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Facile One-pot Synthesis of Macrobicyclic/Macrotricyclic Cryptands: Effect of Reactant Concentrations

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Abstract—Under high concentration conditions, tripodal trialdehyde **1** undergoes [2+3] Schiff base condensation with linear aliphatic diamines at room temperature to form macrobicyclic cryptands while two tripodal trialdehydes **1** or **2** undergo [2+2] Schiff base condensation with two tripodal triamines to form macrotricylic cryptands. Another macrotricyclic cryptand is formed via [4+6] amidation reaction.
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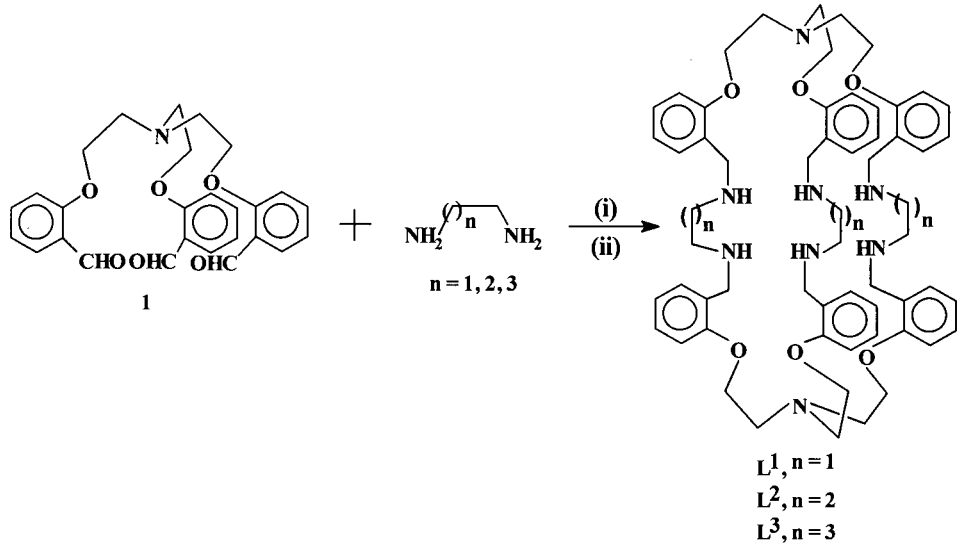
Introduction

Macropolycyclic ligands as synthetic receptors for organic or inorganic cations, anions or neutral molecules play important roles in a number of areas in chemistry as well as biochemistry.[1] Our research efforts[2–5] in this area involve, manipulation of the binding sites and the macropolycyclic architecture with the ultimate aim(s) to effect (i) specificity in the recognition processes, (ii) co-operative binding of different substrates leading to catalysis, (iii) cryptand based molecular photonic devices, (iv) new generation of amphiphiles, etc. The present set of macrobicyclic cryptands were designed to include more than one metal ions inside the cavity in order to study metal–metal interaction(s) which is an area of considerable current interest. Macrotricyclic cryptands[1] have not been used as extensively as the macrobicyclic cryptands owing in part, to the difficulties associated with their synthesis. The usual method of synthesis of these molecules involves linking of two macrocycles through their functionalizable sites with spacers, which delineate the central cavity of the compound. The method of synthesis starting from acyclic precursors, however, usually affords the desired cryptand in low yields. We have reported a synthesis of such molecules taking



Scheme 1. (i) THF, RT, stirring, 20 h. (ii) MeOH, in situ $NaBH_4$.

