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The Synthesis and Structure of Diaza- and Tetraazacoronands

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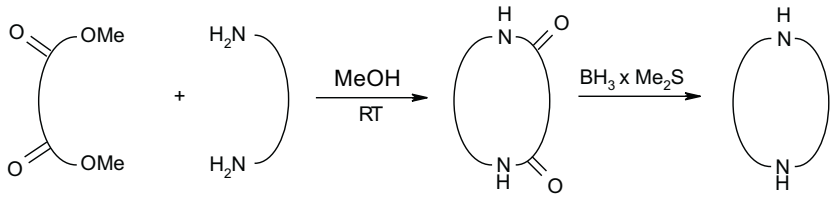
A general method of the synthesis of simple azacoronands *via* the amidation reaction is presented. Several examples of the X-ray structure studies of the compounds obtained are given.

Key words: macrocyclization, molecular receptors, diazacoronands, tetrazacoronands, preorganization, hydrogen bonding, X-ray structure, high pressure

Recently, we have found that α,ω-dicarboxylates react with α,ω-diamines in methanol as a solvent to give the macrocyclic diamides in good yields [1–3]. Their subsequent reduction with a borohydride–dimethyl sulphide complex affords the respective diazacoronands (Scheme 1).

Scheme 1



This fact prompted us to apply such approach to the synthesis of many other types of azacoronands, including variously modified [4–9] and chiral [10,11] macrocycles. The results obtained from these studies allowed for a preliminary description of the course of macrocyclization, according to which the diester and diamine form a linear amido intermediate, able to both – cyclization and linear oligomerization. Both latter processes are competitive, but it is difficult to predict which one should be preferred under the reaction conditions used. We assumed that the hydrogen bonds between the substrates and methanol forces the self assembly of the linear dimers and cause their cyclization. The earlier approaches to similar syntheses have been carried out under

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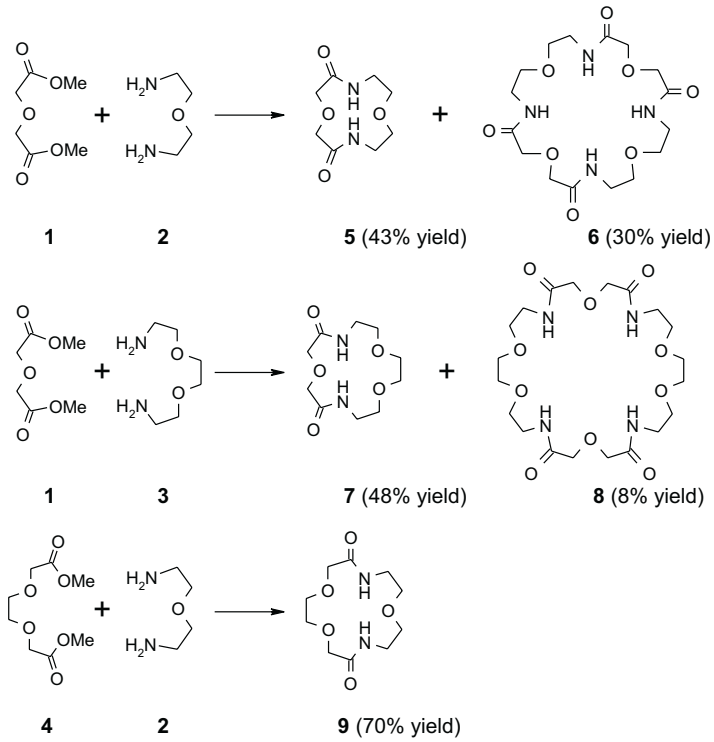
high-temperature [12,13] or high-dilution [14] conditions, and the hydrogen bonding was not taken into account as a crucial point.

For further clarification of the course of the macrocyclization reaction, we decided to investigate more carefully the reactions of diglicolic acid dimethyl ester (**1**) with two homologic α,ω-diamines **2** and **3**. Moreover, we used for comparison triglicolic acid dimethyl ester (**4**) in the reaction with α,ϖ-diamine **2**.

RESULTS AND DISCUSSION

In the reaction of dimethyl ester **1** with diamine **2**, carried out in methanol at room temperature, apart the diamide **5**, a tetraamide **6** was detected and isolated (Scheme 2). In the case of the reaction of **1** with **3**, together with diamide **7**, the tetraamide **8** was formed. It seems to be noteworthy that the reaction of diester **4** with diamine **2** affords exclusively diamide **9**. It indicates that though the macrocycles **7** and **9** are of the same size, the position of ester groups in the substrate plays an important role. Apparently, diester is preorganized better than diamine of the same length, and the intermediately formed linear monoamide reacts intermolecularly the faster the shorter is the distance between amido and amino groups.

