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Synthesis and X-ray crystallographic investigation of a novel indole-based cryptand: structure of a sandwiched cyclic S_6 hexameric methanol cluster

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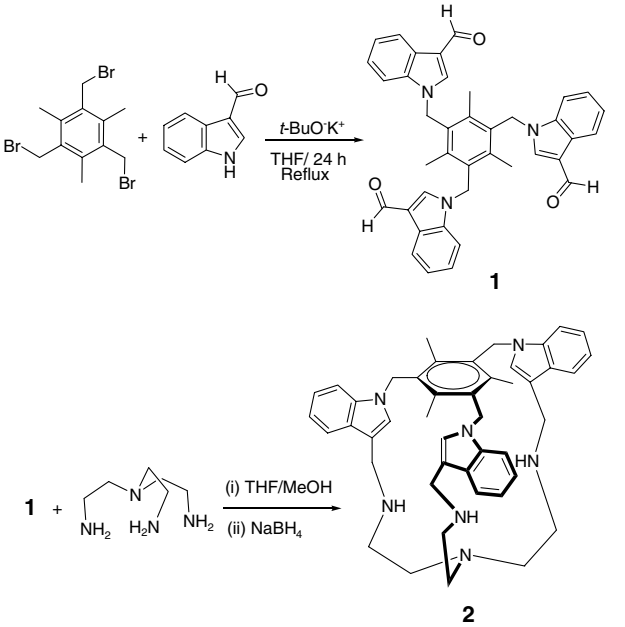
Abstract—Synthesis of a novel cryptand with an indole moiety in its architecture is described. Crystal structures of this newly synthesized cryptand and its trialdehyde precursor have been investigated. In the case of the cryptand molecule, a discrete cyclic S_6-symmetric hexameric methanol cluster sandwiched between the hydrophobic ends of two cryptand units was characterized crystallographically. Moreover, a hexameric cyclic chair conformation composed of methanol and secondary nitrogen atoms from the cryptand skeleton was also identified.

The importance of indoles and their derivatives is well recognized by synthetic as well as biological chemists.[1–7] Though bibrachial lariat ether[4] and cyclophanes[8] with indole rings have been reported, to the best of our knowledge only one cryptand has been synthesized having an indole in its basic skeleton.[9] The use of a McMurry coupling reaction was used in an attempt to synthesize an indole-based bicyclic cage molecule but it was unsuccessful.[8a] In the present study, we report the synthesis and crystal structures of novel indole-based cryptand **2** and its trialdehyde precursor **1**. Moreover, detailed structural analysis of **2** showed a discrete cyclic S_6 symmetric methanol hexamer, sandwiched between the hydrophobic ends of two cryptand units.

The reaction of 1,3,5-tris(bromomethyl)-2,4,6-trimethyl benzene[10] with indole-3-aldehyde in the presence of *t*-BuO^-K^+ as a base in THF afforded trialdehyde **1** as a pale pink colored solid in 90% yield. The 1:1 condensation of **1** with tris(2-aminoethylamine) in THF/MeOH followed by in situ $NaBH_4$ reduction afforded cryptand **2** as a pale yellow solid in 15% yield (Scheme 1). Our attempt to isolate the intermediate Schiff base failed resulting only in the formation of a highly insoluble yellow solid. Crystals of **1** and **2** suitable for X-ray crystallography were obtained on slow evaporation of a methanolic solution of **2** and an acetonitrile solution of **1**. In an attempt to characterize and understand the conformation and molecular packing we have determined the crystal structure of precursor **1** and cryptand **2** by single crystal X-ray diffraction (see Supplementary data).



Scheme 1. Synthesis of cryptand **2** from trialdehyde **1**.