Keywords: macrobicyclic/macrotricyclic cryptands; Schiff base; one-pot synthesis.
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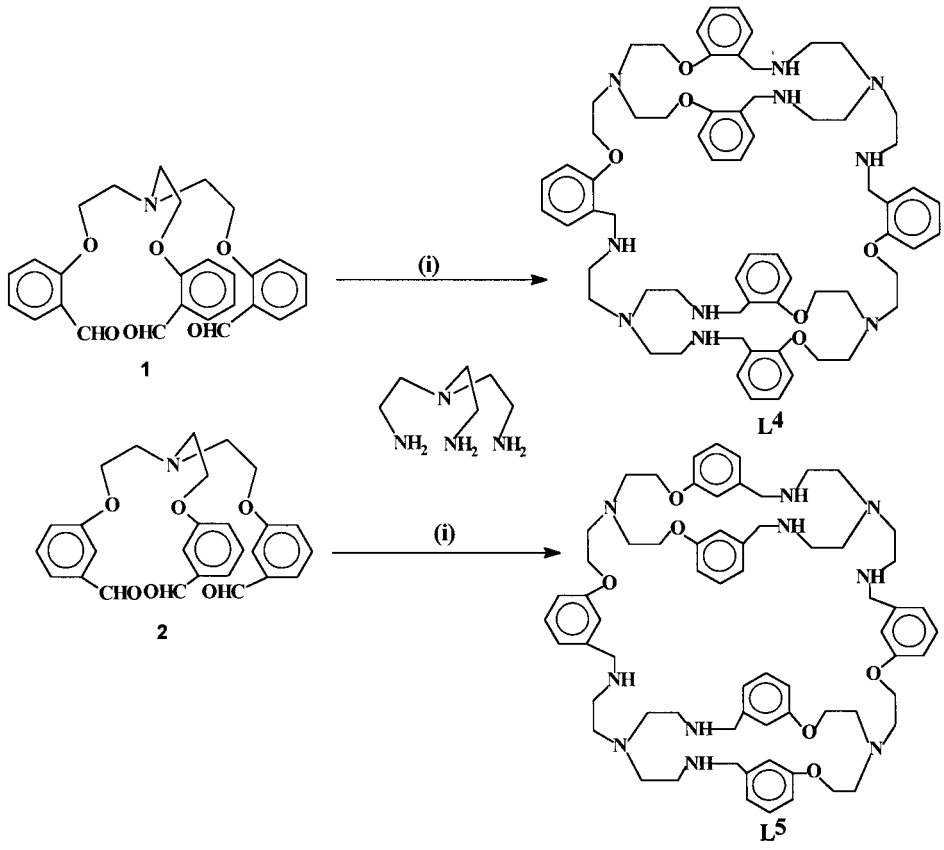


Scheme 2. (i) THF+MeOH, RT, Stirring, 24 h, in situ $NaBH_4$.

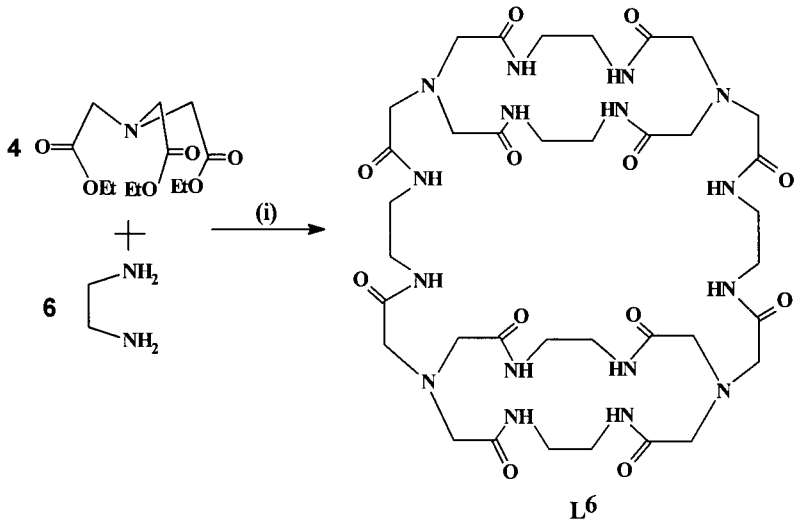
advantages of a size mismatch between two tripodal reactants.[6] We present here a simple method to synthesize macrotricyclic cryptands in one-pot starting from acyclic precursors in high yields.

