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TETRAHEDRON

Synthesis of Some 24-membered Tetralactam Derivatives by an Unexpectedly Simple Route, and Some Macrocyclic Polyether Dilactams

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Abstract: An unexpected reaction of 1,5-bis(arylamino)-3-oxapentanes **4**, **21** and **22** with diglycolyl dichloride gave 24-membered macrocyclic tetralactams **18**, **23** and **24** respectively, in a reaction involving two molecules of each reactant (2:2 process). This was in contrast to closely related reactions of α,ω-bis(arylamino)alkylethers **5** and **6** with diglycolyl, triglycolyl and tetraglycolyl dichlorides which yielded the macrocycles **9-14** by reaction of one molecule of each reactant (1:1 process). The phenyl nuclei in **14** and **18** were formylated to give **34**, **35** and **36**. The aldehydes, **35** and **36** were condensed with a quinoxaline fluorophore to yield the diene **37** and the tetraene **38** respectively.

Macrocycles containing both ether and amide groups are of interest because of their ability to show selectivity in the complexation of alkaline earth metal rather than alkali metal ions.[1] For example, polyether-dilactams[2,3] and polyether-tetralactams[4] have been investigated in some detail and it has been shown that for 18-, 21- and 24-membered tetralactams the carbonyl groups play an important part in the bonding of the complex. However, the 24-membered tetralactams have been accessible only in poor yield or by multi-step syntheses. The macrocyclic amides have the potential to act as precursors of the corresponding amines which possess the property of showing greater selectivity for ammonium ions than the corresponding polyethers.[5] In the course of the preparation of a series of macrocyclic polyether dilactams we have discovered a simple and efficient route to certain 24-membered tetraether-tetralactams.

The amines **4**, **5** and **6** required for the preparation of the macrocyclic amides were prepared by reduction of the corresponding amides **1**, **2** and **3** which, in turn, were obtained by reaction of aniline with di-, tri- and tetra-glycolyl dichlorides, respectively (Scheme 1). Compounds **4** and **5** were also obtained in better yield by reaction of the ditosylates **7** and **8** with aniline.

The diamine **4** reacted with triglycolyl dichloride under high dilution conditions to give **9**. The diamine **5** similarly gave **10**, **11** and **12** on reaction with di-, tri- and tetra-glycolyl dichloride respectively, and **6** gave **13** and **14** on reaction with tri- and tetra-glycolyl dichloride respectively (Scheme 2). The dilactams **9**, **10**, **11**, **12**, **13** and **14** were formed by reaction of one molecule of diacid dichloride with the diamine (1:1 reaction) and TLC analysis of the reaction product showed little evidence of higher molecular weight products.

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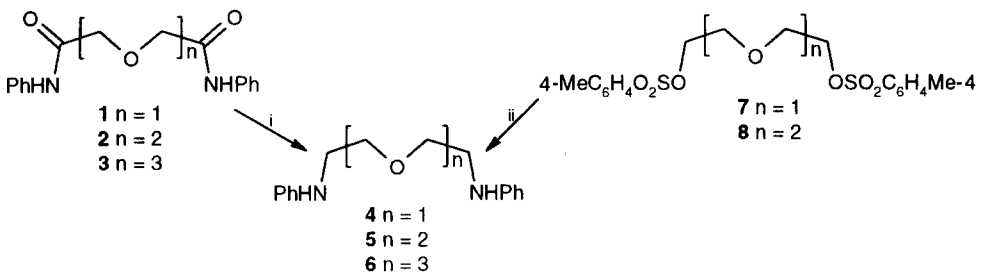
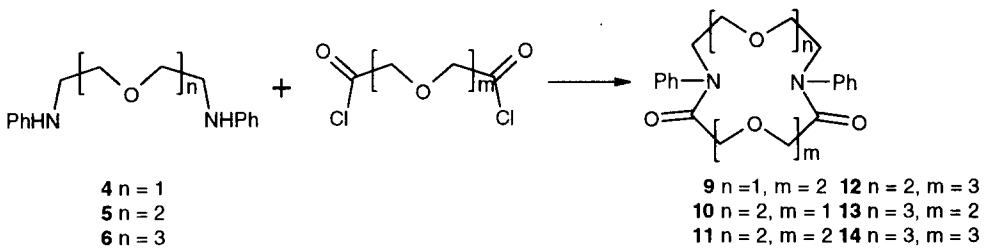
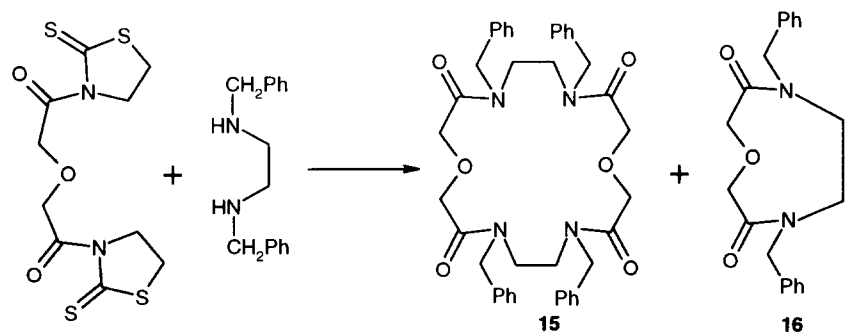


