137. Metal Complexes with Macrocyclic Ligands. IX[1]). Synthesis and Properties of a new Class of Branched N_4-Macrocycles with an Additional Ligating Group in the Side Chain

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Summary

In the presence of Ni^{2+} the template reaction between 2,6-diacetylpyridine and 4-(2-dimethylaminoethyl)- or 4-(2-hydroxyethyl)-1,7-diamino-4-azaheptane yields the complexes of either the open-chain ligand (**3** and **11**) or of the macrocycle (**4** and **12**). Reduction of the imino group in **4** and **12** with PtO_2/H_2 gives **5** and **13**, respectively. In the case of the dimethylamino derivative **5** a mixture of at least four isomers was obtained. These were partially separated by chromatography on *Sephadex* SP-25 cation exchanger. Through demetalation of the Ni^{2+} complexes by cyanide the new macrocycles **7** and **14** were isolated, from which the corresponding Zn^{2+} and Cu^{2+} complexes were prepared.

The macrocyclic Ni^{2+}-complexes **4**, **12**, **5** and **13** can exist in two forms depending on the pH of the solution. At low pH protonation of the dimethylamino or hydroxy group in the side chain occurs. The metal ion is then bound to the four nitrogen atoms of the macrocycle in a square planar ligand field. At higher pH, however, the dimethylamino or hydroxy group (the last one also in its deprotonated form) can coordinate to one of the axial positions, whereby pseudo-octahedral coordination geometry is induced. This reaction can be quantitatively described by a reversible acid-base equilibrium, the pK_H of which greatly depends on the nature of the functional group, the degree of unsaturation of the macrocycle and the metal ion.

The acid-base reaction and the concomitant structural change are a direct consequence of the unique combination of the rigid and kinetically stable structure of the macrocycle and of the flexible and kinetically labile functional group of the side chain.

In most mono- or bicyclic ligands described in the literature the coordinating atoms are an integral part of the ring [2]. Thus rigid structures result which often account for the specific complexation of these ligands with metal ions. In contrast,

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open-chain ligands being more flexible can form complexes with different geometries and can adapt themselves to the specific features of the coordinated metal ion. It would therefore appear interesting to combine the cyclic and open-chain structural elements in one ligand in order to study its coordination properties. Only a few examples of ligands of this type have been described. The Fe^{2+} complex of a porphyrine to which a hystidyl residue is attached through a side chain was synthesized as a model for hemoglobin [3]. The compound prepared by *Busch et al.* [4] from the corresponding unsubstituted macrocycle in the presence of $Fe(CH_3CN)_6^{2+}$ and of two equivalents of base is another example for this type of ligand. The same combination of cyclic and open-chain structural elements is also found in the tetra-*N*-alkylated tetraazacycloalkanes which have interesting properties in regard to the stability [5] and to the structure of their complexes [6].

The metal derivatives of such compounds might also be considered as models for biologically relevant systems since in many cases the metal ion bound to a set of four nitrogen atoms in a square planar arrangement also coordinates to one or two unidentate ligands. It is thought that the nature of the axial group significantly alters the properties of the metal ions [7], thus making the biological system specific for the task for which it was developed.

Thus we have started a synthetic program for the preparation of branched macrocycles in order to study such compounds and to investigate whether they can be considered as models for biologically important molecules. This paper describes the first synthesis and the complexation properties of two new macrocycles with a functional side chain designed in such a way that coordination at one of the axial positions can occur.

Experimental Part

Melting points are uncorrected. IR. spectra (absorption bands in cm^{-1}) were obtained in solution or as KBr discs on a *Perkin-Elmer* 157G spectrophotometer. NMR. spectra were recorded on a *Varian* EM 360 or a WH 90 *Brucker* FT-instrument using tetramethylsilane or 3-(trimethylsilyl)-propanesulfonate as internal standard. Chemical shifts are given in δ-values, the multiplicity, the intensity and the type of protons are indicated in parenthesis (s = singlet, d = doublet, t = triplet, qa = quadruplet, qi = quintuplet, m = multiplet and br. = broad). Abbreviations: HV. = high vacuum.

N,N-*Bis(2-cyanoethyl)-N',N'-dimethylethylenediamine* (**1**). 99 ml (1.5 mol) Acrylonitrile were added to a mixture of 40 ml MeOH and 54.4 ml (0.5 mol) *N,N*-dimethylethylenediamine at such a rate that the temperature did not exceed 20°. The mixture was then heated to 70° for 4 days. Destillation at 0.2 Torr under N_2 gave 77.8 g (80%) of the product: b.p. 144–147°/0,2 Torr; $n_D = 1.467$. – IR. (CCl_4): 2260 (CN).

$C_{10}H_{18}N_4$ (194.28) Calc. C 61.82 H 9.36 N 28.84% Found C 61.65 H 9.06 N 28.62%

1 · Dihydrochloride: m.p. 170–172°.

$C_{10}H_{20}Cl_2N_4$	Calc.	C 44.95	H 7.54	Cl 26.54	N 20.97%
(267.20)	Found	„ 44.78	„ 7.49	„ 26.57	„ 20.66%

N,N-*Bis(3-aminopropyl)*-N',N'-*dimethylethylenediamine* (**2**). 52.3 g (0.27 mol) **1** dissolved in 100 ml abs. ethanol and 70 ml liquid ammonia were hydrogenated with 11 g *Raney*-nickel (W2) at 130 atm H_2. The temperature was gradually increased to 45° (8 h), 56° (22 h), 80° (4 h) and finally to 105° (2 h). After filtration of the catalyst and evaporation of the solvent the residue was distilled under N_2 whereby 44.8 g (82%) product, pure by GC. was obtained. B.p. 94–98°/0.15 Torr; $n_D = 1.481$. – IR. (CCl_4): no

CN band, 3380 and 3280 (NH_2). – NMR. ($CDCl_3$): 1.36 (*s*, 4 H, 2 NH_2); 1.61 (*qi*, 4 H, 2 C–CH_2–C); 2.10 (*s*, 6 H, 2 NCH_3); 2.38–2.84 (*m*, 12 H, 6 NCH_2).