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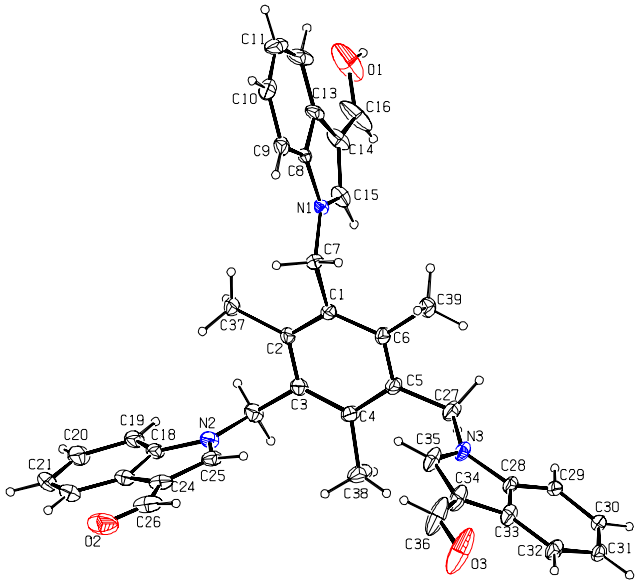

Figure 1. ORTEP diagram of **1** (40% probability factor for the thermal ellipsoids) with atom numbering scheme (the lattice acetonitrile molecules are removed for clarity).

Compound **1** crystallizes in monoclinic space group $P2_1/c$ with acetonitrile as solvent of crystallization. Figure 1 shows the ORTEP diagram of **1** with the atom numbering scheme. As depicted in Figure 1 all the three indole arms of the ligand are spread apart because of the steric constraints imposed by the methyl groups attached to the central phenyl ring at alternate positions and the various H-bonding interactions of the molecule to make an effective packing arrangement. The indole rings are almost orthogonal to the central phenyl moiety and the mean plane angles between the phenyl rings and the indole ring range from 80.55° to 87.68°.

The packing diagram of **1** viewed down the *b*-axis with hydrogen bonding interactions is depicted in Figure 2. The ligand moieties are arranged as bilayers via C–H···O hydrogen bonding interactions and are oriented along the *c*-axis. The layered ligand molecules within the bilayers are oriented in an offset manner with two of the indole arms projected along the *c*-axis and one arm toward the *a*-axis. From the offset ligand moiety within the bilayers, aldehyde oxygen O1 is involved in a bifurcated C–H···O hydrogen bond with the indole hydrogen atoms H25 and H35.

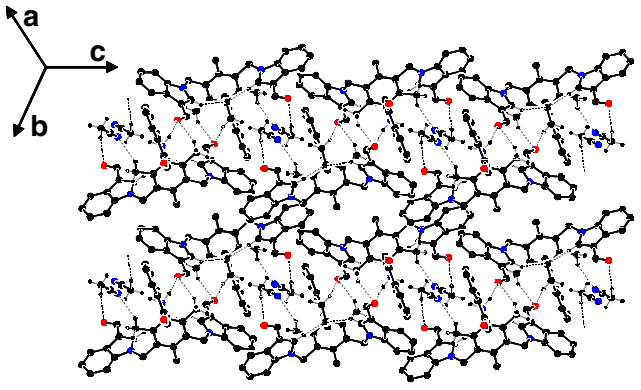

Figure 2. Packing diagram with H-bonding interactions of **1** viewed down the *b*-axis showing the bilayer arrangement of the ligand moiety and the encapsulation of the lattice acetonitrile between the adjacent bilayers via C–H···O and C–H···N hydrogen bonding.

In addition to this C–H···O interaction, the molecules within the bilayers are linked via weak C–H···π interactions from either side along the *c*-axis between the phenyl hydrogen H11 and methyl hydrogen H38A and the aromatic ring (C28–C33) of the indole ring. The pertinent C–H···π interactions with symmetry codes are C11–H11···Cg1: H11···Cg1 = 2.55 Å, C11···Cg1 = 3.314(7) Å, <C11–H11···Cg1 = 139°, symmetry code: $-x$, $1-y$, $-z$. C38–H38A···Cg1: H38A···Cg1 = 2.99 Å, C38···Cg1 = 3.634(5) Å, <C11–H11···Cg1 = 126°, symmetry code: $1-x$, $2-y$, $-z$ where Cg1 is the center of gravity of the phenyl ring C28–C33.

It is interesting to note that in between the neighboring bilayers, the lattice acetonitrile molecule is bound via C–H···N and C–H···O interactions. Thus hydrogen atom H40B from acetonitrile is involved in a C–H···O interaction with the aldehyde oxygen O3, whereas the indole hydrogen H35 is involved in a C–H···N interaction with acetonitrile which firmly encapsulates acetonitrile in the cavity down the *b*-axis.