Results and Discussion

The tripodal trialdehyde, tris{[2-(2′-(oxomethyl)phenyl)-oxy]ethyl}amine,[7] **1** can cap the two ends of a linear diamine in a [2+3] fashion (Scheme 1) to form the corresponding macrobicyclic cryptand. As the reactions are carried out at 5°C, no templating metal ion is necessary[3] due to the decreased degree of movement of the reacting arms. Carrying out these reactions at high concentration does not afford cryptands of higher order. However, when the trialdehyde **1** or **2** is allowed to react with the tripodal triamine, tris(2-aminoethylamine) (tren) the nature of the product is critically dependent on the concentration of the reactants. Under high dilution conditions (each reactant concentration kept at 1 mM) at 5°C they undergo mostly [1+1] Schiff-base condensation forming macrobicyclic cryptands.[3] When the concentrations of the reactants were increased (each reactant concentration 10 M), however, they undergo [2+2] Schiff-base condensation at room temperature in the absence of any templating metal ion mostly forming macrotricyclic cryptands $\mathbf{L^4}$ and $\mathbf{L^5}$ (Scheme 2). The [1+1] condensation product is only obtained as a minor product. The *para*-analogue of the trialdehyde **1**, when allowed to react with tren in the same manner, only yields a polymeric material of indefinite composition. Recently a macrotricyclic cryptand has been reported[8] by allowing two tripodal components to react at high concentration. The macrotricyclic cryptand $\mathbf{L^6}$ is synthesized from the tris-ethylester[9] of nitrilotriacetic acid and ethylenediamine in a [4+6] condensation reaction (Scheme 3). We have not isolated any [2+3] condensation product from this reaction by varying the reactants' concentration.

In high concentration conditions, collision of the reactants has a greater probability and the components react in an intermolecular fashion. The self-complementary nature of the components drive the reaction to the desired product. Interestingly, 1,2-diaminobenzene reacts with the triester in high concentration to yield only the macrobicyclic product.[9] Ethylenediamine being more flexible compared to 1,2-diaminobenzene can orient itself suitably to form the macrotricyclic product $\mathbf{L^6}$.

Cryptand $\mathbf{L^6}$ unlike $\mathbf{L^1}$–$\mathbf{L^5}$ is highly soluble in water as well as in alcohol. Since all the macrobicyclic cryptands have six secondary amino nitrogens, they are excellent complexing agents for transition metal ions. The aliphatic spacers allow an optimal coordination geometry around a metal ion inside the cavity. When treated with $[Cu(H_2O)_6](ClO_4)_2$ or $[Co(H_2O)_6](ClO_4)_2$ mononuclear cryptates are formed with $\mathbf{L^1}$ and $\mathbf{L^2}$. With $\mathbf{L^3}$, however, no well-defined complex could be isolated apparently because of the much higher flexibility and large bite angle of the diamine moiety present in each arm of the cryptand. The Cu(II) cryptate of $\mathbf{L^1}$ showed a broad d–d transition centered around 600 nm



Scheme 3. (i) RT, Stirring, 7 day.

while the cryptate with $\mathbf{L}^2$ showed a broad peak at ~650 nm which are attributable[3] to tetragonal Cu(II)N_6 chromophores. Similarly, each of the Co(II) cryptates exhibited two d–d transitions at about 600 and 650 nm assignable[3] to hexadentate Co(II)N_6 chromophores. The Co(II) cryptates did not give any EPR signal either at 298 or at 77 K while each Cu(II) cryptate in acetonitrile showed a typical four line signal with g_{av}=2.05 at 298 K which changed to an axial one with $g_{II}\approx$2.10 and $g_{\perp}\approx$2.03 in acetonitrile glass at 77 K consistent[3] with tetragonal Cu(II) coordination geometry.

Conclusion

In conclusion, we have reported here the facile one-pot synthesis of three new macrobicyclic and three new macrotricyclic cryptands in high yields. All of them are stable at room temperature for months and show good ligational properties towards transition metal ions. Currently, we are engaged in probing the cryptands for their recognition characteristics towards neutral molecules and anions as well as cations. Functionalization of the cryptands is in progress and will be reported later.

Experimental

General synthesis of $\mathbf{L}^1$–$\mathbf{L}^3$

The tripodal trialdehyde tris{[2-(2′-(oxomethyl)phenyl)-oxy]ethyl}amine, **1** (0.92 g; 2 mmol) was dissolved in 20 mL of THF at room temperature with constant stirring. To this solution was added the linear diamine (3 mmol) all at once. The reaction mixture was kept for another 20 h with constant stirring at room temperature. The Schiff base thus formed was hydrogenated in situ by stirring at room temperature for 4 h with $NaBH_4$ after adding 10 mL of methanol to the reaction mixture. The solvent was evaporated to almost dryness and the residue was shaken with 50 mL of water. The cryptand was extracted from the aqueous medium with $CHCl_3$ (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated completely to obtain the desired product.