$C_{10}H_{26}N_4$ (202.34)	Calc.	C 59.36	H 12.95	N 27.69%	Found	C 59.1	H 12.9	N 27.4%

2 · *Tetraoxalate monohydrate:* m.p. 168–170°.

$C_{18}H_{36}N_4O_{17}$ (580.50)	Calc.	C 37.24	H 6.25	N 9.65%	Found	C 37.37	H 6.30	N 9.65%

2 · *Tetrapicrate:* m.p. 194°.

$C_{34}H_{38}N_{16}O_{28}$ (1118.76)	Calc.	C 36.50	H 3.42	N 20.03%	Found	C 36.41	H 3.72	N 19.87%

[N-{1-(6-Acetylpyrid-2-yl)ethylidene}-4-(2-dimethylaminoethyl)-4-azaheptane-1,7-diamine-nickel(II)] diperchlorate (**3**). 13.08 g (55 mmol) $NiCl_2 \cdot 6\,H_2O$, 9.0 g (55 mmol) 2,6-diacetylpyridine and 11.08 g (55 mmol) **2** were dissolved in 275 ml 50% aqueous EtOH. After addition of 4 ml acetic acid the mixture was kept at 65° during 4½ h, then concentrated to about 100 ml. 15 ml saturated $NaClO_4$-solution and active charcoal were added and the hot solution was filtered over *Celite*. On cooling the product was separated as red flat crystals which were recrystallized twice from water/$NaClO_4$ and then washed with EtOH. After drying them over P_2O_5 in HV. 11.8 g (36.4%) **3** were obtained. *Caution:* the crystals explode upon heating, dec. 253°. – IR. (KBr): 3311 and 3268 (NH_2), 1660 (C=O), 1620, 1580 (C=N, pyridine), 1100 (ClO_4).

$C_{19}H_{33}N_5NiO_9$	Calc.	C 37.31	H 5.50	Cl 11.72	N 11.57%
(605.10)	Found	„ 37.58	„ 5.57	„ 11.75	„ 11.49%

[2,12-Dimethyl-7-(2-dimethylaminoethyl)-3,7,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),2,11,13,15-pentaene-nickel(II)] diperchlorate (**4**). 4.75 g (20 mmol) $NiCl_2 \cdot 6\,H_2O$, 3.26 g (20 mmol) 2,6-diacetylpyridine and 4.05 g (20 mmol) **2** were dissolved in 100 ml EtOH/water 1:1. After addition of 1.5 ml acetic acid the solution was heated to about 80° for 36 h whereby the colour changed from red to violet. The solution was concentrated to about 40 ml and 10 ml saturated $NaClO_4$-solution and active charcoal were added. After heating to 80° for 10 min the mixture was filtered through *Celite*. On cooling the product separated as olive crystals which were washed with EtOH and recrystallized from water/$NaClO_4$. The analytical pure compound was obtained by chromatography on *Sephadex* SP-25 with 0.4M sodium acetate adjusted to pH 5 as eluent. The first fraction containing **4** was evaporated to dryness and taken up with EtOH, then ether was added until no further precipitation of sodium acetate occurred. After filtration the solvent was taken off, the residual oil was dissolved in a little water and the calculated amount of saturated $NaClO_4$-solution was added. The solution was heated to dissolve the precipitate then cooled. 3.64 g (31%) **4** were obtained which were washed with cold EtOH and dried at 120° during 1 h. – IR. (KBr): 3400 (H_2O), 1670, 1615, 1580 (C=N, pyridine), 1100 (ClO_4). – NMR. (CF_3COOH): 2.13 (br., 4 H, 2 C–CH_2–C); 2.55 (*s*, 6 H, 2 CH_3); 3.22 (*d*, 6 H, 2 N–CH_3); 3.64 (*m*, 8 H, 4 N–CH_2); 8.22 (*m*, 3 H, pyridine-H).

$C_{19}H_{31}Cl_2N_5NiO_8 \cdot H_2O$	Calc.	C 37.71	H 5.49	Cl 11.72	N 11.52%
(605.12)	Found	„ 37.64	„ 5.63	„ 11.54	„ 11.35%

[2,12-Dimethyl-7-(2-dimethylammoniumethyl)-3,7,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene-nickel(II)] triperchlorate (**5**). 2.98 g (4.9 mmol) **4**, dissolved in 550 ml water, were hydrogenated with 30 mg PtO_2 at 140 atm H_2 during 48 h. After filtering off the catalyst the solution was concentrated and 5 ml saturated $NaClO_4$-solution were added. The mixture of crystals (1.92 g, 55%) was filtered off and washed with EtOH. The separation of the isomers was accomplished through chromatography on *Sephadex* SP-25. The crude product was applied to a column (70×3 cm) filled with 40 g *Sephadex* SP-25 and eluted with 0.4M sodium acetate adjusted to p*H* 5 with a flow-rate of 1–2 ml/min. The first brown fraction consisted of the only partially reduced compound **17**. – NMR. (CF_3COOH): 1.81 (*d*, 3 H, CH–CH_3); 2.17 (br., 4 H, 2 C–CH_2–C); 2.61 (*s*, 3 H, N=C–CH_3); 3.15–4.0 (br., 12 H, 6 N–CH_2); 3.28 (*d*, 6 H, 2 N–CH_3); 4.5 (br., 1 H, C*H*–CH_3); 7.6–8.5 (*m*, 3 H, pyridine-H).