The adjacent bilayers are also linked via C–H···O interactions between aldehyde oxygen O3 and methylene hydrogen H7B and methyl hydrogen H39B attached to the central phenyl ring along the *a*-axis forming a two-dimensional hydrogen bonding network as depicted in Figure 2. Details of all these intermolecular H-bonding interactions with symmetry code are available in Table 1 of the Supplementary data.

Compound **2** crystallizes in the R-3 space group with two molecules of methanol in the lattice. The ORTEP diagram of the cryptand with the atom numbering scheme is depicted in Figure 3. The cryptand possesses a three fold symmetry passing through N1 of the tren moiety and the centroid of the phenyl bridgehead to which the indole rings are attached. The mean plane between the symmetrically disposed indole rings of the cryptand moiety with respect to the central phenyl ring is orthogonal (89.10°) just as is observed in precursor **1**. The fascinating feature of the structure is the entrapment of the S_6 symmetric methanol molecule between the cryptand units down the *c*-axis (Fig. 4).

The centro-symmetric hexameric methanol cluster with a chair conformation is held by O–H···O hydrogen bonding interactions with an O···O separation distance of 2.603 Å which is well within the range reported by Wieghardt et al.[11] This is also supported by a recent report by Benisvy et al. on a C2-symmetric structure representing the first crystallographic evidence of the second energetically favored form of liquid methanol with a twisted boat conformation with an O···O distance ranging from 2.548 Å to 3.0347 Å, though some

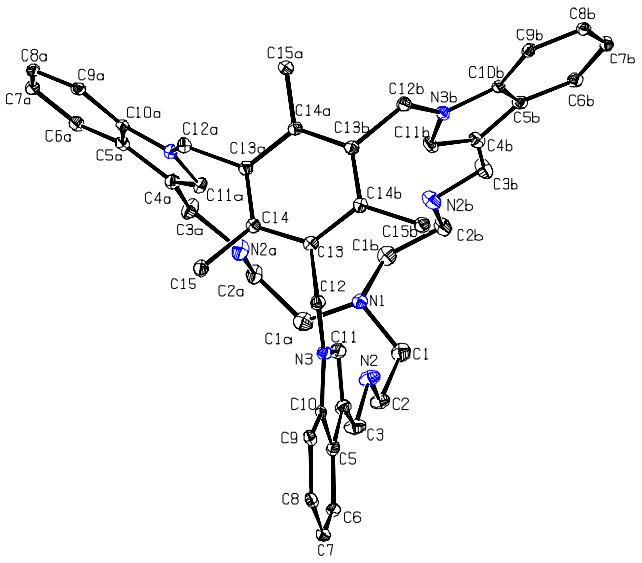

Figure 3. ORTEP diagram of compound **2** (40% probability factor for the thermal ellipsoids) with atom numbering scheme (hydrogen atoms and lattice methanol molecules are omitted for clarity).

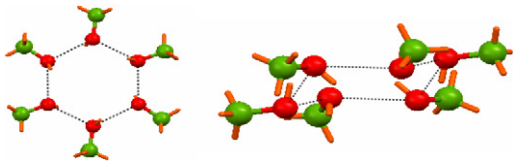

Figure 4. MERCURY diagram depicting, (a) the cyclic methanol hexamer and (b) the S_6 symmetric chair conformation of the cyclic hexameric cluster.

of the methanol molecules in this hexamer were in coordination with the metal center.[12] In our report, the hexameric methanol cluster is sandwiched between the hydrophobic ends of the cryptand moieties (i.e., bridgehead phenyl rings) by van der Waals forces down the *a*-axis which is depicted in the packing diagram of the compound in Figure 5 and the close up view of the haxameric methanol cluster in Figure 6.