$\mathbf{L}^1$ was obtained from **1** (0.92 g) and ethylenediamine (0.18 g) as a pale yellow semi-solid (0.65 g, 65%). [Found C, 71.53; H, 8.08; N, 11.37. $C_{60}H_{78}N_8O_6$ requires C, 71.54; H, 7.80; N, 11.13%]; ν_{max} (neat) 3500–3200 (br), 2945–2855 (br), 1595, 1490, 1455, 1240, 1165, 945 cm^{-1}; δ_H (300 MHz, $CDCl_3$, 25°C) 2.65 (12H, m), 3.20 (12H, t, J=5.0 Hz), 3.72 (12H, t, J=5.5 Hz), 4.30 (12H, s) 6.84–7.30(24H, m). δ_C (75.5 MHz, $CDCl_3$, 25°C): 29.36, 47.45, 53.69, 66.46, 110.9, 120.3, 127.1, 128.4, 130.6, 156.6. ES-Ms m/z (%) 1007(25) $[\mathbf{L}^1+H]^+$.

$\mathbf{L}^2$ was obtained from **1** (0.92 g) and 1,3-diamino propane (0.22 g) as a pale yellow semi-solid (0.6 g; 54%). [Found C, 72.02; H, 8.28; N, 10.97. $C_{63}H_{84}N_8O_6$ requires C, 72.10; H, 8.06; N, 10.68%]; ν_{max} (neat) 3500 – 3200 (br), 2955–2850 (br), 1600, 1495, 1455, 1240, 1165, 940 cm^{-1}; δ_H (300 MHz, $CDCl_3$, 25°C) 1.79 (6H, m), 2.64 (12H, m), 3.21 (12H, t, J=5.0 Hz), 3.75 (12H, t, J=5.5 Hz), 4.12 (12H, s), 4.55 (6H, s br), 6.85–7.36 (24H, m). δ_C (75.43 MHz, $CDCl_3$, 25°C): 24.22, 28.36, 47.32, 53.16, 66.47, 110.8, 120.1, 127.7, 129.5, 132.1, 156.3. ES-Ms m/z (%) 1085(100) $[\mathbf{L}^2+2H_2O]^+$.

$\mathbf{L}^3$ was obtained from **1** (0.92 g) and 1,4-diaminobutane (0.26 g) as a pale yellow semi solid (0.5 g, 45%). [Found C, 72.43; H, 8.53; N, 10.36. $C_{66}H_{90}N_8O_6$ requires C, 72.63; H, 8.31; N, 10.27%]; ν_{max} (neat) 3500–3200 (br), 2950–2840 (br), 1590, 1490, 1455, 1240, 1165, 945 cm^{-1}; δ_H (300 MHz, $CDCl_3$, 25°C) 1.42 (12H, m), 2.58 (12H, s br), 3.22 (12H, t, J=5.0 Hz), 3.67 (12H, t, J=5.5 Hz), 4.12 (12H, s), 6.89–7.34 (24H, m). δ_C (75.43 MHz, $CDCl_3$, 25°C) 24.22, 27.11, 49.43, 53.53, 66.70, 110.8, 120.4, 127.8, 129.3, 132.2, 156.6. ES-Ms m/z (%) 1091(15) $[\mathbf{L}^3+H]^+$.