Scheme 1: Reagents: (i) $LiAlH_4$, THF; (ii) $C_6H_5NH_2$



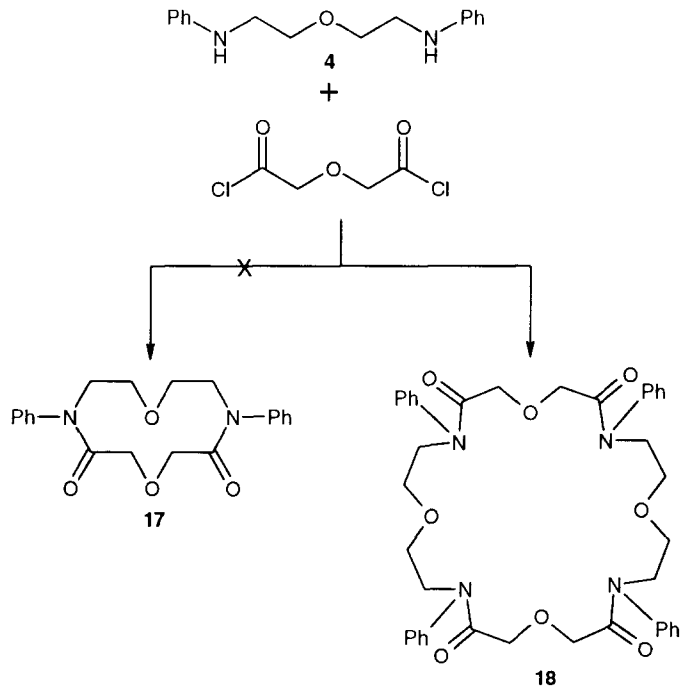
Scheme 2

It is known[6] that a diamine and a diacid dichloride generally give only a small yield of a tetraamide from a reaction of two molecules of each reactant (2:2 reaction). Attempts have been made to increase the yields of tetraamides by the formation of diazasilolidines.[7,8] Reaction of these diazasilolidines with diacid dichloride gave the polymethylene tetramides as the only cyclic product in yields of 12-40%. However, it has been shown that replacement of the methylene groups in the diamine by oxygen atoms leads to a significant decrease in the tetraamide:diamide ratio.[9,10] The best yield of tetraamide **15** was obtained from 1,2-bis(benzylamino)ethylene and the thiazolidine 2-thione derivative of the diacid. However, both the tetraamide (31.3%) and the diamide **16** (22.7%) were produced (Scheme 3). When the acid chloride was used a lower overall yield was obtained with the two products **15** and **16** being obtained in 20.1 and 21% yield, respectively.[10]



Scheme 3

The next preparation we attempted was the formation of **17** by use of the reaction between diglycolyl dichloride and the diamine **4** (Scheme 4). On the evidence of the literature and our own results obtained in the preparation of **9-14**, we expected that **17** would be formed in moderate to good yield by a (1:1 reaction), with **18** being present as only a small proportion of the total product. The reaction was performed under the same high dilution conditions as those used previously. The product (58%) had a molecular ion at 708 daltons by EI mass spectrometry consistant with the tetralactam **18** formed by a 2:2 reaction process (Scheme 4).

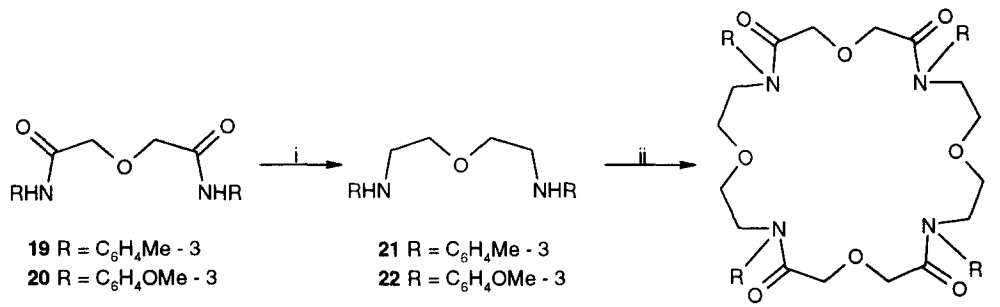


Scheme 4

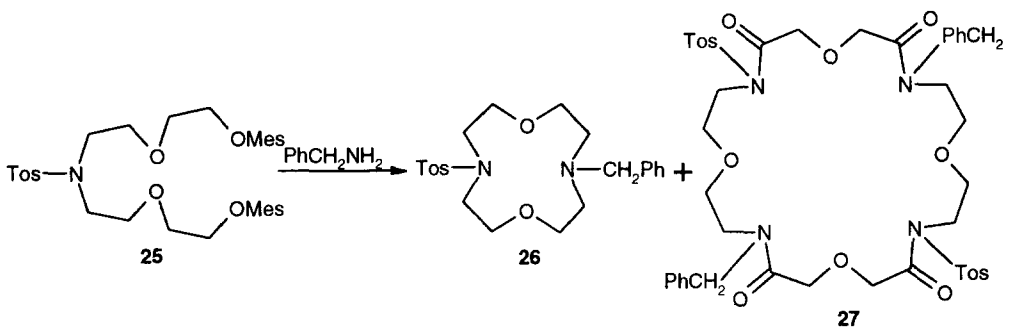
Reduction of amides **19** and **20** gave the diamines **21** and **22** which on reaction with diglycolyl chloride under high dilution conditions afforded the (2:2 reaction) products **23** and **24** (Scheme 5). In neither case was there evidence (TLC) of the presence of a 1:1 reaction product. Thus there appears to be a sharp discontinuity in the type of reaction between the diacid dichlorides and bis(2-[arylamino]ethyl)ether which lead to the 15-membered ring of **10** by a 1:1 process and the reactions which involve a 2:2 process yielding the 24-membered ring of **18**, **23** and **24**. To the best of our knowledge, the 2,6,14,18-tetraoxo-4,10,16,22-tetraoxa-1,7,13,19-tetraazacyclotetraeicosane ring system present in **18**, **23** and **24** has been reported only once and was then obtained by synthesis of an activated 1,17-dicarboxylic acid and its reaction with a 1,7-diamine.[10]