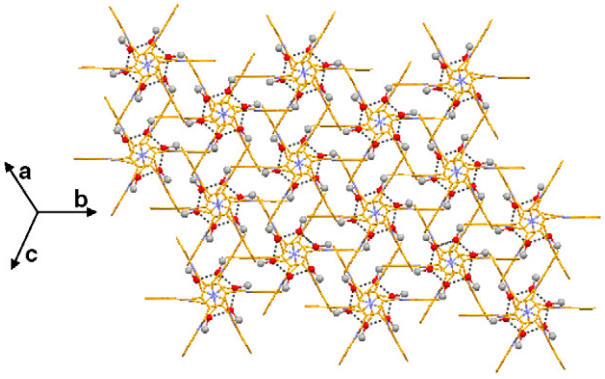

Figure 5. Packing diagram depicting the cryptand moiety (wire frame model) with hydrogen bonded (hydrogen bonding in dotted lines) hexameric methanol cluster (ball and stick model) embedded between the three fold symmetric cryptand moiety down the *c*-axis (the second methanol molecule forming N–H···O interactions with the amino nitrogen of the cryptand ligand is omitted for clarity).

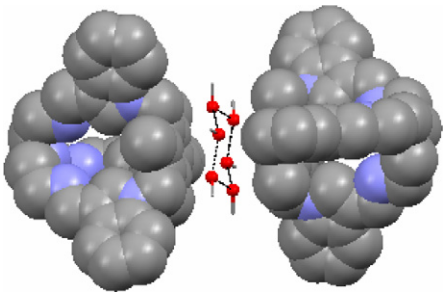

Figure 6. Close-up view of the hydrogen bonded hexameric methanol cluster sandwiched between the cryptand moieties.

In addition to the above hexameric O–H···O interactions of the methanol molecule, the other lattice methanol is involved in hydrogen bonding with the secondary amino hydrogens from the symmetric arms of the cryptand moiety via O–H···N and N–H···O hydrogen bonding. Thus the oxygen atom O1 of the symmetrically disposed methanol molecule acts as a donor in the O–H···N interaction and as an acceptor in the N–H···O interaction with the amino nitrogen N2 which is part of the C_3 symmetric tren arm of the cryptand, generating a chair-shaped cyclic hexameric ring (Fig. 7). Details of the hydrogen bonding interactions with symmetry codes are available in Table 2 of the Supplementary data.

In summary, we have described the synthesis of a novel cryptand molecule with indole moieties in the skeleton and its precursor trialdehyde. The precursor trialdehyde packs in the solid state as a bilayer motif with encapsulation of acetonitrile between the neighboring bilayers. In the case of cryptand **2**, structural evidence for the existence of a methanol cluster in its hexameric chair conformation was demonstrated and is rarely reported previously, even though more theoretical predictions regarding conformations of the cyclic hexameric methanol are available.[13,14] Studies on the synthesis and photophysical properties of this kind of cryptand with special attention toward its guest binding properties are in progress.

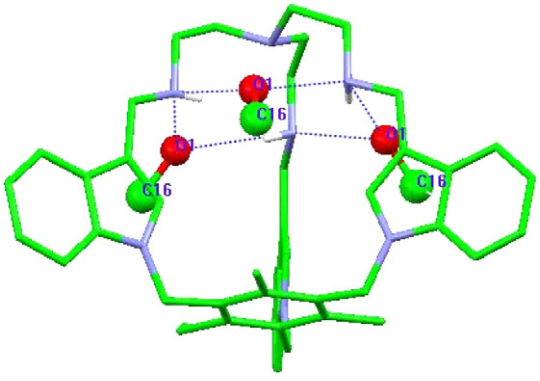

Figure 7. Hydrogen bonding interactions between additional lattice methanol and the amino nitrogen of the cryptand via O–H···N and N–H···O interactions creating a six-membered ring in a chair conformation.

Synthesis of trialdehyde **1**. To a slurry of *t*-BuO$^-$K$^+$ (3.5 mmol, 0.392 g) in 25 mL of dry THF, a solution of indole-3-aldehyde (3 mmol, 0.435 g) in 10 mL of THF was added dropwise under nitrogen. The slurry was allowed to stir for 15 min then 1,3,5-tris(bromomethyl)-2,4,6-trimethyl benzene[10] was added in one portion to the reaction mixture. The reaction mixture was allowed to stir for 4 h. During the reaction potassium bromide precipitated and reaction completion was monitored by TLC. The solvent was evaporated under reduced pressure and the product was extracted with $CHCl_3$ (3×100 mL). The chloroform extract was dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded trialdehyde **1** as a pale pink colored solid in 90% yield. mp: 162–164 °C ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.30 (s, 9H), 5.45 (s, 6H), 7.27–7.54 (m, 12H), 8.29 (m, 3H), 9.92 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 17.20, 46.09, 110.39, 119.19, 122.72, 124.22, 125.06, 126.54, 131.55, 135.57, 138.05, 141.06, 185.01; MS (EI) (*m*/*z*) 592.5 ($M+H^+$) 100%. Anal. Calcd for $C_{43}H_{39}N_5O_3$: C, 76.65; H, 5.83; N, 10.39%. Found: C, 76.48; H, 5.76; N, 10.34%. During the course of this work Rajakumar et al. reported the synthesis of trialdehyde **1** following a different scheme though a detailed procedure was not given.[8a]

