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Synthesis of New Dibenzosulfide and Dibenzosulfoxide Macrocyclic Compounds

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Abstract

Some new dibenzosulfo, dibenzosulfoxo macrocyclic diamides are synthesized.

Introduction

Thousands of crown ethers have been synthesized since Pedersen reported the ability of these macrocyclic ethers to bind alkali metal cations [1, 2]. The search for their applications has solved many significant problems in different fields of science and engineering, such as chemistry, biology, analysis and microanalysis, metal separation and transport, molecular recognition, medical and industrial uses, biophysics, catalysis, agriculture, and ecology [3, 4].

The crown ethers are often synthesized by Williamson's reaction, by direct reaction of glycols with dialkylating agents under moderate or high dilution conditions to restrict linear polymerization [5, 6].

In addition, the preparation of macrocyclic diamides have attracted many attentions recently, because of their significant metal ion complexing as well as being valuable intermediates for the synthesis of aza crown ethers and related compounds such as cryptands [6]. These compounds have wide applications [7]. Macrocyclic diamides are prepared by variety of procedures including reaction of dicarboxylic acid diesters [8], diacid dichlorides [9], bis(α-chloroamide) compounds [10] and activated carboxylic acids [11] with various diamines under high dilution conditions.

In previous work, we have described the synthesis of new macrocycles **11** and **12** in Williamson's reaction of **1** with diethyleneglycol di-*p*-toluenesulfonate and 1,2-dibromoethane (Figure 1) [12, 13]. In this work, we have described the preparation of new macrocyclic diamides **7**–**10** (Figures 2 and 3). For this purpose, **2** was reacted with chloroacetonitrile in the presence of K_2CO_3 and KI in dry acetone to produce dinitrile, 3 (100%, mp 96–98 °C) [14]. Basic hydrolysis of **3** gave diacid, **4** (90%, mp 178–180 °C) [15], which was converted to diacid dichloride, **5** (95%, mp 84–86 °C) by reaction with oxalyl chloride in the presence of catalytic amounts of DMF in CH_2Cl_2 [16] (compounds **3**–**6** are identified with spectroscopic means: IR, ^{1}H NMR, ^{13}C NMR and MS). Cyclization of **5** and **6** with diamines in an appropriate solvent (CH_2Cl_2 or CH_3CN) afforded macrocyclic diamides **7**–**10**. The reactions take place under standard conditions [17] (Figures 2 and 3).

Experimental

The reactions were carried out in an efficient hood. All the materials purchased from Merck, Fluka and Aldrich chemical companies and applied without further purification. The melting points (uncorrected) were measured with a Electrothermal engineering LTD 9100 apparatus. IR spectra were measured 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 with Shimadzu GC-MS-QP 1100 EX model. CH_2Cl_2 was dried over P_2O_5 and then distilled from CaH_2. CH_3CN was dried over CaH_2 and then distilled.

General procedure for the preparation of macrocyclic diamides

A solution of diamine (0.002 mol) and triethylamine (0.004 mol) in an appropriate dried solvent (50 mL, CH_3CN or CH_2Cl_2) was added quickly (5 s) to a vigorously stirred solution of diacid dichloride (0.002 mol) in the same solvent (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

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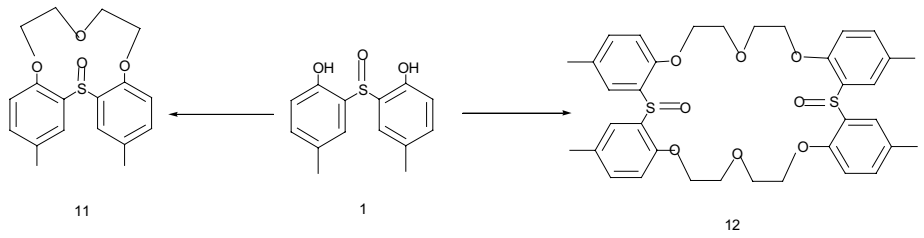

Figure 1.

