Synthesis of New Di- and Tetraazadibenzosulfoxide Macrocycolic Compounds

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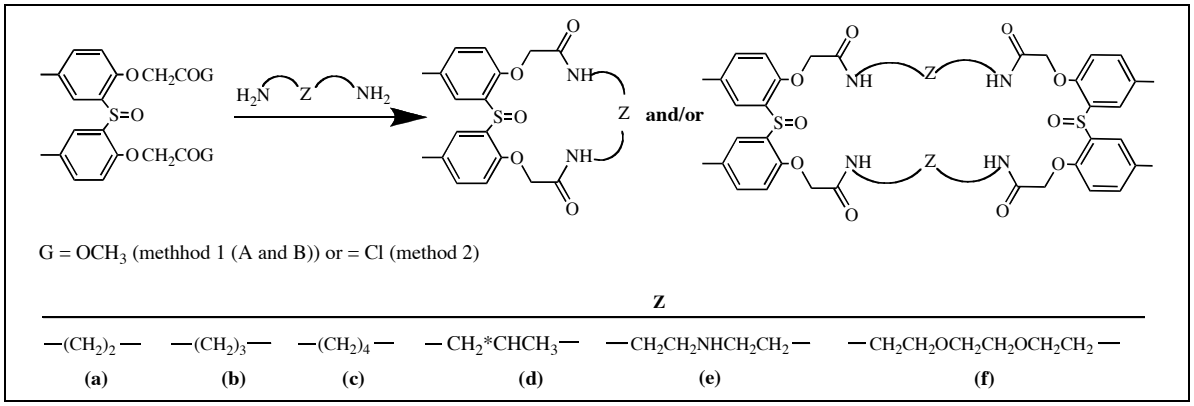

Novel macrocyclic di and tetraamide compounds have been synthesized by the reaction of 2-2'-sulfoxide-bis-(4-methyl phenoxy) aceticester or aceticacid chloride) (obtained from corresponding bisphenol) with appropriate diamines. Also the results of the presence of base as template are discussed and compared.

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INTRODUCTION

Due to their selective cationic binding affinities and their adjustable hydrophobicities, crown ethers [1] have found increasing applications as a phase transfer reagents [2,3], catalysts [2-4], membrane transports [5,6], sensors [7,8], and in separation technologies [9] such as the removal of cesium from the alkaline nuclear waste [10,11].

Convenient methods for preparation of aza-crowns have been extensively reviewed [12-16]. Among these methods, the high-dilution technique [17], the route based on template effect [18], the high pressure approach [19], high concentration technique [20], and diester methods [21] are frequently used as the most versatile procedures.

Using a diester allows the reaction to take place under normal conditions without using the high dilution or high pressure techniques. For application purposes the availability of efficient synthetic methods are everything. Consequently any route that represents a more efficient alternative to a long and tedious process is always welcome. Templating is one such route that engenders, among other things, mass production and the construction of countless architectural designs. In chemical terms, templation involves the use of molecule or ion to promote the formation of one compound from a reaction that would otherwise from a complex mixture [22]. Using a molecular or ionic scaffold in this manner opens up new areas of research, by providing efficient access to compounds that are otherwise hard to synthesize using step-wise syntheses [23]. In this route, the rate of formation of the macrocycles is intimately tied to the nature of the cation that is present [24]. If it can fit snugly in the incipient crown, the reaction rate and the yield will be much greater than in the parallel experiment in which an ill-fitting cation is present [23].

