3. Metal Complexes of Macrocyclic Ligands

Part XXXVII[1])

Synthesis of Heteroditopic Bis-macrocycles and Their Potential for Preparing Heterobinuclear Metal Complexes

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A new and generally applicable synthetic path for the preparation of heteroditopic bis-macrocycles using tri-*N*-protected tetraazacycloalkanes as building blocks and bromoacetyl bromide as bridging reagent is described. In the first step, bromoacetyl bromide is used as acylating agent for one of the macrocycles, whereas in the second step it is used as alkylating agent for the second macrocycle, thus giving protected bis-macrocyclic amides (*e.g.* **6**). After reduction of the amide moiety and deprotection, bis-azamacrocycles with an ethylene bridge are obtained (*e.g.* **8**). The corresponding homoditopic bis-macrocycles **16** and **17** are also prepared for comparison purpose. Spectrophotometric studies indicate that bis-macrocycle **8**, which consists of a 12- and a 14-membered ring, binds two metal ions with equal affinity, whereas compound **13**, in which an unsubstituted (cyclam) and a trimethyl-substituted tetraazacyclotetradecane unit (Me_3cyclam) are bridged, shows selective metal-ion binding. The first metal ion is always incorporated into the cyclam unit, whereas the second one binds to the Me_3cyclam macrocycle. Thus, by sequential addition of two different metal ions, heterobinuclear complexes can easily be prepared. The electrochemistry of the binuclear Ni^{2+} complexes, studied by CV and DPV, as well as the EPR spectra of the binuclear Cu^{2+} complexes clearly indicate metal-metal interactions.

Introduction. – Beside open-chain ligands, macrocycles too were widely used to form binuclear metal complexes [2]. This can be achieved in different ways. One possibility is to use large rings, which are able to accommodate two metal ions: polyazamacrocycles [3], polythioethers [4], but also rings with two or more different donor atoms were synthesized for this purpose [5] [6]. In several cases, an internal bridging group was introduced to coordinate both metal ions so that a strong metal-metal interaction resulted [7]. Although most of these ligands are symmetric, *i.e.* have the same number and type of donor atoms to bind the two metal ions, a few examples of rings having two different sets of donor groups were also prepared [6].

Another way to obtain binuclear metal complexes is to use bis-macrocycles, in which the two rings are interconnected by a bridge starting either from a N- [8] [9] or from C-atom [10] [11]. Whereas this last type of bis-macrocycles leaves the donor atoms unchanged, they are synthetically more difficult to prepare than the *N*-substituted ones. Bis-macrocycles bridged by a chain between two N-atoms of two rings were synthesized using selectively protected compounds in which only one N-atom was available for substitution either by alkylation or acylation [8].

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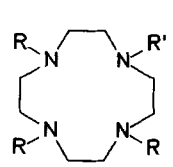
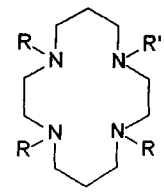
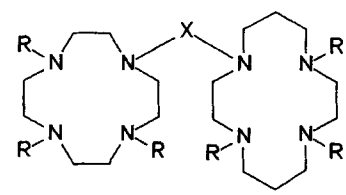


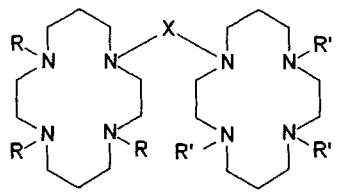
1 R = R′ = H
2 R = Ts, R′ = H
3 R = Ts, R′ = $BrCH_2CO$



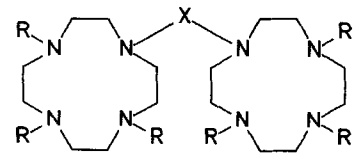
4 R = R′ = H
5 R = Ts, R′ = H
9 R = Ts, R′ = $BrCH_2CO$
10 R = Me, R′ = H



6 R = Ts, X = $C(O)CH_2$
7 R = Ts, X = CH_2CH_2
8 R = H, X = CH_2CH_2



11 R = Ts, R′ = Me, X = $C(O)CH_2$
12 R = Ts, R′ = Me, X = CH_2CH_2
13 R = H, R′ = Me, X = CH_2CH_2
17 R = R′ = H, X = CH_2CH_2



14 R = Ts, X = C(O)C(O)
15 R = Ts, X = CH_2CH_2
16 R = H, X = CH_2CH_2

All ligands of this latter type described up to now are symmetrical and allow to prepare homobinuclear complexes by adding two equiv. of metal ion. The synthesis of heterobinuclear species is possible but difficult and often needs chromatographic separation techniques to isolate the desired heterobinuclear species [11] [12]. We describe here a new synthetic method of general application which allows to prepare heteroditopic bis-macrocycles and thus also heterobinuclear metal complexes in a simple way.

Experimental Part. – The compounds 1,4,7,10-tetraazacyclododecane [13] (**1**), 1,4,8,11-tetraazacyclotetradecane [14] (= cyclam; **4**), 1,4,8-tritosyl-1,4,8,11-tetraazacyclotetradecane [9] (**5**), 1,4,8-trimethyl-1,4,8,11-tetraazacyclotetradecane [15] (**10**), and 1,1′-(ethane-1,2-diyl)bis(1,4,8,11-tetraazacyclotetradecane) (**17**) [9] were prepared according to the literature. Solvent mixtures in *v/v*.