$C_{19}H_{33}Cl_2N_5NiO_8$	Calc.	C 38.74	H 5.64	Cl 12.04	N 11.89%
(589.12)	Found	„ 38.90	„ 5.41	„ 11.86	„ 11.90%

Then tree fractions called A, B, and C in the order of elution were obtained. Each fraction was evaporated to dryness below 40°, the residue taken up with hot EtOH and mixed with so much ether that no more sodium acetate precipitated. After filtration, the solvent was distilled and the oil dissolved in a little water. Addition of saturated $NaClO_4$-solution induced crystallisation. Recrystallisation from water acidified with a drop of conc. $HClO_4$-solution gave the analytical pure compounds. Only isomer **5B** was obtained in quantities large enough for a complete characterisation. – IR. (KBr): 3450 (NH), 2600–2300 (NH^+), 1610, 1580 (pyridine), 1100 (ClO_4). – NMR. (CF_3COOH); 1.78 (*d*, 6 H, 2 CH_3); 2.15 (br., 4 H, 2 C–CH_2–C); 2.5–3.6 (br., 12 H, 6 N–CH_2); 3.31 (*d*, 6 H, 2 NCH_3); 4.30 (*m*, 2 H, 2 C*H*–CH_3); 7.20–8.2 (*m*, 3 H, pyridine-H).

$C_{19}H_{36}Cl_3N_5NiO_{12}$ (Isomer B)	Calc.	C 33.00	H 5.25	Cl 15.38	N 10.13%
(691.56)	Found	„ 32.87	„ 5.39	„ 15.05	„ 9.99%

[2, 12-Dimethyl-7-(2-dimethylaminoethyl)-3, 7, 11, 17-tetraazabicyclo [11. 3. 1]heptadeca-1 (17), 13, 15-triene-nickel(II)] diperchlorate (**6**). When **5B** was dissolved in acetone with more than one equivalent of 2,6-lutidine and ether was added dropwise until a slight turbidity appeared, **6B** was obtained upon cooling. – IR. (KBr): 3287 (NH), 1606, 1584 (pyridine), 1090 (ClO_4).

$C_{19}H_{35}Cl_2N_5NiO_8$ (Isomer B)	Calc.	C 38.61	H 5.97	Cl 11.99	N 11.85%
(591.11)	Found	„ 38.62	„ 6.06	„ 12.23	„ 11.64%

2,12-Dimethyl-7-(2-dimethylaminoethyl)-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**7**). 2.01 g (41 mmol) NaCN were added to 3.89 g (6.6 mmol) **5B** in 200 ml water at 80°. After the typical yellow colour of $Ni(CN)_4^{2-}$ had fully developed (about 20 min), the solution was made strongly alkaline with NaOH and the product was extracted with ether in a *Kutscher-Steudel* apparatus. After taking off the ether two portion of 30 ml benzene were added and evaporated to dryness. The residue was then dissolved in warm ether which upon evaporation gave 1.76 g (80.3%) colourless crystals of **7**, m.p. 64–65°. – IR. (KBr): 3400 (H_2O), 3270 (NH), 1595, 1575 (pyridine). – NMR. ($CDCl_3$): 1.33 (*d*, 6 H, 2 CH_3); 1.67 (*qi*, 4 H, 2 C–CH_2–C); 2.20 (*s*, 6 H, 2 N–CH_3); 2.2–3.0 (*m*, 8 H, 4 N–CH_2); 3.66 (*qa*, 2 H, 2 C*H*–CH_3); 6.83–7.65 (*m*, 3 H, pyridine H).

$C_{19}H_{35}N_5 \cdot H_2O$	Calc.	C 64.91	H 10.61	N 19.92%	
(351.54)	Found	„ 64.98	„ 10.61	„ 20.21%	

7 · *Tetraperchlorate*, m.p. 232–233°.

$C_{19}H_{39}Cl_4N_5O_{16}$	Calc.	C 31.03	H 5.35	Cl 19,28	N 9.52%
(735.36)	Found	„ 31.0	„ 5.5	„ 19.1	„ 9.4%

7 · *Tetrabromide*, dec. 260°.

$C_{19}H_{39}Br_4N_5$	Calc.	C 34.73	H 5.98	Br 48.64	N 10.66%
(657.17)	Found	„ 34.7	„ 6.0	„ 48.4	„ 10.9%

7 · *Trioxalate*, m.p. 221–222°.

$C_{25}H_{41}N_5O_{12}$	Calc.	C 49.74	H 6.85	N 11.60%
(603.63)	Found	„ 49.6	„ 6.9	„ 11.7%

7 · *Tetrapicrate*, m.p. 206–207°.

$C_{43}H_{47}N_{17}O_{28}$	Calc.	C 41.32	H 3.79	N 19.05%
(1249.94)	Found	„ 41.03	„ 3.80	„ 18.82%

[2, 12-Dimethyl-7-(2-dimethylammoniumethyl)-3, 7, 11, 17-tetrabicyclo [11. 3. 1]heptadeca-1 (17), 13, 15-triene-copper(II)] triperchlorate (**8**). 100 mg (0.3 mmol) **7**, in 10 ml EtOH, and 111 mg (0.3 mmol) $Cu(ClO_4)_2 \cdot 6\ H_2O$, also in 10 ml EtOH, were mixed and heated until the precipitate was dissolved. After cooling blue violet crystals were obtained which were dried at 120° for 6 h (yield 131 mg, 73.5%). – IR. (KBr): 3220 (NH), 1605, 1585 (pyridine), 1080 (ClO_4).