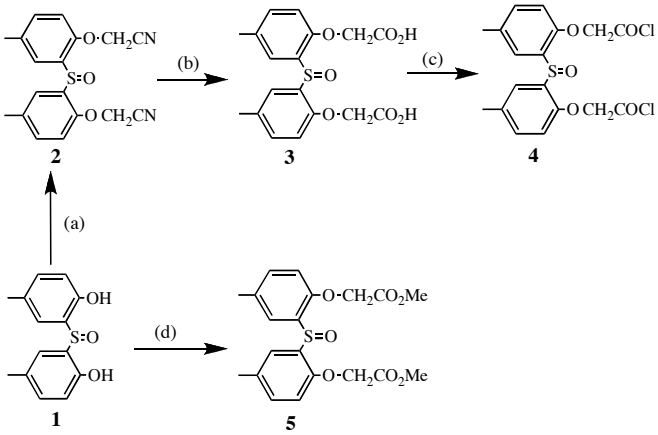
Activated dicarboxylic acid derivatives have also been used for the preparation of macrocyclic diamides in excellent yields under normal reaction conditions [25].

In the previous work, we have described the syntheses of new macrocycles **8** and **11** (Table 1) [25]. The compelexation reactions between 7,10,13-triaza-1-sulfoxo-4,16-dioxa-20,24-dimethyl-2,3;17,18-dibenzo-cyclooctadecane-6,14-dione (**11**) macrocycles with Ag^+, Cd^{2+}, Cu^{2+}, Pb^{2+}, Sr^{2+}, Tl^+ and Zn^{2+} ions have been studied by our research teams. The stability constants of the resulting complexes were determined and found to decrease in the order $Tl^+ > Zn^{2+} > Cd^{2+} > Pb^{2+} > Cu^{2+} > Ag^+ > Sr^{2+}$ [26]. These results encouraged us to synthesis a variety of corresponding macrocycle derivatives with different sizes. Here in continuation of previous works [25,27], we report the preparation of set of new di- and tetraazadibenzosulfoxide macrocyclic compounds *via* different techniques: a diester, a metal template and an activated diacid dichloride. Also the results of methods are discussed and compared.

RESULTS AND DISCUSSION

Dibenzosulfoxide **1** was synthesized based on a reported procedure [28] in 65% yield. Treatment of **1** with chloroacetonitrile and methylchloroacetate in the presence of K_2CO_3 and KI at refluxed in dry acetone afforded dinitrile **2** in 90% yield and dimethyl ester **5** in 95% yield, respectively. Basic hydrolysis of dinitrile **2** in refluxing basic alcoholic solution followed by acidification afforded the diacid **3** in 95% yields [29]. The diacid **3** was converted to diacid dichloride **4** in 90% yield by reaction with oxalyl chloride in the presence of DMF (cat.) in CH_2Cl_2 and used without purification (Scheme I).

Scheme I



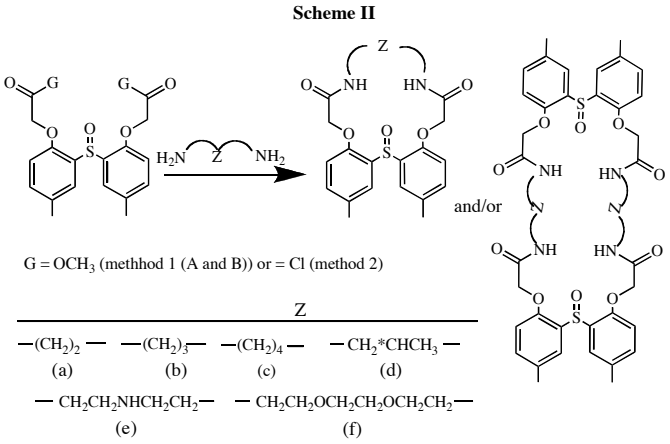
a) $ClCH_2CN$ / K_2CO_3 / KI, CH_3COCH_3, Reflux b) KOH / EtOH / H_2O, Reflux
c) $(COCl)_2$ / DMF, CH_2Cl_2 d) $ClCH_2CO_2Me$ / K_2CO_3 / KI, CH_3COCH_3, Reflux

Our first attempts toward the synthesis of aza macrocycles (method 1-A) generally afforded low to moderate yields of macrocyclic products and long reaction time (up to 3 day) (Scheme 2). These moderate yields were because of factors such as the competition between the formation of linear oligomers and desired macrocycles. There is no restriction of bond rotations in both diacid dichloride, diesters and condensing diamines in these cases. Hence, not much loss in entropy during the cyclization step is expected. This factor does affect the final yields and reaction times in the ring closure processes.

