86. Metal Complexes with Macrocyclic Ligands, XVII[1]). Synthesis of Two Key Intermediates for the Preparation of Mono-*N*-functionalized Tetraazamacrocycles and Their Metal Complexes

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Summary

With a modification of the cyclization procedure of *Richman & Atkins* [8] the two macrocycles 1,4,7-tritosyl-11-benzyl-1,4,7,11-tetraazacyclotetradecane (**8**) and 1,7,11-tritosyl-4-trityl-1,4,7,11-tetraazacyclotetradecane (**15**) were prepared. After selective cleavage of the benzyl and trityl group, respectively, one obtains the two key products 1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane (**9**) and 1,7,11-tritosyl-1,4,7,11-tetraazacyclotetradecane (**16**) which have three N-atoms protected by tosyl groups and one accessible for further reactions.

To test some of the possibilities we have alkylated **9** and **16** with iodoacetamide, 1-tosyl-aziridine and acrylonitrile. After detosylation with HBr in glacial acetic acid in the presence of phenol mono-*N*-functionalized tetraazamacrocycles were thus obtained. The advantage of this synthesis is that the cyclization which is the most difficult step of the whole procedure, has to be done only once, regardless of the nature of the pendant arm. In addition a large number of derivatives can be prepared by varying the alkylation component.

With Ni^{2+}, Cu^{2+} and Zn^{2+} metal complexes of these new ligands were prepared and their IR. and VIS. spectra studied. In the case of the carbamoyl derivatives **12**, **14** and **18** the Cu^{2+}-complexes exist in two forms. Whereas at low pH the carboxamide group of the pendant arm is probably not bound to the metal ion, at high pH after deprotonation it coordinates in one of the axial positions.

In contrast to open-chain ligands tetraazamacrocycles often form kinetically stable complexes even with metal ions which give tipically labile complexes [2]. This allows to study these metal complexes in strongly acidic or alkaline solutions. Moreover it is often also possible to assume that the coordination geometry and stoichiometry remains the same in the solid state and in solution. Thus one can study and correlate structures and reactivities in a simple way, similarly to what has been done for the kinetically stable Cr(III) and Co(III) complexes.

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We wish to study the influence of axial ligands on the properties of the coordinated metal ion and the effect of the metal ion on the reactivity of an organic group which is either coordinated or at least very close to the metal ion. For both aspects of this research functionalized tetraazamacrocycles seem ideal to us since the macrocycle occupies four coordination sites of the metal ion leaving the other two positions open for further binding in an octahedral geometry.

Persubstituted tetraazamacrocycles have previously been described [3] but their coordination properties are relatively complicated [4]. In the case of the tetraacetates there are eight potential coordinating groups, the four amino N-atoms of the macrocycle and the four carboxylate groups of the side chains so that several structures are possible. Monofunctionalized derivatives are more appropriate for our purpose, but a synthetic route had to be devised for their preparation. Of the different synthesis of macrocycles, such as template reactions [5], cyclization at high dilution [6], zip reaction [7] we have chosen and modified the cyclization procedure of *Richman & Atkins* [8] in such a way that selectively protected products can be prepared.

Experimental Part

General remarks. Melting points obtained on a *Büchi* apparatus are uncorrected. IR.-spectra were run in KBr pills on a *Perkin-Elmer 157G* or on a *Beckman 4240* spectrophotometer. ^{1}H-NMR. spectra were obtained on a *Varian EM 360* or on a *Brucker WH 90 FT* instrument using TMS as internal standard. MS. and elemental analysis were performed by the analytical laboratory of *Ciba-Geigy AG*, Basel. Thin layer chromatography (TLC.) was run on *Merck* silica gel sheets (*60 F 254*, 0.25 mm).

Preparation of N,N-*Bis(2-cyanoethyl)benzylamine* (**1**) [9], N,N-*bis(3-aminopropyl)benzylamine* (**2**) [10], N,N-*bis(3-tosylaminopropyl)benzylamine hydrochloride* (**3**) [11], N,O,O'-*tritosyldiethanolamine* (**4**) [12], *dipropylenetritosylamide* (**5**) [13], N-*trityl-diethanolamine* (**6**) [14] and N-*trityl*-O,O'-*dimesyldiethanolamine* (**7**) [14] follows the literature and their purity was checked by m.p., IR.- and/or NMR.-spectra.

Preparation of 11-benzyl-1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane (**8**). To 84.9 g (150 mmol) of **3** dissolved in 1.5 l abs. DMF 23.6 g (540 mmol) of NaH (55% oil dispersion) were added under Ar and the solution was heated to 50° so that a controlled H_2-evolution took place. The temp. was then increased to 110° in about 1 h until the H_2-evolution practically stopped. During 45 min a solution of 102.2 g (180 mmol) of **4** in 200 ml of DMF was added under stirring. The mixture was then cooled to r.t. and evaporated in a RV. to give a thick oily residue which was taken up with 500 ml of H_2O. The aqueous suspension was extracted three times with 250 ml of CH_2Cl_2, the org. phase was dried over Na_2SO_4, filtered and evaporated, whereby the last traces of solvent (also some DMF) were taken off at 1 Torr. The residue was then dissolved in 45 ml of CH_2Cl_2 to which 150 ml of CH_3OH were slowly added at 40°. After several hours at r.t. 63.0 g of **8** were obtained. These were recrystallized from 80 ml of CH_2Cl_2 and 200 ml of CH_3OH to give 56 g (50%) of white crystals of **8**, m.p. 162–163.5°. TLC. ($CHCl_3$/AcOEt 1:1) Rf 0.55. – IR. (KBr): 2930 (CH), 1598 and 1495 (arom.), 1340 and 1185 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 1.7 (*qi*, 4 H, 2 C–CH_2C); 2.45 (*s*, 9 H, 3 CH_3Ar); 2.45 (*m*, 4 H, 2 N–CH_2); 3.3 (*m*, 12 H, 6 SO_2N–CH_2); 3.5 (*s*, 2 H, ArCH_2–N); 7.5 (*m*, 17 H, 17 arom. H).

