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SYNTHESIS OF *N,N'*-DIMETHYL DIAZACORONANDS *VIA* DOUBLE-QUATERNIZATION REACTION[1]

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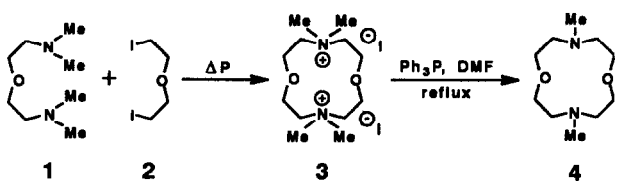
Abstract - *α,ω-Tertiary diamines react under high pressure with α,ω-di-iodo compounds to give the cyclic bis-quaternary salts in almost quantitative yields It is also shown that the same reaction can be carried out under atmospheric-pressure conditions with slightly lower yields. Subsequent demethylation of the bis-quaternary salts with triphenylphosphine affords N,N'-dimethyl diazacoronands in high yield*

Owing to the importance of diazacoronands as building blocks for the synthesis of more complex molecular receptors, the studies on the methods of their preparation lay within the scope of interest of supramolecular chemistry The methods for the formation of diazacoronands have recently been reported [2,3] In principle, high-dilution techniques[4] and "template effect" procedures[5] provide the most useful methods It was recently found that *N,N'*-dimethyl diazacoronands reacted under high-pressure conditions with various α,ω-di-iodo compounds to afford the respective bis-quaternary salts, whose demethylation led to the corresponding cryptands in very good yields [6,7] The experience gained from these studies paved the way for the high-pressure synthesis of diazacoronands Very recently we presented a preliminary information on this new application of the high-pressure quaternization-demethylation procedure [1] We now report the extension of these studies on the synthesis of diazacoronands as well as an atmospheric-pressure modification of the procedure

We found that the α,ω-tertiary diamine **1** reacted smoothly with 1 equiv of bis-(2-iodoethyl) ether (**2**) to give product **3** as a colourless solid (Scheme 1)

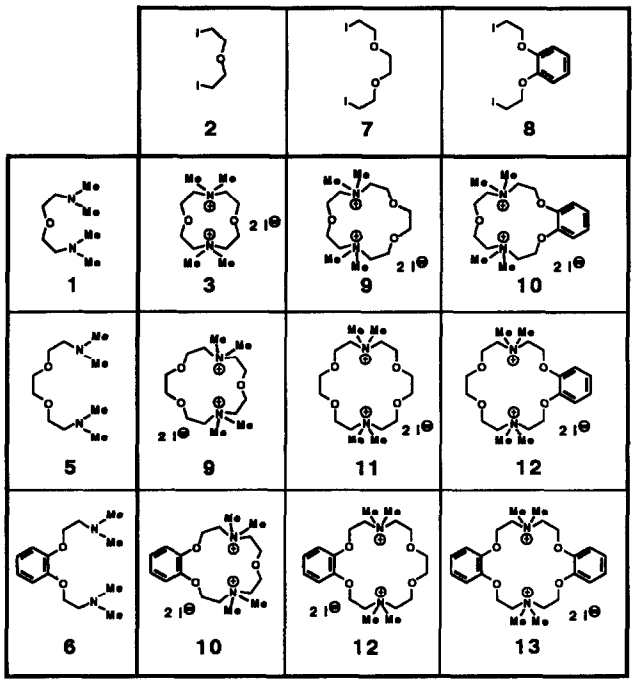


1 **2** **3** **4**

Scheme 1

Demethylation performed by treatment of **3** with triphenylphosphine in boiling DMF, afforded the *N,N'*-dimethyl diazacoronand **4** in 81% yield

The same procedure was applied for preparation of other bis-quaternary salts starting from α,ω-tertiary diamines (**1**, **5**, **6**) and α,ω-di-iodides (**2**, **7**, **8**) the appropriate macrocyclic salts were obtained (Scheme 2) The yields of these reactions are shown in Table 1

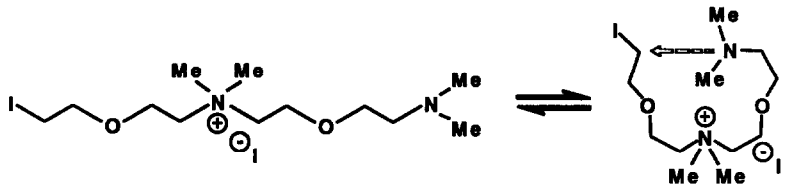


Scheme 2

Table 1

Compound / Yield	2	7	8
1	99%	95%	96%
	3	**9**	**10**
5	95%	97%	99%
	9	**11**	**12**
6	92%	96%	91%
	10	**12**	**13**