To minimize these difficulties, we have used different conditions including high-concentration method (method 2), as well as the presence of variety of alkali metal cations to evaluate the "template" and "salt" effects in the macrocyclization step (method 2-B) (Scheme II).

The "template effects" of different cations (Na^+, K^+ and Cs^+) were studied by using their carbonate salts. The study proved that these salts are effective in macrocyclization steps in both the yields (~60%) and the length of times (~12 h), but did not indicate considerable

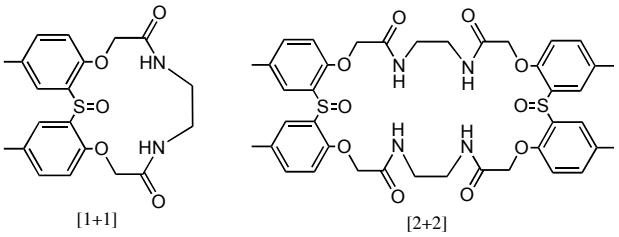
Scheme II



differences for these different alkali metal ions. Because these cations are able to interact with the reacting functional groups in a manner that keeps them together during the macrocyclization step, higher yields of cyclocondensation reaction were expected.

In the macrocyclization reaction with diamine **a** a "dimerization" reaction was observed in which a 30 membered macrocyclic tetraamide (**7**) was isolated as the main product in method 1-A, and by-product in method 1-B, while in method 2 only regular macrocyclization was occurred (**6**) and no dimerization was observed (Scheme III).

Scheme III



Template effect caused an increase in the [1+1] product (**6**) and a decrease in the [2+2] product (**7**), which may be the result of a stabilizing interaction in the incipient hetromacrocycle in the [1+1] product. Also we observed a more enhanced template effect for diamine **f**, likely due to the existence of two highly electron pair donating oxygen atoms [Table 1].

Results indicate that the diacid dichloride method shows better macrocylization yields than the diester method and template effect but this method also has some difficulties such as diacid dichloride instability.

EXPERIMENTAL

The reactions were carried out in an efficient hood. All the materials purchased from Merck, Fluka and Aldrich chemical companies and used without further purification. CH_2Cl_2 was dried over P_2O_5 and then distilled from CaH_2. Both CH_3CN and CH_3OH were dried over CaH_2 and then distilled. Triethylamine

Table 1

Synthesis of different macrocyclic compounds by three methods

Macrocycle	Z	Yield (%)		
		Method 1		Method 2
		A	B	
6	CH_2CH_2 [1+1]	25%	50%	80%
7	CH_2CH_2 [2+2]	40%	20%	-----
8	$CH_2CH_2CH_2$[a]	45%	55%	65%
9	CH_2*$CHCH_3$[b]	40%	50%	75%
10	$CH_2CH_2CH_2CH_2$	45%	60%	65%
11	$CH_2CH_2NHCH_2CH_2$[a]	50%	65%	80%
12	$CH_2CH_2OCH_2CH_2OCH_2CH_2$	40%	70%	80%

[a]See reference [26].

[b]The only isolated product is [2+2].

[b]The only isolated product is [2+2].

was distilled from CaH_2 and stored over 4 Å molecular sieves. The melting points (uncorrected) were measured by an Electrothermal engineering LTD 9100 apparatus. Ir spectra were recorded on a Perkin-Elmer model 543, the ^{1}H nmr and ^{13}C nmr spectra were obtained using BRUKER AVANCE DRX 500 and BRUKER AVANCE DPX 250 MHz apparatus and mass spectra were obtained by an electron ionization Varian Incos 50 and JEOL JMS-700 and the MULDI spectra BRUKER Biflex.