1,4,7-Tritosyl-1,4,7,10-tetraazacyclododecane (**2**). To **1** (5.04 g, 29.3 mmol) and Et_3N (25 ml, 180.4 mmol) in $CHCl_3$ (200 ml), a soln. of TsCl (11.10 g, 58.2 mmol) in $CHCl_3$ (400 ml) was added at 40° in 7 h. The mixture was stirred at 40° for 1 h and, after cooling to r.t., was left overnight. The org. phase was washed with H_2O (100 ml), dried (Na_2SO_4), and evaporated. The residue was dissolved in warm CH_2Cl_2 to which so much MeOH was added that crystallization took place. A second crop of **2** was obtained by evaporating the mother liquor of the first crop, dissolving the oil in $CHCl_3$ (200 ml) and Et_3N (16 ml, 115.4 mmol) and adding a new soln. of TsCl (1.88 g, 9.9 mmol) in $CHCl_3$ (100 ml) at 40° in 90 min. Standard workup of this mixture gave **2**. Yield 8.4 g (5.6 g and 2.8 g, 45%). IR (KBr): 1350, 1165 (SO_2N). ^{1}H-NMR ($CDCl_3$): 1.25 (*s*, NH); 2.4 (*s*, 3 MeC_6H_4); 2.9–3.5 (*m*, 8 CH_2N); 7.2–7.4 (*d*, 6 arom. H); 7.5–7.8 (*t*, 6 arom. H). Anal. calc. for $C_{29}H_{38}N_4O_6S_3 \cdot 0.1\,H_2O$ (636.64): C 54.71, H 6.05, N 8.80, O 15.33, S 15.11, H_2O 0.28; found: C 54.50, H 6.07, N 8.95, O 15.25, S 15.09, H_2O 0.38.

2-Bromo-1-(4,7,10-tritosyl-1,4,7,10-tetraazacyclododec-1-yl)ethan-1-one (**3**). To a soln. of **2** (9.97 g, 15.7 mmol) and Et_3N (4 ml, 28.9 mmol) in dry CH_2Cl_2 (80 ml), a soln. of bromoacetyl bromide (2 ml, 23.0 mmol) in dry CH_2Cl_2 (10 ml) was added at 0° in 30 min. The mixture was kept at 0° for 15 min and then slowly heated to r.t. The org. phase was washed with sat. $NaHCO_3$ soln. (2 × 50 ml) and 0.2M HCl (50 ml) dried (Na_2SO_4), and evaporated. The brown product was dissolved in hot MeOH to which hot H_2O was added to induce crystallization: 9.9 g (83%) of **3**. IR (KBr): 1645 (CON). ^{1}H-NMR ($CDCl_3$): 2.45 (3*s*, 3 MeC_6H_4); 3.2–4.1 (*m*, 8 CH_2N, $BrCH_2CO$); 7.3–7.4 (*m*, 6 arom. H); 7.6–7.75 (*m*, 6 arom. H). ^{13}C-NMR ($CDCl_3$): 21.7, 26.2 (MeC_6H_4); 49.6–

55.0 (CH_2N, $BrCH_2CO$); 127.7–130.6, 144.5, 145.1 (arom. C); 168.3 ($BrCH_2CO$). Anal. calc. for $C_{31}H_{39}Br_{0.91}N_4O_7S_3(OH)_{0.09}\cdot 0.15H_2O$ (752.82): C 49.46, H 5.27, Br 9.66, N 7.44, O 15.39, S 12.78, H_2O 0.36; found: C 49.19, H 5.18, Br. 9.69, N 7.55, O 15.51, S 12.63, H_2O 0.13.

1-(4,7,10-Tritosyl-1,4,7,10-tetraazacyclododec-1-yl)-2-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradec-1-yl)-ethan-1-one (**6**). A suspension of **3** (9.10 g, 12.0 mmol), **5** (7.98 g, 12.0 mmol), and dried Na_2CO_3 (2.53 g, 23.9 mmol) in dry MeCN (200 ml) was refluxed for 4 d. After cooling to r.t., CH_2Cl_2 (200 ml) was added, the soln. washed with H_2O (2 × 100 ml), dried (Na_2SO_4), and evaporated, and the residue recrystallized twice from CH_2Cl_2/EtOH: 12.6 g (78%) of **6**. ^{1}H-NMR ($CDCl_3$): 1.75 (*q*, C–CH_2–C); 2.0 (*q*, C–CH_2–C); 2.35–2.45 (6*s*, 6 *Me*C_6H_4); 2.7–3.95 (*m*, 16 CH_2N, C(O)CH_2); 7.25–7.35 (*m*, 2 arom. H); 7.6–7.75 (*m*, 12 arom. H). Anal. calc. for $C_{62}H_{80}N_8O_{13}S_6\cdot H_2O$ (1355.75): C 54.93, H 6.10, N 8.27, O 16.52, S 14.19; found: C 55.03, H 6.10, N 8.28, O 16.56, S 14.23.

1,4,8-Tritosyl-11-[2-(4,7,10-tritosyl-1,4,7,10-tetraazacyclododec-1-yl)ethyl]-1,4,8,11-tetraazacyclotetradecane (**7**). To a soln. of **6** (12.1 g, 9.0 mmol) in dry THF (60 ml), 1M BH_3 in THF (90 ml, 90 mmol) was added at 0°. The resulting soln. refluxed for 1 d, cooled to r.t., quenched with MeOH/H_2O 3:1 (40 ml), and evaporated. The residue was stirred in CH_2Cl_2 (100 ml) and filtered; this procedure was repeated twice. The combined org. fractions were dried (Na_2SO_4) and evaporated: 17.42 g of **7**.

1-[2-(1,4,7,10-Tetraazacyclododec-1-yl)ethyl]-1,4,8,11-tetraazacyclotetradecane (**8**). A soln. of **7** (16.70 g, *ca.* 9.0 mmol) was heated in 96% H_2SO_4 (40 ml) to 100° for 4 d. To the black soln., 36% HCl soln. (40 ml) was very slowly given at –20°. After addition of Et_2O (150 ml), the mixture was left at –20° overnight. The solid was filtered off and extracted with hot H_2O (2 × 500 ml). The combined aq. fractions were concentrated to *ca.* 300 ml, treated with decolorizing charcoal, and evaporated. Two crystallizations from HCl/H_2O/EtOH gave **8** as hydrochloride: 1.40 g (21% rel. to **6**). ^{1}H-NMR ($CDCl_3$, free base): 1.7–1.8 (*m*, 2 C–CH_2–C); 2.5–2.9 (*m*, 18 CH_2N, 6 NH). ^{13}C-NMR ($CDCl_3$, free base): 25.9, 28.1 (C–CH_2–C); 45.1–54.8 (CH_2N). Anal. calc. for $C_{20}H_{46}N_8\cdot 6.8HCl\cdot 3.7H_2O$ (713.23): C 33.68, H 8.51, Cl 33.80, N 15.71, O 8.30, H_2O 9.35; found: C 33.49, H 8.57, Cl 33.67, N 15.62, O 8.21, H_2O 9.26.

