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Diazacoronands—synthesis, structure and inclusion properties

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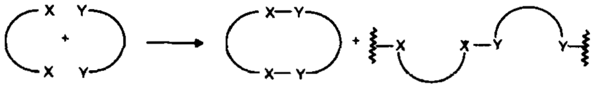
Two general methods of the synthesis of diazacoronands: the high-pressure approach and that *via* bisamidation are presented. Several examples of the X-ray structure studies of the compounds obtained are given.

INTRODUCTION

Crown ethers form a clearly organized family of compounds. Their structural and complexing properties have been described and reviewed several times.[1] Diazacoronands, a sub-branch of crown ethers, occupy a specific place in the family since their natural abilities to serve as basis for construction of many more complex structures. Efforts undertaken by many authors during the last 35 years result in few general methods for the synthesis of crown ethers. They are either already commonly used or seem to possess proper attributes to find wide application. Most of them consist of a reaction of two molecules which form bonds between their termini to form the macrocyclic ring (Scheme 1).



Scheme 1

The formation of the needed product stays in competition with formation of linear oligomers. All the procedures elaborated until now either enhance the probability of desired reaction or force appropriate preorganization of the substrates. The self-assembly phenomena seem to play an important role when preorganization is to be achieved. In the diazacoronands synthesis the necessary domination of the desired product is realized in various ways which can be grouped according to the structure of the adducts and reaction mechanism or according to the methodology applied during the synthesis. For several years our interest has focussed on two methods.[2,3] The double alkylation and the double acylation of α,ω-diamines derived from ethylene glycols. Both methods, though they are efficient enough in many cases, are supported by possibility of application of the high pressure technique.

Double alkylation

The formation of charged products from neutral substrates usually results in increased solvation. Thus, when the charge develops along the reaction coordinate the activation volume is often large and negative. For example the formation of quaternary ammonium salts from a tertiary amine and alkylating agent (the Menshutkin reaction) has an activation volume within the range of -20 to -50 cm^3/mol.[4] Such reactions should be dramatically accelerated by pressure. High pressure not only accelerates the Menshutkin reaction, but also influences the reaction selectivity. It was expected that N,N,N',N'-tetramethyl α,ω-diamine would react under high-pressure conditions with an α,ω-diiodo compound to form the macrocyclic quaternary salts. Indeed, the reaction of tertiary amines of type **1** with diiodo derivative **2** under a 10 kbar pressure afforded the desired crystalline bis-quaternary salt of the type **3** in a quantitative yield (Scheme 2).[2,5]

Subsequent demethylation of compounds **3** by treatment with triphenylphosphine in boiling DMF gave N,N'-dimethyl diazacoronands of general structure **4** in a good yield.[2,5]

The investigation of the influence of changes in pressure on yield and purity of products indicates that this reaction is stepwise and consists of two pressure-accelerated processes: the first intermolecular quaternization is slow, and the second intramolecular quaternization is fast. The linear conformation of the

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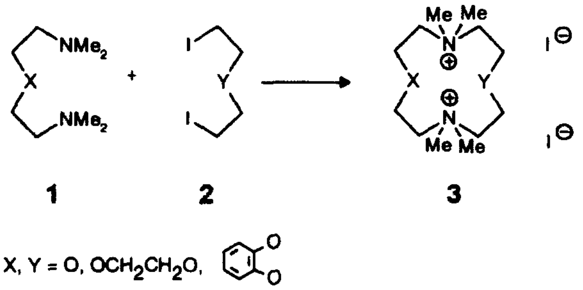
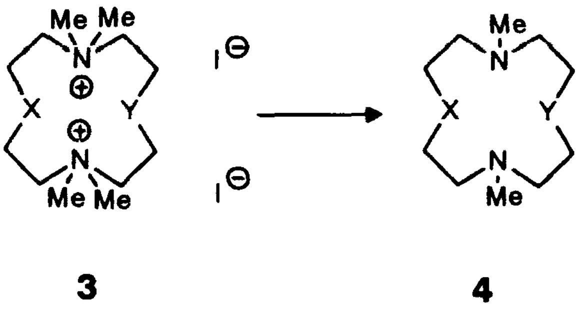


