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The Use of tris(2-Aminoethyl)amine in Macrocyclization Processes

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Abstract: Reactions of tripodal amine **1** with tripodal esters **2** and **4**, carried out in methanol under ambient conditions, afforded - as single products - tricyclic cryptands **3** and **5**, respectively. Under the same conditions, the amine **1** reacted with dipodal esters **6** and **7** to give bis-macrocycles **9** and **10**, respectively.

Supramolecular chemistry deals with more or less rigid and organized molecules, called molecular devices.[1] Owing to their noncovalent bonding, these species exhibit special abilities to be properly organized in space. This specific organization can theoretically be achieved *via* step-by-step synthesis. The complexity of target molecules acting as molecular devices is, however, often too high to allow a chemist to build up the molecule stepwise. The rational route to obtain this type of compounds seems to be to design a system procure components, and then to create suitable conditions to allow the system to preorganize.[2] The self-assembly approaches to the synthesis of various molecular devices, such as diazacoronands[3,4] and bicyclic[5,6] or tricyclic[6,7] cryptands have been reported by us. There are several other known reactions of tripodal reagents with dipodal components, leading mainly to bicyclic compounds.[8-11] Interesting example of the synthesis of bicyclic cryptands is the reaction of two molecules of tripodal acetylenic derivatives, carried out in the presence of Cu(I) salts, to afford the desired cyclodimerization product.[12] It has recently been found by us that dimethyl α,ω-dicarbocylate reacted under ambient conditions with α,ω-diamino aliphatic ethers in methanol as solvent, to afford the macrocyclic diamides in good yields.[13-15]

These results prompted us to apply tripodal amine **1** to the reaction with tripodal tricarboxylate **2**. When the reaction was carried out in methanol as solvent and at room temperature for 30 days, the crystalline tricyclic cryptand **3**[16] was formed as a single product, in 51% yield (Scheme 1). The proposed structure of compound **3**[17] was based on spectral analysis (^{1}H and ^{13}C NMR and mass spectrometry). The ^{13}C NMR spectrum is very characteristic: it consists of four pairs of signal in a 1:2 ratio (Figure 1). The final proof of the structure was based on the X-ray analysis. Figure 2a shows a projection of the molecule of compound **3**.

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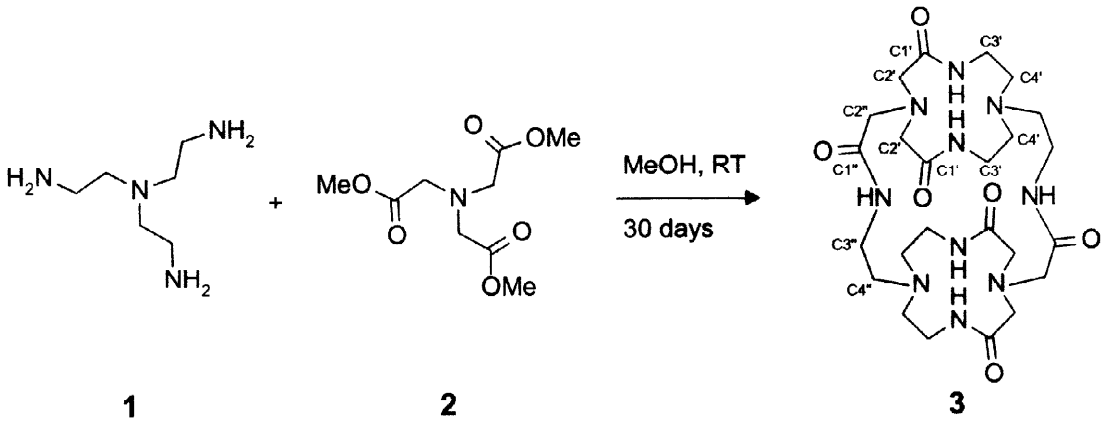