Scheme 2



Application of the high-pressure technique [15] to three of the above-mentioned reactions, namely of diester **1** with diamines **2** and **3**, and of diester **4** with diamine **2** afforded the same products with different yields and diamide-tetraamide ratios as shown in Table 1.

Table 1. The results of the high-pressure macrocyclization reaction.

Entry	Substrates	Products	
		Diamide (yield)	Tetraamide (yield)
1	**1** + **2**	**5** (18%)	**6** (12%)
2	**1** + **3**	**7** (30%)	**8** (12%)
3	**4** + **2**	**9** (40%)	

We are able to obtain compounds **5–9** as monocrystals suitable for X-ray analysis. Figure 1 shows conformations of these compounds along with numbering scheme adopted in structure determination.

Hydrogen bonding is one of the major noncovalent interactions that may provide conformational stability to the ring system, both in solution and in solid state. In the case of azacoronands, possessing both proton donors and proton acceptors, dynamic interactions with the solvent molecules are deduced readily from the ^{1}H NMR spectra. The azamacrocyclic compounds containing by definition two-fold or higher symmetry show in solution dynamically averaged symmetrical structures. The presented solid state data, however, show the unsymmetrical molecules (*i.e.* not possessing crystallographic two-fold symmetry). That concerns general symmetry of the ring system and often symmetry of the intra- and intermolecular hydrogen bond patterns.

Recently, it has been found that formation of an intramolecular hydrogen bond of the type **A** (Fig. 2) is one of the characteristic features of the azamacrocyclic compounds in the solid state [16]. Due to two-fold symmetry of all these compounds usually, two five-membered rings are formed inside of the 12- to 30-membered macrocycles. Typically, the number of proton acceptors significantly exceeds the number of proton donors. Therefore, water or other solvent molecules are quite often incorporated into the crystals, affording quite complex hydrogen bonding patterns.

It is apparent from the projection shown in Fig. 1 and data presented in Table 2 that in the case of compound **5**, possessing the smallest possible, strained 12-membered ring, formation of the intramolecular hydrogen bond of type **A** is restricted to one per ring. The other amide group forms intermolecular, polar hydrogen bonded chains.

Table 2. Hydrogen-bonds for **5** [Å and deg.].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(1)–H(1)...O(13)#1	0.83(3)	2.13(3)	2.815(3)	140(3)
N(1)–H(1)...O(4)	0.83(3)	2.31(3)	2.707(2)	110(2)
N(7)–H(7)...O(14)#1	0.69(4)	2.22(4)	2.883(3)	159(5)

Symmetry transformations used to generate equivalent atoms: #1 x + 1, y, z.