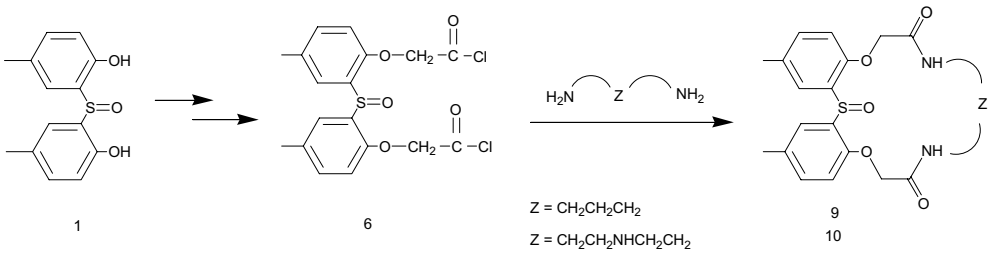

Figure 2.

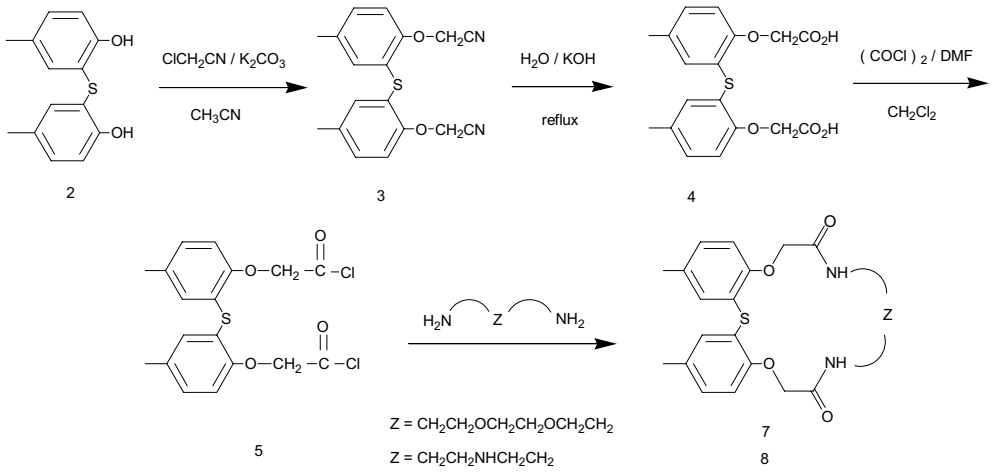

Figure 3.

evaporated to afford solid products which was purified with recrystallization or column chromatography.

*7,16-Diaza-1-thia-4,10,13,19-tetraoxa-23,27-dimethyl-2,3;20,21-dibenzo-cyclouneicosane-6,17-dione (**7**)*

This compound was purified by column chromatography on silica gel using EtOAc/MeOH (10:1) as eluent and then recrystallized from $CHCl_3$/***n***-hexane to afford white needle crystals, mp 148–150 °C; IR (KBr) 3440, 3040, 2920, 2880, 1680, 1520, 1480, 1440, 1350, 1300, 1280, 1240, 1150, 1115, 1080, 1040, 895, 800, 545, 440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 6H), 3.55 (s, 4H), 3.62 (s, 8H), 4.56 (s, 4H), 6.84 (d, $J = 8.1$ Hz, 2H), 6.88 (s, 2H), 7.08 (d, $J = 7.75$ Hz, 2H), 7.43 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.37, 153.94, 132.88, 132.78, 129.8, 123.1, 113.35, 70.75, 70.18, 68.64, 39.28, 20.96 ppm; MS (EI) m/z 474 $(M)^+$, 475 $(M + 1)^+$, 476 $(M + 2)^+$, 477 $(M + 3)^+$, 335, 307, 257, 241, 228, 190, 151, 121, 119, 108, 105, 91, 85, 56, 44.

*7,10,13-Triaza-1-thia-4,16-dioxa-20,24-dimethyl-2,3;17,18-dibenzo-cyclooctadecane-6,14-dione (**8**)*

This compound was purified by column chromatography on silica gel using EtOAc/MeOH (3:1) or CH_2Cl_2/MeOH (10:1) as eluent and then recrystallized from $CHCl_3$/MeOH to afford colorless crystals, mp 220–222 °C; IR (KBr) 3420, 3360, 3040, 2940, 2880, 1680, 1570, 1490, 1280, 1250, 1210, 1080, 1050, 830, 800, 770, 680, 590, 560, 438 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 6H), 2.78–2.8 (m, 4H), 3.39–3.4 (m, 4H), 4.6 (s, 4H), 6.82 (d, $J = 8.29$ Hz, 2H), 6.9 (s, 2H), 7.1 (d,

