson, C.J. *J. Am. Chem. Soc.* 1967, **89**, 7017.
2. Lehn, J. M. *Acc. Chem. Res.* 1978, **11**, 50.
3. Park, C. H. ; Simmons, H. E. *J. Am. Chem. Soc.* 1968, **90**, 2431.
4. Graf, E. ; Lehn, J.M. *J. Am. Chem. Soc.* 1975, **27**, 5022.
5. (a) Richmann, J.; Atkins, T. J. *J. Am. Chem. Soc.* 1974, 96, 2268 (b) Rossa, L.; Vogtle, F. *Topics in Curr. Chem.* 1983, **113**, 1 (c) Krakowiak, K. ; Bradshaw, J.S.; Zamecka-krakowiak, D.J. *Chem. Rev.* 1989, **89**, 929.
6. (a) Ilioudis, C. A.; Steed, J.W. *J. Supramol. Chem, 1.* 2001, 165 and references sited therein (b) Ghosh, P. ; Shukla, R.; Chand, D.K.; Bhardwaj, P. K. *Tetrahedron* 1995, **51**, 3265 (c) Chen, D.; Martell, A.E. *Tetrahedron* 1991, **47**, 6895.
7. Dietrich, B.; Hosseini, M. W.; Lehn, J. M.; Sessions, R.B. *Helv. Chimica. Acta.* 1985, **68**, 289.
8. (a) Qian, M.; Gou, S.; Chantrapromma, S.; Raj, S. S. S.; Fan, H. K.; Zang, Q.; Yu, Z.; You, X. *Inorg. Chimica. Acta.* 2000, **305**, 83 (b) Adams, H.; Elsegood, M. R. J.; Fanton, D. E.; Heath, S. L.; Ryan, S. J. *J.Chem.Soc.,Dalton Trans.* 1999, 2031.
9. Munif, R.; Reibenspies, J.; Martell, A. E., *Inog. Chem.,* 1991, **30**, 3446.
10. (a) Scrimin, P.; Veronese, A.; Tecilla, P.; Tonellato, U.; Monaco, V.; Formaggio, F.; Crima, M.; Toniolo, C. *J.Am. Chem. Soc.* 1996, **118**, 2505 (b) Vanhest, J. C. M.; Delnoye, D. A. P.; Baars, M. W. P. L.; Vangenderen, M. H. P.; Meijer, E. W. *Macromolecules* 1995, **28**, 6689 (c) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polymer J.* 1985, **17**, 117.

11. (a) Drew, M. G. B.; Marrs, D.; Hunter, J.; Nelson, J. *J. Chem. Soc., Dalton Trans.* 1992, 11 (b) Jazwinski, J.; Lehn, J.M.; Meric, R.; Vigneron, J.P. *Tet. Lett.* 1987, **28**, 3489 (c) Jazwinski,, J.; Lehn, J.M.; Lilienbaum, D.; Ziessel, R.; Guilhem, J.; Picard, C.J. *J. Chem. Soc. Chem. Comm.* 1987,1691(d) Drew, M. G. B.; McDowell, D.; Nelson, J. Polyhedron 1988, 7, 2229 (e) Mckee, V.; Dorrity, M. R. J.; Malone, J. F.; Marrs, D.; Nelson, J. *J. Chem. Soc. Chem. Comm.* 1992, 383.

12. Howarth, O.W.; Morgan, G. G.; Mckee, V.; Nelson, J. *J.Chem.Soc.,Dalton Trans.* 1999, 2097.

13. Drew, M. G. B.; Farrell, D.; Morgan, G. G.; Mckee, V.; Nelson, J. *J.Chem.Soc.,Dalton Trans.* 2000, 1513.

14. Avecilla, F.; Platas-Iglesias, C.; Rodriguez-Cortinas, R.; Guillemot, G.; Bunzli, J.G.; Brondino, C. D.; Garaldes Blass Ade C. F. G. C.; Blas, A. *J.Chem.Soc.,Dalton Trans.* 2002, 4658.

15. Sureshan, C.A.; Bhattacharya, P. K. *Polyhedron* 1997, **16**, 489.

16 Drew,M.G.B.;Howarth,O.W.;Martin,N.;Morgan,G.G.;Nelson,J. . *J.Chem.Soc.,Dalton Trans.* 2000, 1275.

17. Marvel, C. S.; Tarkoy, N. *J.Am. Chem. Soc.* 1957, **79**, 6000.

18. Ghosh, P.; Shukla, R.; Chand, D. K.; Bhardwaj, P. K. *Tetrahedron* 1995, **51**, 3265.