Synthetic Route To Produce Giant-Size Azamacrocycles

Carla Bazzicalupi,† Andrea Bencini,† Vieri Fusi,† Mauro Micheloni,*,‡ Piero Paoletti,*,† and Barbara Valtancoli†

Department of Chemistry, University of Florence, Via Maragliano 75, I-50132 Florence, Italy, and Institute of Chemical Sciences, University of Urbino, Italy

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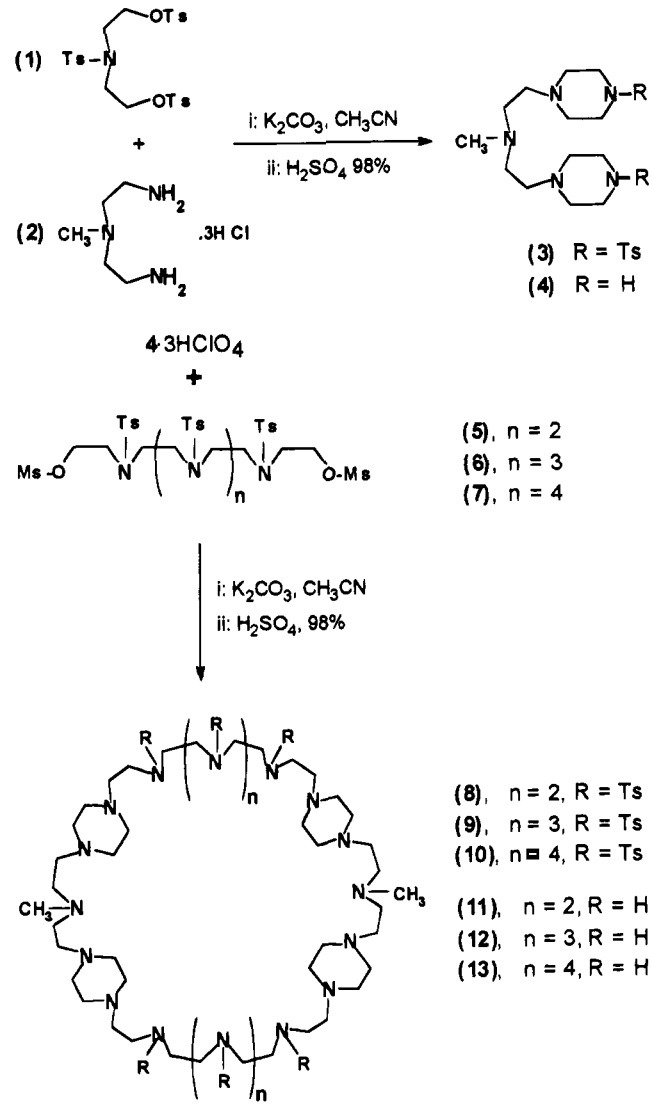
Introduction

In the last few years there has been considerable interest in the development of new aza macrocyclic receptors.[1] Macrocyclic molecules containing appropriate binding sites and cavities of suitable size and shape may be designed to form selective inclusion complexes. Actually, the molecular topology of the host molecule can be synthetically modulated in order to bind many different chemical species. For this purpose, aza macrocyclic receptors able to bind different kinds of substrates, such as inorganic or organic cations[2–7] or anionic species,[5–8] have been studied to elaborate their use as selective host molecules, molecular carriers, and catalysts.

In spite of the great effort dedicated to the synthesis of new azamacrocycles very few attempts have been successful in obtaining very large macrocyclic compounds containing more than 50 atoms in their framework.[9] The synthetic difficulties are the main reason for the scarce attention paid to this potentially interesting topic.

Scheme 1



So far polyazamacrocycles have been synthesized by using the Richman and Atkins method[10] or its modifications. Usually 1:1 cyclizations occur and the overall yield rapidly decreases when reactants are characterized by elongated and flexible structures.[11] We have therefore devised a synthetic procedure able to produce, in high yield, very large azamacrocycles (see Scheme 1).

Results and Discussion

All new compounds have been fully characterized by standard techniques (see Experimental Section); in the case of compound **12** the crystal structure of its binuclear cadmium complex has been solved.[12] As far as we know compound **13** is the largest azamacrocycle ever synthesized.

† University of Florence.
‡ University of Urbino.