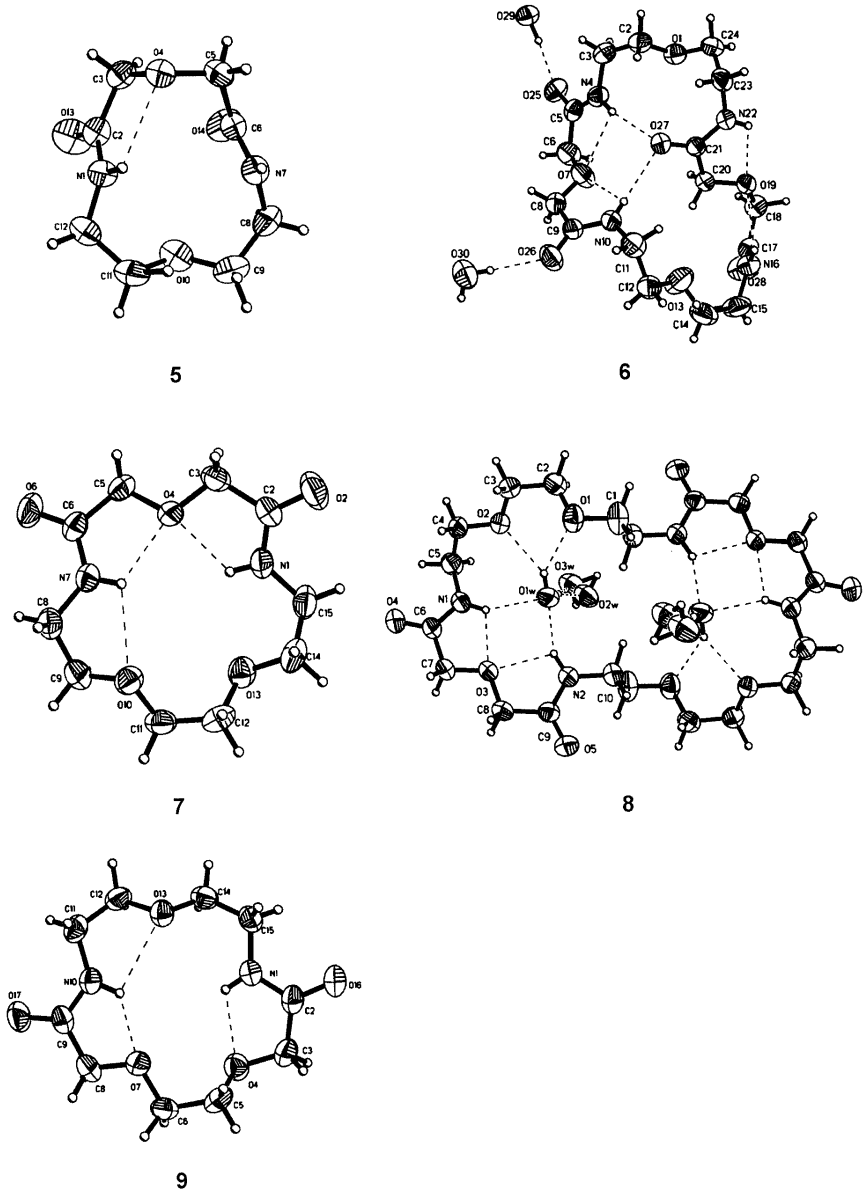


Figure 1. ORTEP diagrams of compounds **5–9** showing labelling scheme and intramolecular hydrogen bonding patterns

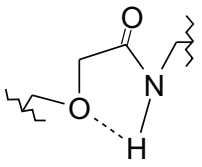


Figure 2. Hydrogen bonding of type **A**.

In tetrazacompound **6**, four intramolecular hydrogen bonds of type **A** are formed. The dimeric molecule **6** represents, to our knowledge, the first example of a free ligand, where the ring collapsed and the carbonyl group is involved in an intramolecular hydrogen bond formation. Intermolecular weak interactions, allowing crystal formation, exploit hydrogen bonding *via* inclusion of the two additional water molecules. As shown in Table 3, the intramolecular H-bond formed by N(22) is one of the strongest found in this class of compounds.

Table 3. Hydrogen-bonds for **6** [Å and deg.].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(22)–H(25)...O(19)	0.87(4)	2.12(3)	2.589(3)	113(3)
N(22)–H(25)...O(29)#1	0.87(4)	2.23(4)	3.010(3)	149(3)
N(16)–H(26)...O(28)#2	0.86(5)	2.08(5)	2.799(3)	142(4)
N(10)–H(27)...O(27)	0.84(4)	2.24(4)	2.993(3)	151(3)
N(4)–H(28)...O(27)	0.84(5)	2.22(5)	3.041(3)	166(4)
O(29)–H(29)...O(25)	0.96(5)	1.87(5)	2.829(3)	177(4)
O(29)–H(30)...O(30)#3	0.84(7)	1.98(7)	2.805(4)	166(6)

Symmetry transformations used to generate equivalent atoms: #1 x + 1/2, y – 1/2, z; #2 x + 1, y, z; #3 x – 1, y, z.

The compound **7** (structural details concerning this compound will be published later) and **9**, shown in Fig. 1, both containing 15-membered rings, are interesting examples of the same number and types but different topology of the intramolecular hydrogen bonds (see Table 4 for geometry of H-bonding of **9**).

Table 4. Hydrogen-bonds for **9** [Å and deg.].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(1)–H(1)...O(4)	0.83(5)	2.20(6)	2.676(5)	117(4)
N(10)–H(10)...O(7)	0.85(5)	1.93(5)	2.541(5)	127(4)

Compound **8**, being formal dimer of compound **7**, has the largest 30-membered ring with four amide units as shown in Fig. 1. The ring is large enough to adopt conformation allowing formation of the maximal number of hydrogen bonds of type **A** without folding. The remaining etheral oxygen atoms form hydrogen bonded network with four water molecules (see Table 5).

