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Synthesis of Hetero-Polytopic Cryptands Incorporating Hard and Soft Donor Atoms Via Tripod-Tripod Schiff Base Condensation: Versatile Ligands for Transition Metal Ions

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Abstract: Template synthesis of four new cryptands has been described. In each of these cryptands, there are three distinct compartments. These cryptands readily make mono- as well as binuclear cryptates with transition metal ions like copper, nickel etc. The dicopper cryptates reduce in solution to the Cu(I) state.

A lot of interest is currently devoted to the synthesis of macrobicyclic cryptands and to the use of such compounds as hosts for a variety of metal ions as well as organic guests. Cryptands with more than one distinct compartment are able to provide suitable frameworks for arrangement in space of one or more receptor sites to bind together different metal ions, organic guests or both. Incorporation of both hard as well as soft donors at strategic positions can discriminate the affinities of these sites towards different metal ions. The metal ion recognition of such cryptands can be useful in areas like selective binding and transport, catalysis, mimicry of the intrinsic active sites of metalloproteins[1], metal-metal interactions[2] inside the cavity to have molecular magnets, molecular wires as well as molecular switches. With transition metals like copper, these multi-receptors can form inclusion complexes and can be potential small molecular weight probes for the active sites of proteins like hemocyanin [3], dopamine-β-hydroxylase[4] etc. With organic guests, contribution in areas like mechanism of drug action, enzyme-substrate interactions etc. can be made possible. Also, the cryptands described here can be used to make artificial membranes, micelles[5] etc. attaching long alkyl chains to the three secondary amino groups present in each of them. We have been able to attach three palmityl groups to a similar cryptand[6]. These systems should be amenable to studies as their Langmuir-Blodgett films and when paramagnetic metal ions are incorporated inside the cavity, the systems can be of use in materials research. Besides, due to higher lipid solubility, such metal cryptates can be used as potential anthelmintic agents [7]. We are interested in some of the aforesaid areas of research. In order to realize our goals, we have designed and synthesized a number of cryptands having distinct compartments and more importantly having three secondary amino groups for functionalization. Our synthetic method involves Schiff base condensation of two tripodal units in the presence of Cs^+ ion as the template. This synthetic strategy affords a high yield of the desired product in pure forms. Moreover, the cumbersome procedure involved in the high-dilution synthesis of the macrobicycles can be circumvented. In the present paper, we have described the synthesis and characterisation of four new macrobicyclic cryptands. A preliminary report on using these cryptands as ligands for transition metal ions like Cu and Ni is also described.

RESULTS AND DISCUSSION

All the macrobicycles were obtained in good yields (40-60%) although the corresponding Schiff bases were found to be slightly unstable in nature. When the two tripodal components were allowed to react in absence of the Cs^+ ion, no product of definite composition could be isolated. Our choice of Cs^+ ion as the template was based on the fact that it can bring the two tripodal components together in suitable orientation without strongly binding to either of them or the cryptand formed. High yields of the desired product supports our assumption. Besides, the cryptands can be easily recovered from the reaction mixture in pure form. The Cs^+ ion templated Schiff base condensation of two tripodal units is thus proved to be a very effective one considering the wide structural varieties of the cryptands synthesized. We have not tested the suitability of other alkali metal ions like Rb^+ or any other type of metal ion as the template. However, when the X-ray crystallographically characterised Ni(II)-complexes[8,9] of the triamines **1** or **2** were allowed to react with the tripodal trialdehyde **5**, the desired cryptand was not formed and the Ni(II)-complex decomposed during reaction.

The cryptands were found to be good ligands for transition metal ions like Cu, Ni, etc. The Cu(II) cryptates of **6**,**7** & **9** show interesting physicochemical and redox properties. The UV-Vis spectra in acetonitrile showed two d-d transitions centred around 900 and 600 nm consistent[10] with the distorted octahedral geometry around the metal ion. The strong near-UV band (360 nm) in those complexes indicate LMCT transitions involving thioether sulfur and Cu(II) while the strong absorption near 280 nm is indicative[10] of LMCT transition from secondary amino nitrogen to Cu(II). The solid state as well as solution (acetonitrile) EPR spectra at 298 K and at 77 K gave only a broad signal with $g_{av} = 2.15$ without any hyperfine structures. The EPR data is typical of magnetically concentrated Cu(II) systems. Based on these physicochemical studies and comparing with other mononuclear Cu(II) complexes, it is concluded that the Cu(II) ion is bonded to the three thioether sulfurs and three nitrogen donors in a distorted octahedral fashion at one end of the cavity. The electron transfer properties of the cryptates were studied by cyclic voltammetry at 293 K. The mononuclear Cu(II)-cryptates showed a quasi-reversible couple (ΔE_p = 140 -180 mV at the scan rate of 100 mVs^{-1}) with the $E_{1/2}$ value in the range, (0.5- 0.6 V) vs. Ag/AgCl. This quasi-reversible cycle is attributable to Cu(II)/Cu(I) couple which indicates theses systems are strong reducing agents. Not surprisingly, when a further equivalent of $[Cu(H_2O)_6].(ClO_4)_2$ is added to a solution of the mononuclear cryptate, the colour of the solution changed immediately to dark green and within hours colourless crystals appeared at the bottom of the reaction vessel. Single crystal X-ray analysis of this product revealed its identity as $[Cu(CH_3CN)_4].ClO_4$. When excess of cupric perchlorate hexahydrate (greater than 10 equivalent) is added to this system, more of the cuprous salt is deposited. This kind of behaviour has been reported[11] in modelling the active sites of binuclear copper centres present in metalloenzymes like hemocyanin and dopamine β-hydroxylase. The copper cryptates are presently under investigation as active site models of the copper-proteins mentioned above.