A derivative of the corresponding amine ring system has been reported twice as a minor product (5%)[5,11] in a reaction of the bis(methanesulfonate) **25** with benzylamine. The product of the reaction was mainly the 12-membered ring **26** (51%[6] and 60%[7]) (Scheme 6). The later paper[7] gives an alternative five step route to

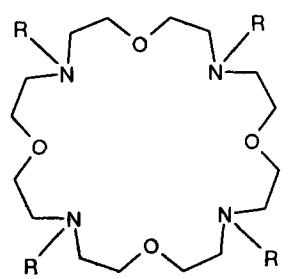
27 from **25** which provides a 45% yield in the final step. Also, a four step route to **28** from **25** is described and **27** is used as an intermediate in the preparation of the parent ring system **29** (Fig. 1). Few studies have been made of the properties of this ring system because of its inaccessibility.[5]



Scheme 5: Reagents: (i) $LiAlH_4$, THF; (ii) $(ClCOCH_2)_2O$, toluene, high dilution, r.t.



Scheme 6



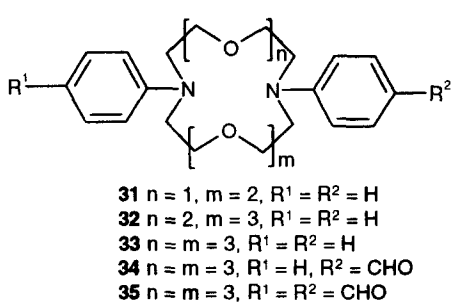


Figure 1

The new and efficient route to **18** provided the opportunity to prepare **30** by reduction of the amide function. The reduction of **11** by lithium aluminium hydride has been reported to proceed more smoothly than when diborane was used.[12] However, in our hands, borane in THF smoothly reduced **9**, **12** and **14** to the corresponding amines, **31**, **32** and **33**, respectively. Similar reduction of the tetralactam **18** gave **30**.

It seemed likely that the aromatic rings in the amines might be functionalised by use of the Vilsmeier-Haack reaction. The mono- and di-aldehydes, **34** and **35** were obtained from **33** in a controlled manner by use of slightly more than one and two molar equivalents of phosphorus oxychloride, respectively. More interestingly, the tetraaldehyde **36** was obtained by using an excess of phosphorus oxychloride in a Vilsmeier-Haack reaction of **30**. The dialdehyde **35** and tetraaldehyde **36** were condensed with the fluorophores, 5,8-dimethoxy- and 6,7-dimethoxy-1,3-dimethylquinoxalin-2-one[13] respectively to give the di- and tetra-olefin **37** and **38** (Fig. 2). The tetraaldehyde **36**, now relatively readily available, is a useful starting material for the preparation of derivatives of the 24-membered ring macrocyclic derivatives including those containing fluorophores.

The fluorescence of **37** was low (λ_{ex} 444 and λ_{em} 589 nm, ϕ_f 0.05) and showed little change on the addition of alkali metal or alkaline earth ions. Similar fluorescence properties were found for **38** (λ_{ex} 446 and λ_{em} 555, ϕ_f 0.04) but in the presence of Ba^{2+} and Ca^{2+} a marked decrease in λ_{em} was observed (λ_{ex} 446 and λ_{em} 514, ϕ_f 0.03). This shift in λ_{em} was not observed in the presence of Li^+, Na^+, K^+, Cs^+. A small shift (λ_{ex} 452 and λ_{em} 546, ϕ_f 0.04) was observed in the presence of Mg^{2+}.

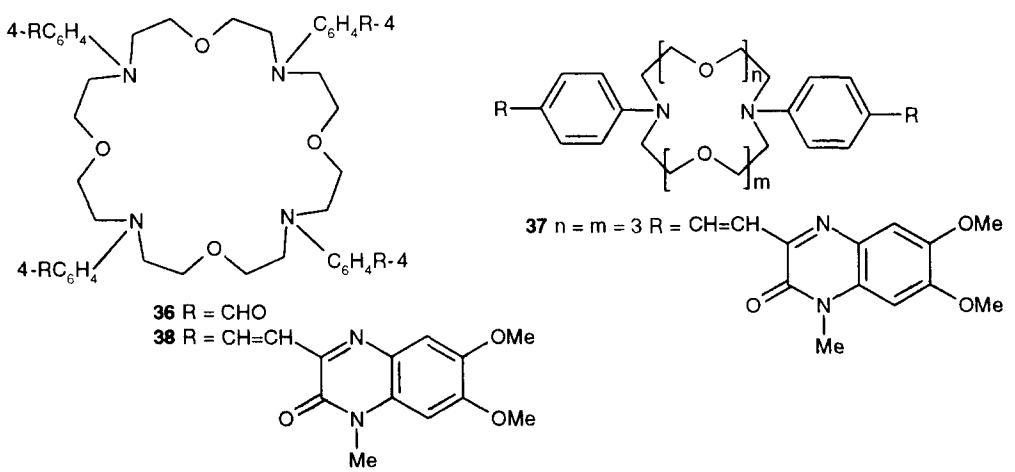


Figure 2

EXPERIMENTAL

The determination of m.p., IR, NMR, fluorescence and mass spectra were made using the instruments and procedures described[13] together with addition of a Bruker AM 360 MHz NMR instrument.