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The procedure developed for synthesis of the giant-size aza macrocycles utilizes the simple starting material **1**, which can be obtained by tosylation of diethanolamine in high yields. Reaction of **2** with 2 equiv of **1** in the presence of base (K_2CO_3) easily gives the bis-piperazinyl derivative **3** which affords, after removal of the tosyl groups, the compound **4**. Reaction of **4** with the tosylated polyamines **5**, **6**, and **7** in CH_3CN in the presence of K_2CO_3, a modification of the method of Richman and Atkins, affords, after purification by chromatography, the tosylated macrocycles **8**, **9**, and **10**, respectively. Finally, the removal of the tosyl groups in H_2SO_4 leads to the giant size macrocycles **11**, **12**, and **13** in good yields.

Yields of tosylated derivatives in the critical cyclization step are in the range of 20–40% allowing reasonable quantities of final compounds to be prepared and their chemical properties investigated. The preferential formation of macrocycles having 54, 60, and 66 atoms, respectively, in the cycle, over those with half atoms in the macrocyclic framework is the surprising result of the present synthetic procedure, in which four reactant molecules are cyclically assembled together.

Alcock et al. reported the synthesis of an octaaza-macrocycle by using 1,4-bis(3′-aminopropyl)piperazine in the cyclization reaction. Such a precursor contains one piperazine backbone.[13] The preferred chair conformation of the 1,4-piperazine ring and the consequent trans orientation of the two side arms bearing the NH_2 reactive functions would explain the observed "two plus two" cyclization.

In our case, it is hard to ascribe the 2 + 2 cyclizations simply to the conformation of the piperazine rings. The observed reaction pathway must be related to the presence of two piperazine rings in one of the synthetic fragments which increases its rigidity and therefore the probability of 2 + 2 cyclizations. The absence of any cation–template effect contributes to support this hypothesis. Indeed, the same type of cyclization reaction, when carried out with linear, not reinforced, polyaminic fragments yields only macrocycles made by 1 + 1 fragments and half overall backbone.[11]

It is also of interest that the yield of the present cyclization decreases as the length of the tosylated polyamines **5**–**7** increases. Furthermore, when the fragments are long enough to contain more than six nitrogen atoms the cyclization yield becomes too low and one unresolvable reaction mixture is obtained. Most likely, the increased length of the tosylated polyamines represents an unfavorable factor for the assembly of four reactants together.

In conclusion, the reinforcement of one synthetic fragment, which represents a relatively small structural variation, has a profound influence upon the reaction products.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 200.13 and 50.33 MHz, respectively. Compounds **2**, **5**, **6**, and **7** were synthesized as previously described.[14]

***N,O,O′*-Tritosyldiethanolamine (1).** Diethanolamine (50.3 g, 0.5 mol) was dissolved in 600 mL of triethylamine. To this solution was added tosyl chloride (286 g, 1.5 mol) in small portions at room temperature. After the addition was completed, cold water was added to give a colorless precipitate which was filtered off and recrystallized from ethanol (206 g, 72%): mp 101–102 °C (lit.[15] mp 78–79 °C). Anal. Calcd for $C_{25}H_{29}NS_3O_8$: C, 52.89; H, 5.15; N, 2.47. Found: C, 52.8; H, 5.1; N, 2.5.

***N,N′*-Ditosylbis(2-piperazinylethyl)methylamine (3).** Amine hydrochloride **2** (4.7 g, 0.02 mol) and K_2CO_3 (27.6 g, 0.2 mol) were suspended in refluxing CH_3CN (200 mL). To this mixture, was added a solution of **1** (23.4 g, 0.04 mol) in CH_3CN (200 mL) dropwise in 7 h. After the addition was completed, the suspension was refluxed for 12 h and then filtered. The solution was vacuum evaporated to yield the crude product which was recrystallized from ethanol (8.5 g, 74%): mp 144–145 °C; ^1H NMR ($CDCl_3$) 2.15 (s, 3H), 2.42 (m, 22 H), 2.90 (m, 4H), 3.22 (t, 2H), 3.40 (t, 2H), 7.37 (d, 4H), 7.63 (d, 4H); ^{13}C NMR 21.4, 42.8, 45.8, 55.4, 55.1, 55.6, 127.7, 129.5, 131.9, 143.6. Anal. Calcd for $C_{27}H_{41}N_5O_4S_2$: C, 57.50; H, 7.33; N, 12.43. Found: C, 57.5; H, 7.3; N, 12.3.