General procedure for the preparation of macrocyclic diamides.

Diester method (1-A). A mixture of diamine **a-f** (1 mmol) and dimethyl esters **5** (1 mmol, 0.406 g) in dry methanol (80 mL) was refluxed for 3 days. Then the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel and/or recrystallization.

Diester Method and Salt Effect (1-B). A mixture of diamine **a-f** (1 mmol), dimethyl esters **5** (1 mmol, 0.406 g) and K_2CO_3 or Cs_2CO_3 (0.5 mmol) in dry methanol (80 mL) was refluxed for 12 h. Then the resulting precipitate was filtered off and the solvent was evaporated under reduced pressure to give crude product that was purified by column chromatography on silica gel and/or recrystallization.

Method (2). A solution of diamine **a-f** (2 mmol) and triethylamine (4 mmol, 0.55 mL) in dry CH_2Cl_2 (50 mL) was added quickly (5 sec.) to a vigorously stirred solution of diacid chloride **4** (2 mmol, 0.993 g) in dry CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. The precipitate was filtered off and the filtrate was washed with water (2×50 mL), 10% aqueous NaOH solution (50 mL) and then with water (100 mL). The organic layer was dried (Na_2SO_4), and evaporated to afford a solid product that was purified by recrystallization or column chromatography.

7,10-Diaza-1-sulfoxo-4,13-dioxa-17,21-dimethyl-2,3;14,15-dibenzocyclopentadecane-6,11-dione (6). This compound was purified by column chromatography on silica gel using petroleum ether/EtOAc (1:5) as eluent and then recrystallized from CH_2Cl_2/*n*-hexane to afford white powder, mp 245-248 °C; ir (KBr): 3400, 3050, 2965, 2935, 1705, 1600, 1530, 1485, 1440, 1255, 1215, 1070, 1040, 960, 890, 835, 820, 545, 500 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.28(s, 6H), 3.29-3.34(m, 4H), 4.53-4.69(m, 4H), 6.54-7.27(m, 8H) ppm; ^{13}C nmr ($CDCl_3$) δ 167.2, 153, 134.4, 133.5, 131.5, 121.6, 112.5, 68.2, 38.5, 20.6 ppm; MS (EI) m/z 402(M^+), 386, 355, 337, 331, 281, 151, 149, 105, 91, 77, 71, 45, 30.

7,10,22,25-Tetraaza-1,16-disulfoxo-4,13,19,28-tetraoxa-32,36,41,44-tetramethyl-2,3;14,15;17,18;29,30-tetrabenzo-cyclotriacontane-6,11,21,26-tetraone (7). This compound was purified by column chromatography on silica gel using EtOAc/MeOH (4:1) as eluent and then recrystallized from CH_2Cl_2/*n*-hexane to afford white powder, mp 322-324 °C; ir (KBr): 3410, 3250, 2955, 1685, 1535, 1495, 1430, 1285, 1245, 1230, 1160, 1035, 1045, 1025, 810, 725 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.24(s, 6H), 2.28(s, 6H), 3.46-3.71(m, 8H), 4.42-4.53(m, 8H), 6.69-6.7(m, 4H), 7.12-7.14(d, J=10Hz, 4H), 7.21-7.37(m, 4H), 8.85(s, 2H), 9.02(s, 2H) ppm; ^{13}C nmr ($CDCl_3$) δ 168.1, 168, 153.4, 133.8, 133.6, 131.5, 131.4, 128.4, 128.2, 128, 127.7, 112.7, 112.6, 68.2, 68, 39.5, 39.3, 20.6 ppm; MS m/z 804.1 (M^+), 805.1 $(M+1)^+$, 806.1 $(M+2)^+$, 536.2, 331, 298, 151, 122, 105, 91, 71, 69, 56, 45.