From the point of view of reaction mechanism, it has been postulated[8] that this reaction consists in two steps The first intermolecular quaternization leads to a linear salt which then reacts intramolecularly, affording a cyclic bis-quaternary product The second intramolecular step is in competition with the possible reaction of chain elongation (polymerization) The linear compound obtained in the first step is in equilibrium with the quasi-cyclic form which seems to be favoured by high pressure (Scheme 3)



Scheme 3

It was expected that under increasingly high pressure the reaction leading to linear polymers is disfavoured because of the increase in solvent viscosity that prevents intermolecular collisions In our opinion, the preference for formation of a quasi-cyclic intermediate is due not only to high pressure but, first and foremost, to self-assembly of the linear conformer High pressure only slows down the transport processes According to Menger's postulate,[9] the reacting groups remain in proximity (in the absence of intermolecular reactions prevented by high pressure) long enough for the reaction to occur

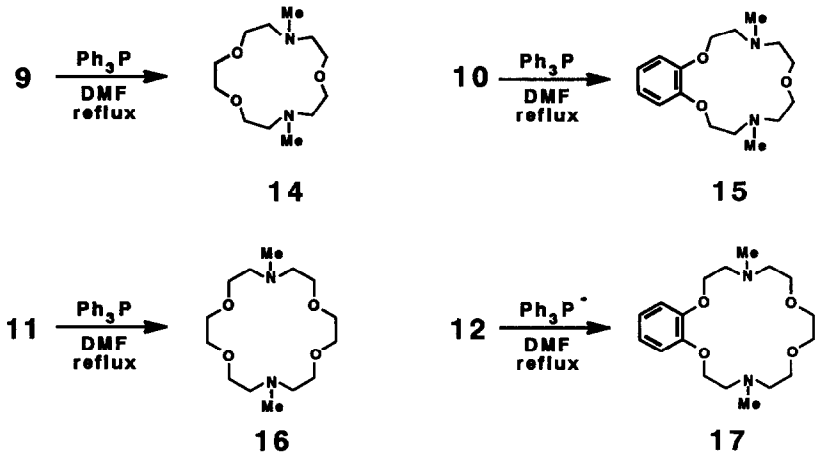
The question arises whether high pressure is indispensable for enforcing the cyclization of these substrates To check this assumption it was resolved to perform under normal pressure exactly the same reactions as specified in Scheme 2 The yields of these reactions are presented in Table 2

Table 2

Yield / Compound	2	7	8
1	79%	74%	66%
	3	**9**	**10**
5	85%	68%	66%
	9	**11**	**12**
6	48%	53%	36%
	10	**12**	**13**

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

The bis-quaternary salts can be directly transformed into the corresponding *N,N'*-dimethyl diazacoronands (Scheme 4) which are well known from the literature [10-12] The transformation was performed using triphenylphosphine in boiling DMF [13] The yields of these reactions are presented in Table 3



Scheme 4

Table 3

Compound	14	15	16	17
Yield	74%	70%	59%	64%

All the presented cyclization reactions proceed efficiently under high-pressure conditions as well as under normal pressure The course of the reactions is assumed to depend on the occurrence of self-assembly phenomena which are probably stimulated by a properly selected solvent and the yields are improved by application of high pressure The performed experiments allow for the following conclusions

1 The application of the high-pressure technique results with 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 macrocyclic bis-quaternary ammonium salts can be easily transformed into corresponding *N,N'*-dimethyl diazacoronands

4 The bis-quaternarization reaction, under high pressure and normal conditions as well, can be recommended for obtainment of more elaborated structures, including chiral compounds

EXPERIMENTAL

General

^{1}H NMR spectra were recorded at 500 MHz with a BRUKER AM 500 spectrometer ^{13}C NMR spectra were measured at 125 MHz with a BRUKER AM 500 spectrometer Elemental analyses were performed on a micro scale

All high-pressure reactions were carried out in a piston-cylinder type apparatus with an initial working volume of about 90 mL Construction details of the apparatus have been reported previously [14]

General procedure for preparation of *N,N,N',N'*-tetramethyl diazacoronands under high pressure