Diglycolyl dichloride, 3,6-dioxaoctanedioic acid (triglycolic acid) and 3,6,9-trioxadecandioic acid (tetraglycolic acid) were purchased from the Aldrich Chemical Company. Triglycolyl dichloride and tetraglycolyl dichloride were prepared from the corresponding dicarboxylic acids by literature methods.[14] Compounds **3**, **5**,[14] **7**, **8**[15] and **11**[12] were prepared by known routes.

General method for the preparation of the diamides 1, 2, 19 and 20

A mixture of the primary aromatic amine (107 mmol), triethylamine (214 mmol) and dry THF (150 ml) was added dropwise over 8 h to a stirred solution of the appropriate diacid dichloride (54 mmol) in dry THF (150 ml) at 0 °C under a nitrogen atmosphere. After the addition was complete, the mixture was allowed to warm up to room temperature and stirred overnight. The mixture was evaporated to dryness and the residue dissolved in dichloromethane, washed consecutively with dilute hydrochloric acid, dilute sodium hydroxide solution and water. The organic layer was dried (Na_2SO_4) and evaporated. The compounds were purified by crystallisation to give the white diamides. The physical data are reported in Tables 1 and 2.

General method for the preparation of the diamines 4, 6, 21 and 22 from the diamides

The diamide (7 mmol) was added portionwise to a slurry of lithium aluminium hydride (2.7 g, 71 mmol) in THF (100 ml) and the mixture was then refluxed for 6 h. After cooling the stirred mixture to 0 °C, dilute sodium hydroxide (5%) was added dropwise to deactivate the excess of hydride. The solid was filtered off and the filtrate evaporated *in vacuo* to remove THF. The residue was extracted with chloroform, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude diamine residue was dissolved in dichloromethane and extracted with dilute hydrochloric acid. The aqueous extract was basified with sodium hydroxide solution to pH 9. Extraction with dichloromethane, and evaporation of the solvent gave the colourless diamine which was purified and characterised (Tables 1 and 2).

General procedure for the preparation of the diamines 4 and 5 from the ditosylates 7 and 8, respectively

A mixture of the appropriate glycol ditosylate and freshly distilled amine (20 molar equivalents) under a nitrogen atmosphere was heated at 100 °C for 6 h. After cooling the mixture and the addition of diethyl ether, the solid was filtered off. The filtrate was distilled to remove the ether and aniline. The residue was dissolved in ethyl acetate, filtered through alumina, and the solvent evaporated to give the crude product, which was purified by column chromatography using ethyl acetate and chloroform (1:4) to give diamines identical to those obtained from the amides.

General method for the synthesis of diamides 9, 10, 12-14

A mixture of a secondary diamine (12 mmol), dry pyridine (49 mmol) and dry toluene (240 ml) and a solution of diacid dichloride (12 mmol) in dry toluene (320 ml) were added simultaneously and dropwise to stirred dry toluene (1 L) over 10 h at room temperature under a nitrogen atmosphere. After standing overnight, the solid was filtered off and the filtrate concentrated *in vacuo* to give the crude product. Purification of the product was achieved by chromatography and crystallisation to give the white diamides (Tables 3 and 4).

General method for the preparation of 1,7,13,19-tetraaryl-2,6,14,18-tetraoxo-4,10,16,22-tetraoxa-1,7,13,19-tetraazacyclotetraeicosanes, 18, 23 and 24

The appropriate 1,7-diaryl-4-oxa-1,7-diazaheptane and diglycolyl dichloride were used in the procedure described for the preparation of **9-14**. The physical data for **18**, **23** and **24** are reported in Tables 3 and 4.

General procedure for the reduction of the macrocyclic diamides 9, 12 and 14 and the tetraamide 18 to give the amines 31, 32, 33 and 30, respectively

To a stirred solution of the amide (8 mmol) in THF (50 ml) under an argon atmosphere at room temperature was added a solution (1 M) of borane-THF complex (40 ml, 40 mmol for the diamide and 60 ml, 60 mmol for the tetraamide). The reaction mixture was refluxed for 10 h. After cooling the mixture, water (100 ml) was added and the mixture evaporated to dryness. The residue was triturated with chloroform and the solid filtered off. The filtrate was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude amine. The amines were purified by column chromatography to give white solids.

1,7-Diphenyl-4,10,13-trioxa-1,7-diazacyclopentadecane (31): Yield: 44% (eluted with ethyl acetate : petroleum spirit (b.p. 60-80 °C), (7:3); m.p. 101-104 °C; IR (KBr): ν_{max} 3056, 2876, 1600, 1504, 1382 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21 (m, 4H, 2x3- and 2x5-ArH), 6.67 (m, 6H, 2x2-, 2x4- and 2x6-ArH), 3.67 (m, 20H, 10xCH_2); EIMS m/z: 370 (M^+, 30%), 177 (39), 150 (100), 119 (63). Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.26; H, 8.21; N, 7.55.