Synthesis of $\mathbf{L}^4$

The tripodal trialdehyde **1** (3.69 g; 8 mmol) was dissolved in 20 mL dry THF and stirred at RT. Tris(2-aminoethyl)amine

(1.3 mL; 8 mmol) taken in 10 mL of MeOH was added to the stirred solution of trialdehyde all at once. Then the mixture was stirred for another 24 h at room temperature. The Schiff base so formed was hydrogenated in situ by stirring with excess of $NaBH_4$ at room temperature for 4 h followed by refluxing for another 1 h. The solvent was evaporated almost to dryness and the residue was shaken with 100 mL of water. The desired cryptand was extracted from the aqueous medium with $CHCl_3$ (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain a yellow semisolid. It was stirred with acetone (25 mL) and the resulting solution left at 5°C overnight to obtain colorless crystals whose spectral characteristics were found to be identical to those obtained with the macrobicyclic cryptand. After complete removal of acetone, the viscous liquid was dissolved in mixed solvent system of acetonitrile: hexane: ethyl acetate (1:1:1 by vol). After keeping overnight at RT, the macrotricyclic cryptand could be obtained as a colorless semi-solid (0.93 g, 21%). [Found: C, 70.78; H, 8.04; N, 12.56. $C_{66}H_{90}N_{10}O_6$ requires C, 70.81; H, 8.10; N, 12.51%]; ν_{max}(KBr) 3295, 3030, 2925, 2870, 2820, 1595, 1240, 1110, 1045, 950 cm^{-1}; δ_H (80 MHz, $CDCl_3$): 2.5 (24H, m), 3.2 (12H, t, J=6.0 Hz,), 3.6 (12H, s), 4.1 (12H, t, J=6.0 Hz), 6.8–7.2 (24H, m). ES-MS m/z (%) 1119(10) $[\mathbf{L^4}]^+$.

Synthesis of $\mathbf{L^5}$

The tripodal trialdehyde **2** (3.69 g; 8 mmol) was dissolved in 20 mL dry THF and stirred at RT. A solution of tris-(2-aminoethylamine) (1.3 mL; 8 mmol) taken in 10 mL of MeOH was added all at once to the stirred solution of the trialdehyde. After 30 min of stirring some white solids precipitated from the reaction mixture, which were collected by filtration. The filtrate was then stirred for another 24 h at room temperature. The Schiff-base thus formed was hydrogenated in situ by stirring with an excess of $NaBH_4$ at room temperature for 4 h followed by refluxing for another 1 h. The solvent was evaporated almost to dryness and the residue was shaken with 100 mL of water. The desired cryptand was extracted from the aqueous medium with $CHCl_3$ (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain a yellow semi-solid of $\mathbf{L^5}$. The compound could be obtained as a colorless microcrystalline solid by crystallization from acetonitrile: hexane: ethyl acetate (1:1:1 by vol) solvent system (0.9 g, 23%), mp decomposed at 165°C. [Found: C, 70.65; H, 7.97; N, 12.63. $C_{66}H_{90}N_{10}O_6$ requires C, 70.81; H, 8.10; N, 12.51%]; ν_{max}(KBr) 3425, 3300, 3045, 2815, 1610, 1580, 1450 1320, 1270, 1160, 1125, 1060, 940 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 1.90 (3H, s), 2.65 (12H, s), 3.05 (6H, t, J=3.0 Hz), 3.60 (6H, s), 4.01 (6H, t, J=3.5 Hz), 6.90 (12H, m); ES-MS m/z (%) 1119(30) $[\mathbf{L^5}]^+$.

Synthesis of $\mathbf{L^6}$

The triester (5.5 g, 20 mmol) and ethylenediamine (1.8 g, 30 mmol) were mixed and stirred at room temperature for 7 days. Then the mixture was evaporated to dryness in vacuo. The oily residue was then washed with $CHCl_3$ (3×50 mL) and ether (3×50 mL). The macrotricyclic cryptand ($\mathbf{L^6}$) was extracted with 10 mL of water. Complete removal of water in vacuo gave a thick pale yellow oily product in (1.7 g 38%). [Found: C, 47.37; H, 6.74; N, 24.52. C_{36} H_{60} $N_{16}O_{12}$ requires C, 47.57; H, 6.65; N, 24.66 %]; ν_{max} (neat) 3300, 2995, 1645, 1595, 1500, 1400, 1240, 1100, 990 cm^{-1}; δ_H (80 MHz, D_2O) 2.9 (12H, m), 3.8 (12H, m); δ_C (20.1 MHz, D_2O) 38.82, 39.96, 58.57, 173.47. ES-MS m/z (%) 910.4(15) $[\mathbf{L^6}+H]^+$.

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