$J = 8.17$ Hz, 2H), 7.48 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.27, 153.58, 132.61, 132.51, 129.7, 122.19, 112.29, 67.88, 49.33, 39.25, 20.97 ppm; MS (EI) m/z 429 $(M)^+$, 430 $(M + 1)^+$, 431 $(M + 2)^+$, 386, 360, 316, 303, 257, 241, 228, 180, 178, 164, 151, 121, 108, 105, 91, 85, 84, 56, 49, 43, 30.

*7,11-Diaza-1-sulfoxo-4,14-dioxa-18,22-dimethyl-2,3;15,16-dibenzo-cyclohexadecane-6,12-dione (**9**)*

This compound was purified by column *chromatography* on silica gel using EtOAc/MeOH (3:1) as eluent and then recrystallized from $CHCl_3$/MeOH to afford white needles, mp 276–278 °C, IR (KBr) 3424, 3387, 3335, 3028, 2929, 1674, 1603, 1535, 1490, 1430, 1281, 1239, 1232, 1153, 1069, 1034, 879, 807, 713, 660, 600, 565, 466 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.83–1.93 (m, 2H), 2.3 (s, 6H), 3.24–3.32 (m, 2H), 3.51–3.59 (m, 2H), 4.43–4.6 (q, 4H), 6.84–6.88 (d, $J = 8.25$ Hz, 2H), 7.24–7.32 (m, 4H), 7.48 (s, 2H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.3, 152.6, 133.8, 132.5, 130.7, 127.5, 112.8, 67.7, 38.6, 27.2, 24 ppm ; MS (EI) m/z 416 $(M)^+$, 417 $(M + 1)^+$, 418 $(M + 2)^+$, 419 $(M + 3)^+$, 398, 357, 316, 303, 259, 246, 228, 151, 121, 113, 108, 99, 91, 85, 77, 65, 56, 43, 30.

*7,10,13-Triaza-1-sulfoxo-4,16-dioxa-20,24-dimethyl-2,3;17,18-dibenzo-cyclooctadecane-6,14-dione (**10**)*

This compound was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (2:1) as eluent and then recrystallized from acetone/MeOH to afford a white solid, mp 220–222 °C, IR (KBr) 3437, 3403, 3042, 2933, 2861, 1681, 1534, 1495, 1446, 1289, 1285, 1054, 1033, 815, 761, 680, 588, 482 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.32 (s, 6H), 2.77–2.87 (m, 4H), 3.36–3.42 (m, 4H), 4.58 (s, 4H), 6.9–6.93 (d, $J = 7.5$ Hz, 2H), 7.27–7.31 (m, 4H), 7.8 (s, 2H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.1, 152.8, 133.6, 132.1, 129.7, 127.5, 115.3, 67.3, 47.2, 38, 20.2 ppm; MS (EI) m/z 445 $(M)^+$, 446 $(M + 1)^+$, 447 $(M + 2)^+$, 448 $(M + 3)^+$, 377, 360, 319, 257, 246, 178, 121, 113, 107, 91, 85, 77, 56, 43, 30.

Results and discussion

The essential problem in the synthesis of the title macrocycles is Williamson's reaction of the phenoxide groups with chloroacetonitrile, 1,2-dibromoethane and diethyleneglycol di-*p*-toluenesulfonate. This problem was partially solved by the use of the LiCl, NaOH, KOH in the synthesis of macrocycles **11** and **12** [12, 13], and increase of yield due to template effect (in the absence of this compounds the yields was very low), and the syntheses of diamides **7**–**10** was performed by standard conditions to obtain desired dinitriles. Reaction of **1** and **2** with chloroacetic acid lead to low yields of diacids so this reaction was not useful for this purpose. Basic hydrolysis of dinitriles and then synthesis of diacid dichlorides was performed in high yields and the products were obtained in high purity by simple recrystallization (H_2O/Ethanol). In addition, in the preparation of the macrocyclic diamides **7**–**10** the cyclization reaction between diacid dichlorides and diamines did not need high-dilution method or template effect and takes place in short time.