1,10-Diphenyl-4,7,13,16,19-pentaoxa-1,10-diazacyclouneicosane (32): Yield: 41% (eluted with ethyl acetate:methanol, 97:3); m.p. 93-95 °C; IR (KBr): ν_{max} 3026, 2868, 1598, 1504, 1354 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.20 (m, 4H, 2x3- and 2x5-ArH), 6.65 (m, 6H, 2x2-, 2x4- and 2x6-ArH), 3.65 (m, 28H, 14xCH_2); EIMS m/z: 459 (M^++H, 77%), 458 (M^+, 100%), 397 (72), 353 (63). Anal. Calcd for $C_{26}H_{38}N_2O_5$: C, 68.10; H, 8.35; N, 6.11. Found: C, 68.14; H, 8.32; N, 5.99.

1,13-Diphenyl-4,7,10,16,19,22-hexaoxa-1,3-diazacyclotetraeicosane (33): Yield: 50% (eluted with ethyl acetate:petroleum spirit (b.p. 60-80 °C), 4:6); m.p. 58-59 °C; IR (KBr): ν_{max} 2870, 1600, 1504, 1354, 1286 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.20 (m, 4H, 2x3- and 2x5-ArH), 6.68 (m, 6H, 2x2-, 2x4- and 2x6-

ArH), 3.63 (m, 32H, 16xCH_2); EIMS m/z: 503 (M^++H, 84%), 502 (M^+, 100%), 397 (70), 221 (68). Anal. Calcd for $C_{28}H_{42}N_2O_6$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.07; H, 8.55; N, 5.48.

1,7,13,19-Tetraphenyl-4,10,16,22-tetraoxa-1,7,13,19-tetraazacyclotetraeicosane (30): Yield: 63% (eluted with dichloromethane:ethyl acetate, 95:5); m.p. 105-107 °C; IR (KBr): ν_{max} 3020, 2950, 1615, 1520, 1405, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.19 (m, 8H, 4x3- and 4x5-ArH), 6.68 (m, 12H, 4x2-, 4x4- and 4x6-ArH), 3.58 (s, 32H, 8xNCH_2 and 8xOCH_2); EIMS m/z 652 (M^+, 10%), 163 (12), 134 (14), 83 (100). Found (FAB; NOBA): M^+ 652.3988; $C_{40}H_{52}N_4O_4$ requires 652.3982.

1-(4-Formylphenyl)-13-phenyl-4,7,10,16,19,22-hexaoxa-1,13-diazacyclotetraeicosane (34)

Redistilled phosphorus oxychloride (0.18 g, 1.2 mmol) was added dropwise to dry DMF (0.55 g, 7.5 mmol) at 0 to -5 °C and stirred for 15 min. A solution of **33** (0.5 g, 1 mmol) in DMF (25 ml) was added dropwise with stirring under a nitrogen atmosphere at 0 to -5 °C . The reaction mixture was then heated on a steam-bath for 4 h, cooled and poured onto ice (250 g). A saturated aqueous solution of sodium acetate was added dropwise to the vigorously stirred reaction mixture while the temperature was kept below 20 °C and until the pH was 7. The neutral reaction mixture was kept in the fridge overnight and the precipitate filtered off. The crude product was purified by chromatography (ethyl acetate:petroleum spirit, 8:2) and crystallised from a mixture of chloroform and petroleum spirit to afford the white solid of **34** (0.25 g, 47%), m.p. 156-158 °C; IR (KBr): ν_{max} 2866, 1664, 1596, 1558, 1506, 1398 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.72 (s, 1H, CHO), 7.71 (d, 2H, J = 8.5, 2xArH), 7.20 (m, 2H, 3xArH), 6.70 (m, 5H, 5xArH), 3.66 (m, 32H, 16xCH_2); EIMS m/z: 530 (M^+, 100%), 425 (24), 149 (31). Found (FAB; NOBA): M^+ 530.2990; $C_{29}H_{42}N_2O_7$ requires 530.2989; Anal. Calcd for $C_{29}H_{42}N_2O_7$: C, 65.64; H, 7.98; N, 5.28. Found: C, 65.15; H, 8.41; N, 4.84.

1,13-Bis(4-formylphenyl)-4,7,10,16,19,22-hexaoxa-1,13-diazacyclotetraeicosane (35)

Redistilled phosphorus oxychloride (0.36 g, 2.4 mmol) was added dropwise to dry DMF (1.1 g, 12 mmol) a 0 to -5°C and stirred for 15 min. A solution of **33** (0.5 g, 1 mmol) in DMF (25 ml) was added dropwise with stirring under a nitrogen atmosphere at 0 to -5 °C. The procedure was then as described above for **34** and chromatography using ethyl acetate:petroleum spirit, 95:5, gave the pale yellow solid of **35** (0.23 g, 41%), m.p. 95-96 °C; IR (KBr): ν_{max} 2868, 1668 1596, 1554, 1438, 1400, 1354 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.73 (s, 2H, 2xCHO), 7.71 (s, 4H, J = 8.5, 2x3- and 2x5-ArH), 6.73 (d, 4H, J = 8.5, 2x2- and 2x6-ArH), 3.70 (s, 24H, 12xOCH_2), 3.62 (s, 8H, 4xNCH_2); EIMS m/z: 558 (M^+, 16%), 83 (100). Anal. Calcd for $C_{28}H_{38}N_2O_7$: C, 65.35; H, 7.44; N, 5.39. Found: C, 65.33; H, 7.47; N, 5.39.