The UV-Vis spectra of the corresponding nickel cryptates show d-d transitions near 1050 and 680 nm and LMCT transitions around 320 and 240 nm consistent with distorted octahedral coordination of Ni(II) by three thioether sulfurs and three nitrogens[12]. The Ni(II)-cryptates do not show any characteristic redox coupling in their cyclic voltammograms due to rapid decomposition of the oxidized/reduced species generated electrochemically.

EXPERIMENTAL

Triethanolamine, thionyl chloride, AIBN, NaN_3, triethylamine, $NaBH_4$, and all the solvents were obtained from SD Fine Chemicals, India. Mesyl chloride, salicylaldehyde, tris(2-aminoethyl)amine, 2-aminothiophenol, 1,1,1-tris (hydroxymethyl) ethane, mesitylene and N-bromosuccinimide were acquired from Aldrich Chemical Co., USA. The solvents, thionyl chloride, AIBN and NBS were purified prior to use employing standard methods of purification. All other reagents were used as received.

Synthesis of the tripodal amines, **1-4**

Syntheses of **1-3** were achieved following published procedures[8,9,13]. The tripodal amine **4** was synthesized by allowing 1,3,5-trisbromomethylbenzene to react with 2-aminothiophenol at elevated temperature. 1,3,5-trisbromomethylbenzene was prepared according[14] to Vogtle et. al. by brominating mesitylene with NBS in the presence AIBN and light. m. pt. 93° (lit. 94°). To a solution of sodium n-propoxide (4.5 mmol) generated by dissolving sodium in n-propanol (20 ml) was added 2-aminothiophenol (4.5 mmol) and the reaction mixture was allowed to reflux . After an interval of 10 min., solid 1,3,5-tris-bromomethylbenzene (1.5 mmol) was added in small portions to the refluxing solution over a period of 5 min. The mixture was then allowed to reflux for a further 4 h. period. The entire operation was done in an atmosphere of dry nitrogen gas. It was then allowed to cool to room temperature and poured into 40 ml water with constant stirring. The resulting oily mass was extracted with 3 x 20 ml of chloroform, dried over anhydrous sodium sulphate and upon evaporation of the chloroform, the desired tripodal amine was obtained as a yellow viscous oil in 70% yield. The product was almost pure and was used in the cryptand synthesis as isolated.