Scheme 2

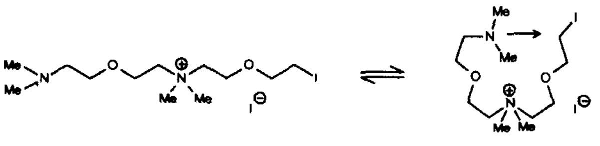
quaternary salt formed at the first stage is in an equilibrium with the quasi-cyclic conformation which should be favored by high pressure and could easily react intramolecularly (Scheme 4).[6]

On the other hand the linear conformation can react with a second molecule of the substrate to form the linear bis-quaternary salt. However, under increasingly high pressure, the reaction leading to linear polymers should be disfavoured because of the increasing viscosity that would prevent intermolecular collisions. The high-pressure double quaternization reaction, carried out in aprotic solvents, is characterized by a complex mechanism in which—apart from molecular processes like conformational changes of substrates and/or intermediates—some macroscopic processes, e.g. changes in viscosity of the reaction media, play prominent role. N,N'-Dimethyl diazacoronands were also obtained by a double-alkylation reaction involving secondary α,ω-diamines and typical α,ω-diiodo compounds. For example, the secondary amines of type **5** reacted with diiodo ethers **2** under high-pressure conditions (acetonitrile as solvent, 11kbar, 50°C, 20h) to give the respective salts of the type **6** in a very good yield.[7] Neutralization of salts **6** by potassium hydroxide, followed by pyrolysis of the complex formed, lead to the desired N,N'-dimethyl diazacoronand of the type **7** in good overall yield (Scheme 5).

The further experience proved that application of high pressure is in many cases not necessary to obtain satisfactory results. The polyethylene ether systems seems to possess a well pronounced tendency to self-assemble (e.g. favored gauche conformation of ethylene moiety). This feature can be supported by the influence of a polar protic solvent (methanol), which, thanks to strong interaction *via* hydrogen bonds, organizes the whole system. It seems to assure the appropriate proximity of the reacting terminal groups, during long enough times. Thus, following Menger's postulate,[8] this is sufficient for the reaction to occur.



Scheme 3



Scheme 4

Although the cyclic products of the high-pressure reactions are far more pure, in both cases (normal and high-pressure conditions) the desired compounds can be isolated by one or two crystalizations after which the yields are still reasonably high.

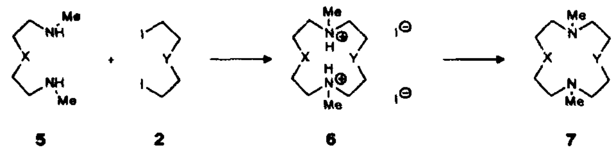
Double acylation

Another useful method for the synthesis of diazacoronands is the reaction between primary α,ω-diamines and dimethyl esters of α,ω-dicarboxylic acids.[3] Tabushi *et al.*[9] have reported a general synthetic method to prepare polyazacoronands by reacting polyamines with dimethyl esters of oligoglycolic acids. The reaction resulted in cyclic bisamide compounds similar to those obtained in Lehn's classical high-dilution bisacylation. Some changes incorporated into the procedure allowed us to elaborate an easy synthetic method.[10]

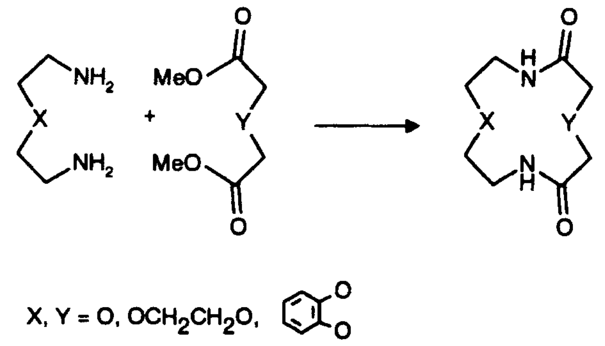
Diamides leading to the known diazacoronands were selected, as the targets of the preliminary synthetic investigations (Scheme 6).