Scheme 1

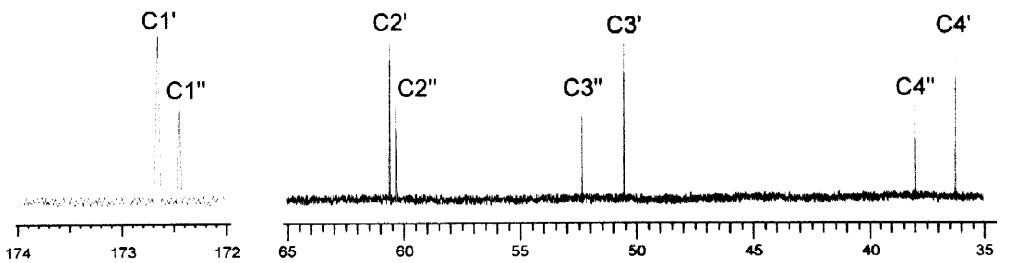
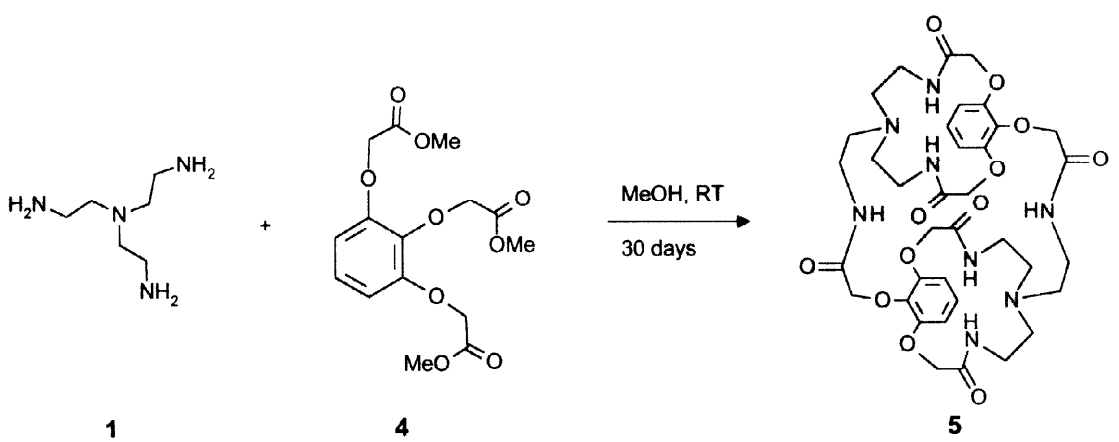


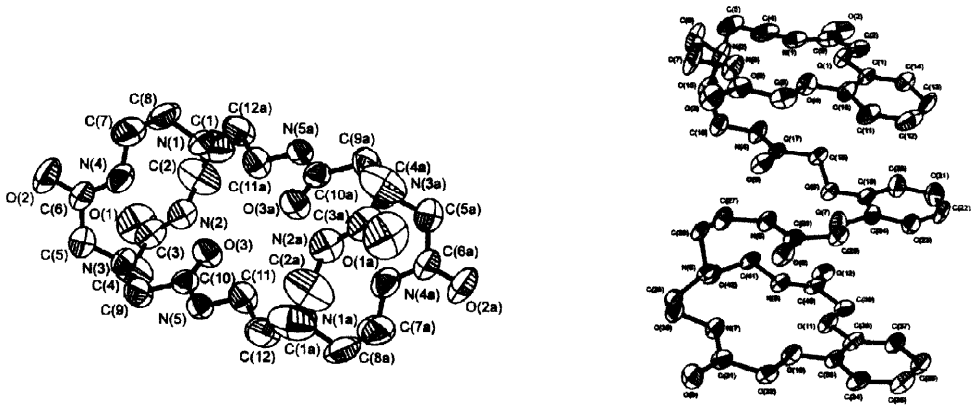
Figure 1. Fragments of ^{13}C NMR spectrum of tricyclic cryptand **3**

It is interesting that in the crystal structure of **3** (Figure 2a) there are no intramolecular hydrogen bonds and we did not observe molecules of solvent included. We observed, however, formation of molecular channels stabilized by intermolecular hydrogen bonds with participation of the solvent.

A similar product, the tricyclic cryptand **5**,[18] was obtained in 39% yield from the reaction of tripodal amine **1** with another tripodal ester **4**, carried out under similar conditions as in the former case (Scheme 2).



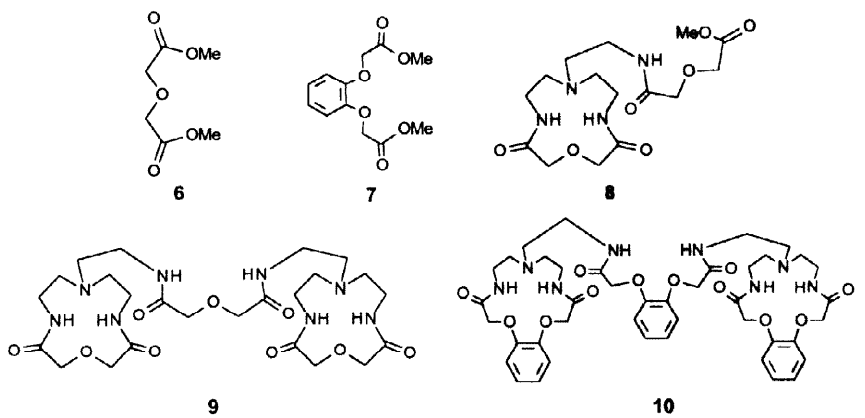
Scheme 2



a) b)