Table 5. Hydrogen-bonds for **8** [Å and deg.].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
N(1)–H(1N)...O(1W)	0.867(18)	2.152(19)	2.9424(16)	151.4(16)
O(1W)–H(1W1)...O(2W)	0.92(3)	1.80(3)	2.694(5)	165(2)
O(1W)–H(1W1)...O(3W)#2	0.92(3)	1.83(3)	2.741(6)	173(2)
N(1)–H(1N)...O(3)	0.867(18)	2.187(17)	2.6271(15)	111.1(14)
N(2)–H(2N)...O(1W)	0.909(18)	2.006(19)	2.8496(16)	153.6(15)
O(1W)–H(2W1)...O(2)	0.87(3)	2.21(3)	2.9201(15)	139(2)
O(1W)–H(2W1)...O(1)	0.87(3)	2.44(3)	3.2008(18)	147(2)
O(3W)–H(2″)...O(4)#3	0.94(3)	1.90(3)	2.787(5)	157(3)
O(3W)–H(1′)...O(5)	0.92(3)	1.95(3)	2.829(5)	159(2)

Symmetry transformations used to generate equivalent atoms: #1 –x + 1, –y + 1, –z + 1; #2 –x, –y + 1, –z + 1; #3 –x, –y + 2, –z + 1.

Contrary to numerous crystal structures of azacoronands, that have been investigated up to date, three out of the five compounds crystallize in noncentrosymmetric space groups and their molecules do not show any strict or approximate elements of symmetry. One can assume that dissymmetry of hydrogen bonding creates an unsymmetrical object that pack in the noncentrosymmetric fashion. The presented structures show that two factors are shaping the molecular conformation during crystal formation: ability for hydrogen bonding (*i.e.* stoichiometry of hydrogen bond donors and acceptors) and steric hindrance introduced by the presence of H-bonded rings of type **A**. When intramolecular strain is significant, hydrogen bonded 5-membered ring is twisted out of the molecular plane (the case of 24-membered ring in compound **6**). When the ring is larger, the void space is filled by hydrogen bonded water molecules (the case of compound **8**).

EXPERIMENTAL

General: ^{1}H NMR spectra were recorded with Varian Gemini (200 MHz) and/or Bruker AM500 (500 MHz) spectrometers in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. ^{13}C NMR spectra were also recorded with Varian Gemini (50 MHz) and/or Bruker AM500 (125 MHz) spectrometers. High-resolution mass spectrometry (HRMS) experiments were performed on an AMD-604 Intectra instruments. Column chromatography was carried out on silica gel (Kieselgel-60, 200–400 mesh).

General procedure for synthesis of cyclic diaza- and tetraazacoronands under atmospheric pressure conditions: An equimolar 0.1 M methanolic solution (5 mmol) of α,ω-diamine and α,ω-diester was left at room temperature for 7 days. Then the solvent was evaporated and the residue was chromatographed on a silica gel column using 0.5–5% mixtures of methanol in chloroform.

General procedure for synthesis of cyclic diaza- and tetraazacoronands under high pressure conditions: An equimolar 0.1 M methanolic solution (5 mmol) of α,ω-diamine and α,ω-diester was filled into a Teflon ampoule, placed in a high-pressure vessel filled with ligroine as a transmission medium and compressed (12 kbar) at room temperature for 48 h. After decompression, the residue was chromatographed on a silica gel column using 0.5–5% mixtures of methanol in chloroform.

Diazacoronand **5** [3], m.p. 178–180°C: ^{1}H-NMR (200 MHz, $CDCl_3$): 3.49 (*dt*, 4H); 3.65 (*t*, 4H); 4.12 (*s*, 4H); 7.27 (*bm*, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): 38.7; 68.6; 74.0; 170.0.

Tetraazacoronand **6**, m.p. 194–195°C: Anal. Calcd. for $C_{16}H_{28}N_4O_8$: C, 47.5; H, 6.9; N, 13.8; Found: C, 47.5; H, 6.9; N, 13.6; HRMS m/z (M^+, $C_{16}H_{28}N_4O_8$) Calcd. 404.19071; Found: 404.19082; ^{1}H-NMR (200 MHz, $CDCl_3$): 3.51 (*dt*, 8H); 3.58 (*t*, 8H); 4.08 (*s*, 8H); 7.15 (*bs*, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): 38.9; 69.4; 70.9; 168.9.

Diazacoronand **7** [3], m.p. 146–148°C: ^{1}H-NMR (200 MHz, $CDCl_3$): 3.53 (*m*, 4H); 3.55 (*s*, 4H); 3.59 (*m*, 4H); 4.05 (*s*, 4H); 7.09 (*m*, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): 38.2; 68.5; 69.9; 70.0; 167.6.

Tetraazacoronand **8**, m.p. 198–200°C: Anal. Calcd. for $C_{20}H_{36}N_4O_{10}$: C, 48.7; H, 7.3; N, 11.4; Found: C, 48.2; H, 7.3; N, 11.1; HRMS m/z (M^+, $C_{20}H_{36}N_4O_{10}$) Calcd. 493.25096; Found: 493.25115; ^{1}H-NMR (200 MHz, $CDCl_3$): 3.51 (*m*, 8H); 3.59 (*m*, 8H); 3.62 (*s*, 8H); 4.01 (*s*, 8H); 7.33 (*bs*, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$): 38.7; 69.9; 71.0; 168.7.