$C_{19}H_{35}Cl_3CuN_5O_4 \cdot H_2O$	Calc.	C 31.94	H 5.35	Cl 14.88	N 9.80%
(714.47)	Found	„ 32.21	„ 5.24	„ 14.80	„ 9.96%

[2, 12-Dimethyl-7-(2-dimethylaminoethyl)-3, 7, 11, 17-tetraazabicyclo[11.3.1]-heptadeca-1(17), 13, 15-triene-zinc(II)] diperchlorate (**9**). The complex was obtained by mixing 150 mg (0.45 mmol) **7**, in 10 ml EtOH, with 168 mg (0.45 mmol) $ZnClO_4 \cdot 6\ H_2O$, also in 10 ml EtOH, and heating the solution until the precipitate was completely dissolved. 213 mg (yield 86.2%) **9** were so obtained on cooling the solution. – IR. (KBr): 3285 (NH), 1610, 1582 (pyridine), 1090 (ClO_4). – NMR. (d_6-DMSO): 1.45 (*d*, 6 H, 2 CH_3); 2.0 (br., 4 H, 2 C–CH_2–C); 2.5–3.4 (br., 12 H, 6 N–CH_2); 2.78 (*s*, 6 H, 2 N–CH_3); 4.20 (*qa*, 2 H, 2 C*H*–CH_3); 7.6–8.4 (*m*, 3 H, pyridine-H).

$C_{19}H_{35}Cl_2N_5O_8Zn$	Calc.	C 38.18	H 5.90	Cl 11.86	N 11.72%
(597.80)	Found	„ 37.97	„ 5.99	„ 11.73	„ 11.68%

N,N-*Bis(3-aminopropyl)-ethanolamine* (**10**). 700 ml THF, 60 g Rh-catalyst (5% on alumina) and 500 g liquid ammonia were placed in a nickel autoclave under 170 atm H_2. 267.6 g (1.6 mol) *N,N*-bis(2-cyanoethyl)-ethanolamine [8] were added over 3 h through pumping. The reaction was stopped after the theoretical amount of H_2 had been taken up (14 hours). The ammonia was evaporated and the catalyst filtered off. The residual oil obtained after distillation of the THF was fractionated at 0.08–0.1 Torr under N_2. A large amount (53%) of *N*-(3-aminopropyl)-ethanolamine [NMR. ($CDCl_3$): 1.65 (*qi*, 2 H, C–CH_2–C); 2.27 (*s*, 4 H, NH_2, NH and OH); 2.59–2.9 (*m*, 6 H, 3 N–CH_2); 3.65 (*t*, 2 H, O–CH_2)] came over at 70–80°, and then, at 108–112°, 48 g (17%) of **10** were obtained. – NMR. ($CDCl_3$): 1.60 (*qi*, 4 H, 2 C–CH_2–C); 1.94 (*s*, 5 H, 2 NH_2 and OH); 2.46–2.90 (*m*, 10 H, 5 N–CH_2); 3.61 (*t*, 2 H, CH_2–O).

$C_8H_{21}N_3O$ (175.28) Calc. C 54.82 H 12.08 N 23.98% Found C 54.50 H 12.10 N 23.88%

10 · *Tripicrate*, m.p. 223° (233–238° [8]).

$C_{26}H_{30}N_{12}O_{22}$ (862.58) Calc. C 36.20 H 3.52 N 19.49% Found C 36.26 H 3.60 N 19.44%

[N-{1-(6-Acetylpyrid-2-yl)ethylidene}-4-(2-hydroxyethyl)-4-azaheptane-1,7-diamine-nickel(II)] diperchlorate (**11**). Its preparation is similar to that of **3**. Yield 49%. *Caution:* the compound explodes upon heating. – IR. (KBr): 3592 (OH), 3301, 3258 (NH), 1661 (C=O), 1626, 1601 (C=N, pyridine), 1080 (ClO_4).

$C_{17}H_{28}Cl_2N_4NiO_{10}$	Calc.	C 35.32	H 4.88	Cl 12.27	N 9.69%
(578.05)	Found	„ 35.16	„ 5.08	„ 12.51	„ 9.43%

[2, 12-Dimethyl-7-(2-hydroxyethyl)-3, 7, 11, 17-tetraazabicyclo[11.3.1]heptadeca-1(17), 2, 11, 13, 15-pentaene-nickel(II)] diperchlorate (**12**). Its synthesis is similar to that of **4**. Yield 65%. – IR. (KBr): 3340 (OH), 1615, 1580 and 1570 (C=N, and pyridine), 1080 (ClO_4).

$C_{17}H_{26}Cl_2N_4NiO_9$	Calc.	C 36.46	H 4.68	Cl 12.66	N 10.00%
(560.03)	Found	„ 36.54	„ 4.64	„ 12.98	„ 10.10%

[2, 12-Dimethyl-7-(2-hydroxyethyl)-3, 7, 11, 17-tetraazabicyclo[11. 3. 1]-heptadeca-1(17), 13, 15-triene-nickel(II)] diperchlorate (**13**). 4.01 g (7.15 mmol) **12** were dissolved in 200 ml water and hydrogenated with 40 mg PtO_2 at 110 atm H_2 during 48 h. After filtering off the catalyst 5 ml saturated $NaClO_4$-solution were added and the mixture concentrated until the first crystals formed. After cooling these were collected and recrystallized from acetone/ether whereby 2.36 g (58.5%) **13** were obtained. – IR. (KBr): 3420 (OH), 3255 (NH), 1605, 1580 (pyridine), 1100 (ClO_4).