2-Bromo-1-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradec-1-yl)ethan-1-one (**9**). A soln. of **5** (5.05 g, 7.62 mmol) and Et_3N (1.3 ml, 9.38 mmol) in dry CH_2Cl_2 (50 ml) was cooled to –7°. After addition of bromoacetyl bromide (1 ml, 11.49 mmol) in dry CH_2Cl_2 (10 ml) over 35 min, the mixture was stirred for 30 min at –7° before it was slowly heated to r.t. and extracted with sat. $NaHCO_3$ soln. (2 × 25 ml), 1M HCl (10 ml), and H_2O (40 ml). The org. phase was dried (Na_2SO_4) and evaporated and the residue chromatographed (silica gel (*Merck 60*, 70–230 mesh), CH_2Cl_2/acetone 100:2.5): 4.30 g (72%) of pure **9**. IR (KBr): 1645 (CON). ^{1}H-NMR ($CDCl_3$): 1.9–2.1 (*m*, 2 C–CH_2–C); 2.4–2.45 (3*s*, 3 *Me*C_6H_4); 2.95–4.0 (*m*, 8 CH_2N, $BrCH_2CO$); 7.3–7.4 (*m*, 6 arom. H); 7.7–7.8 (*m*, 6 arom. H). Anal. calc. for $C_{33}H_{43}BrN_4O_7S_3$ (783.82): C 50.57, H 5.53, Br 14.29, N 7.15, O 12.27, S 10.19; found: C 50.69, H 5.69, Br 14.19, N 7.03, O 12.22, S 9.98.

2-(4,8,11-Trimethyl-1,4,8,11-tetraazacyclotetradec-1-yl)-1-(4,8,11-tritosyl-1,4,8,11-tetraazacyclotetradec-1-yl)ethan-1-one (**11**). A suspension of **9** (5.53 g, 7.06 mmol), **10** (1.71 g, 7.05 mmol), and dried Na_2CO_3 (1.50 g, 14.15 mmol) in dry MeCN (100 ml) was refluxed for 1 d. After cooling to r.t., H_2O (50 ml) was added, the soln. extracted with CH_2Cl_2 (4 × 50 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue chromatographed (silica gel (*Merck 60*, 70–230 mesh), CH_2Cl_2/MeOH/25% NH_3 100:10:1): 4.28 g (64%) of pure **11**. IR (KBr): 1640 (CON). ^{1}H-NMR ($CDCl_3$): 1.75 (*m*, 2 C–CH_2–C); 2.05 (*m*, 2 C–CH_2–C); 2.1–3.8 (*m*, 3 MeN, 3 *Me*C_6H_4, 16 CH_2N, C(O)CH_2); 7.35–7.45 (*m*, 6 arom. H); 7.7–7.85 (*m*, 6 arom. H). Anal. calc. for $C_{46}H_{72}N_8O_7S_3\cdot 0.25CH_2Cl\cdot 0.15HBr\cdot H_2O$ (996.70): C 55.73, H 7.55, Br 1.20, Cl 1.78, N 11.24, O 12.84, S 9.65; found: C 55.66, H 7.41, Br 0.98, Cl 1.73, N 11.11, O 12.89, S 9.70.

1,1'-(Ethane-1,2-diyl)-4,8,11-trimethyl-4',8',11'-tritosylbis(1,4,8,11-tetraazacyclotetradecane) (**12**). To a soln. of dried **11** (2.96 g, 3.13 mmol) in dry CH_2Cl_2/THF 2:1 (30 ml), 1M BH_3 in THF (60 ml, 60 mmol) was added during 30 min at 0°. The mixture was refluxed for 1 d, then cooled to r.t., and 6M HCl (100 ml) was added. The soln. was refluxed for 1 h and evaporated. The residue was dissolved in H_2O, conc. NaOH soln. added to pH 10, the aq. phase extracted with CH_2Cl_2, and the org. phase dried (Na_2SO_4) and evaporated: 2.00 g (*ca.* 68%; not anal. pure). IR (KBr): no CON at 1640.

1,1'-(Ethane-1,2-diyl)-4,8,11-trimethylbis(1,4,8,11-tetraazacyclotetradecane) (**13**). A suspension of crude **12** (0.50 g, *ca.* 0.54 mmol) and phenol (0.60 g, 6.38 mmol) in 96% H_2SO_4 (5 ml) was kept at 100° for 3 d. After cooling to r.t., Et_2O was added and the mixture left at –20° overnight. The black solid was filtered off and dissolved in H_2O, the soln. treated with decolorizing charcoal and evaporated, and the resulting oil recrystallized from 47% HBr/H_2O/EtOH: **13** as hydrobromide (0.39 g, 58%). ^{1}H-NMR ($CDCl_3$, free base): 1.65 (*q*, 2 C–CH_2–C); 1.75 (*q*, 2 C–CH_2–C); 2.2 (3*s*, 3 MeN); 2.4–2.75 (*m*, 18 CH_2N, 3 NH). ^{13}C-NMR ($CDCl_3$, free base): 24.3, 26.4, 28.7 (C–CH_2–C); 43.5–43.8 (MeN); 47.8–55.4 (CH_2N). Anal. calc. for $C_{25}H_{56}N_8\cdot 8HBr\cdot 7.5H_2O$ (1251.19): C 24.00, H 6.36, Br 51.09, N 8.96, O 9.59, H_2O 10.80; found: C 24.14, H 6.39, Br 50.86, N 9.15, O 9.75, H_2O 10.90.