0 1M Solution of α,ω-tertiary diamine (1 equiv) and α,ω-di-iodide (1 equiv) in acetonitrile was charged into a Teflon ampoule which was placed in a high-pressure vessel filled with pentane as a transmission medium, and compressed (10 kbar) at room temperature for 48 h After decompression, the crystals were filtered off, the solvent was evaporated from the filtrate, and the combined solid was twice recrystallized from methanol

General procedure for preparation of *N,N,N',N'*-tetramethyl diazacoronands under atmospheric pressure

0 1M Solution of α,ω-tertiary diamine (1 equiv) and α,ω-di-iodide (1 equiv) in acetonitrile was left at room temperature for 6 days After filtration of crystals and evaporation of the solvent from the filtrate, the combined solid was twice recrystallized from methanol

N,N,N',N'-Tetramethyl-1,7-diaza-4,10-dioxacyclododecane di-iodide (**3**)

Anal calcd for $C_{16}H_{28}N_2O_2I_2 \times H_2O$ C, 28 6, H, 6 0, N, 5 6 Found C, 28 5, H, 5 9, N, 5 7

^{1}H NMR (D_2O) δ 3 08(s, 12H), 3 55-3 60(m, 8H), 3 81-3 83(m, 8H)

^{13}C NMR (D_2O) δ 52 2, 63 8, 63 9, 64 1, 64 3, 64 4, 71 1

N,N,N',N'-Tetramethyl-1,10-diaza-4,7,13-trioxacyclopentadecane di-iodide (**9**)

Anal calcd for $C_{14}H_{32}N_2O_3I_2$ C, 31 7, H, 6 1, N, 5 3 Found C, 31 7, H, 6 3, N, 5 4

^{1}H NMR (D_2O) δ 3 16 3 18(m, 12H), 3 59 3 67(m, 12H), 3 88 2 93 (m, 8H)

^{13}C NMR (D_2O) δ 51 7, 63 3, 63 6, 63 8, 63 9, 69 2

N,N,N',N'-Tetramethyl-5,6-benzo-1,10-diaza-4,7,13-trioxacyclopentadecane di-iodide (**10**)

Anal calcd for $C_{16}H_{32}N_2O_3I_2$ C, 37 4, H, 5.6, N, 4 9 Found C, 37 1, H, 5 8, N, 5 2

^{1}H NMR (DMSO-d_6 D_2O,1 1) δ 3 30(s, 12H), 3 83(m, 4H), 3 94 (m, 4H), 4 02(m, 4H), 4 48(m, 4H), 6 97 7 15(m, 4H)

^{13}C NMR (DMSO-d_6 D_2O,1 1) δ 52 0, 62 6, 63 2, 63 5, 64 0, 114 4, 115 4, 121 9, 122 4, 147 1, 147 6

N,N,N',N'-Tetramethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane di-iodide (**11**)

Anal calcd for $C_{16}H_{36}N_2O_4I_2$ C, 33 5, H, 6 3, N, 4 9 Found C, 33 6, H, 6 5, N, 4 9

^{1}H NMR (D_2O) δ 3 28(s, 12H), 3 74(s, 8H), 4 05(s, 8H)

^{13}C NMR (D_2O) δ. 55 1, 66 9, 72 4

N,N,N',N'-Tetramethyl-5,6-benzo-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane di-iodide (**12**)

Anal calcd for $C_{20}H_{36}N_2O_4I_2$ C, 38 0, H, 5 9, N, 4 4 Found C, 38 1, H, 6 3, N, 4 5

^{1}H NMR (DMSO-d_6 D_2O,1 1) δ 3 10(s, 12H), 3 56(m, 4H), 3 60(m, 4H), 3 76(t, J=4 9Hz, 4H), 3 88(m,4H), 4 36(m, 4H), 6 95 - 7 02(m,4H)

^{13}C NMR (DMSO-d_6.D_2O,1 1) δ 51 8, 62 0, 62 7, 63 7, 64 6, 69 5, 113 8, 122 3, 146 5

N,N,N',N'-Tetramethyl-5,6,14,15-dibenzo-1,10-diaza-4,7,13,16-tetraoxacyclooctadecane di-iodide (**13**)

Anal calcd for $C_{24}H_{36}N_2O_4I_2$ C, 43 0, H, 5 4, N, 4 2 Found C, 43 1, H, 5 4, N, 4 3

^{1}H NMR (DMSO-d_6 D_2O,1 1) δ 3 31(s, 6H), 3 35(s, 6H), 3 97(m, 8H), 4 48(m, 8H), 6 95 - 7 3(m,8H)