Synthesis of cryptand **2**. Trialdehyde **1** (1 mmol, 0.591 g) was dissolved in 300 ml of a 3:1 dry CH_3OH/THF mixture in a 1 L round bottom flask at 40 °C. After complete dissolution by warming, the solution was cooled to room temperature. TREN (0.15 ml, 1 mmol) was dissolved in 250 ml of dry MeOH and added dropwise at a rate of 2–3 drops/min with vigorous stirring at room temperature. The color of the solution changed from pale pink to pale yellow as the addition continued. After complete addition of TREN, the reaction mixture was allowed to stir overnight. Then, excess sodium borohydride was added in portions to the reaction mixture for complete reduction and the mixture allowed to stir for 4 h at room temperature. The color of the solution changed from yellow to colorless upon reduction. A pale yellow solid was obtained after $CHCl_3$ work-up. Cryptand **2** was isolated by neutral alumina column chromatography where 8:2 hexane/chloroform was used as eluent. Yield of **2**: 15%; mp: 156–158 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.22 (s, 9H), 2.56 (t, $J = 3.4$, 6H), 2.92 (t, $J = 3.4$, 6H), 3.30 (br s, 3H), 3.92 (s, 6H), 5.27 (s, 6H), 6.92–7.56 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 16.69, 44.85, 46.56, 47.94, 53.87, 114.62, 109.47, 119.33, 119.85, 122.25, 123.20, 128.07, 131.96, 136.92, 140.00; MS (EI) (*m*/*z*): 690.5 (M^+) 100%. Due to the six methanol molecules present in the system, elemental data were not obtained.

Crystal data for **1**. Crystal dimensions of $C_{43}H_{39}N_5O_3$: $0.48 \times 0.38 \times 0.32$; $M_w = 673.79$, monoclinic, space group $P2_1/c$, $a = 12.4485(11)$, $b = 11.2059(10)$, $c = 25.365(2)$ Å, $V = 3537.9(5)$ Å^3, $D_c = 1.265$ g cm^{-3}, $Z = 4$, μ(Mo-K$_\alpha$) = 0.081 mm^{-1}, total reflections = 17,277, 6226 unique reflections ($R_{int} = 0.0337$), largest difference peak and hole = 0.979 and −0.489 e Å^{-3}. Final $R_1[I > 2\sigma(I)] = 0.0835$, $wR_2 = 0.2333$, goodness of fit on $F^2 = 1.084$. CCDC 627146 contains the Supplementary data for **1**.

Crystal data for **2**. Crystal dimensions of $C_{51}H_{75}N_7O_6$: $0.23 \times 0.13 \times 0.06$; $M_w = 882.18$, hexagonal, space group R-3, $a = 17.4063(9)$, $b = 17.4063(9)$, $c = 27.718(3)$ Å, $V = 7272.9(9)$ Å^3, $D_c = 1.209$ g cm^{-3}, $Z = 6$. μ(Mo-K$_\alpha$) = 0.080 mm^{-1}, total reflections = 12,228, 2846 unique reflections ($R_{int} = 0.0569$), largest difference peak and hole = 0.825 and −0.523 e Å^{-3}. Final $R_1[I > 2\sigma(I)] = 0.0801$, $wR_2 = 0.2082$, goodness of fit on $F^2 = 1.037$. CCDC 627145 contains the Supplementary data for **2**.

Acknowledgements

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Supplementary data

^{1}H NMR, ^{13}C NMR, LC–MS, X-ray data (CIF), and hydrogen bonding parameters for compounds **1** and **2**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.083.

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