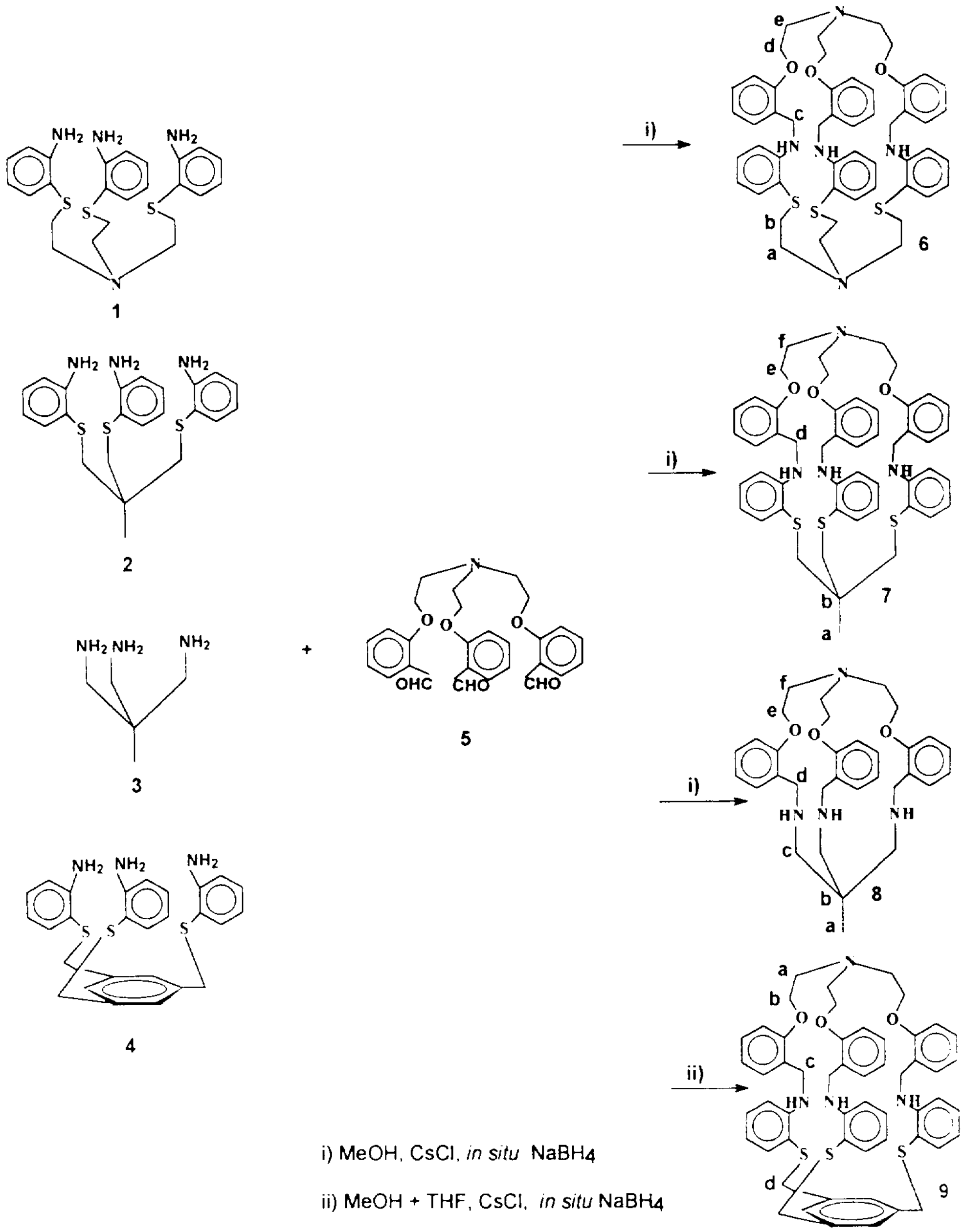
^1H-NMR (80 MHz, $CDCl_3$, ppm): 3.75 (s, 6H, CH_2); 4.57 (sb, 6H, NH_2); 6.9 (m, 15H, aromatic).

Synthesis of the trialdehyde **5** was achieved following our published procedure[6] .

General synthesis of the cryptands, **6-8**

A general method of synthesis was adopted for all the cryptands. The trialdehyde (1 mmol) and CsCl (1 mmol) were dissolved in methanol (200 ml) at 50°C. To this solution was added a solution of the corresponding tripodal amine (1 mmol) dissolved in methanol (200 ml) in a dropwise manner with stirring over a period of 6 h under a dry dinitrogen blanket. The temperature of the reaction mixture was maintained at ~50° C. After the addition was complete, the reaction mixture was allowed to reflux for about 3 h. The Schiff base thus formed was reduced *in situ* with $NaBH_4$ in refluxing methanol for 4 h. The resulting pale yellow solution was concentrated to almost dryness, poured into 50 ml of cold water and well shaken for about 10 min. The product was extracted with chloroform (3 x 20 ml) , dried over anhydrous sodium sulfate and finally the chloroform was removed to yield the desired product as pale yellow to colourless high viscous liquid. The cryptands were characterised by ^1H-NMR, ^{13}C-NMR and FAB-mass spectroscopy.

For the synthesis of the cryptand **9**, the procedure was slightly modified. In this case, the triamine was templated with CsCl in 200 ml methanol and THF mixture (3:1 ratio by vol). The trialdehyde taken in the solvent of above composition (200 ml) was added dropwise at 50°C with constant stirring. All the cryptands solidified as colourless to almost colourless crystalline solids on keeping in the freeze at ~2°C for



i) MeOH, CsCl, *in situ* $NaBH_4$

ii) MeOH + THF, CsCl, *in situ* $NaBH_4$

Fig. 1. Synthetic scheme for the cryptands

five days. However, they melted quickly when allowed to warm upto the room temperature.

General synthesis of the metal-cryptates

1 mmol of $[Cu(H_2O)_6].2ClO_4$ dissolved in dry methanol (20 ml) was added dropwise with constant stirring at RT to the methanolic solution (20 ml) of the cryptand (1 mmol). After the addition was complete, the reaction mixture was warmed upto 50°C for 15 minutes and finally allowed to cool to 5°C. Powdered solid that settled at the bottom was collected and air-dried. No solid could be isolated in case of **8**.