Bis(2-piperazinylethyl)methylamine (4). A 5 g (0.009 mol) sample of **3** was dissolved in 15 mL of H_2SO_4 (96%), and the resulting solution was kept at 110 °C for 70 h. The solution was cooled and added dropwise to 200 mL of diethyl ether, with stirring, to give a thick oil which was separated and washed with diethyl ether. The residue was dissolved in the minimum amount of water, and the solution was made alkaline with concentrated aqueous NaOH. The alkaline solution was extracted with chloroform (5 × 100 mL). The organic solution was dried over anhydrous Na_2SO_4 and evaporated to dryness to afford **4** as a colorless oil (1.7 g, 72%): ^1H NMR (D_2O, pD = 5.1) 2.94 (m, 8 H), 2.99 (t, 4 H), 3.06 (s, 3 H), 3.40 (m, 8 H) 3.48 (t, 4 H); ^{13}C NMR, 42.2, 44.6, 50.4, 52.2, 53.6; MS *m/z* (FAB) 256 ($[M + H]^+$).

Bis(2-piperazinylethyl)methylamine Triperchlorate (4·3HClO₄). The pentamine **4** was dissolved in ethanol and treated with 65% perchloric acid to give the triperchlorate salt as a white solid in almost quantitative yield. Anal. Calcd for $C_{13}H_{32}Cl_3N_5O_{12}$: C, 28.04; H, 5.79; N, 12.57. Found: C, 28.1; H, 5.7; N, 12.4.

Caution: Perchlorate salts of organic ligands are potentially explosive; these compounds must be handled with great caution!

13,16,19,22,40,43,46,49-Octatosyl-4,31-dimethyl-1,4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52-octadecazatricyclo[50.2.2.2.2.2^{7,10,25,28,34,37}]tetrapentacontane (8). Amine triperchlorate **4**·3HClO₄ (8.3 g, 0.015 mol) and K_2CO_3 (20.6 g, 0.15 mol) were suspended in refluxing CH_3CN (750 mL). To this mixture, a solution of **5** (15.0 g, 0.015 mol) in CH_3CN (200 mL) was added dropwise in 6 h. After the addition was completed, the suspension was refluxed for 48 h and then filtered. The solution was vacuum evaporated to yield the crude product which was chromatographated on neutral alumina (CH_2Cl_2/MeOH 100/1.5). The eluted fractions were collected and evaporated to dryness to afford pure **8** as a colorless solid (6.7 g, 42%): mp 104–106 °C; ^1H NMR ($CDCl_3$) 2.22 (s, 6H), 2.42 (m, 80 H), 3.35 (m, 32 H), 7.32 (d, 8 H), 7.39 (d, 8 H), 7.68 (d, 8 H), 7.78 (d, 8 H); ^{13}C NMR, 21.4, 43.3, 47.3, 48.2, 49.0, 49.6, 52.9, 53.0, 54.2, 56.5, 57.4, 127.2, 127.3, 129.6, 129.7, 135.0, 135.7, 143.2, 143.6. Anal. Calcd for $C_{102}H_{150}N_{18}O_{16}S_8$: C, 57.23; H, 7.06; N, 11.78. Found: C, 57.5; H, 7.1; N, 11.9.

4,31-Dimethyl-1,4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52-octadecazatricyclo[50.2.2.2.2.2^{7,10,25,28,34,37}]tetrapentacontane (11). A 6.7 g (0.0032 mol) sample of **8** was dissolved in 15 mL of H_2SO_4 (96%), and the resulting solution was kept at 110 °C for 70 h. The solution was cooled and added dropwise to 200 mL of diethyl ether, with stirring, to give a thick oil which was separated and washed twice with diethyl ether. The residue was dissolved in a minimum amount of water, and the solution was eluted through an ionic exchange resin (Dowex, 1 × 8, anionic form). The solution containing the free amine was vacuum evaporated to dryness to afford a colorless solid (1.8 g, 63%): mp 40–42 °C; ^1H NMR ($CDCl_3$) 2.19 (s, 6 H), 2.44–2.50 (m, 56 H), 2.7 m, 32 H); ^{13}C NMR, 43.5, 46.0, 48.9, 49.1, 49.2, 53.1, 53.4, 54.3, 58.0, 57.6; MS *m/z* (FAB) 908 ($[M + H]^+$). Anal. Calcd for $C_{46}H_{102}N_{18}$: C, 60.89; H, 11.33; N, 27.78. Found: C, 60.4; H, 11.5; N, 27.5.