$C_{38}H_{48}N_4O_6S_3$	Calc.	C 60.61	H 6.43	N 7.44	N 12.77%
(753.01)	Found	„ 60.66	„ 6.49	„ 7.40	„ 12.73%

Preparation of 1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane (**9**). In a hydrogenation flask 37.7 g (50 mmol) of **8** were dissolved in 400 ml of glacial acetic acid and after purging with N_2 2.5 g of Pd/C (10%) suspended in 100 ml of glacial acetic acid were added. The hydrogenation was carried out at 20°/760 Torr. After three days 1.3 l (58 mmol) of H_2 were taken up and a TLC.($CHCl_3$/AcOEt/CH_3OH 7:7:2, Rf 0.85 for **8** and 0.25 for **9**) showed no starting material any more. The catalyst was filtered off over *Celite* and washed with 50 ml of glacial acetic acid. The solution was then rotatory evaporated.

The white residue was dissolved in 250 ml of $CHCl_3$ which were extracted with 140 ml of 1N NaOH and 100 ml of water. The $CHCl_3$ phase was dried, filtered and concentrated to about 150 ml. Then 120 ml of ether and 20 ml of CH_3OH were added. After standing at r.t. 31.4 g (95%) white crystals of **9** were obtained, m.p. 179–181°. – IR. (KBr): 3005 (NH), 2950 (CH), 1600 and 1495 (arom.), 1345 and 1160 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 1.0 (*s*, 1 H, NH); 1.65 (*qi*, 4 H, 2 C–CH_2–C); 2.6 (*t*, 4 H, 2 N–CH_2); 2.4 (*s*, 9 H, 3 CH_3Ar); 3.25 (*m*, 12 H, 6 SO_2N–CH_2); 7.5 (*m*, 12 H, 12 arom. H).

$C_{31}H_{42}N_4O_6S_3$ (662.88) Calc. C 56.17 H 6.39 N 8.45% Found C 55.79 H 6.45 N 8.48%

Preparation of 1,4,7,11-tetraazacyclotetradecane (**10**). The hydrolysis of 232 mg (0.35 mmol) of **9** in 1.25 ml conc. sulfuric acid was performed for 3 days at 100°. After cooling 3 ml abs. ether were added and over night a precipitate was formed at 0°. The brownish product was filtered off, dissolved in 0.2 ml of water and 0.9 ml of 5N NaOH and evaporated to dryness. The residue was extracted with four portions of 5 ml $CHCl_3$. The organic phase was dried and evaporated. The oil was taken up with 5 ml of ether, from which at 0° white hygroscopic needles formed. Recrystallization from ether afforded 23 mg of the pure product **10**, m.p. 84–88° ([15]: 75–77°). – IR. (KBr): 3210 (NH), 2920 and 2830 (CH). – ^{1}H-NMR. ($CDCl_3$): 1.7 (*qi*, 4 H, 2 C–CH_2–C); 2.0 (*s*, 4 H, 4 NH); 2.7 (*m*, 16 H, 8 C–CH_2–N).

$C_{10}H_{24}N_4$ (200.33) Calc. C 59.95 H 12.08 N 27.97% Found C 59.65 H 12.00 N 27.70%

Preparation of 11-carbamoylmethyl-1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane (**11**). In a reaction flask 33.1 g (50 mmol) of **9**, 8 g (43 mmol) of iodoacetamide and 10 ml of NEt_3 were dissolved in 380 ml of DMF and the solution was heated for 4 h at 90°. Then an additional 4.9 g (27 mmol) of iodoacetamide and 6.9 ml of NEt_3 were added and the mixture was heated for another 12 h at 90°. The DMF was rotatory evaporated and the residue was taken up with 300 ml of $CHCl_3$, extracted once with 200 ml of 1N NaOH and twice with 100 ml of water. The organic phase was dried over Na_2SO_4, treated with a slurry of silica gel, to which a brown product sticked, and concentrated to about 100 ml. After addition of 50 ml of ether the solution left at r.t. over night afforded yellow crystals of **11**. Recrystallization from 2-propanol yields 37 g (88%), m.p. 209–211°. – IR. (KBr): 3460, 3330 (NH), 2930 (CH), 1680 ($CONH_2$), 1600, 1490 (arom.), 1340, 1160 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 1.7 (*qi*, 4 H, 2 C–CH_2–C); 2.45 (*s*, 9 H, 3 ArCH_3); 2.5 (*m*, 4 H, 2 N–CH_2); 3.2 (*m*, 14 H, 6 SO_2N–CH_2 and CH_2CONH_2); 6.8 (*s*, 2 H, $CONH_2$); 7.45 (*m*, 12 H, arom. H).