1,7,13,19-Tetrakis(4-formylphenyl)-4,10,16,22-tetraoxa-1,7,13,19-tetraazacyclotetraeicosane (36)

Redistilled phosphorus oxychloride (0.72 g, 4.8 mmol) and dry DMF (2.20 g, 30 mmol) and **30** (0.65 g, 1 mmol) in DMF (25 ml) were used in the procedure as described above for the preparation of **34**. The crude product was purified by column chromatography (ethyl acetate) to give the white solid of **36** (0.24 g, 32%), m.p. 177-180 °C; IR (KBr): ν_{max} 2380, 1654 1592, 1532, 1522, 1348 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.73 (s, 4H, 4xCHO), 7.70 (d, 8H, *J* = 8.5, 4x3- and 4x5-ArH), 6.68 (d, 8H, *J* = 8.5, 4x2- and 4x6-ArH), 3.65 (t, 32H, *J* = 3.7, 8xOCH_2 and 8xNCH_2). Anal. Calcd for $C_{44}H_{52}N_4O_8$: C, 67.50; H, 6.95; N, 7.16. Found: C, 67.26; H, 6.78; N, 7.07.

1,13-Bis(4-[2-{5,8-dimethoxy-1-methyl-2(1*H*)-quinoxalinon-yl}ethenyl]phenyl)-4,7,10,16,19,22-hexaoxa-1,13-diazacyclotetraeicosane (37)

A mixture of 1,13-bis(4-formylphenyl)-4,7,10,16,19,22-hexaoxa-1,13-diazacyclotetraeicosane (**35**) (0.28 g, 0.5 mmol), 5,8-dimethoxy-1,3-dimethyl-2(1*H*)-quinoxalinone[13] (0.23 g, 1 mmol), glacial acetic acid (0.8 ml), piperidine (1 ml) and toluene (35 ml) was refluxed in a flask fitted with a Dean and Stark apparatus for 24 h. The solvent was evaporated *in vacuo*, the residue purified by column chromatography (ethyl acetate) and crystallised from a mixture of methanol and dichloromethane to give **37** as an orange solid (0.23 g, 46%), m.p. 173-175 °C; IR (KBr): ν_{max} 2896, 1650 1600, 1518, 1492, 1430, 1392 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, 2H, *J* = 16.1, 2xCH), 7.55 (d, 4H, *H* = 9.3, 4xArH), 7.51 (d, 2H, *J* = 16.1, 2xCH), 6.93 (d, 2H, *J* = 9.3, 2xArH), 6.69 (d, 4H, *J* = 8.8, 4xArH), 6.68 (d, 2H, *J* = 8.8, 2xArH), 4.0 (s, 12H, 4xOCH_3), 3.86 (s, 6H, 2xNCH_3), 3.63 (m, 32H, 4xNCH_2 and 12xOCH_2). Anal. Calcd for $C_{54}H_{66}N_6O_{12}$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.38; H, 6.91; N, 8.16.

1,7,13,19-Tetrakis(4-[2-{6,7-dimethoxy-1-methyl-2(1*H*)-quinoxalinon-3-yl}ethenyl]phenyl)-4,10,16,22-tetraoxa-1,7,13,19-tetraazacyclotetraeicosane (38)

A mixture of the tetraaldehyde **36** (0.38 g, 0.5 mmol), 6,7-dimethoxy-1,3-dimethyl-2(1*H*)-quinoxalinone[13] (0.47 g, 2 mmol), dry toluene (35 ml), glacial acetic acid (0.8 ml) and piperdine (1 ml) was refluxed in a Dean and Stark apparatus for 24 h. After cooling, the mixture was evaporated *in vacuo*, the residue purified by preparative TLA (ethyl acetate) and crystallised form a mixture of methanol and dichloromethane to give **38** as an orange solid (0.38 g, 47%), m.p. 191 °C (decomp.); IR (KBr): ν_{max} 2862, 1642, 1598, 1518, 1462, 1386 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.93 (d, 4H, *J* = 15.6, 4xCH), 7.48 (m, 12 H, 4xCH and 8-ArH), 6.63 (m, 16H, 16xArH), 3.98 (s, 12H, 4xOCH_3), 3.97 (s, 12H, 4xOCH_3), 3.71 (s, 12H, 4xNCH_3), 3.53 (m, 32H, 8xNCH_2 and 8xOCH_2). Found (FAB, NOBA): M^++H 1629.7411; $C_{92}H_{101}N_{12}O_{16}$ required 1629.7452.