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13,16,19,22,25,43,46,49,52,55-Decatosyl-4,34-dimethyl-1,4,7,-10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58-eicosazatricyclo[56.2.2.2.2.2^{7,10,28,31,37,40}]hexacontane (9). This compound was synthesized from **4**·3$HClO_4$ (9.5 g , 0.017 mol) and **6** (20.0 g, 0.017 mol) following the procedure reported for **8**, obtaining pure **9** as a colorless solid (6.3 g, 29%): mp 116–118 °C; ^{1}H NMR ($CDCl_3$), 2.18 (s, 6 H), 2.43 (m, 86 H), 3.35 (m, 40 H), 7.30 (d, 8 H), 7.37 (d, 12 H), 7.68 (8 H), 7.76 (d, 12 H); ^{13}C NMR, 21.4, 43.1, 47.1, 48.7, 49.4, 49.6, 49.8, 52.9, 53.1, 54.3, 56.0, 57.1, 127.2, 127.3, 129.6, 129.7, 134.8, 135.0, 135.7, 143.2, 143.6, 143.7. Anal. Calcd for $C_{120}H_{172}N_{20}O_{20}S_{10}$: C, 56.84; H, 6.84; N, 11.04. Found: C, 56.6; H, 6.7; N, 10.9.

4,34-Dimethyl-1,4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,-49,52,55,58-eicosazatricyclo[56.2.2.2.2.2^{7,10,28,31,37,40}]-hexacontane (12). This compound was synthesized from **9** (6.3 g, 0.0025 mol) following the procedure reported for **11**, obtaining pure **12** as a colorless oil (1.6 g, 64%); ^{1}H NMR ($CDCl_3$) 2.18 (s, 6 H), 2.40–2.50 (m, 56 H), 2.7 (m, 40 H); ^{13}C NMR 43.5, 46.1, 49.1, 49.2, 49.3, 49.4, 53.1, 53.4, 54.5, 56.0, 57.6; MS *m/z* (FAB) 994 ([M + H]$^+$). Anal. Calcd for $C_{50}H_{112}N_{20}$: C, 60.44; H, 11.36; N, 28.20. Found: C, 60.3; H, 11.2; N, 28.1.

13,16,19,22,25,28,46,49,52,55,58,61-Dodecatosyl-4,37-dimethyl-1,4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,49,52,55,58,-61,64-docosazatricyclo[62.2.2.2.2.2^{7,10,31,34,40,43}]-hexahexacontane (10). This compound was synthesized from **4**·3$HClO_4$ (2.8 g , 0.005 mol) and **7** (7.0 g, 0.005 mol) following the procedure reported for **8**, obtaining pure **10** as a white solid: mp 123–125 °C (1.4 g, 19%); ^{1}H NMR ($CDCl_3$) 2.18 (s, 6 H), 2.42 (m, 92 H), 3.35 (m, 48 H), 7.30 (d, 8 H), 7.39 (d, 16 H), 7.68 (8 H), 7.78 (d, 16 H); ^{13}C NMR 21.4, 43.1, 47.2, 48.5, 49.2, 49,3, 49.6, 49.8, 52.8, 53.0, 54.1, 55.8, 57.0, 127.2, 127.3, 129.6, 129.7, 135.0, 135.7, 143.2, 143.6. Anal. Calcd for $C_{138}H_{194}N_{22}O_{24}S_{12}$: C, 56.57; H, 6.67; N, 10.52. Found: C, 56.8; H, 6.9; N, 10.7.

4,37-Dimethyl-1,4,7,10,13,16,19,22,25,28,31,34,37,40,43,46,-49,52,55,58,61,64-docosazatricyclo[62.2.2.2.2.2^{7,10,31,34,40,43}]-hexahexacontane (13). This compound was synthesized from **10** (1.4 g, 0.0005 mol) following the procedure reported for **11**, obtaining pure **13** as a colorless oil (0.32 g, 62%): ^{1}H NMR ($CDCl_3$) 2.15 (s, 6 H), 2.35–2.45 (m, 56 H), 2.7 (m, 48 H); ^{13}C NMR 43.6, 46.1, 49.2, 49.3, 49.3, 49.4, 49.5, 53.0, 53.6, 54.6, 56.4, 57.6; MS m/z (FAB): 1080 ([M + H]$^+$). Anal. Calcd for $C_{54}H_{122}N_{22}$: C, 60.07; H, 11.39; N, 28.54. Found: C, 59.9; H, 11.2; N, 28.3.

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