$C_{17}H_{30}Cl_2N_4NiO_9$	Calc.	C 36.20	H 5.36	Cl 12.57	N 9.93%
(564.04)	Found	„ 36.01	„ 5.32	„ 12.77	„ 10.16%

2,12-Dimethyl-7-(2-hydroxyethyl)-3,7,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene (**14**). The compound was prepared as described for **7**. Yield 67.3%, m.p. 124–125°. – IR. (KBr): 3280 (OH), 3150 (NH), 1587 and 1575 (pyridine). – NMR. ($CDCl_3$): 1.37 (*d*, 6 H, 2 CH_3); 1.72 (*qi*, 4 H, 2 C–CH_2–C); 2.2–2.6 (*m*, 10 H, 5 N–CH_2); 3.6 (*m*, 4 H, 2 C*H*–CH_3 and CH_2O); 6.85–7.68 (*m*, 3 H, pyridine-H).

$C_{17}H_{30}N_4O$ (360.45) Calc. C 66.33 H 9.87 N 18.28% Found C 66.33 H 9.97 N 18.23%

14 · *Trihydrobromide*, dec. 277–278°.

$C_{17}H_{33}BrN_4O$	Calc.	C 37.18	H 6.06	Br 43.65	N 10.20%
(549.19)	Found	„ 36.88	„ 5.84	„ 43.75	„ 10.07%

14 · *Triperchlorate*, dec. 250°.

$C_{17}H_{33}Cl_3N_4O_{13}$	Calc.	C 33.59	H 5.47	Cl 17.50	N 9.22%
(607.83)	Found	„ 33.25	„ 5.68	„ 17.59	„ 9.15%

[2,12-Dimethyl-7-(2-hydroxyethyl)-3,7,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene-copper(II)] diperchlorate (**15**). The complex was obtained as described for **8**. Yield 88%. – IR. (KBr): 3420 (OH), 3200 (NH), 1602 and 1580 (pyridine) 1090 (ClO_4).

$C_{17}H_{30}Cl_2CuN_4O_9$	Calc.	C 35.89	H 5.32	Cl 12.46	N 9.85%
(568.90)	Found	„ 35.80	„ 5.26	„ 12.33	„ 9.86%

[2, 12-Dimethyl-7-(2-hydroxyethyl)-3, 7, 11, 17-tetraazabicyclo [11. 3. 1]-heptadeca-1 (17), 13, 15-triene-zinc(II)] diperchlorate (**16**). The complex was preparated analogously to **9**. Yield 67%. – IR. (KBr): 3460 (OH), 3195 (NH), 1608 and 1582 (pyridine), 1090 (ClO_4). – NMR. (D_2O): 1.52 (*d*, 6 H, 2 CH_3); 2.12 (br., 4 H, 2 C–CH_2–C); 2.5–3.3 (*m*, 10 H, 5 N–CH_2); 4.13 (br., 4 H, 2 C*H*–CH_3 and O–CH_2).

$C_{17}H_{30}Cl_2N_4O_9Zn$	Calc.	C 35.78	H 5.30	Cl 12.42	N 9.82%
(570.73)	Found	„ 35.98	„ 5.33	„ 12.33	„ 9.98%

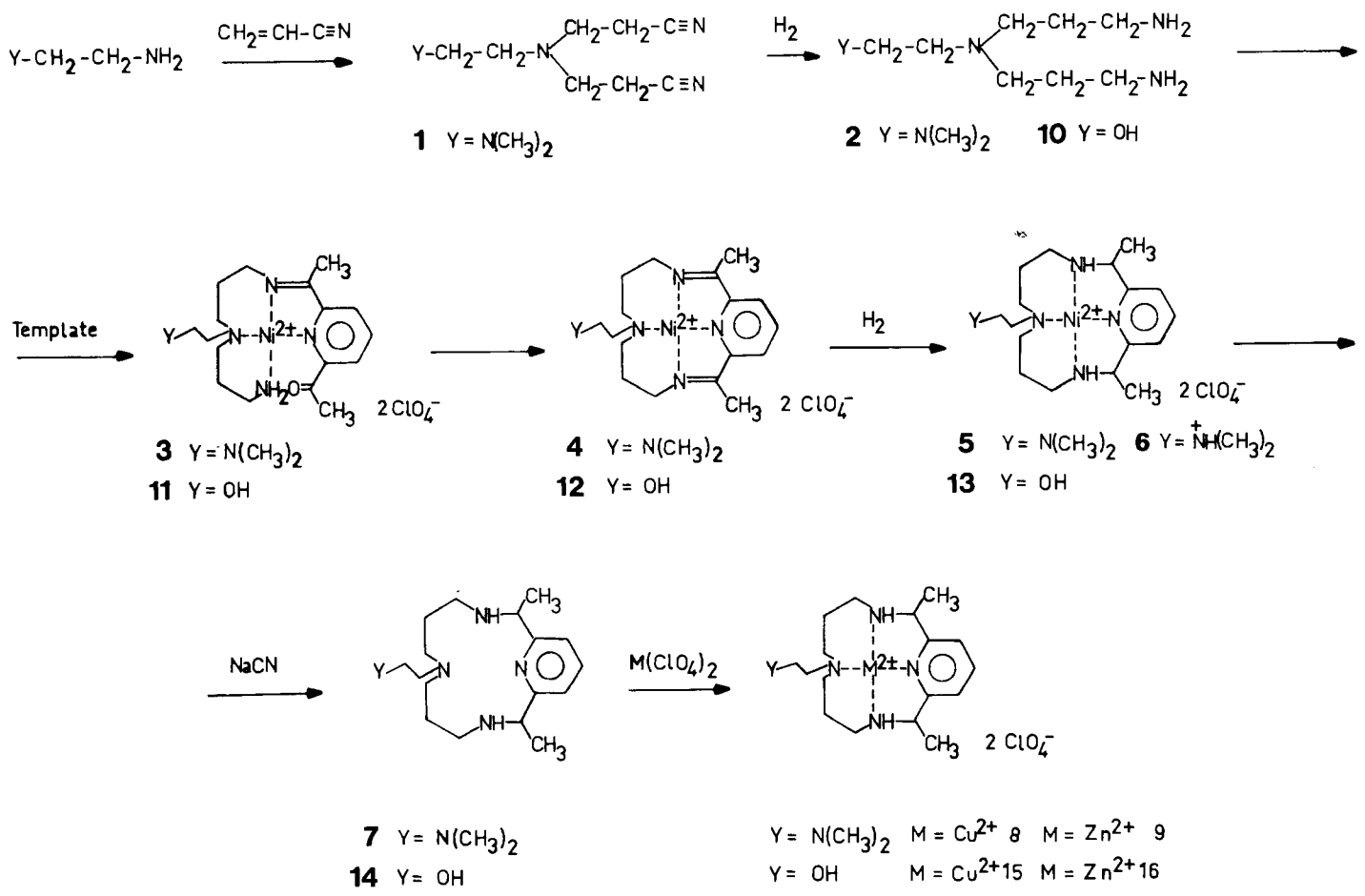
[2,12-Dimethyl-7-(2-oxyethyl)-3,7,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene-nickel-(II)] perchlorate (**18**). Olive crystals of **18** were isolated by treating **13** with one equivalent of NaOH and by carefully concentrating the aqueous solution. – IR. (KBr): 3520 (OH), 3250 (NH), 1590, 1575 (pyridine), 1090 (ClO_4).