$C_{33}H_{45}N_5O_7S_3$	Calc.	C 55.06	H 6.30	N 9.73	S 13.36%
(719.93)	Found	„ 54.89	„ 6.52	„ 9.61	„ 13.40%

Preparation of 11-carbamoylmethyl-1,4,7,11-tetraazacyclotetradecane (**12**). To 30.1 g (320 mmol) of phenol in 125 ml 40% HBr/glacial acetic acid 33.5 g (40 mmol) of **11** were added and the solution stirred for 0.5 h at r.t. Then the temp. was increased to 65° for 24 h, whereby after 10 h an additional 50 ml 40% HBr/glacial acetic acid was added. After cooling to r.t. and addition of 350 ml ether the suspension was stirred for 1 h at 0°. The yellow tetrahydrobromide was filtered off and washed with 30 ml of ether. To remove phenol the solid was dissolved in 100 ml of water and the solution was extracted with 3 × 40 ml of ether. The aqueous layer was then cooled to 0°, made alkaline with 5 ml of 6N NaOH and 85 ml of 60% K_2CO_3-solution and extracted with 3 × 180 ml of $CHCl_3$. The $CHCl_3$ phase was dried and concentrated to about 50 ml. Addition of 150 ml of ether gave at 0° a crop of yellow crystals, which were recrystallized from 100 ml of CH_2Cl_2/ether 7:3. Yield 6.95 g (68%), m.p. 167–170°, TLC. ($CHCl_3$/CH_3OH 4:1) Rf 0.5. – IR. (KBr): 3330, 3270 (NH), 2920, 2820 (CH), 1670 ($CONH_2$). – ^{1}H-NMR. ($CDCl_3$): 1.8 (*qi*, 4 H, 2 C–CH_2–C); 2.7 (*m*, 16 H, 8 N–CH_2–); 3.05 (*s*, 2 H, CH_2–$CONH_2$). – MS.: 258 ($[M+1]^+$), 257 (M^+).

$C_{12}H_{27}N_5O$ (257.38) Calc. C 56.00 H 10.57 N 27.21% Found C 56.00 H 10.30 N 26.80%

Alternative procedure. In a reaction flask with a 1-cm-thick mercury cathode and a graphite anode protected through a ceramic diaphragm filled with 0.1N HCl, 671 mg (0.8 mmol) of **11** were suspended in 30 ml CH_3OH with 2.5 g $(CH_3)_4NCl$ as electrolyte. The electrolysis took place at 0–5° with 24 V and 0.9 A, whereby the insoluble starting compound slowly went into solution. Because of the pulses of the mercury surface a stirrer was not necessary as long as the distance between the two electrodes was 6 mm. The methanolic solution was evaporated, the residue taken up with 25 ml of 30% K_2CO_3-solution and the aqueous layer was extracted with 3 × 8 ml of $CHCl_3$. The organic phase was dried, evaporated

and the residue dissolved in 8 ml of CH_2Cl_2 and 3.5 ml of ether. Over night 105 mg (51%) of **12** were obtained. M.p., Rf-value and IR.-spectrum were identical to those given above.

Preparation of 11-(2-cyanoethyl)-1,4,7-tritosyl-1,4,7,11-tetraazacyclotetradecane (**13**) In 125 ml freshly distilled acrylonitrile 43.75 g (66 mmol) of **9** were suspended, heated and stirred at 70° for 3 days under N_2. The mixture was then rotatory evaporated and the residue taken up with 120 ml of CH_2Cl_2. Addition of 100 ml of ether afforded 40.6 g (86%) white crystals of **13**, m.p. 156–159°. – IR. (KBr): 2930 (CH), 2250*w* (CN), 1600 and 1495 (arom.), 1345 and 1160 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 1.7 (*qi*, 4 H, 2 C–CH_2–C); 2.45 (*s*, 9 H, 3 CH_3Ar); 2.5 (*m*, 8 H, 3 CH_2–N and CH_2CN); 3.3 (*m*, 12 H, 6 CH_2SO_2); 7.5 (*m*, 12 H, arom. H).

$C_{34}H_{15}N_5O_6S_3$ (715.94) Calc. C 57.04 H 6.34 N 9.78% Found C 56.96 H 6.46 N 9.59%

Preparation of 11-(2-carbamoylethyl)-1,4,7,11-tetraazacyclotetradecane (**14**). In 63 ml of 40% HBr/glacial acetic acid 10.7 g (15 mmol) of **13** and 8.5 g (90 mmol) of phenol were dissolved and heated to about 60° for 20 h. After cooling to r.t. 110 ml of ether was added. The mixture was kept at 0° for about 1 h, then the crystals were filtered off and washed with 40 ml of ether. The crude product contained beside **14** about 20% of partially tosylated derivatives. The raw product was dissolved in 35 ml of ice/water and extracted twice with 30 ml of ether. The water phase was then mixed with 35 ml of CH_3OH. At 0° over night a first fraction (1.4 g) of the partially tosylated product was obtained. To the filtrate 30 ml of EtOH and 40 ml of ether were added, whereby at 0° a second fraction of 5.9 g (66%) light yellow crystals of **14** was obtained. The hydrochloride was prepared by dissolving the product in 60 ml of 2N NaOH, which were extracted three times with 40 ml of $CHCl_3$. Then 39 g of K_2CO_3 were added to the aqueous phase and the saturated solution was extracted with 4×20 ml of $CHCl_3$. From it 2 g of a chromatographic pure oil were obtained and by addition of ethanolic HCl-solution the hydrochloride was prepared as usually. Dec. 237°. TLC. (conc. NH_3-solution/CH_3OH 2:7) Rf 0.4. – IR. (KBr): 3400 (NH), 2930 and 2800 (CH), 2700 (NH^+), 1670 ($CONH_2$). – MS. of the free base: 272 ($[M+1]^+$), 271 (M^+).