The starting materials for the preparation of target macrocyclic diamides are commercially available or procurable with minimal expenditure of work. The established optimal reaction conditions are as follows: solvent—methanol, temperature—ambient, time—seven days, concentration—0.1 M. The typical reaction has been performed as a bath process. This implies that the values of effective molarity (EM) of substrates reacting under these conditions are high enough to afford the desired product in a reasonable yield.

All products were crystalline, and except for one example, all yields were higher than 50%. It seems that the reaction yield is slightly higher when at least one of substrates is a derivative of catechol. The phenyl ring increases the rigidity of the molecule and at the same



Scheme 5



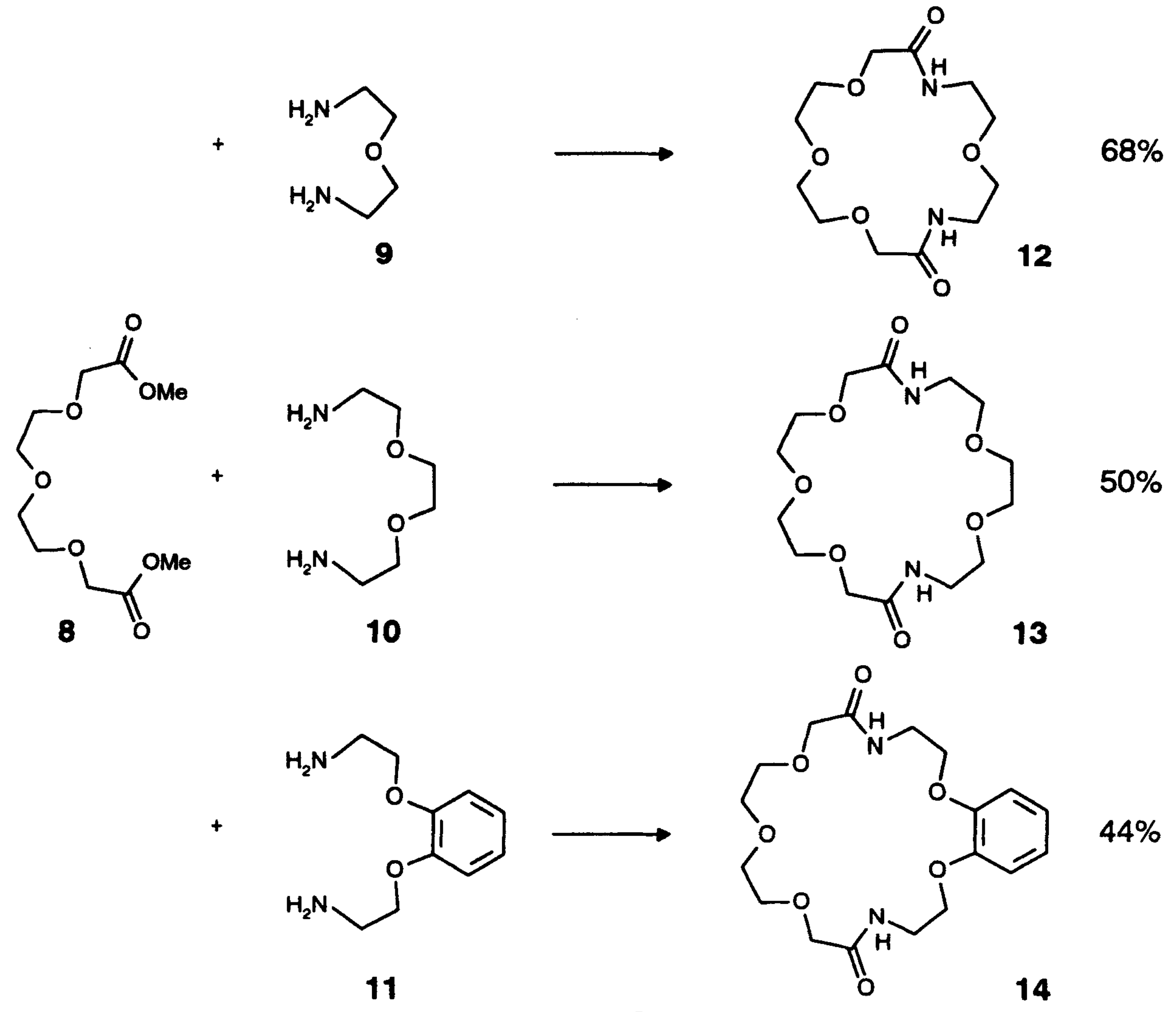
Scheme 6

time improves preorganization of the whole system. Moreover, the products with the phenyl subunit partly precipitated from the reaction mixture.

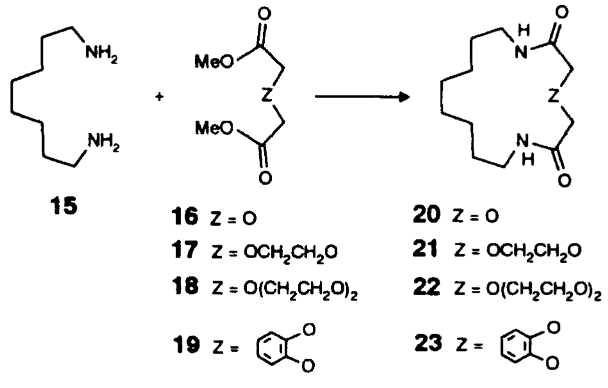
The yield of reactions seems to be sufficiently high for most practical purposes; it appears to be slightly dependent on the size of the macrocycle. In order to prove this relationship we performed a series of reactions of diester **8** with diamines **9**, **10** and **11**, leading to products with 18- and 21-membered rings (Scheme 7).

These results indicate that indeed the yields of the reactions performed depend on the ring size of the products; the preference to form 18-membered rings is evidenced by the present and the previous series of reactions. The long aliphatic chain of substrate **8** forming a 21-membered ring seems to be more resistant to preorganization, owing to its higher flexibility. Here again, the catechol derivative **14** partly crystallized from the reaction mixture.