$C_{17}H_{31}ClN_4NiO_6$	Calc.	C 42.40	H 6.49	Cl 7.36	N 11.63%
(481.62)	Found	„ 42.19	„ 6.23	„ 7.63	„ 11.61%

Measurements. – Visible absorption spectra were run in silica cells on a *Cary* 118 spectrophotometer. Spectroscopic pure solvents *(Merck)* were used. Reflection spectra were measured using the nujol mull-technique [9]. The spectrophotometric titrations were carried out using a self-developed apparatus, consisting of a 1 cm silica cell with a small magnetic stirrer, a *Metrohm* microelectrode and an *Agla* micrometer siringe, through which the reagent was added. The whole titration set-up was placed into the cell-housing compartment of the *Cary* 118. The absorbance was followed at 450 nm for **4**, 476 nm for **5B** and 464 for **5C**. pH-Titration with standard acid or base were recorded on a *Metrohm* potentiograph E436 with a combined glass electrode, calibrated with two standard buffer solutions. The pK_H values were calculated using a nonlinear least square program for a *Hewlett Packard* HP 9821 computer [10].

Results and discussion. – *Syntheses.* The two new macrocycles **7** and **14** were prepared following the synthetic route outlined in the *Scheme*. The first step consists in the addition of 2 mol acrylonitrile to either *N,N*-dimethylaminoethylamine or ethanolamine, using reaction conditions known to produce mainly the bis-products [8] [11]. In the case of ethanolamine the dinitrile cannot be distilled, since it decomposes [12], and was used directly for the next step. The reduction of the dinitriles was achieved in ethanol and ammonia with *Raney*-nickel or rhodium on alumina as catalyst. The reduction of **1** gives, as expected, mainly the bis-product. In contrast the monoderivative is obtained in high yield from the reduction of the hydroxy compound. Although a patent for the synthesis of **10** has appeared

Scheme


Y-CH2-CH2-NH2
CH2=CH-C≡N
Y-CH2-CH2-N(CH2-CH2-C≡N)2
1 Y = N(CH3)2
H2
Y-CH2-CH2-N(CH2-CH2-CH2-NH2)2
2 Y = N(CH3)2
10 Y = OH
Template
3 Y = N(CH3)2
11 Y = OH
4 Y = N(CH3)2
12 Y = OH
H2
5 Y = N(CH3)2
6 Y = NH+(CH3)2
13 Y = OH
NaCN
7 Y = N(CH3)2
14 Y = OH
M(ClO4)2
Y = N(CH3)2 M = Cu2+ 8 M = Zn2+ 9
Y = OH M = Cu2+ 15 M = Zn2+ 16

[13], we were unable to reach the yield given therein. A possible reason for the large amount of mono-product obtained in the case of *N, N'*-bis(2-cyanoethyl)-ethanolamine could be that under the condition of hydrogenation a *retro*-condensation takes place. The mono- and bis-products can easily be distinguished either by titration with acid or by the relative intensity of the peaks in their NMR. spectra.