$C_{13}H_{33}Cl_4N_5O \cdot 1.25\,H_2O$ (417.25) Calc. C 34.82 H 5.90 N 10.15% Found C 34.63 H 6.03 N 10.38%

Preparation of 4-trityl-1,7,11-tritosyl-1,4,7,11-tetraazacyclotetradecane (**15**). To 44 g (69 mmol) of disodium salt of **5** [13] in 550 ml of abs. DMF a solution of 34.8 g (69 mmol) of **7** in 210 ml of DMF was added during 3.5 h at 100°. After cooling to 60° the mixture was diluted with 250 ml of water and the supernatant liquid was decanted. The solid was dissolved in 150 ml of CH_2Cl_2 to which 150 ml of benzene and 150 ml of EtOH were added. Cooling to 0° afforded a first crop of crystals. From the decanted solution more product could be isolated by adding 300 ml water and extracting three times with 250 ml of CH_2Cl_2. After drying over Na_2SO_4 the CH_2Cl_2-phase was concentrated to about 100 ml. By addition of 250 ml of benzene a further crop was obtained at 0°. Crystallization from 100 ml of CH_2Cl_2 and 150 ml of ether gave 25.2 g (40%) of **15**, m.p. 170°–180° (dec.). – IR. (KBr): 2950 (CH), 1600 and 1495 (Arom.), 1345 and 1160 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 2.0 (*m*, 8 H, 2 CH_2–N-trityl and 2 C–CH_2–C); 2.4 (*s*, 9 H, 3 CH_3Ar); 3.2 (*m*, 12 H, 6 SO_2N–CH_2); 7.25 (*m*, 27 H, arom. H).

$C_{50}H_{56}N_4O_6S_3$	Calc.	C 66.34	H 6.24	N 6.19	S 10.67%
(905.20)	Found	„ 66.44	„ 6.19	„ 5.96	„ 10.37%

Preparation of 1,7,11-tritosyl-1,4,7,11-tetraazacyclotetradecane (**16**). To cleave the trityl group 13.6 g (15 mmol) of **15** dissolved in 60 ml of $CHCl_3$ and 18 ml of MeOH were cooled to about 0° and reacted with 18 ml of cold 17% HCl-solution in ether for 1 h. By addition of 900 ml of ether 10.1 g (96%) of **16** were obtained, m.p. 212–220°. For the analysis 1 g of **16** · HCl was dissolved in 60 ml of $CHCl_3$ and 0.5 ml of CH_3OH to which 30 ml of ether were added, whereby 0.97 g analytical pure product crystallized. – IR. (KBr): 3005 (NH), 2930 (CH), 2700 (NH^+), 1600 and 1495 (Arom.), 1345 and 1160 (SO_2N).

$C_{31}H_{43}ClN_4O_6S_3$	Calc.	C 53.24	H 6.20	N 8.01	S 13.75%
(699.34)	Found	„ 53.38	„ 6.31	„ 8.02	„ 13.90%

The free base **16** was obtained by treating 0.7 g of **16** · HCl in 55 ml of $CHCl_3$ with 30 ml of 2.5N NaOH and twice with 20 ml of water. The organic phase was dried and rotatory evaporated. The oil was crystallized from CH_2Cl_2/ether to give 0.48 g of **16**, m.p. 187–189°. – ^{1}H-NMR. ($CDCl_3$): 1.5

(*s*, 1 H, NH); 2.0 (*m*, 4 H, 2 C–CH_2–C); 2.45 (*s*, 9 H, 3 CH_3Ar); 3.05 (*m*, 16 H, 6 SO_2N–CH_2 and 2 –CH_2–N); 7.5 (*m*, 12 H, arom. H).

Hydrolysis of **16** · HCl with conc. sulfuric acid in an analogous procedure as described for **9** gave **10**.

Preparation of 4-carbamoylmethyl-1,7,11-tritosyl-1,4,7,11-tetraazacyclotetradecane (**17**). A solution of 7.2 g (10.3 mmol) of **16**, 1.5 g (8.1 mmol) of iodoacetamide and 2 ml of NEt_3 in 65 ml of DMF was heated to 80° for 6 h. Then 1.4 g (7.6 mmol) of idoacetamide and 2 ml of NEt_3 were added once more and the solution was kept for 12 h at 90°. The mixture was then evaporated and the residue taken up with 120 ml of $CHCl_3$ which were extracted with 80 ml of 0.5N NaOH and twice with 80 ml of water. The organic phase was dried over Na_2SO_4 and concentrated to about 50 ml. Addition of 40 ml ether afforded 4.6 g (62%) of **17**, m.p. 160–165°. For the analysis the crude product was recrystallized from $CHCl_3$/ether. – IR. (KBr): 3420 and 3350 ($CONH_2$), 2920 (CH), 1680 ($CONH_2$), 1600 and 1490 (Arom.), 1340 and 1160 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 2.0 (*qi*, 4 H, 2 C–CH_2–C); 2.4 (*s*, 9 H, 3 CH_3Ar); 2.6–3.3 (*m*, 18 H, 2 –CH_2–N, 6 SO_2N–CH_2 and CH_2–$CONH_2$); 6.9 (*s*, 2 H, $CONH_2$); 7.5 (*m*, 12 H, arom. H).