Preorganization of substrate molecules, which we believe to be crucial for the formation of the presented macrocycles, is probably achieved via hydrogen bonds formed between the molecules of methanol and the



Scheme 7



Scheme 8

ethereal oxygen atoms of substrate. In this case a drop in the number of ethereal binding sites in the substrates would probably decrease the yields of macrocyclic diamides.

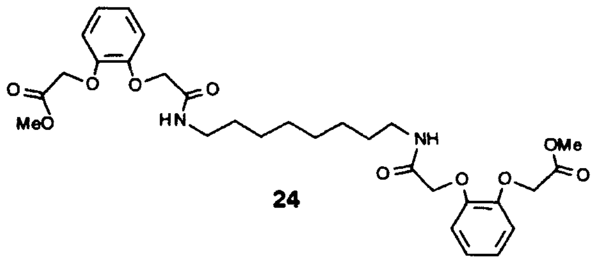
In order to confirm this assumption, the reactions of diesters **16**, **17**, **18** and **19** with 1,8-diaminooctane (**15**) were performed (Scheme 8).

The yields of diamides **20**, **21**, **22** and **23** are indeed substantially lower, in comparison to their fully ethereal counterparts. Moreover, the products are highly contaminated with login oligomeric substances. ^{1}H NMR analysis showed that the major by-products of these reactions consist of two subunits of diester and of one subunit of diamine in the form of a linear diamide-diester. In the reaction between **15** and **19**, leading to **23**, the presence of the contaminating product **24** was confirmed by ^{1}H NMR investigations (Scheme 9).

This seems to be consistent with the assumed course of the reaction, according to which the diester and diamine form a linear amido compound which then undergoes the cyclization or oligomerization. Both latter processes are competitive and the EM values indicate which one is preferred under the reaction conditions used.[11]

In the case of fully ethereal compounds, the hydrogen bonds between the substrates and solvent force the self-assembly of the linear dimers and cause theirs cyclization. A compound without oxygen binding sites is poorly preorganized by methanol.