The third step in the synthesis is a template reaction in which 2,6-diacetylpyridine and the corresponding amine component are cyclized in the presence of Ni^{2+} following the procedure of *Busch et al.* [14]. After a reaction time of 5 h one can isolate products which, according to their chemical and physical properties, are non-cyclic. The IR. of **3** shows bands at 3311 and 3268 cm^{-1}, which are assigned to NH_2-stretching vibrations, at 1660 cm^{-1} assignable to a ketonic function and at 1620 and 1580 cm^{-1} corresponding to the C=N and pyridine absorptions. Similarly the analogous open chain compound **11** has bands at 3301, 3258 and 1661 cm^{-1}. In addition both **3** and **11** are not stable against acid. The spectroscopic and analytical results of **3** and **11** are best explained by open chain structures with only one imino group. We were able to show that **3** is an intermediate in the cyclisation process since it can be converted into the cyclic product under more sharp conditions such as higher temperature and longer reaction time. The macrocyclic Ni^{2+}-complexes, however, can also be obtained directly, using similar conditions, from 2,6-diacetylpyridine and the amine component in the presence of Ni^{2+}. These compounds are characterized by the lack of NH_2- and CO-stretching bands in their IR. spectra and the greater stability against acid. The NMR. spectrum of **4** in CF_3COOH is also fully compatible with the cyclic structure.

The catalytic reduction of the *Schiff* bases **4** and **12** in the presence of PtO_2 gives the saturated cyclic Ni^{2+}-complexes **5** and **13**. It has been previously shown that for this system up to 14 isomers can occur [15]. The isomerism originates from the relative position of the two α-methyl groups, of the two hydrogen atoms of the secondary amines and of the alkyl group in position 7. Three isomers were observed when the crude mixture of **5** was run on a *Sephadex* SP-25 column using sodium acetate as eluent. For **13**, however only one component was isolated which did not separate in fractions on analogous chromatographic analysis.

The final step of the synthesis is the displacement of the macrocycle from the reduced Ni^{2+}-complexes by cyanide. The NMR. of both **7** and **14** are consistent with the macrocyclic structures proposed.

Nickel(II) complexes. The IR. spectra of the Ni^{2+}-complexes of the *Schiff* bases **4** and **12** exhibit no NH bands, but absorptions at 1670, 1615 and 1580 cm^{-1} typical for the imino groups and the pyridine ring and at 1100 cm^{-1} characteristic for the perchlorate ion. Complex **12** has an additional band at 3340 cm^{-1} due to the presence of an OH-group.

For **4** it was possible to obtain a ^{1}H-NMR. spectrum under strongly acidic conditions indicating that the complex in CF_3COOH is diamagnetic, whereas under other pH conditions both **4** and **12** are paramagnetic. The VIS. spectra also reflect the change in multiplicity which occurs on going from acidic to alkaline solution (see *Table 1*). In acids the complexes **4** and **12** exhibit one absorption band typical for square planar coordination geometry of the Ni^{2+}-ion [16]. At neutral or alkaline pH several weak bands can be observed in the visible spectrum.

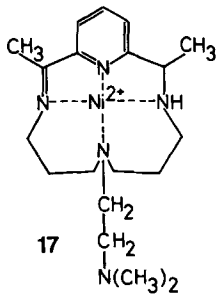
These results indicate that the Ni^{2+}-ion is in a pseudooctahedral environment with the macrocycle occupying five coordination positions, whereas the sixth is probably taken up by a solvent molecule. This is reflected by the small shifts observed in band position when the complexes are dissolved in different solvents *(Table 1)*.

The coordination-geometry change induced by the pH can best be explained by assuming that an acid-base equilibrium involving the side chain occurs (1), since the corresponding unsubstituted ligand does not show a similar reaction.

$$Ni(L)^{n+} + H^+ \rightleftharpoons Ni(LH)^{(n+1)+} \qquad : K_H \tag{1}$$

For **4** only one spectral change has been observed. The quantitative evaluation of the spectrophotometric titration gives $pK_H = 2.46$. For **12**, however two spectral changes occur: one between 11 M and 1 M $HClO_4$, the other with pK_H 10.33.

During the chromatographic separation of the isomers **5** an additional Ni^{2+}-complex was detected especially when solutions of **5** were left for longer time at room temperature or were heated for some time above 40° in the presence of dioxygen. Its ^{1}H-NMR. spectrum shows two methyl resonances, a doublet at 1.81 ppm and a singlet at 2.61 ppm. In addition the three pyridine proton appear as an *ABC*-pattern. Structure **17** is consistent with the ^{1}H-NMR. spectrum and the analytical results.



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The Ni^{2+} complexes of the reduced macrocycles (**5**, **6** and **13**) do not show the imino band in their IR. spectra any more. The pyridine ring absorbs at 1600–1430 cm^{-1}, the NH at 3250 cm^{-1} and the perchlorate ion at 1100 cm^{-1}. The hydroxy derivative **13** has an additional band at 3420 cm^{-1} due to the OH-group. In the IR. spectrum of **5B** we also observe the typical intercombination bands for an ammonium group at 2300–2100 cm^{-1} which are missing in that of **6** and **13**.

Solution of **5B** and **5C** in CF_3COOH give ^{1}H-NMR. spectra indicating that these complexes are diamagnetic. At higher p*H*, however, a change in multiplicity similar to the one observed for **4** with a concomitant spectral change occurs. The spectral properties of the Ni^{2+}-complexes with the saturated macrocycles *(Table 1)* indicate that at acidic pH a square planar species exists, whereas in alkaline solutions octahedral geometry is present. In the solid state different geometries are also observed, **5B** having a Ni^{2+} in D_{4h}-geometry whereas in **6B** the Ni^{2+}-ion is in a

ligand field with O_h-symmetry. For **13** as for **12** again two spectral changes were found. The first in strong acid the second with $pK_H = 10.5$.