$C_{33}H_{45}N_5O_7S_3$ (719.93) Calc. C 55.06 H 6.30 N 9.73% Found C 54.91 H 6.49 N 9.53%

Preparation of 4-carbamoylmethyl-1,4,7,11-tetraazacyclotetradecane (**18**). A solution of 3.3 g of phenol and 4.2 g (5.8 mmoll) of **17** in 25 ml 40% HBr/glacial acetic acid was stirred for 1.5 h at r.t. and then 28 h at 65°. After cooling 120 ml of ether were added and the precipitate was filtered off and washed with ether. The solid was dissolved in 30 ml of water and the excess phenol was extracted twice with 50 ml of ether. By addition of 20 ml of sat. K_2CO_3-solution the solution was made alkaline and then extracted with three portions of 35 ml of $CHCl_3$. The organic phase was dried, treated with active charcoal and evaporated to dryness. After three crystallizations from CH_2Cl_2/ether one obtained 560 mg (37%) of **18**, m.p. 110–111°. – IR. (KBr): 3420 and 3300 ($CONH_2$ and NH), 2920 and 2820 (CH), 1670 ($CONH_2$). – ^{1}H-NMR. ($CDCl_3$): 1.75 (*qi*, 4 H, 2 C–CH_2–C); 2.7 (*m*, 16 H, 8 CH_2–N); 3.15 (*s*, 2 H, CH_2–$CONH_2$); 5.38 (br., NH). – MS.: 258 ([M+1]), 257 (M^+).

The trihydrobromide was prepared from alkoholic HBr-solution.

$C_{12}H_{30}Br_3N_5O$ (500.12) Calc. C 28.81 H 6.04 N 14.00% Found C 28.87 H 6.27 N 13.80%

Preparation of 4-(2-cyanoethyl)-1,7,11-tritosyl-1,4,7,11-tetraazacyclotetradecane (**19**). In a reaction flask with stirrer 2.35 g (3.5 mmol) of **16**, 10 ml freshly distilled acrylonitrile, 5 ml of DMF and 0.03 ml of acetic acid were refluxed for 4 days at 100°. The mixture was rotatory evaporated and the residue taken up with 35 ml of $CHCl_3$. These were washed with 20 ml of 0.5N NaOH and twice with 10 ml of water. After drying the organic phase over Na_2SO_4 the solution was concentrated to about 5 ml and fractionated by addition of 8, 10 and 15 ml of ether. The first fraction was chromatographed on silica gel (*Merck 60*) with $CHCl_3$/CH_3OH 99:1. Beside 183 mg starting material (**16**) 651 mg (28%) of **19** were also obtained, m.p. 203–206°. – IR. (KBr): 2920 (CH), 2270*w*, (CN), 1600 and 1495 (Arom.), 1340 and 1160 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 1.95 (*qi*, 4 H, 2 C–CH_2–C); 2.4 (*s*, 9 H, 3 CH_3–Ar); 2.45–2.8 (*m*, 6 H, 2 CH_2–N and CH_2CN); 3.15 (*m*, 12 H, 6 SO_2N–CH_2); 7.45 (*m*, 12 H, arom. H).

$C_{34}H_{45}N_5O_6S_3 \cdot 0.25\ H_2O$	Calc.	C 56.33	H 6.40	N 9.66%
(724.44)	Found	„ 56.32	„ 6.33	„ 9.59%

Preparation of 4-(2-tosylaminoethyl)-1,7,11-tritosyl-1,4,7,11-tetraazacyclotetradecane (**20**). In 6 ml acetonitrile 199 mg (0.3 mmol) of **16** and 79 mg (0.4 mmol) of 1-tosyl-aziridine [16] were refluxed until no starting material could be detected any more. The solution was then rotatory evaporated and the residue chromatographed on a short silica gel (*Merck 60*) column with $CHCl_3$. The product was crystallized from THF with a small addition of ether. Yield: 74 mg (29%), m.p. 186–188°. TLC. ($CHCl_3$/CH_3OH 20:1) Rf 0.6 (Rf 0.45 (**16**), Rf 0.9, 1-tosyl-aziridine). – IR. (KBr): 3250 ($SONH_2$), 2940 (CH), 1600 and 1495 (Arom.), 1335 and 1160 (SO_2N). – ^{1}H-NMR. ($CDCl_3$): 1.85 (*qi*, 4 H, 2 C–CH_2–C); 2.4 (*s*, 12 H, 4 CH_3–Ar); 2.65 (*t*, 6 H, 3 CH_2–N); 3.1 (*m*, 14 H, 7 SO_2N–CH_2); 5.4 (*t*, 2 H, SO_2NH_2); 7.45 (*m*, 16 H, arom. H).