7,10,22,25-Tetraaza-1,16-disulfoxo-4,13,19,28-tetraoxa-8,23,32,36,41,44-hexamethyl-2,3;14,15;17,18;29,30-tetrabenzocyclotriacontane-6,11,21,26-tetraone (9). This compound was purified by column chromatography on silica gel using EtOAc / MeOH (5:1) as eluent, mp 211-213 °C; ir (KBr): 3430, 3345-3290, 2990, 2950, 1690, 156, 1505, 1450, 1300, 1270, 1230, 1170, 1080, 1050, 1030, 830, 615 cm^{-1}; ^{1}H nmr ($CDCl_3$): Crowded spectrum is obtained for ^{1}H nmr, but selected data are reported as following; δ 0.63 (b, 3H), 1.17 (b, 3H), 2.34 (b, 12H), 2.23-3.41(b, 2H), 4.11 (b, 2H), 4.28 (b, 2H), 4.54-4.93 (m, 8H), 6.69-7.44 (m, 12H), 7.71 (b, 1H), 8.94 (b, 1H) ppm; ^{13}C nmr ($CDCl_3$): 168.5, 168, 166.4, 154.6, 151.9, 135.4, 134.3, 132.2, 131.1, 129.8, 128.7, 127.8, 129.6, 125.8, 114.7, 113.8, 113.4, 112, 68.6, 68, 67.7, 45.5, 44.7, 43.4, 42.5, 41.9, 21, 20.7, 20.6, 20.5, 17.7, 17.4 ppm; MS m/z 831.1 (M^+), 832.1 $(M+1)^+$, 833.1 $(M+2)^+$,552.2, 536.2, 523.2, 417.2, 154.1.

7,12-Diaza-1-sulfoxo-4,15-dioxa-19,23-dimethyl-2,3;16,17-dibenzo-cycloheptadecane-6,13-dione (10). This compound was purified by column chromatography on silica gel using EtOAc/MeOH (5:1) as eluent, mp 285-288 °C; ir (KBr): 3425, 3285, 3240, 3080, 2955, 2880, 1690, 1550, 1450, 1440, 1285, 1250, 1215, 1155, 1070, 1045, 1010, 885, 820, 740, 560cm^{-1}; ^{1}H

nmr ($CDCl_3$) □ 1.62-1.63(m, 4H), 2.29(s, 6H), 3.193-3.198(m, 4H), 4.51-4.52(m, 4H), 7.239-7.241(m, 2H), 7.269-7.273(m, 4H), 8.3(s, 2H) ppm; ^{13}C nmr ($CDCl_3$) δ 167.6, 155, 134.7, 132.5, 129.8, 128.1, 113.9, 68, 38.3, 26, 20.7 ppm; MS (EI) m/z 430 (M^+), 331, 298, 271, 248, 151, 122, 106, 84, 78, 71, 56, 40.

7,16-Diaza-1-sulfoxo-4,10,13,19-tetraoxa-23,27-dimethyl-2,3; 20,21-dibenzo-cyclouneicosane-6,17-dione (12). This compound was purified by column chromatography on silica gel using EtOAc/MeOH (10:1) as eluent, mp 196.5-198 °C; ir (KBr): 3430, 3330, 3115, 2960, 2940, 2870, 1700, 1615, 1580, 1540, 1500, 1440, 1315, 1295, 1235, 1150, 1055, 1030, 830, 820, 735, 610, 580 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.32(s, 6H), 3.55-3.61(m broad, 12H), 4.51-4.56(m, 4H), 6.88-6.91(m, 2H), 7.30(s, 2H), 7.51-7.55(m, 2H) ppm; ^{13}C nmr ($CDCl_3$) □ 167.7, 153.1, 133.9, 132.9, 131.7, 127.2, 113.2, 70.3, 68.7, 68.1, 39.2, 20.7 ppm; MS m/z 490.2 (M^+), 491.2 (M^++1), 371.2, 298.2, 271.1, 248.2, 211.1, 162.1.

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