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Size Mismatch Between Two Tripodal Units: A New Synthetic Strategy for Macrotricyclic Cryptand

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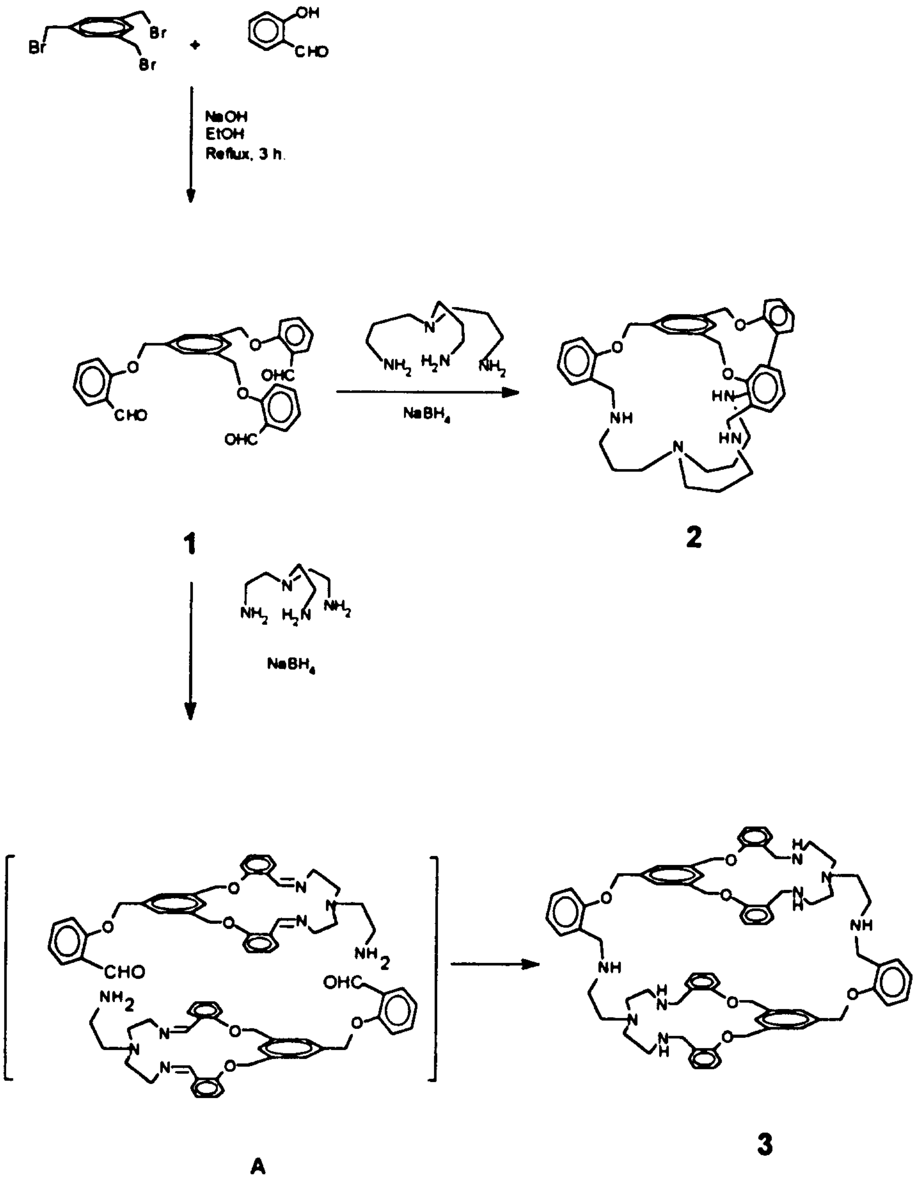
Abstract : Tripods of matched/mismatched sizes lead to a macrobicyclic/macrotricyclic cryptand in high yield by Schiff base condensation at 5° C in the absence of any templating metal ion.

Design and synthesis of macropolycyclic receptor molecules for selective recognition of organic as well as inorganic cations,[1] anions,[2] and neutral molecules[3] is the most basic requirement of supramolecular chemistry. We are involved in the syntheses and utilisation of heterotopic cryptands for molecular recognition,[4] metal ion recognition[5] etc. Further derivatization of these cryptands lead to interesting results such as photochemical switches,[6] vesicle formation,[7] monolayer formation in a Langumir trough etc. Encouraged by our above mentioned findings we are now aiming at the syntheses of new host molecules of different shapes, sizes and topology. Macrotricyclic cryptands have several important features which should make them very useful in many areas of chemistry and biochemistry. The architecture of these molecules consists of two lateral macrocyclic cavities linked through spacers that delineate the central cavity. Such systems can be useful as carriers for translocation of substrates across biological membranes, as binuclear metal cryptates to transfer several electrons to the substrate bound in the central cavity , for the activation of small molecules, for signal and energy transduction, etc. However, no good synthetic method is available which can produce macrotricycles in high yields. The construction of macrotricyclic molecules are generally carried out by connecting two macrocycles by two bridges[8] where each macrocycle possesses two derivatizable sites The yields reported are quite low. Our initial synthetic approach for macrobicyclic cryptand has been [1+1] Schiff base condensation of two matching tripodal units. We are reporting here a new method of synthesis that takes place readily due to size mismatch of two tripodal units leading to a macrotricyclic cryptand. This method affords the cryptand in pure form and in high yields.