$C_{40}H_{53}N_5O_8S_4$ (860.13) Calc. C 55.86 H 6.21 N 8.14% Found C 55.99 H 6.32 N 8.34%

Metal complexes. A solution of 0.25 mmol of ligand in 2 ml of EtOH was mixed with 0.25 mmol of metal diperchlorate in 2 ml of EtOH and heated to about 50°. Depending on the metal ion and the ligand the complex either directly crystallized on cooling or could be brought to cristallization by adding a less polar organic solvent. The exact solvent mixture is given for each complex below. The UV./VIS. and IR. spectra of the complexes are given in *Table 1.*

Ni(**10**)$(ClO_4)_2 \cdot 0.4\ H_2O$. Precipitates from EtOH. Orange-red crystals. Yield: 89%.

$C_{10}H_{24}Cl_2N_4NiO_8 \cdot 0.4\ H_2O$	Calc.	C 25.81	H 5.40	N 12.04	H_2O 1.61%
(465.50)	Found	„ 25.62	„ 5.31	„ 11.63	„ 1.60%

Cu(**10**)$(ClO_4)_2$. Precipitates from EtOH. Violett crystals. Yield: 89%.

$C_{10}H_{24}Cl_2CuN_4O_8$ (462.77) Calc. C 25.95 H 5.23 N 12.11% Found C 26.12 H 5.22 N 12.26%

Zn(**10**)$(ClO_4)_2$. Precipitates from EtOH. White crystals. Yield: 65%.

$C_{10}H_{24}Cl_2N_4O_8Zn \cdot 0.75\ H_2O$	Calc.	C 25.12	H 5.40	N 11.72	H_2O 2.78%
(464.61)	Found	„ 24.94	„ 5.40	„ 11.80	„ 2.80%

Ni(**12**)$(ClO_4)_2$. Precipitates from 4 ml of EtOH and 3 ml of ether. Violett crystals. Yield: 74%.

$C_{12}H_{27}Cl_2N_5NiO_9$ (514.99) Calc. C 27.99 H 5.28 N 13.60% Found C 27.70 H 5.40 N 13.51%

Cu(**12**)$(ClO_4)_2$. Precipitates from 4 ml of EtOH and was recrystallized from 11 ml of CH_3CN/EtOH/Et_2O 1:3:7. Blue crystals. Yield: 81%.

$C_{12}H_{27}Cl_2CuN_5O_9$	Calc.	C 27.73	H 5.24	N 13.47	Cu 12.23%
(519.82)	Found	„ 27.92	„ 5.09	„ 13.75	„ 12.30%

Zn(**12**)$(ClO_4)_2$. Precipitates from 4 ml of EtOH and was recrystallized from 14 ml of H_2O/EtOH/Et_2O 3:7:4. White crystals. Yield: 61%.

$C_{12}H_{27}Cl_2N_5O_9Zn$ (521.66) Calc. C 27.63 H 5.22 N 13.43% Found C 27.76 H 5.38 N 13.47%

Ni(**14**)$(ClO_4)_2$. Precipitates from 2 ml of EtOH. Violett crystals. Yield: 52%.

$C_{13}H_{29}Cl_2N_5NiO_9$ (529.04) Calc. C 29.52 H 5.53 N 13.24% Found C 29.81 H 5.53 N 12.92%

Cu(**14**)$(ClO_4)_2$. Precipitates from 4 ml of EtOH. Blue crystals. Yield: 55%.

$C_{13}H_{29}Cl_2CuN_5O_9$ (533.85) Calc. C 29.25 H 5.48 N 13.12% Found C 29.38 H 5.48 N 12.73%

Zn(**14**)$(ClO_4)_2$. Precipitates from 4 ml of EtOH and was recrystallized from 3.5 ml of CH_3CN/EtOH/Et_2O 1:3:3, 1,5 ml EtOH and 1.5 ml ether. White crystals. Yield: 51%.

$C_{13}H_{29}Cl_2N_5O_9Zn$ (535.69) Calc. C 29.15 H 5.46 N 13.07% Found C 29.24 H 5.49 N 12.95%

Ni(**18**)$(ClO_4)_2$. Precipitates from 4 ml of EtOH and 3 ml of ether. Violett crystals. Yield: 43%.

$C_{12}H_{27}Cl_2N_5NiO_9$ (514.99) Calc. C 27.99 H 5.28 N 13.60% Found C 27.99 H 5.32 N 13.50%

Cu(**18**)$(ClO_4)_2$. After evaporation of the EtOH the blue oil crystallized upon addition of 3 ml of CH_2Cl_2. Blue crystals. Yield: 43%.

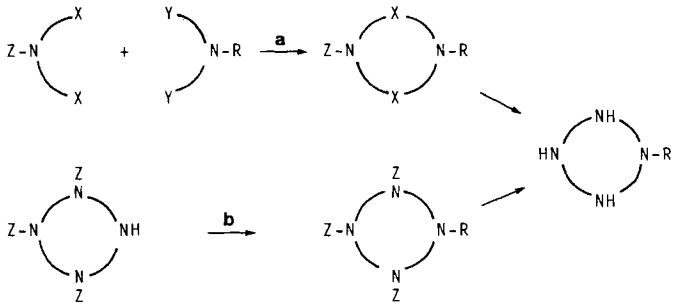
$C_{12}H_{27}Cl_2CuN_5O_9 \cdot 0.5\ H_2O$	Calc.	C 27.26	H 5.34	N 13.24%	
(528.83)	Found	„ 26.92	„ 5.06	„ 12.93%	

Zn(**18**)$(ClO_4)_2$. Precipitates from 4 ml of EtOH and was recrystallized from 24.5 ml of H_2O/EtOH/Et_2O 1:2:4. White crystals. Yield: 41%.