The three isomers of **5** obtained through chromatographic separation on *Sephadex* SP-25 have been characterized by their UV./VIS., IR. and ^{1}H-NMR. spectra. **5A** turned out to be a mixture of two components, which were not further separated due to the small amount of the substance. In contrast the main products **5B** and **5C** are pure isomers as indicated by all physical measurements. Up to now we are not able to determine the absolute configuration of the products isolated. However, one of the component of **5A**, isomer **5B** and **5C** must be related to each other by having the same configuration at the carbon atoms and at the tertiary nitrogen atom. They only differ by the relative configuration at the secondary amino groups. This can be shown by dissolving either **5A** or **5B** or **5C** in 0.2 M NaOH over night and running the mixture over *Sephadex* SP-25. By elution with 0.4 M sodium acetate at p*H* 5 the three components **A**, **B** and **C** are obtained again. Only *N*- but not *C*-isomerisation would be expected to take place under these conditions [17].

Other metal complexes. The Cu^{2+}- and Zn^{2+}-complexes were synthesized from the ligands and the respective metal perchlorates. All are diperchlorates with the exception of the Cu^{2+}-complex **8** which, according to the analytical results, is a triperchlorate. The IR. spectra do not markedly differ from those of the corresponding Ni^{2+}-complexes. The ^{1}H-NMR. spectra of the Zn^{2+}-complexes obtained in

Table 1. *UV./VIS. spectra of the macrocyclic complexes with Ni^{2+}* (**4**, **12**, **5**, **6** and **13**) *and with Cu^{2+}* (**7** and **15**)

Compound	λ_{max} in nm (ε in $mol^{-1}\,l\,cm^{-1}$)				
	11 M $HClO_4$	Water pH < 2	Water pH > 10	Acetone	Reflectance[a]
4		433*s* (300)	719 (23)	711 (25)	708
			~500*s* (58)	482 (84)	491
12	455 (575)	715 (27)	730 (24)	723 (35)	712
	392 (1660)	506 (45)	500*s* (62)	485*s* (45)	~500
5B		476 (45)		476 (120)	482
		350*s*		370*s*	
5C		464 (82)		469 (113)	461
				367*s*	360*s*
6B			746 (11)	754 (13)[b]	708
			534 (9.6)	632 (11)	546
			355*s*	480 (15)	~350*s*
				367*s*	
6C			~750 (12)	745 (13)[b]	
			560 (24)	603 (15)	
			464 (18)	528 (18)	550
			358 (194)	350*s*	350*s*
13	466 (2700)	724 (18)	744 (16)	722 (35)	710
		508 (13)	529 (12)	~475 (46)	502
		356 (83)	368 (105)	350*s*	350*s*
7				590 (82)	572
15				612 (80)	575

[a] In nujol according to [9].
[b] A drop of 2,6-lutidine was added.

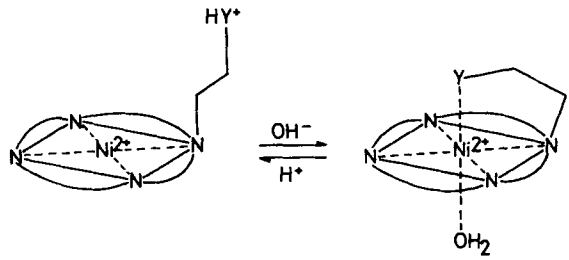

Fig. *pH induced structural rearrangement for the macrocyclic Ni^{2+}-complexes. $Y = -N(CH_3)_2$ or $-OH$.*

DMSO and D_2O are also similar to those of the analogous Ni^{2+}-compounds. The absorption spectra of the Cu^{2+}-complexes are also given in *Table 1*.

pH-Induced coordination-geometry change. The colour change of the Ni^{2+}-complexes of the unsaturated and saturated macrocycles, which is observed when the pH is shifted from acidic to alkaline indicates a change in coordination geometry from square planar to octahedral. The structural rearrangement can be explained as shown in the *Figure* [18]. At low pH the ligating group of the side chain is protonated and therefore blocked for a coordinative bond to the metal ion. The Ni^{2+}-ion is then surrounded by the four nitrogen atoms of the macrocycle in a square planar arrangement similar to that of the unsubstituted parent compound Ni(CRH) $(ClO_4)_2$ [15]. Deprotonation of the functional group gives a potential ligand, which coordinates to one of the axial positions, whereby a pseudo octahedral species is formed. In the case of **12** and **13** a second spectral change takes place, which, however, is not accompanied by a structural reorganisation. We think that this is due to the deprotonation of the coordinated hydroxy group, although we cannot rule out hydrolysis of the water molecule bound at the sixth coordination position. Complex **18** was isolated under these conditions.

The pK_H values for the acid base reaction (1) are given in *Table 2* and show that the nature of the metal ion and the degree of unsaturation of the macrocycle play an important role in determining their values. The p*H* induced structural changes in these complexes resembles in some respect that observed for metalloprotein when external conditions are altered. So for example tyrosine 248 in carboxypeptidase is about 14 Å apart from the active Zn^{2+}-ion in the crystalline state. Upon dissolving the crystals the same tyrosine binds to the metal ion [19]. Tyrosine 248 located in a flexible part of the amino acid sequence of the protein can approach the metal ion in a similar way the ligating group of the side chain of

Table 2. *pK_H values of the Ni^{2+} complexes* **4**, **5**, **12** *and* **13** *and of the Zn^{2+}-complex* **9** *for reaction (1) at 25° and $I = 0.5$*

	4	**12**	**5B**	**5C**	**13**	**9**
$pK_{H,1}$[a])	2.46	< 1	6.29	6.21	< 1	7.11
$pK_{H,2}$[a])		10.33			10.45	

[a]) All values with ±0.02.

these macrocycles does. The *pH* induced structural change results from the unique combination of the rigid and kinetically stable structure of the macrocycle and the flexible and kinetically labile side chain unit.

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