1,2-Bis(4,7,10-tritosyl-1,4,7,10-tetraazacyclododec-1-yl)ethane-1,2-dione (**14**). To a soln. of **2** (4.53 g, 7.14 mmol) and Et_3N (3 ml, 21.64 mmol) in dry CH_2Cl_2 (35 ml), oxalyl chloride (0.31 ml, 3.61 mmol) in dry CH_2Cl_2 (5 ml) was added over 30 min at 0°. The mixture was stirred at 0° for 30 min before it was allowed to reach r.t. The org. phase was then washed with sat. Na_2CO_3 soln. (25 ml), 1M HCl (30 ml), and H_2O (30 ml), dried (Na_2SO_4), and evaporated and the residue recrystallized from CH_2Cl_2/EtOH: pure **14** (4.25 g, 90%). IR (KBr): 1645 (CON). ^{1}H-NMR ($CDCl_3$): 2.4, 2.45 (2*s*, 6 *Me*C_6H_4); 3.25–4.0 (*m*, 16 CH_2N); 7.25–7.35 (*m*, 12 arom. H); 7.65–7.75 (*m*, 12 arom. H). Anal. calc. for $C_{60}H_{74}N_8O_{14}S_6 \cdot 0.9\,H_2O$ (1339.88): C 53.78, H 5.70, N 8.36, O 17.79, S 14.36; found: C 53.59, H 5.68, N 8.40, O 17.58, S 14.47.

1,1'-(Ethane-1,2-diyl)-4,4',7,7',10,10'-hexatosylbis(1,4,7,10-tetraazacyclododecane) (**15**). To a soln. of **14** (4.20 g, 3.17 mmol) in dry THF (15 ml) was added at 0° dropwise 1M BH_3 in THF (70 ml, 70 mmol). The resulting soln. was refluxed for 1 d, cooled to r.t., quenched with MeOH/H_2O 4:1 (50 ml) and evaporated. The residue was stirred in CH_2Cl_2 (100 ml) and filtered and the residue stirred once again with CH_2Cl_2 (100 ml). The combined org. fractions were dried (Na_2SO_4) and evaporated: 1.50 g of CH_2Cl_2-soluble fraction (not anal. pure) and 8.00 g of CH_2Cl_2-insoluble fraction (not anal. pure). IR (KBr): no CON at 1645.

1,1'-(Ethane-1,2-diyl)bis(1,4,7,10-tetraazacyclododecane) (**16**). The CH_2Cl_2-soluble fraction of **15** (1.50 g) was kept in 96% H_2SO_4 (15 ml) at 100° for 4 d. After cooling to 0°, Et_2O was added, the mixture left at −20° overnight, the black solid filtered off and dissolved in H_2O, and the dark soln. treated with decolorizing charcoal and evaporated. Recystallization from HCl/H_2O/EtOH gave **16** as hydrochloride. A second crop of **16** was obtained by heating the CH_2Cl_2-insoluble fraction of **15** (8.00 g) in 96% H_2SO_4 (40 ml), followed by standard workup. Yield: 1.00 g (0.45 g and 0.55 g, 51%). ^{1}H-NMR ($CDCl_3$, free base): 2.4–2.9 (*m*, 18 CH_2N, 6 NH). ^{13}C-NMR ($CDCl_3$, free base): 45.3, 46.1, 47.1, 52.4, 53.5 (CH_2N). Anal. calc. for $C_{18}H_{42}N_8 \cdot 5.9\,HCl \cdot 2\,H_2O$ (621.74): C 34.77, H 8.41, Cl 33.64, N 18.02, H_2O 5.80; found: C 34.93, H 8.44, Cl 33.65, N 18.06, H_2O 5.70.

Measurements. All measurements were done at 25° and $I = 0.5$M (KNO_3), if not stated otherwise.

Spectrophotometric Titrations. Ligands **16**, **17**, **8**, and **13** were titrated with Cu^{2+} on the fully automated titration unit based on a *Philips-Pye-Unicam-PU8800* UV/VIS spectrophotometer [16] in 1-cm cells. The calculations were performed with the program SPECFIT [17]. Typical conditions were: buffered solns. (AcOH/AcONa, 0.1M) at pH 4.8 with [ligand] = $1.00 \cdot 10^{-3}$ M and [Cu^{2+}] = $2.01 \cdot 10^{-2}$ M.

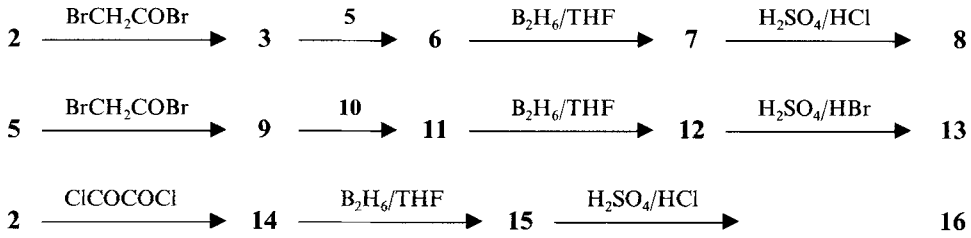
Cyclic Voltammetry (CV) *and Differential Pulse Polarography* (DPP). They were run with a *Metrohm-VA* scanner *E612*, a *Metrohm-VA* detector *E611*, and a *Hewlett-Packard x–y* recorder *HP 7044A* using a conventional three-electrode cell with a Pt or a glassy carbon electrode as working electrode, surrounded by a Pt spiral as auxiliary electrode and a Ag/AgCl sat./LiCl in abs. EtOH as reference electrode with a salt bridge. The experiments were carried out in dry MeCN with $LiClO_4$ (0.1M) as supporting electrolyte and $0.5–1.0 \cdot 10^{-3}$ M complex under N_2. The complexes [Ni(**1**)]$(ClO_4)_2$, [Ni(**4**)]$(ClO_4)_2$, [Ni_2(**8**)]$(ClO_4)_4$, [Ni_2(**13**)]$(ClO_4)_4$, [Ni_2(**16**)]$(ClO_4)_4$, [(Zn,Ni)(**13**)]$(ClO_4)_4$, and [(Ni,Zn)(**13**)]$(ClO_4)_4$ were prepared in H_2O. To a soln. of the ligand was added the desired amount of $Ni(ClO_4)_2$ and for the last two complexes that of $Zn(ClO_4)_2$, obtained by dissolving ZnO in dil. $HClO_4$ soln. The pH was adjusted with NaOH to ensure full complex formation, and the soln. was evaporated. The residue was taken up in dry Me_3CN, filtered, and evaporated. The resulting solid was dissolved again in dry Me_3CN and filtered to give the final soln. Ferrocene was added as internal standard to eliminate the effects of the diffusion potential. The ferrocene-ferrocenium couple has a constant potential of +400 mV *vs.* NHE in all solvents [18]. Cyclic voltammograms were recorded at scan rates of 10–15 mV/s, whereas the differential pulse polarograms were run at 1 mV/s with a pulse amplitude of 10 mV. The scan range was 200–2000 mV for both methods.