More careful investigation of the reactions of diglicolic acid dimethyl ester **16** with diamines **9** and **10** revealed that the expected derivatives of diaza coronands **25** and **27** respectively, are not the only cyclic products formed in detectable amounts.[12] In the first case apart the diamide **25**, a tetraamide **26** was detected and isolated. In the second case together with the diamide **27**, the tetraamide **28** was formed (Scheme 10).



Scheme 9

It seems to be noteworthy that the reaction of diester **17** with diamine **9** produces exclusively diamide **29**. It indicates that though the macrocycles **27** and **29** are of the same size, position of an ester groups in the substrate plays a crucial role. Apparently diester is preorganized better than diamine of the same length, and intermediately formed linear monoamide reacts intramolecularly the faster the shorter is the distance between amide and amine groups.

Macrocyclic diamides can be readily transformed into macrocyclic diamines[13] which are of great importance in the chemistry of molecular receptors. All the reductions of the obtained diamides were conducted using the $BH_3 \times Me_2S$ complex as a reducing agent in boiling THF (Scheme 11).

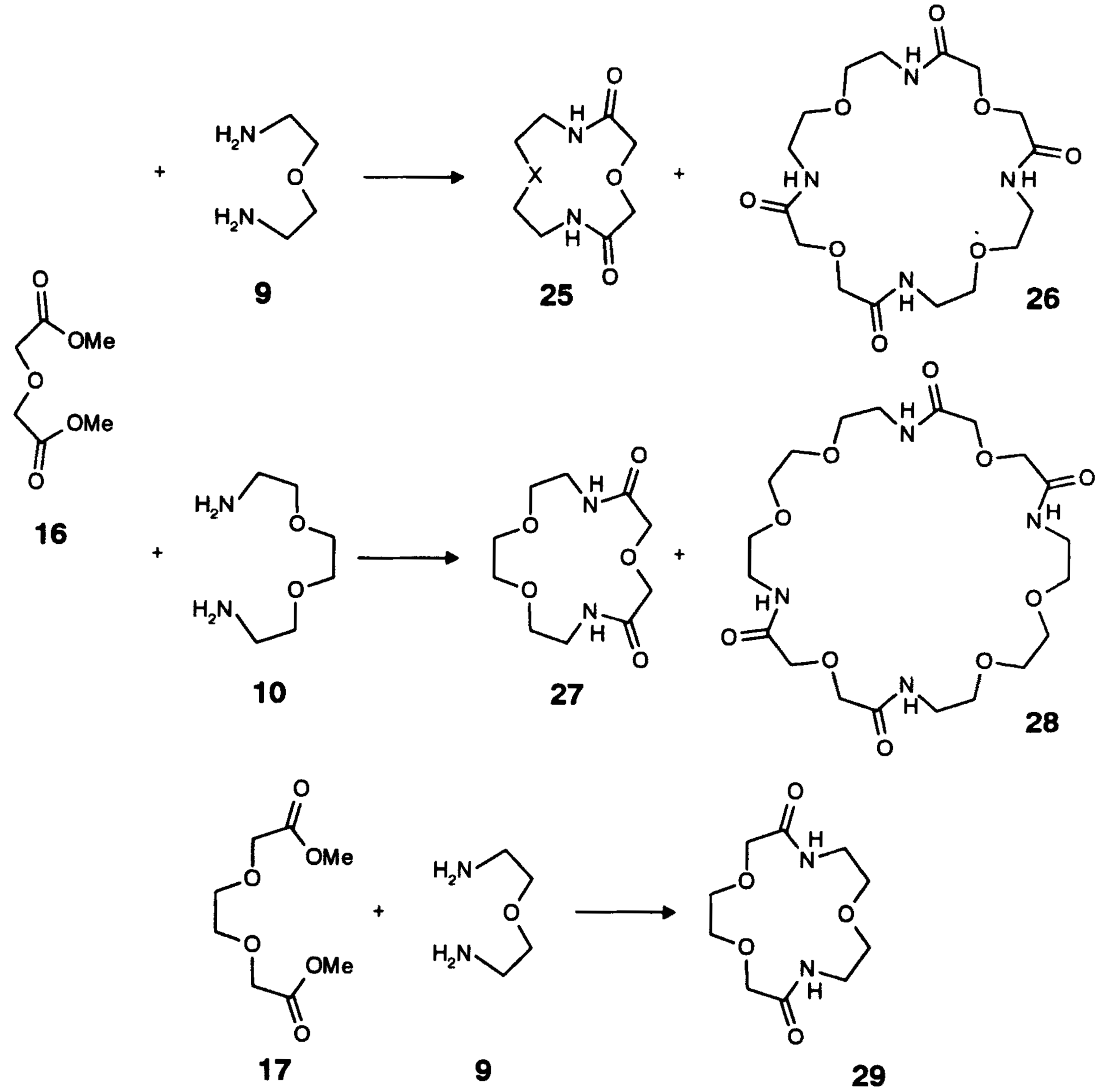
Most of the diamides obtained were crystallized successfully allowing for suitable crystallographic investigations.