The most interesting point in this research was found in the structure determination of these macrocycles. The larger the macrocycle the more flexible is the cavity. The flexibility and rigidity of these macrocycles affect the diastereotopic character of methylene groups, especially methylenes adjacent to carbonyl groups. This is obvious by analysis of ^1H NMR spectra (in the methylene region a few groups of peaks were observed at 3.90–4.05 and 4.05–4.20 ppm (for **11**) also 3.85–3.89, 3.98–4.00 and 4.06–4.13 ppm (for **12**) which were unexpected, the similar unexpected patterns for macrocycles **7**–**10** in methylene region were obtained, especially for methylenes adjacent to carbonyl groups). The macrocycles are twisted due to the repulsion effects of sulfoxide group (S=O) either with oxygens, nitrogens, carbonyl groups or another sulfoxide group in the cavity in sulfoxides macrocycles, or because of repulsions between different groups involved in the cavity in the sulfides macrocycles. The more twisted the cavity or macrocycle, the more difference in the diastereotopic character of CH_2 protons (see Ref. [12a] for more evidence, spectral data of **11** and **12**, and spectral data for **7**–**10**, in methylene regions). This difference also results in the their difference of the chemical shifts. The more rigid the macrocycle the more difference in the chemical shifts of the protons. The splitting patterns follow as AA′BB′ and 'ddd', etc.

In conclusion, we have described the synthesis of new benzosulfoxides and benzosulfides diamides **7**–**10** macrocycles. Synthesis of these macrocycles was performed in simple conditions without using template effect and high dilution conditions. Syntheses of new macrocycles of this family, conformational analysis and dynamic studies of these macrocycles are under study in our laboratory.

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13 2,3,5,6,14,15,17,18-Tetrabenzo-27,30,35,38-tetramethyl-4,16-disulfoxo-24-crown-6 (**12**) and 2,3,5,6-dibenzo-15,18-dimethyl-4-sulfoxo-12-crown-3 (**11**): To a solution of 1.48 g (0.004 mL) of 1 in acetonitrile (300 mL) 4 g (0.028 mol) of K_2CO_3, 0.09 g NaOH and 0.24 g LiCl were added. The mixture was refluxed for 15 min and then 1.528 g (0.004 mol) diethylene glycol di-*p*-toluenesulfonate was added dropwise (1 drop/s). The reflux was continued for 30 h and then 200 mL of distilled water and 20 g of K_2CO_3 was added to the reaction mixture and then extracted with chloroform (5×20 mL). The combined chloroform layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product. The crude product was purified by column chromatography on silica gel 40 (70–230 mesh) and eluted by petroleum ether/ethyl acetate (4:1) to give two macrocycles, **11** and **12**. The yield was 55% (the yield of **11** was 62% and **12**, 38%) and melting points for **11** and **12** were 205–207 °C and 171–172 °C, respectively.

Spectral data for **11**: IR (KBr) 3005, 1600, 1475, 1000, 1300, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.84 (s, 6H), 3.90–4.05 (ddd, 4H, $J = 1.42$, 2.85, 12.8 Hz), 4.05–4.20 (ddd, 4H), 6.73 (d, $J = 8.79$ Hz, 2H), 7.12 (dd, $J = 8.79$, 2.17 Hz, 2H), 7.63 (d, $J_M = 2.17$ Hz, 2H); MS (EI) m/z 333 ($M^+ + 1$, calcd. M = 332), 262, 244, 228, 201, 151, 110, 108, 77, 49.

Spectral data for **12**: IR (KBr) 3000–3200, 2900–2980, 1500, 1450, 1250, 1050 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 12H), 3.85–3.89 (ddd, $J = 10$, 10 Hz, 4H), 3.98–4.00 (ddd, $J = 10$, 1.5 Hz, 4H), 4.06–4.13 (ddd, $J = 35_{\text{geminal}}$, 15, 10 Hz, 8H), 6.63–6.65 (d, $J = 10$ Hz, 4H), 7.05–7.06 (dd, $J = 10$ Hz, 4H), 7.57 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.55, 69.17, 72.17, 95.96, 111.66, 125.25, 130.89, 131.89, 134.47, 153.25; MS (EI) m/z 666 ($M^+ + 2$, calcd. M = 664), 568, 513, 453, 406, 386, 333, 262, 177, 151, 110, 77, 45.

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