Spectrophotometric Investigations. The heterobinuclear complexes of ligand **13** ($3.9 \cdot 10^{-3}$ M) with the pairs Cu^{2+}/Ni^{2+}, Cu^{2+}/Co^{2+}, Ni^{2+}/Cu^{2+}, Ni^{2+}/Co^{2+}, Zn^{2+}/Cu^{2+}, Zn^{2+}/Ni^{2+}, and Zn^{2+}/Co^{2+} were examined in a 1-cm cuvette using a *Perkin-Elmer-Lambda-2* UV/VIS spectrophotometer.

EPR Spectra. The binuclear Cu^{2+} complexes were examined on a *Varian-E-9* spectrometer using $1 \cdot 10^{-3}$ M solns. in H_2O/DMF 2:1 frozen at −120°. No external reference was used since the absolute values of the frequency and the magnet field were known.

Results and Discussion. – *Synthesis.* The strategy for the synthesis of heteroditopic bis-macrocycles here described in the *Exper. Part* is based on the use of a bifunctional reagent, which can react in an acylation and an alkylation step (*Scheme*). Our studies indicate that bromoacetyl bromide has ideal properties for this purpose. The second condition necessary for this synthesis is the availability of triprotected tetraazamacro-

Scheme



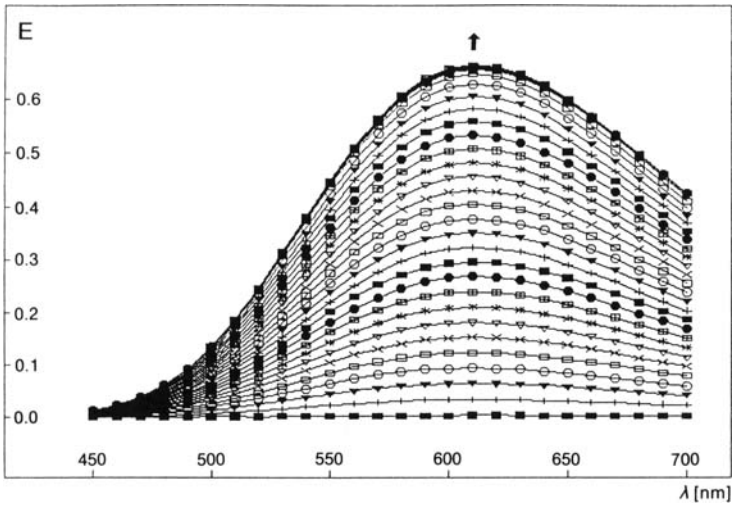
cyles, since we want to selectively substitute only one of the N-atoms in order to build the bridge. Compounds of this type are known. Thus, the trimethyl derivative **10** was previously used for monoalkylation studies with good success [19]. Also the tritosyl derivative **5** was described for the synthesis of homoditopic bis-macrocycles [9]. A synthesis similar to [9] leads to the tritosyl derivative **2** of the 12-membered tetraazamacrocycle with relatively good yields.

Although the acylation/alkylation method is generally applicable to whatever components one wishes to couple, there are some restrictions which must be noted. *E.g.*, the tritosyl derivative **2** can easily be acylated, however, its alkylation is more difficult. Thus, for building bis-macrocyles with a 12-membered ring, the latter unit is better introduced in the acylation step (*e.g.* **2** → **3**). In contrast to that, 14-membered derivatives can easily be either acylated or alkylated. Both bromoacetyl bromide or chloroacetyl chloride are equally well suitable for the acylation step. However, for the subsequent alkylation, the bromo derivative seems to be better and more reactive. On the other hand, the higher reactivity of the bromo derivatives makes it more difficult to purify these compounds. Thus, recrystallization of **3** or **9** from $MeOH/H_2O$ always gives some hydrolyzed compound, whereas chromatography on silica gel with $CH_2Cl_2/MeOH/NH_3$ is somewhat milder and yields a purer product. The first method is used for **3**, the second for **9**.

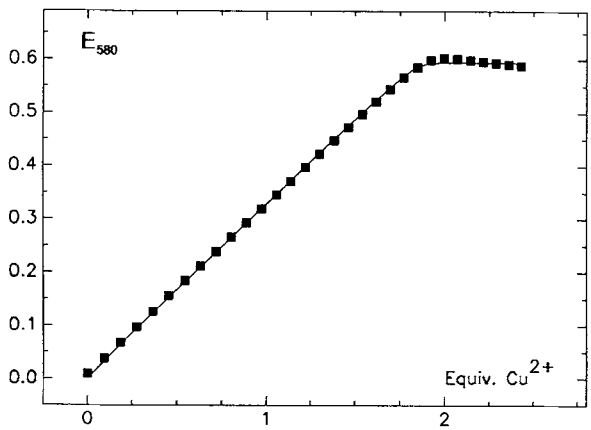
The alkylation with the bromoacetyl derivative gives relatively good yields when a 14-membered ring is to be alkylated (**3** → **6**, **9** → **11**). The following reduction of the amide group is performed with B_2H_6 in THF using a 10–20-fold excess of reagent and standard workup (see *Exper. Part*; **6** → **7**, **11** → **12**). The products **7** and **12** were then detosylated using conc. H_2SO_4 and the final product crystallized as hydrochloride (**8**) or hydrobromide (**13**), respectively.