$C_{12}H_{27}Cl_2N_5O_9Zn$ (521.66) Calc. C 27.63 H 5.22 N 13.43% Found C 27.40 H 5.01 N 13.44%

Discussion. – In contrast to the synthesis of tetrafunctionalized tetraazamacrocycles which can easely be prepared by reacting the unsubstituted macrocycle with an excess of alkylating agent [3], the synthesis of mono-substituted derivatives requires a more selective route. Schematically there are two ways to introduce a pendant side chain into a tetraazamacrocycle (s. *Scheme 1*): *a)* Let us start with two

Scheme 1. *Strategy for the synthesis of mono-N-functionalized tetraazamacrocycles:* a) *cyclization with side chain included in one reaction component,* b) *alkylation of a selectively protected tetraazamacrocycle.*

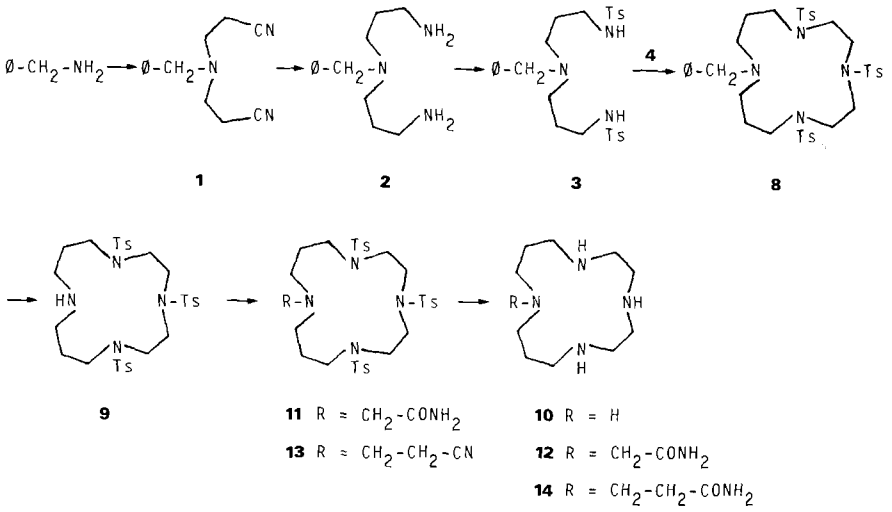


components, one of which already has the side chain, and react them according to one of the typical cyclization procedures. The resulting macrocycle will then have the side attached as a pendant arm. An example of this type of synthesis has been described in the cyclization of 2,6-diacetylpyridine with *N,N*-bis(3-aminopropyl)-*N',N'*-dimethylethylenediamine or *N,N*-bis(3-aminopropyl)ethanolamine using Ni^{2+} as a template [17]. The main disadvantage of this synthetic route, however, is that the cyclization, which generally is the most difficult step of the whole synthesis, has to be repeated for each new side chain, thus requiring a large investment of time and labour. Of course one way to avoid this difficulty would be to prepare a functionalized cyclic product which offers the possibility of selective modifications to new derivatives by simple chemical reactions. From the macrocycle with the 2-hydroxyethyl pendant side chain described in [17] we have prepared the 2-chloroethyl, the 2-cyanoethyl and the 2-carboxyethyl derivatives in this way [18]; *b)* the second synthetic route consists in the preparation of a selectively protected tetraazamacrocycle with only one N-atom accessible for alkylation. Thus the cyclization must be done only once and it can therefore be optimized. In this work we have changed *Richman & Atkins* [8] cyclization method which has been shown to give good yields for a large number of polyazamacrocycles with different ring sizes by replacing of one of the tosyl groups by a benzyl or a trityl group. These two groups were selected because we felt that they also would force as the tosyl group the open chain component into a favourable conformation for the cyclization so that dilution techniques are not necessary.

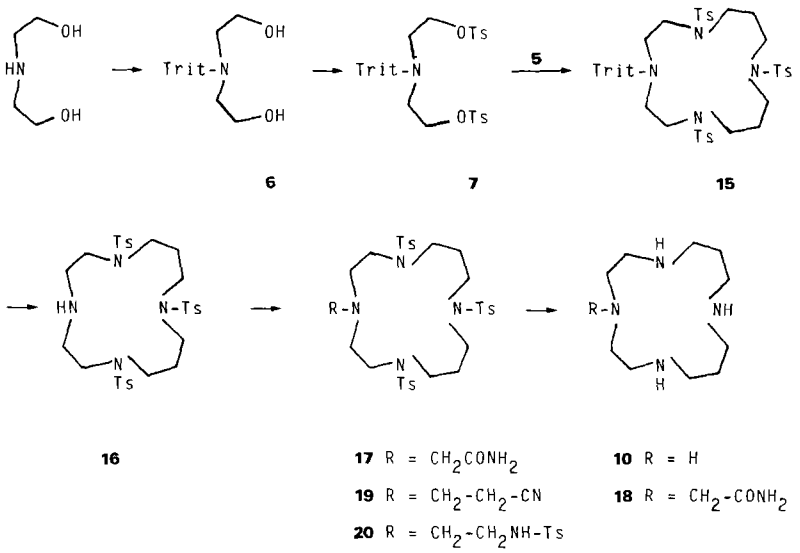
Thus the two starting compounds **3** *(Scheme 2)* and **7** *(Scheme 3)* were prepared and cyclized with **4** and **5**, respectively. Tosyloxy or mesyloxy groups were used since they were shown to be the most effective leaving groups in similar processes [19]. Both cyclizations with a benzyl or a trityl group in 4 or 11 position to give the selectively protected tetraazamacrocycles proceed with reasonable yields (40–60%).