Table 1 Physical Constants of **1**, **2**, **4**, **6**, **19-22**

Compd.	Yield (%)	m.p. (°C)	Molecular Formula	Elemental Analysis (%)/ Accurate Mass Found (Required)		
				C	H	N
1	33[a,b]	153-155	$C_{16}H_{16}N_2O_3$	67.58 (67.59)	5.61 (5.67)	9.86 (9.85)
2	28[b,c]	127-130	$C_{18}H_{20}N_2O_4.H_2O$	62.58 (62.40)	5.91 (5.82)	8.35 (8.09)
4	78[d]	168-169	$C_{16}H_{20}N_2O$	74.89 (74.97)	7.80 (7.86)	10.81 (10.93)
6	67[e]	155-157	$C_{20}H_{28}N_2O_3$	69.46 (69.74)	7.80 (7.86)	10.81 (10.93)
19	52[a,b]	160-162	$C_{18}H_{20}N_2O_3$	69.09 (69.20)	6.48 (6.47)	8.93 (8.97)
20	63[a,b]	132-134	$C_{18}H_{20}N_2O_5$	62.64 (62.77)	5.86 (5.87)	8.08 (8.14)
21	28	oil	$C_{18}H_{22}N_2O_4$	284.1887[f] (284.1889)		
22	56	oil	$C_{18}H_{24}N_2O_3$	316.1784[f] (316.1787)		

[a] Obtained from diglycolyl dichloride, [b]Crystallised from aqueous methanol, [c]Obtained from triglycolyl dichloride, [d]Purified by column chromatography (chloroform), [e]After column chromatography (ethyl acetate:petroleum spirit, 2:3), [f]Accurate mass by EI

Table 2: Spectral data of **1**, **2**, **4**, **6**, **19-22**

Compd.	IR ν_{max}/cm^{-1}	EI-Mass Spectral data m/z (%)	^{1}H-NMR δ from TMS, *J* (Hz)
1	3310, 2950, 1690, 1575, 1460	284 (M^+, 31), 259 (22), 241 (30), 147 (36), 129 (100)	9.98 (brs, 2H, 2xNH), 7.66 (m, 4H, 2x2- and 2x6-ArH), 7.33 (m, 4H, 2x3- and 2x5-ArH), 7.08 (m, 2H, 2x4-ArH), 4.27 (s, 4H, 2xOCH_2)
2	3328, 2913, 1680, 1580, 1455	328 (M^+, 65), 193 (50), 120 (100)	8.70 (brs, 2H, 2xNH), 7.66 (m, 4H, 2x2- and 2x6-ArH), 7.45 (m, 4H, 2x3- and 2x5-ArH), 7.28 (m, 2H, 2x4-ArH), 4.11 (s, 4H, 2xOCH_2)
4	3420, 1620, 1520, 1335, 1200	256 (M^+, 84), 137 (61), 119 (54), 106 (100)	7.18 (m, 4H, 2x2- and 2x6-ArH), 6.67 (m, 6H, 2x3-, 2x4- and 2x5-ArH), 3.82 (m, 2H, 2xNH), 3.75 (t, 4H, *J* = 5.2, 2xOCH_2), 3.29 (t, 4H, *J* = 5.2, NCH_2)
6	3385, 1603, 1506, 1460, 1322, 1102	344 (M^+, 32), 225 (91), 137 (26), 106 (100)	7.17 (m, 4H, 2x2- and 2x6-ArH), 6.66 (m, 6H, 2x3-, 2x4- and 2x5-ArH), 4.10 (brs, 2H, 2xNH), 3.68 (m, 12H, 6xOCH_2), 3.28 (t, 4H, *J* = 5.3, 2xNCH_2)
19	3302, 1672, 1591, 1437, 1307	312 (M^+, 93), 178 (21), 107 (100)	8.19 (brs, 2H, 2xNH), 7.43 (2H, s, 2x2-ArH), 7.38 (d, 2H, *J* = 8.2, 2x6-ArH), 7.24 (t, 2H, *J*= 7.1, 2x5-ArH), 6.99 (d, 2H, *J* = 7.5, 2x4-ArH), 4.26 (s, 4H, 2xOCH_2), 2.36 (s, 6H, 2xCH_3)
20	3302, 1684, 1604, 1523, 1437, 1276	344 (M^+, 93), 123 (100)	8.43 (brs, 2H, 2xNH), 7.32 (s, 2H, 2x2-ArH), 7.23 (t, 2H, *J* = 8.2, 2x5-ArH), 7.06 (d, 2H, *J* = 7.8, 2x6-ArH), 6.70 (d, 2H, *J* = 8.3, 2x4-ArH), 4.20 (s, 4H, 2xOCH_2), 3.79 (s, 6H, 2xOCH_3)
21	3394, 1616, 1600, 1470, 1227	284 (M^+, 29), 120 (100)	7.07 (t, 2H, *J* = 8.1, 2x5-ArH), 6.55 (d, 2H, *J* = 8.1, 2x4-ArH), 6.44 (m, 2H, 2x2- and 2x6-ArH), 3.68 (t, 4H, *J* = 5.2, 2xOCH_2), 3.30 (t, 2H, *J* = 5.2, 2xNCH_2), 2.27 (6H, s, 2xCH_3)
22	3407, 1622, 1612, 1502, 1217	316 (M^+, 47), 136 (100)	7.08 (t, 2H, *J* = 8.1, 2x5-ArH), 6.26 (m, 4H, 2x4- and 2x6-ArH), 6.18 (m, 2H, 2x2-ArH), 4.02 (brs, 2H, 2xNH), 3.75 (s, 6H, 2xOCH_3), 3.68 (t, 4H, *J* = 5.1, 2xOCH_2), 3.30 (t, 4H, *J* = 5.1, 2xNCH_2)