The homoditopic derivatives were prepared using the procedure of *Fabbrizzi* and coworkers [9] for **17** or, in the case of the 12-membered ring, using oxalyl chloride (→ **14**) with subsequent reduction (→ **15**) and deprotection to give **16**, since 1,2-bis(tosyloxy)ethane was not successful as dialkylating agent.

Spectrophotometric Studies. The homo- and heteroditopic ligands were titrated at constant pH with Cu^{2+} to investigate whether two Cu^{2+} per ligand can be bound and if yes, whether the complexation takes place in separate steps. For the homoditopic bis-macrocycles **16** and **17**, the absorbance steadily increases at 610 nm and 530 nm, respectively, indicating that the affinity of the two binding sites for Cu^{2+} is equal or at least very similar (*Figs. 1–4*). The absorption maxima of the Cu^{2+} complexes of these two bis-macrocycles can be compared to those of the corresponding monocycles **1** and **4** which absorb at 590 [20] and 510 nm [21], respectively. The small bathochromic shift of *ca.* 20 nm observed in

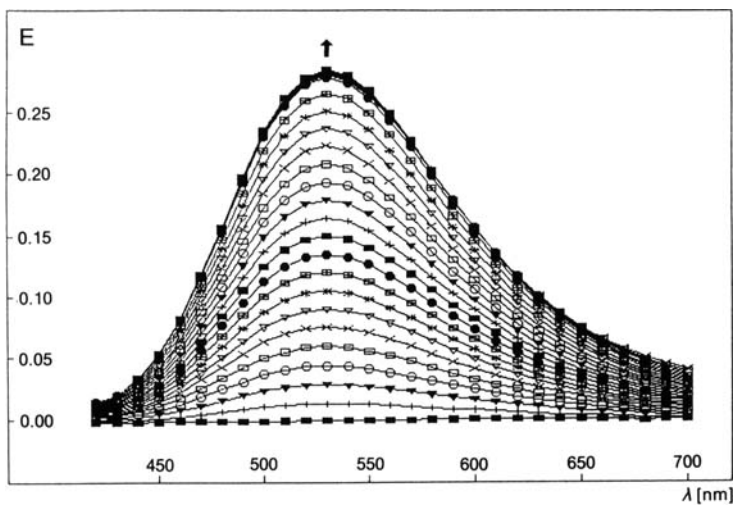


↑ Fig. 1. *Titration of* **16** ($c_L = 1.13 \cdot 10^{-3}$ M) *with* Cu^{2+} (0.01 ml addition with $c_{Cu} = 2 \cdot 10^{-2}$ M) *at pH 4.8*



← Fig. 2. *Plot of E against* Cu^{2+} *equivalents for* **16** *at λ 580 nm*

↓ Fig. 3. *Titration of* **17** ($c_L = 0.97 \cdot 10^{-3}$ M) *with* Cu^{2+} (0.01 ml addition with $c_{Cu} = 2.1 \cdot 10^{-2}$ M) *at pH 4.8*



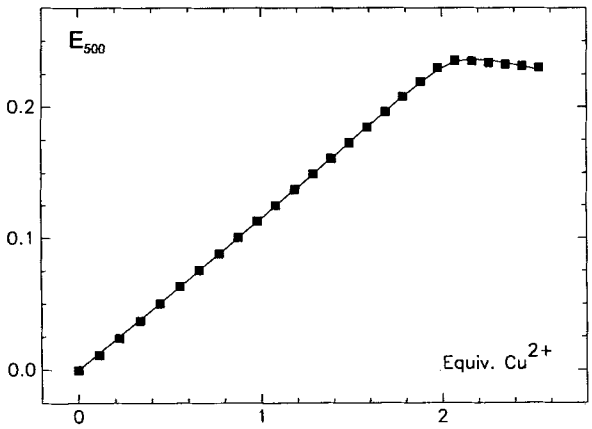


Fig. 4. *Plot of E against Cu^{2+} equivalents for* **17** *at λ 500 nm*

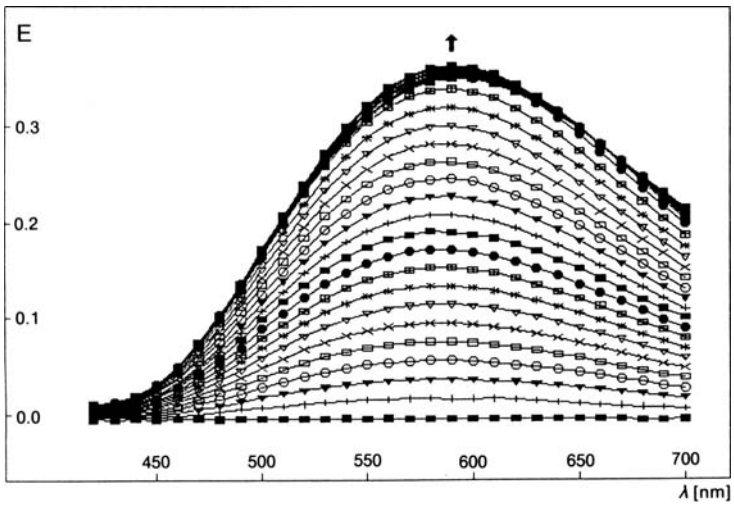


Fig. 5. *Titration of* **8** ($c_L = 1.00 \cdot 10^{-3}$ M) *with* Cu^{2+} (0.01 ml addition with $c_{Cu} = 2 \cdot 10^{-2}$ M) *at pH 4.8*