^{13}C NMR (DMSO-d_6 D_2O,1 1) δ 12 7, 23 6, 24 6, 75 4, 83 2, 108 3

General procedure for demethylation of bis-quaternary salts with trimethylphosphine

Bis-quaternary salt (0 6 mmol) and triphenylphosphine (0 314 g, 1 2 mmol) were refluxed in DMF (10 mL) for 8 h The isolation of the *N,N'*-dimethyl diazacoronands from the reaction mixture appeared troublesome These compounds strongly complex the methyltriphenylphosphonium iodide which is one of the side products The complex was decomposed by treatment of the reaction mixture with the diluted hydrochloric acid, and then the liberated phosphonium iodide was removed by extraction with chloroform The aqueous solution contains only the desired product, and after evaporation of water the *N,N'*-dimethyl diazacoronand was isolated by distillation in vacuum on a bubble-to-bubble type apparatus

N,N'-Dimethyl-1,7-diaza-4,10-dioxacyclododecan (**4**)

^{1}H NMR ($CDCl_3$) δ 2 37(s, 6H), 2 66(t, J=6Hz, 8H), 3 58(t, J=6Hz, 8H) [Lit [10]]

N,N'-Dimethyl-1,10-diaza-4,7,13-trioxacyclopentadecan (**14**)

^{1}H NMR ($CDCl_3$) δ 2 29(s, 6H), 2 83(m, 8H), 3 5 3 7(m, 12H) [Lit [11]]

N,N'-Dimethyl-5,6-benzo-1,10-diaza-4,7,13-trioxacyclopentadecan (**15**)

^{1}H NMR ($CDCl_3$) δ 2 3(s, 6H), 2 7(t, J=5Hz, 4H), 2 8(t, J=4Hz, 4H), 3 6(t, J=5Hz, 4H), 4 05(t, J=4Hz, 4H), 6 8 6 9(m, 4H) [Lit [12]]

N,N'-Dimethyl-1,10-diaza-4,7,13,16-tetraoxacyclooctadecan (**16**)

^{1}H NMR ($CDCl_3$) δ 2 31(s, 6H), 2 69(t, J=5 5Hz, 8H), 3 62(m, 16) [Lit [12]]

N,N'-Dimethyl-5,6-benzo-1,10-diaza-4,7,13,16-tetraoxacyclooctadecan (**17**)

^{1}H NMR ($CDCl_3$) δ 2 3(s, 6H), 2 7-3 05(t, J=6Hz, 4H), 2 87(t, J=6Hz, 4H), 3 55-3 80(m, 8H), 4 1(t, J=6Hz, 4H), 6 85-6 95(m, 4H)

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REFERENCES

1 For the preliminary communication see Jurczak, J , Ostaszewski, R , Sałański, P *J Chem Soc , Chem Commun* **1989**, 184

2 Gokel, G W , Korzeniowski, S H *Macrocyclic Polyether Synthesis*, Springer Verlag, Berlin-Heidelberg-New York, 1982

3 Krakowiak K E , Bradshaw, J S , Zamecka-Krakowiak, D J *Chem Rev* **1989**, *89*, 929

4 Dietrich, B , Lehn, J M , Sauvage, J P *Tetrahedron Lett* **1969**, 2885

5 Kulstadt, S , Malmsten, L.A *Acta Chem Scand* **1979**, *B33*, 469

6 Jurczak, J , Pietraszkiewicz, M *Top Curr Chem* **1985**, *130*, 183

7 Jurczak, J , Ostaszewski, R , Piertaszkiewicz, M , Sałański, P *J Incl Phenom* **1987**, *5*, 553

8 Jurczak, J , Kasprzyk, S , Mąkosza, M , Ostaszewski, R , Sałański, P *High Press Res* **1990**, *5*, 641

9 Menger, F M *Acc Chem Res* **1985**, *18*, 128

10 Metcalfe, J C , Stoddart, J F , Jones, G *J Am Chem Soc* **1977**, *99*, 8317

11 Luteri, G F , Ford, W T *J Organometal Chem* **1976**, *105*, 139

12 Hodgkinson, L C , Johnson, M R , Leigh, S J , Spencer, N , Sutherland, I O , Newton, R F *J Chem Soc , Perkin Trans 1* **1979**, 2193

13 Tse-Lok Ho, *Synth Commun* **1973**, *3*, 99

14 Jurczak, J , Chmielewski, M , Filipek, S *Synthesis* **1979**, 41