In the molecular design of receptor molecules that can precisely recognize various ions or neutral molecules, knowledge of the precise molecular geometry is indispensable. Therefore, X-ray diffraction studies performed by our group focussed on the following goals:

- — describing conformational differences between coronands and azacoronands and looking for common structural elements characteristic for azacoronands
- — evaluation of inter- and intramolecular interactions and their potential role in the process of ring formation, and possibly future complexation properties.

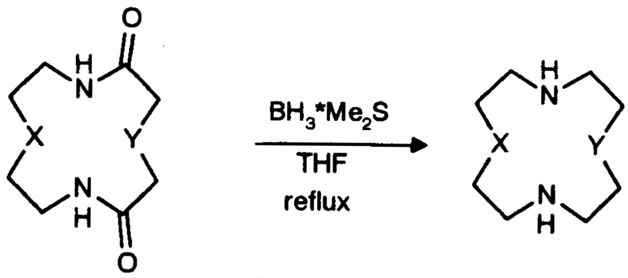
Conformational studies of molecules of the diazacoronands in the solid state

The conformation of the typical coronand molecule is torus-like, which is a consequence of the repulsion between lone electron pairs belonging to the ether oxygen atoms. In the case of diazacoronands synthesized in our laboratory, the molecular shape was more variable and depended on the number of planar elements i.e. amide units and/or phenyl rings fused with the macrocyclic ring, the number of oxygen atoms in the ring, and finally, length of the multimethylene spacer between heteroatoms. Usually, in the vicinity of the amide bonds, intracyclic torsion angle values are far from 180 or 60°. The phenyl ring fused with the macrocyclic ring forms an additional "wing" pointing toward the exterior of the ring. Another factor characteristic for this group of compounds is conformational flexibility, demonstrated in