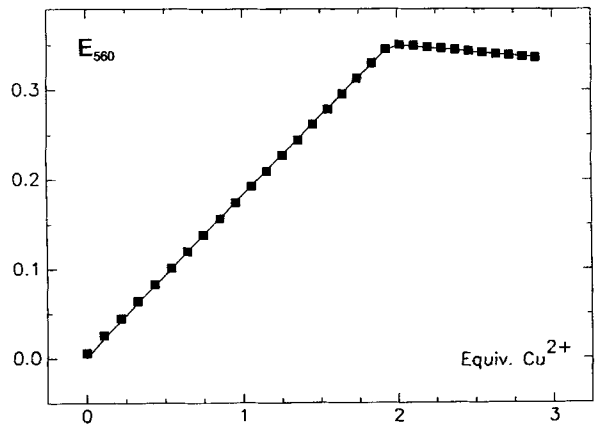


Fig. 6. *Plot of E against Cu^{2+} equivalents for λ 560 nm*

the complexes with **16** and **17** is probably due to a somewhat weaker ligand field because of the substituent at one N-atom.

The titration of the heteroditopic bis-macrocycle **8** is unexpected, since here too the absorbance steadily increases with an absorption maximum at 590 nm (*Figs. 5* and *6*). This indicates that the Cu^{2+} incorporation in the two sites proceeds concomitantly. Probably the incorporation kinetics and/or the thermodynamic stability of the two subunits do not differ enough to obtain a stepwise binding.

The last compound tested shows the expected effect. If one titrates **13** with Cu^{2+}, one observes an increase at 530 nm, corresponding to the incorporation of the first Cu^{2+} into the unsubstituted 14-membered unit (cyclam unit), before the absorptivity starts to increase at 640 nm, which corresponds to the Cu^{2+} chromophore of the methylated ring (Me_3cyclam unit) [22] (*Fig. 7*). The plot of the absorbance at 630 nm against the equivalents of Cu^{2+} clearly shows a break after one Cu^{2+} per bis-macrocycle has been added, followed by a second break two Cu^{2+} per bis-macrocycle are present (*Fig. 8*). In this

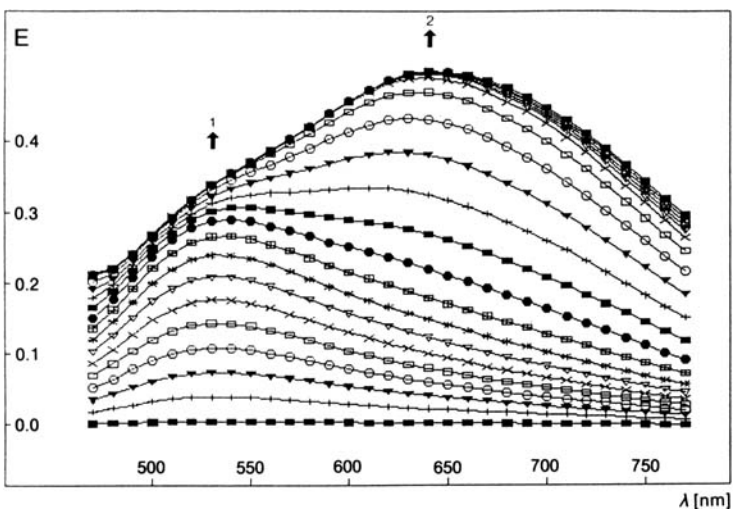


Fig. 7. *Titration of* **13** ($c_L = 1.70 \cdot 10^{-3}$ M) *with* Cu^{2+} (0.01 ml addition with $c_{Cu} = 9.9 \cdot 10^{-2}$ M) *at pH 4.8*

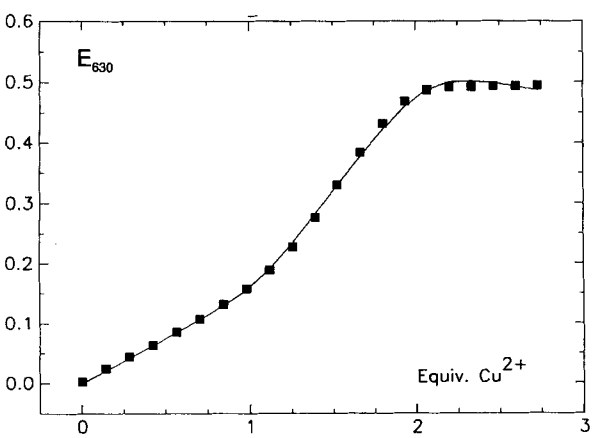


Fig. 8. *Plot of E against* Cu^{2+} *equivalents for* **13** *at λ 630 nm*

system, the two binding sites have affinities different enough to selectively bind the metal ion in a stepwise mechanism.

Qualitative measurements with Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} showed that in all these cases, the first metal ion always binds to the cyclam unit, whereas the second is coordinated by the Me_3cyclam unit. *Table 1* summarizes the results. If Cu^{2+} is added as the first metal ion, the typical band at 530 nm is observed, independent of the addition of a second metal ion, which has to bind to the Me_3cyclam unit. The effect is seen very clearly if Zn^{2+}, a colorless ion, is used in the first addition step. The spectra of the heterobinuclear species, in these instances, are the typical ones for the corresponding colored metal ion which is added in the second step in the Me_3cyclam unit. So isomers of the type $[(Zn,Cu)L]^{4+}$ and $[(Cu,Zn)L]^{4+}$ (L = **13**) with absorption maxima at 650 nm and 530 nm, respectively, can be prepared.