[a]200 MHz, [b]$(CD_3)_2SO$, [c]$CDCl_3$, [d]360 MHz

Table 3: Physical constants of **9**, **10**, **12-14**, **18**, **23**, **24**

Compd.	Yield (%)	m.p. (°C)	Molecular Formula	Elemental Analysis (%)/ Accurate Mass Found (Required)		
				C	H	N
9	33[a]	216-218	$C_{16}H_{16}N_2O_3$	66.08 (66.32)	6.59 (6.58)	7.02 (7.03)
10	48[b]	211-213	$C_{18}H_{20}N_2O_4.H_2O$	66.52 (66.32)	6.68 (6.58)	6.90 (7.03)
12	67[b]	113-115	$C_{16}H_{20}N_2O$	64.62 (64.18)	7.27 (7.04)	5.64 (5.76)
13	71[c]	99-100	$C_{20}H_{28}N_2O_3$	64.31 (64.18)	7.42 (7.04)	5.39 (5.76)
14	54[c]	115-117	$C_{18}H_{20}N_2O_3$	63.28 (63.38)	7.26 (7.22)	5.23 (5.28)
18	58[a]	207-209	$C_{18}H_{20}N_2O_5$	67.83 (67.78)	6.45 (6.26)	7.64 (7.90)
				[d]M^++H 709.3237 (709.3251)		
23	50[a]	193-194	$C_{18}H_{22}N_2O_4$	68.74 (69.10)	6.91 (6.80)	7.04 (7.33)
				[d]M^++H 765.3925 (765.3863)		
24	55[a]	186-187	$C_{44}H_{52}N_4O_{12}$	63.33 (63.77)	6.36 (6.28)	6.54 (6.76)
				[d]M^++H 829.3651 (829.3659)		

[a]From ethyl acetate, [b] From a mixture of ethyl acetate and petroleum spirit, [c]Purified by column chromatography (ethyl acetate:methanol, 97:3), [d]Accurate mass by FAB

Table 4: Spectral data of **9**, **10**, **12-14**, **18**, **23**, **24**

Compd.	IR ν_{max}/cm^{-1}	EI-Mass Spectral data m/z (%)	^{1}H-NMR δ from TMS, *J* (Hz)
9	3060, 2930, 1690, 1670, 1605, 1505	398 (M^+, 81), 354 (28), 341 (70), 252 (42), 177 (49)	7.42 (m, 10H, 10xArH), 4.03 (s, 4H, 2x$COCH_2O$), 3.97 (s, 4H, 2xOCH_2), 3.63 (s, 4H, CH_2OCH_2), 3.53 (t, 4H, 2xNCH_2)
10	3316, 2894, 1678, 1592, 1492	398 (M^+, 72), 342 (63), 280 (54), 177 (65), 119 (100)	7.43 (m, 10H, 10xArH), 4.10 (s, 4H, 2x$COCH_2O$), 3.66 (s, 8H, 4xOCH_2), 3.51 (s, 4H, 2xNCH_2)
12	3056, 2874, 1660, 1592, 1494	486 (M^+, 26), 368 (21), 266 (35), 83 (100)	7.43 (m, 10H, 10xArH), 4.04 (m, 8H, 2x$COCH_2O$ and OCH_2CH_2O), 3.65 (m, 16H, 6xOCH_2 and 2xNCH_2)
13	3052, 2920, 1662, 1592, 1492	486 (M^+, 82), 368 (93), 340 (51), 310 (99), 222 (69), 83 (100)	7.39 (m, 10H, 10xArH), 3.90 (m, 8H, 2xOCH_2O and OCH_2CH_2O), 3.63 (m, 16H, 6xOCH_2 and 2xNCH_2)
14	3058, 2916, 1650, 1594, 1492	530 (M^+, 100), 486 (34), 412 (32), 310 (62), 178 (30), 106 (39)	7.37 (m, 10H, 10xArH), 3.90 (s, 4H, 2x$COCH_2O$), 3.88 (s, 4H, 2xOCH_2), 3.62 (s, 16H, 8xOCH_2), 3.58 (s, 4H, 2xNCH_2)
18	2975, 1675, 1650, 1600, 1495	708 (M^+, 16), 690 (35), 652 (41), 590 (100)	7.34 (m, 20H, 20xArH), 3.92 (s, 8H, 4x$COCH_2O$), 3.75 (t, 8H, *J* = 5.1, 4xOCH_2), 3.37 (t, 8H, *J* = 5.1, 4xNCH_2)
23	3067, 2919, 1672, 1630, 1495	765 (M^++H, 100), 737 (10), 707 (5)	7.15 (m, 16H, 16xArH), 3.95 (s, 8H, 4xOCH_2CO), 3.82 (s, 8H, 4xOCH_2), 3.47 (s, 8H, 4xNCH_2), 2.32 (s, 12H, 4xCH_3)
24	3067, 2937, 1696, 1597, 1493	829 (M^++H, 100), 801 (10), 771 (7), 680 (5)	7.26 (m, 4H, 4xArH), 6.85 (m, 12H, 12xArH), 3.99 (s, 8H, 4x$COCH_2O$), 3.80 (m, 20H, 4xOCH_2 and 4xOCH_3), 3.47 (s, 8H, 4xNCH_2)

[a]200 MHz, [b]$CDCl_3$, [c]$(CD_3)_2SO$, [d]360 MHz

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