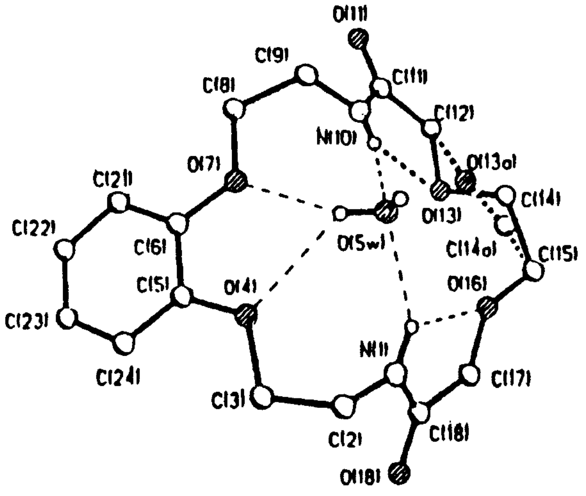


Scheme 10

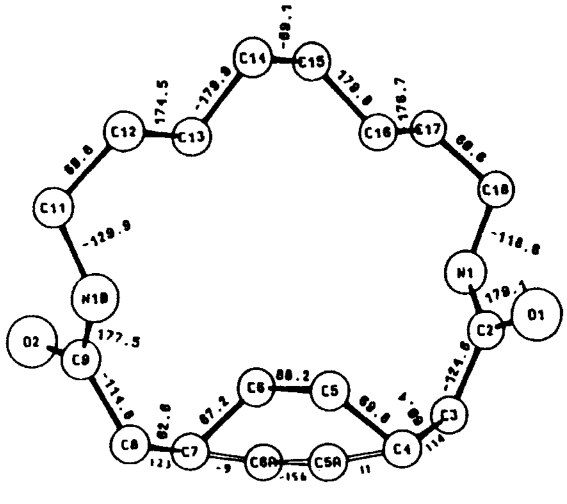
the crystal by the presence of more than one conformer. The most flexible element was usually the intra-ring oxygen bearing a lone pair of electrons which is sterically less voluminous comparing to hydrogen. In several structures the ethereal oxygen atom was found in two different positions in the molecule (see molecule **I**).[14,15] In the case when long multimethylene bridge were incorporated into the ring, as in the case of compound **II**[16], half of the crystal lattice is occupied by the molecules with folded, and a half with extended conformation of this part of the molecule. Another reason why two molecular conformations are preserved in the crystal, is their different pattern of incorporation of solvent molecules into the ring system[17]. This situation is present for compound **III** where stronger and weaker systems of hydrogen bonds formed between 21-membered ring and



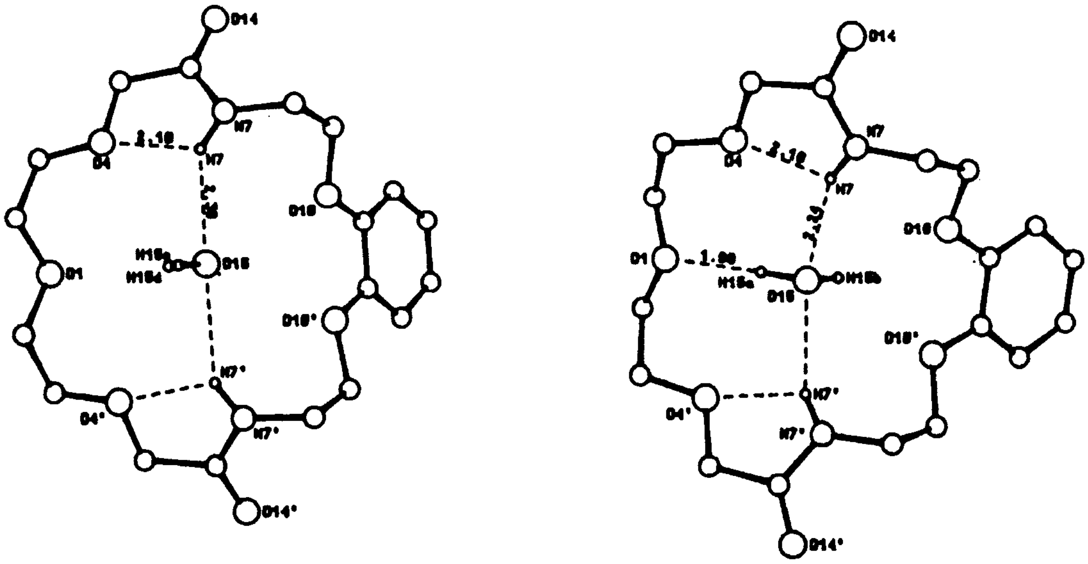
Scheme 11



I (ref. 13)



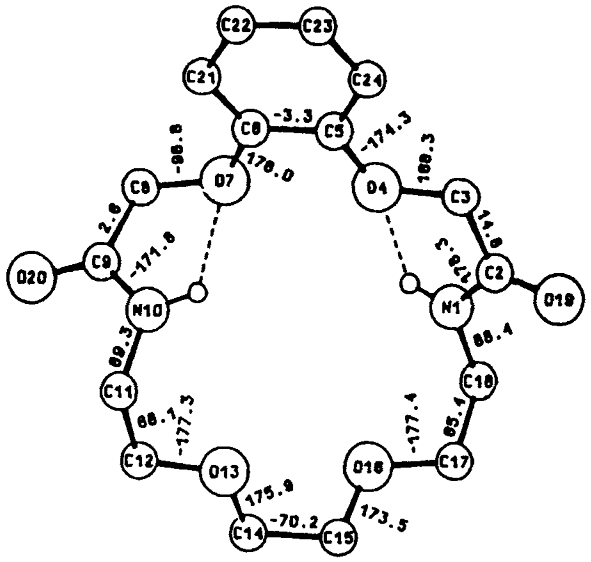
II (ref. 14)