Figure 2. Molecular structure in the crystal: a) compound **3**, b) compound **10**

The reaction of tripodal amine **1** with diester **6**, carried out in methanol under ambient conditions,[19] afforded two products: armed mono-macrocycle **8**[20] (11% yield), and bis-macrocycle **9**[21] (4% yield) (Scheme 3).



Scheme 3

The reaction of the same amine **1** with benzo diester **7**, carried out under analogous conditions, afforded only one product - crystalline bis-macrocycle **10**[22] (34% yield) (Scheme 3). The compound **10** partly precipitated from the reaction mixture, and after a few attempts, we managed to obtain well shaped crystals suitable for X-ray analysis. Figure 2b shows a projection of the molecule.

The present work deals with syntheses of complex tricyclic cryptands *via* the amidation reaction, controlled by self-assembly phenomena which are probably stimulated by methanol used as a solvent as we proposed for preparation of diazacoronands.[13-15] The same concept can be extended to the synthesis of more elaborated structures, e.g. tricyclic chiral cryptands; the project is now in progress.

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16. Typical procedure: A mixture of tripodal amine (1 mmol) and tricarboxylate (1 mmol), dissolved in methanol (15 ml), was left at room temperature for 30 days. The precipitated colorless crystals were recrystallized from a mixture of water, methanol and acetone, to afford pure crystalline product.
17. Analytical data for **3**: m.p. 258°C (decomp.); ^{1}H-NMR (200 MHz, D_2O): 2.70 (*m*, 14H), 3.30 (*bm*, 24H), 3.64 (*s*, 4H); ^{13}C-NMR (200 MHz, D_2O): 36.2, 37.9, 50.6, 52.3, 60.3, 60.7, 172.5, 172.7.
18. Analytical data for **5**: m.p. 305°C (decomp.); ^{1}H-NMR (200 MHz, DMSO-d_6): 3.33 (*m*, 24H), 4.15 (*s*, 4H), 4.44 (*d*, 8H), 6.31 (*d*, 2H), 6.60 (*d*, 2H), 6.74 (*t*, 2H), 7.44 (*bs*, 2H), 7.55 (*bs*, 2H),7.62 (*bs*, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6): 34.8, 35.4, 35.9, 48.5, 50.6, 50.9, 51.5, 67.7, 71.7, 106.6, 107.4, 123.8, 135.9, 149.4, 150.6, 166.6, 167.5, 168.5.
19. Typical procedure: A mixture of tris(2-aminoethyl)amine **1** (1 mmol) and dimethyl dicarboxylate **6** (2 mmol), dissolved in methanol (10 ml), was left at room temperature for 21 days. Then the reaction mixture was evaporated in vacuo, and the residue was subjected to high performance liquid chromatography (HPLC), using a preparative RP18 column and water-ethanol 95:5 v/v as an eluent to afford pure products **8** (11% yield) and **9** (4% yield).
20. Analytical data for **8**: ^{1}H-NMR (200 MHz, $CDCl_3$): 3.32 (*m*, 12H), 3.68 (*s*, 3H), 3.94 (*s*, 4H), 4.02 (*s*, 2H), 4.23 (*s*, 2H), 7.71 (*bs*, 2H), 8.04 (*bs*, 1H).
21. Analytical data for **9**: ^{1}H-NMR (200 MHz, $CDCl_3$): 3.31 (*bm*, 24H), 3.91 (*s*, 8H), 3.96 (*s*, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): 36.0, 38.2, 51.2, 52.7, 70.4, 72.9, 168.8, 169.1.
22. Analytical data for **10**: m.p.185-186°C; ^{1}H-NMR (200 MHz, $CDCl_3$): 2.81 (*m*, 12H), 3.49 (*m*, 12H), 4.22 (*s*, 4H), 4.35 (*s*, 8H), 6.50 (*m*, 2H), 6.76 (*m*, 4H), 6.85 (*m*, 2H), 6.96 (*m*, 4H), 7.5 (*m*, 6H); ^{13}C-NMR (50 MHz, $CDCl_3$): 35.9, 36.9, 51.5, 53.4, 67.4, 68.6, 113.1, 114.2, 122.3, 122.7, 146.4, 147.1, 167.6, 168.6.