Diazacoronand **9** [3], m.p. 173–175°C: ^{1}H-NMR (200 MHz, $CDCl_3$): 3.53 (*m*, 4H); 3.60 (*t*, 4H); 3.72 (*s*, 4H); 4.02 (*s*, 4H); 7.17 (*m*, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$): 38.1; 68.9; 70.1; 70.2; 169.0.

X-ray structure investigations: Single crystals of compounds **5**, **6**, **8** and **9** were obtained by slow crystallization from methanol solution. X-ray diffraction experiments were performed on a Enraf-Nonius CAD4 diffractometer. Details of data collection and structure refinement are shown in Table 6. Lattice constants for the above compounds were determined by a least-squares fit of setting angles of 25 reflections. Intensities of three standard reflections measured every 2 h did not show significant fluctuations for either of the four compounds. Structure factors used for structure solution and refinement were not corected for absorption effects. The structures have been solved by SHELXS86 [17] and refined with

SHELXL97 [18] programs. Both centrosymmetric and non-centrosymmetric space groups were considered throughout crystal structure analysis. Hydrogens attached to C-atoms were included at their geometrical positions and refined in riding mode. Amine, and water H-atoms were located from Δρ maps and refined with isotropic thermal parameters and no restrictions put on the D-H distance. CCDC 178282–178285, respectively for compounds **5**, **6**, **8** and **9** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.camac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223 336033; or deposit@ccdc.cam.ac.uk.

Table 6. Details of data collection and structure refinement.

Identification code	**5**	**6**	**8**	**9**
Empirical formula	$C_8H_{14}N_2O_4$	$C_{17}H_{32}N_4O_9$	$C_{20}H_{42}N_4O_{14}$	$C_{10}H_{18}N_2O_5$
Formula weight	202.21	442.47	562.58	246.26
Crystal system	Monoclinic	Monoclinic	Triclinic	Orthorhombic
Space group	$P2_1$	Cc	$P(-)1$	$Pca2_1$
Unit cell dimensions				
a (Å)	4.9937(8)	4.9933(9)	8.3562(10)	8.6100(10)
b (Å)	7.3464(5)	20.412(3)	9.2815(10)	16.635(2)
c (Å)	13.2619(8)	21.349(3)	10.7366(10)	8.4320(10)
α (°)	90	90	99.010(10)	90
β (°)	98	93.220(10)	97.640(10)	90
γ (°)	90	90	115.881(10)	90
Volume (Å^3)	481.14(9)	2172.5(6)	720.71(13)	1207.7(2)
Z	2	4	1	4
Calculated density (Mg m^{-1})	1.396	1.353	1.296	1.354
Absorption coeff. (mm^{-1})	0.952	0.925	0.940	0.920
F(000)	216	948	302	528
Crystal size (mm)	0.21×0.14×0.14	0.54×0.33×0.21	0.21×0.14×0.14	0.35×0.21×0.21
Theta range for data collection (°)	3.37 to 74.90	4.33 to 74.72	4.33 to 74.88	2.66 to 74.79
Index ranges	$0 \le h \le 6$	$0 \le h \le 6$	$0 \le h \le 10$	$-10 \le h \le 0$
	$0 \le k \le 9$	$0 \le k \le 25$	$-11 \le k \le 10$	$-20 \le k \le 0$
	$-16 \le l \le 16$	$-26 \le l \le 26$	$-13 \le l \le 13$	$-10 \le l \le 0$
Reflections collected/unique	1160/1042 [Rint = 0.0077]	2450/2450 [Rint = 0.000]	3176/2965 [Rint = 0.0249]	1174/1174 [Rint = 0.000]
Data/restraints/parameters	1042/0/183	2450/0/398	2965/0/206	1174/0/226
Goodness-of-fit on F^2	1.065	1.036	0.507	1.169
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0342, wR2 = 0.0950	R1 = 0.0357, wR2 = 0.0987	R1 = 0.0396, wR2 = 0.1229	R1 = 0.0523, wR2 = 0.1440
R indices (all data)	R1 = 0.0342, wR2 = 0.0950	R1 = 0.0357, wR2 = 0.0988	R1 = 0.0414, wR2 = 0.1254	R1 = 0.0528, wR2 = 0.1446
Extinction coefficient	0.053(4)	0.035(4)	0.0032(2)	0.0000(7)

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