The corresponding Ni(II)-cryptates were synthesized following the above procedure using $[Ni(H_2O)_6].2ClO_4$ instead of the Cu(II)-salt. Solid Ni(II)-cryptates could be isolated only in case of **6** & 7.

Macrobicycle **6**. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 2.6 (m, 12H, a & e); 3.05 (t, 6H, b); 4.15 (t, 6H, d); 4.35 (sb, 3H, NH); 4.5 (s, 6H, c); 7.0 (m, 24H, aromatic). ^{13}C-NMR (20.1 MHz, $CDCl_3$): 32.17, 53.19, 54.05, 60.91, 65.89 (aliphatic carbons); 111.69, 114.73, 117.36, 118.11, 120.86, 128.19, 128.64, 129.04, 129.44, 129.96, 135.46, 156.47 (aromatic carbons). FAB-mass: The molecular ion peak was not observed due to fragmentation. Yield ~ 58%.

Macrobicycle 7. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 1.15 (s, 3H, a); 3.2 (t, 6H, f); 3.3 (s, 6H, c); 4.15 (m, 12H, d & e); 4.35 (sb, 3H, NH); 7.1 (m, 24H, aromatic). ^{13}C-NMR (20.1 MHz, $CDCl_3$): 36.98, 41.74, 53.42, 54.33, 67.44, 99.22 (aliphatic carbons); 111.75, 112.61, 115.19, 117.99, 118.51, 120.34, 126.47, 127.38, 129.60, 129.78, 135.57, 136.67 (aromatic carbons). FAB-mass : The molecular ion peak was not observed due to fragmentation. Yield ~ 47%.

Macrobicycle **8**. ^{1}H-NMR (80 MHz, $CDCl_3$, ppm) : 1.2 (s, 3H, a); 3.0 (t, 6H, f); 3.7 (s, 6H, c); 4.20 (t, 6H, e); 4.58 (s, 6H, d); 7.1 (m, 12H, aromatic). ^{13}C-NMR (20.1 MHz, $CDCl_3$): 30.12, 50.14, 54.81, 62.43, 66.20 (aliphatic carbons); 111.02, 121.20, 127.40, 129.60,130.60, 156.43 (aromatic carbons). FAB-mass: The strong peak corresponds to $[M+1]^+$ ion appears at 531. Yield ~ 53%.

Macrobicycle 9. ^{1}H-NMR (80 MHz, $CDCl_3$, ppm) : 3.0 (t, 6H, a); 3.75 (s, 6H, d); 4.1 (t, 6H, b); 4.5 (s, 6H, c); 6.8 (m, 27H, aromatic). ^{13}C-NMR (20.1 MHz, $CDCl_3$): 39.46, 54.60, 61.50, 66.24 (aliphatic carbons); 111.30, 112.05, 112.30, 115.00, 118.55, 121.20, 128.20, 129.12, 129.45, 130.15, 130.55, 136.61, 138.62, 156.80 (aromatic carbons). FAB-mass : The strong peak that appears at 903 corresponds to $[M+1]^+$. Yield ~ 41%.

$[Cu(\mathbf{6})].(ClO_4)_2$. Dark brown solid. Yield 63%. Anal. Calcd. for $C_{51}H_{57}N_5O_3S_3.\ Cu(ClO_4)_2$: C, 53.42; H, 5.01; N, 6.11. Found : C, 52.91; H, 5.22; N, 6.02.

$[Cu(7)].(ClO_4)_2$. Dark brown solid. Yield 69%. Anal. Calcd. for $C_{50}H_{54}N_4O_3S_3.\ Cu(ClO_4)_2$: C, 53.73; H, 4.87; N, 5.01. Found : C, 53.43; H, 5.01; N, 5.13.

$[Cu(9)].(ClO_4)_2$. Dark brown solid. Yield 43%. Anal. Calcd. for $C_{54}H_{54}N_4O_3S_3.\ Cu(ClO_4)_2$: C, 55.64; H, 4.67; N, 4.81. Found : C, 55.17; H, 4.45; N, 4.89.

[Ni(**6**)] $(ClO_4)_2$. Brown solid. Yield 39%. Anal. Calcd. for $C_{51}H_{57}N_5O_3S_3 \cdot Ni(ClO_4)_2$: C, 53.65; H, 5.03; N, 6.13. Found : C, 53.34; H, 5.09; N, 6.19.

[Ni(**7**)] $(ClO_4)_2$. Brown solid. Yield 37%. Anal. Calcd. for $C_{50}H_{54}N_4O_3S_3 \cdot Ni(ClO_4)_2$: C, 53.97; H, 4.89; N, 5.03. Found : C, 54.02; H, 4.93; N, 5.11.

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