The synthetic procedure adopted for the cryptands is illustrated in Scheme 1.The tripodal trialdehyde 1,3,5-tris[(2-(oxomethyl)phenyl)oxymethyl]benzene, **1** was synthesized by refluxing 1,3,5-trisbromomethylbenzene[9] with the sodium salt of salicylaldehyde in ethanol[10]. This trialdehyde undergoes [1+1] Schiff base


Br
Br
Br
OH
CHO
NaOH
EtOH
Reflux, 3 h.
CHO
OHC
OHC
1
NH$_2$
H$_2$N
NH$_2$
NaBH$_4$
NH
HN
HN
N
2
NH$_2$
H$_2$N
NH$_2$
NaBH$_4$
CHO
NH$_2$
NH$_2$
OHC
A
NH
NH
3

Scheme 1

condensation with the tripodal triamine, tris(3-aminopropyl)amine (trpn). However, with the tripodal triamine, tris(2-aminoethyl)amine (tren) due to size mismatch, it undergoes [2+2] Schiff base condensation leading to the formation of a macrotricyclic compound.[11]

Our earlier method was to use an alkali metal ion as the template at ~ 40° C for the condensation of two tripodal units. Subsequently, we[5] and others[12] have found that if the reactants were allowed to react at low temperature (~ 5 °C), no templating metal ion was necessary apparently because of decreased degrees of movement of the reacting arms. It is not surprising that macrobicyclic cryptand **2** is formed by the condensation of **1** and trpn. However, formation of the macrotricyclic cryptand when trpn is replaced by tren deserves a special comment. We believe that as there is a size mismatch between **1** and tren the complete [1+1] condensation of the two units is not facile; rather the intermediate **A** as shown in Scheme 1 is forming and dimerising to give **3** before it can collapse to the macrobicyclic cryptand. Cryptand **3** forms both mono- and dinuclear cryptates with first-row transition metal ions depending upon the reaction conditions and the metal ion involved.

In conclusion, we have reported two new cryptands which can be synthesized at low temperature without using any templating metal ion. The yields are high in both the cases. We have also provided a new synthetic strategy for obtaining macrotricyclic cryptands readily from two tripodal reactants. Currently our efforts are to extend this synthetic strategy to obtain some other cryptands by varying the hetero-atoms and chain lengths. We are also probing the cryptand **3** for its recognition characteristics towards organic molecules and for its usefulness in forming cascade complexes.

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10. Sodium salt of 2-hydroxybenzaldehyde was prepared by adding NaOH (0.12 g, 3 mmol) to a solution of 2-hydroxybenzaldehyde (0.37 g, 3 mmol) in 50 mL of ethanol and stirring at RT for 1/2 h. To this solution

1,3,5-trisbromomethyl benzene (0.36 g, 1mmol) was added and refluxed for 3 h. The reaction mixture was cooled to RT and the white solid was collected by filtration, washed with cold ethanol and finally dried to obtain the tripodal trialdehyde **1** in 85% yield: mp 135-137 °c ; ^{1}H NMR δ 5.4 (s, 6H), 7.5 (m, 15H), 10.7 (s, 3H).

11. General method for the synthesis of **2** and **3** is as follows. The tripodal trialdehyde (1mmol) was dissolved in 100 mL of the solvent system 1:1 methanol:THF and cooled to ~5° C in an ice bath. To this solution was added solution of the triamine (1 mmol) in 100 mL of the solvent system 1:1 methanol:THF over a period of 3 h while stirring the reaction mixture continuously and maintaining the low temperature. After the the addition was complete, the reaction mixture was allowed to warm to RT and kept for another 12 h with constant stirring. The Schiff base so formed was hydrogenated *in situ* with excess of $NaBH_4$ at RT for 2 h followed by refluxing for another 1 h. The solvent was evaporated to almost dryness and the residue was shaken with 20 mL of cold water. The desired cryptand was extracted from the aqueous medium with $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and evaporated to obtain a yellow solid/semisolid. **2** was obtained from **1** and tris(3-aminopropyl)amine in 45% yield: m.pt. 45-47° C ; ^{1}H NMR δ 1.4 (q, 6H), 2.2 (t, 6H), 2.5 (t, 6H), 3.8 (s, 6H), 5.2 (s, 6H), 7.4 (m, 15H); ^{13}C NMR δ 25.99, 47.69, 50.15, 52.09, 70.48, 112.26, 121.48, 127.09, 128.87, 131.27, 138.26, 157.49; FAB-mass m/z (%) 621 (90) (**2**$^+$). **3** was obtained similarly from **1** and tris(2-aminoethyl)amine in 50% yield: m.pt. 85-86° C ; ^{1}H NMR δ 2.5 (s, 24H), 3.8 (s, 12H), 5.0 (s, 12H), 7.2 (m, 30H); ^{13}C NMR δ 47.57, 49.40, 54.67, 70.30, 112.09, 121.14, 125.89, 128.47, 129.15, 130.64, 138,37, 157.03; FAB-mass m/z (%) 1157 (80) (**3**$^+$). The dicobalt cryptate, $Co_2(3)(H_2O)_2(picrate)_4$ gave satisfactory elemental (C,H,N) analysis. The FAB-mass spectrum of this complex showed prominent peaks at 1308, 1251 and 1214 corresponding to the ions formed after liberation of four picrates, one cobalt and two water molecules respectively.
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