The benzyl as well as the trityl group were then cleaved off by hydrogenolysis with Pd/C in glacial acetic acid and by acid hydrolysis with HCl in CH_3OH, respectively. In this manner the two key products **9** and **16** were obtained. They both have three N-atoms protected by tosyl rests and one N-atom (N^4 or N^{11}) accessible for further reactions.

Scheme 2



Scheme 3



Both products proved to be ideal for the introduction of a functionalized side chain and their versatility was demonstrated by reacting **16** *(Scheme 3)* and in part also **9** *(Scheme 2)* with iodoacetamide, acrylonitrile and 1-tosyl-aziridine. The yields varied from 29% up to 92% for the different reactands.

The last step of the synthesis consists in the detosylation of the functional derivatives. Of the different methods described in [20] we have used the hydrolysis

with conc. sulfuric acid for the unsubstituted ligand **10** and the milder reductive cleavage with HBr/glacial acetic acid and phenol for the other compounds. Using this method, however, often after the cleavage of one or more tosyl groups had occurred insoluble hydrobromides were formed which precipitated from the solution thus preventing the further cleavage of the remaining tosyl groups. This is the reason why partially tosylated products were found and the yields were sometimes relatively low. Only in one case we have studied the detosylation by electrochemical means as described by *Horner et al.* [21] for open-chain tosylamides. The main difficulty in this method was that the protected derivatives are only slightly soluble in polar solvents such as CH_3OH so that we had to work with a suspension of the starting compound. The cyano derivatives **13** and **19** do not withstand the detosylation in HBr/acetic acid and phenol, but react to give the corresponding amides. In conclusion we can say that starting from **9** or **16** a combination of alkylation and detosylation allows to synthesize a series of mono-*N*-substituted and functionalized tetraazamacrocycles with nearly every side-chain length and containing a large variety of functional groups.

The metal complexes of the final products were prepared in the usual way by reacting equimolar amounts of the metal perchlorate with the free ligand in EtOH or EtOH and a less polar solvent to induce crystallization.

The IR. spectra of the Ni^{2+}-, Cu^{2+}- and Zn^{2+}-complexes with **12**, **14**, and **18** *(Table)* show the typical amide bands at 1650–1665 cm^{-1} which have to be compared to those of the free ligand at 1670 cm^{-1}.

The VIS. absorption spectra of the complexes with **10**, **12**, **14**, and **18** are also given in the *Table*. The unsubstituted ligand **10** forms with Ni^{2+} and Cu^{2+} complexes which in the solid state and in solution are clearly square planar. The Ni^{2+}-complex exhibits one absorption band at 460 nm and the Cu^{2+}-complex one at 551 nm which is expected for a CuN_4-chromophore [22]. The spectra of the Ni^{2+}- and Cu^{2+}-complexes of the macrocycles **12**, **14** and **18**, however, are very different from those of the complexes with **10**. Whether this is due to a weakening of the ligand field by

Table. *IR.- and VIS.-spectra of the Ni^{2+}-, Cu^{2+}- and Zn^{2+}-complexes with the ligands* **10**, **12**, **14** *and* **18**

	IR.[a]) (cm^{-1})					VIS.[b])
	ClO_4^-	CO–N	CH	NH	H_2O	λ_{max} in nm (M^{-1} cm^{-1})
Ni(**10**)	1100	–	2900	3200	3400	460 (58)
Cu(**10**)	1100	–	2900	3200	–	551 (154)
Zn(**10**)	1100	–	2900	3180, 3250	3400	–
Ni(**12**)	1100	1660	2860, 2920	3270	3300	348 (31), 537 (17), 740 (6)
Cu(**12**)	1100	1665	2870, 2920	3220, 3350	3305	712 (195); 800 (195)[c])
Zn(**12**)	1100	1655	2900	3200	3450	–
Ni(**14**)	1100	1655	2900	3270	3430	351 (41), 550 (18), 800
Cu(**14**)	1100	1660	2900	3250	3450	587 (171)[d]); 770 (200)[c])[d])
Zn(**14**)	1100	1650	2900	3080	3400	–
Ni(**18**)	1100	1660	2900	3270	3400	355 (34), 553 (18), 750 (9)
Cu(**18**)	–					590 (166); 790 (196)[c])[d])
Zn(**18**)	1100	1665	2900	3210	3350	–

[a]) In KBr pill. [b]) In water. [c]) At pH ≈ 12. [d]) With additional shoulder.

introducing a tertiary amino group or whether this is due to the interaction of the functional group of the pendant arm with an apical position of the metal ion is difficult to say as long as no X-ray structure determination is available.

The observation that the absorption maximum of the Cu^{2+}-complexes with **12**, **14** and **18** shifts to longer wavelengths when the pH of the solution is increased to 12 whereas that of the Cu^{2+}-complex with **10** does not show any pH dependence, clearly indicates that the amide group at the end of the side chain can coordinate in its deprotonated form with the metal ion. The shift to longer wavelengths is indicative for apical interaction [22].

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