Pattern I

Pattern II

III (ref. 15)



IV (ref. 17)

the water molecule are observed. The above observation suggests that both in solution and in solid state more than one conformation of almost equal energy are present. Some of them can be stabilized by interactions with solvent molecules.

Substrates used for reaction of the ring closure (i.e. in our case, diamines and methyl esters of dicarboxylic acids) have two-fold symmetry, therefore, by definition, also macrocyclic rings should exhibit this symmetry. All NMR spectra showed a reduced number of peaks, corresponding to the dynamically averaged structure of the two halves of the molecule. In the solid state, however, the crystallographic two-fold symmetry is often reduced, so an entropy factor could contribute to the overall energy of the system.

Inter- and intramolecular interactions

Unlike typical coronands, where intramolecular interactions are limited to repulsion between lone electron pairs belonging to the ring oxygens, diazacoronands exhibit numerous intra- and intermolecular interactions between amide and other groups. Among them, hydrogen bonding interactions play a central role. It is without question that the hydrogen bond is important in the multipoint interaction between host and guest molecules, mostly because of its directional character. In the case of diazacoronands, the presence of a hydrogen bond can stabilize some conformations of the ring, or even promote ring formation during the cyclization reaction. On the other hand, strong intramolecular hydrogen bonds can reduce a ring's flexibility, and disturb the coordination process. Taking into account the above considerations, we were particularly interested to see if there is any hydrogen bonding pattern characteristic for this group of compounds with intra- and/or intermolecular character. Graph-set methodology used for the classification of various hydrogen bonds found in the crystallographically investigated molecules revealed several regularities.[18] The basic pattern which stabilizes conformation of the macro-ring is that between amide hydrogen and ring oxygen located in the β-position to the carbonyl C-atom (see compound **IV**). In the case of diazacoronands, two five-membered rings are formed due to such interactions, with quite stable geometry.[19] Moreover, we found the above pattern in all crystal structures investigated, if only the structural requirements are fulfilled. For smaller rings, or rings where there were no oxygen atoms located suitably for the hydrogen bond formation, usually intermolecular hydrogen bonds were formed between amide nitrogen and carbonyl oxygen atoms belonging to different molecules.[14,20] In the case of larger ring size (18-membered and 21-membered) one water molecule co-crystallized with one diazacoronand molecule. In such case, a water molecule was extensively incorporated into the system of the intramolecular hydrogen bonds.[17] The results presented deal with the synthesis and structural investigations of derivatives of diazacoronands. Compounds obtained differ in molecular size and in the number of oxygen atoms incorporated into the macrocyclic ring. The reactions proceed efficiently under ambient or under high-pressure conditions. The course of the reactions is assumed to depend on the occurrence of self-assembly phenomena which are probably stimulated by physico-chemical properties of the selected solvents.

The experiments performed suggest the following conclusions:

1. The application of the high-pressure technique results in a very good yield and high purity of the products.
2. The use of high pressure can be dispensed with, when the slightly lower yield and lower purity of the products are acceptable.
3. The bis-quaternarization reaction, as well as double alkylation of secondary amines under high pressure and also under normal conditions, can be recommended for obtaining more elaborated structures, including chiral compounds.
4. Diamidation reactions can be utilized for preparation of simple diazacoronands of various molecular sizes.
5. The reactions are effective and proceed under ambient conditions.

6. No additional external cyclization factors (such as the high-dilution approach or template effect) is required for obtaining satisfactory results.
7. The self-assembly approach to investigations of the macrocyclization reactions may provide satisfactory explanations, and leads to constructive conclusions concerning the course and yield of examined processes.

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