Table 1. *Absorption Maxima and Shoulders* (sh) [nm] *of the Homo- and Heterobinuclear Complexes with* **13**, *Obtained by Sequential Addition of Two Metal Ions* M^1 *and* M^2

M^1	M^2				
	no metal	Cu^{2+}	Ni^{2+}	Co^{2+}	Zn^{2+}
Cu^{2+}	530	540 (sh), 640	530, 650 (sh)	530[a])	530
Ni^{2+}	460	450 (sh), 660	395, 460, 660	460, 550 (sh)	460
Zn^{2+}	–	650	390, 510, 640	510	–

[a]) The absorption bands of Co^{2+} are too weak to be seen and are hidden by those of the Cu^{2+} chromophore.

Electrochemical Studies. The binuclear Ni^{2+} complexes were studied by electrochemical methods and compared to the results obtained for the mononuclear ones. Cyclic voltammetry (CV) showed that the reversibility decreases from the 14- to the 12-membered ring systems in the mono- as well as in the binuclear-compounds. Beside CV, also differential pulse polarography (DPV) was used since it allows an easier determination of the potential of each step, especially in the case of the binuclear complexes. The $E_{1/2}$ values are calculated from the peak potentials E_p^1 and E_p^2, using the working curve (*Eqn. 1*) of *Richardson* and *Taube* [23].

$$E_{1/2}^1 = E_c + \frac{\Delta E_{1/2} + \Delta E_{puls}}{2}, \text{ with } E_c = \frac{E_p^1 + E_p^2}{2} \qquad (1)$$

$$E_{1/2}^2 = E_{1/2}^1 - \Delta E_{1/2}$$

Our results with ligands **1**, **4**, and **17** compare well with the corresponding literature values (see [24], [25], and [9], resp.). The $E_{1/2}^1$ values of the binuclear Ni^{2+} complexes are all shifted to more positive values (50–150 mV) than the corresponding values for the mononuclear species (*Table 2*). This results because of the additional positive charge of the second Ni^{2+}, which makes the oxidation $Ni^{2+} \rightarrow Ni^{3+}$ more difficult. Also the separation between $E_{1/2}^1$ and $E_{1/2}^2$ of 90–100 mV (*Table 2*) in the homoditopic ligands can be understood in the same way. The large separation between $E_{1/2}^1$ and $E_{1/2}^2$ of 413 mV in case of **8** is due to the ditopic nature of the bis-macrocycle and indicates that the two Ni^{2+} have a very different environment (*Fig. 9*).

Table 2. *Peak and Half-Wave Potentials* (in mV, against NHE) *for the* Ni^{2+}/Ni^{3+} *Oxidation in the Complexes with* **1**, **4**, **16**, **17**, *and* **8** *Obtained from DPV in Acetonitrile*

Ni^{2+} Complex with	Experimental				Calculated		
	E_p^1	E_p^2	ΔE_p	E_c	$E_{1/2}^1$	$E_{1/2}^2$	$\Delta E_{1/2}$
1 (Cyclen)	1413	–	–	–	1413	–	–
4 (Cyclam)	996	–	–	–	996	–	–
16	1460	1550	90	1505	1460	1560	100
17	1180	1250	70	1215	1175	1265	90
8	1150	1563	413	–	1150	1563	413

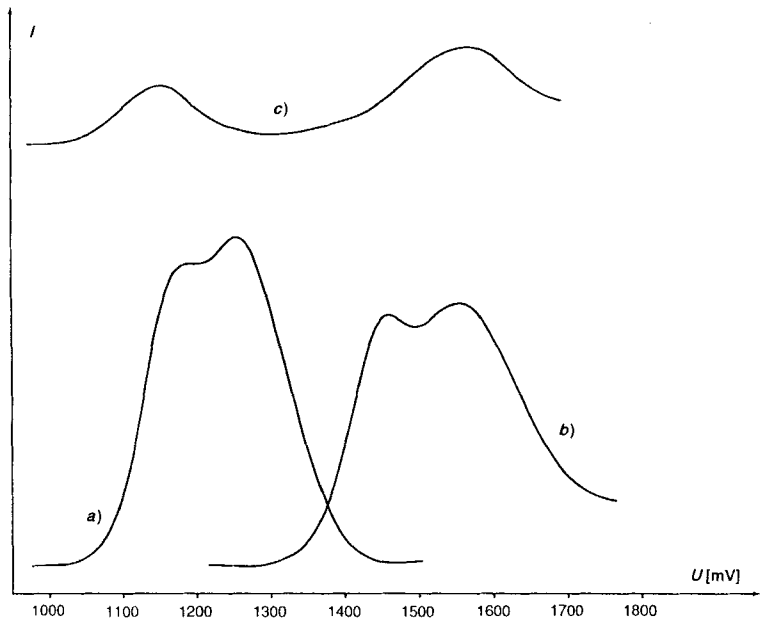


Fig. 9. *DPV of the dinickel(II) complexes of* a) **17**, b) **16**, *and* c) **8** *in acetonitrile*

The binuclear complex with **13** gives CV and DPV which can not be interpreted, since they are irreversible, and absorption phenomena occur with Pt- and glassy carbon electrodes.

EPR Spectra. Another technique to study metal-metal interactions is EPR of paramagnetic ions. *Fig. 10* shows a series of EPR spectra of Cu^{2+} complexes with our new ligand **13**. The EPR spectrum of **13** with only one Cu^{2+} per ligand ([Cu^{2+}(**13**)]) gives the typical pattern for a tetragonal CuN_4 unit with four peaks corresponding to $g_\parallel$ and one to $g_\perp$ [26] (*Fig. 10a*). The spectrum of [(Cu^{2+},Zn^{2+})(**13**)] (obtained by addition of Cu^{2+} followed by that of Zn^{2+}; *Fig. 10b*) closely resembles that of [Cu^{2+}(**13**)]. The former spectrum and that of [(Zn^{2+},Cu^{2+}(**13**)] (obtained by addition of Zn^{2+} and then of Cu^{2+}; *Fig. 10c*) are again typical for a tetragonal geometry of the central ion, but distinctly differ from each other, indicating that the Cu^{2+} is in two different coordination environments.

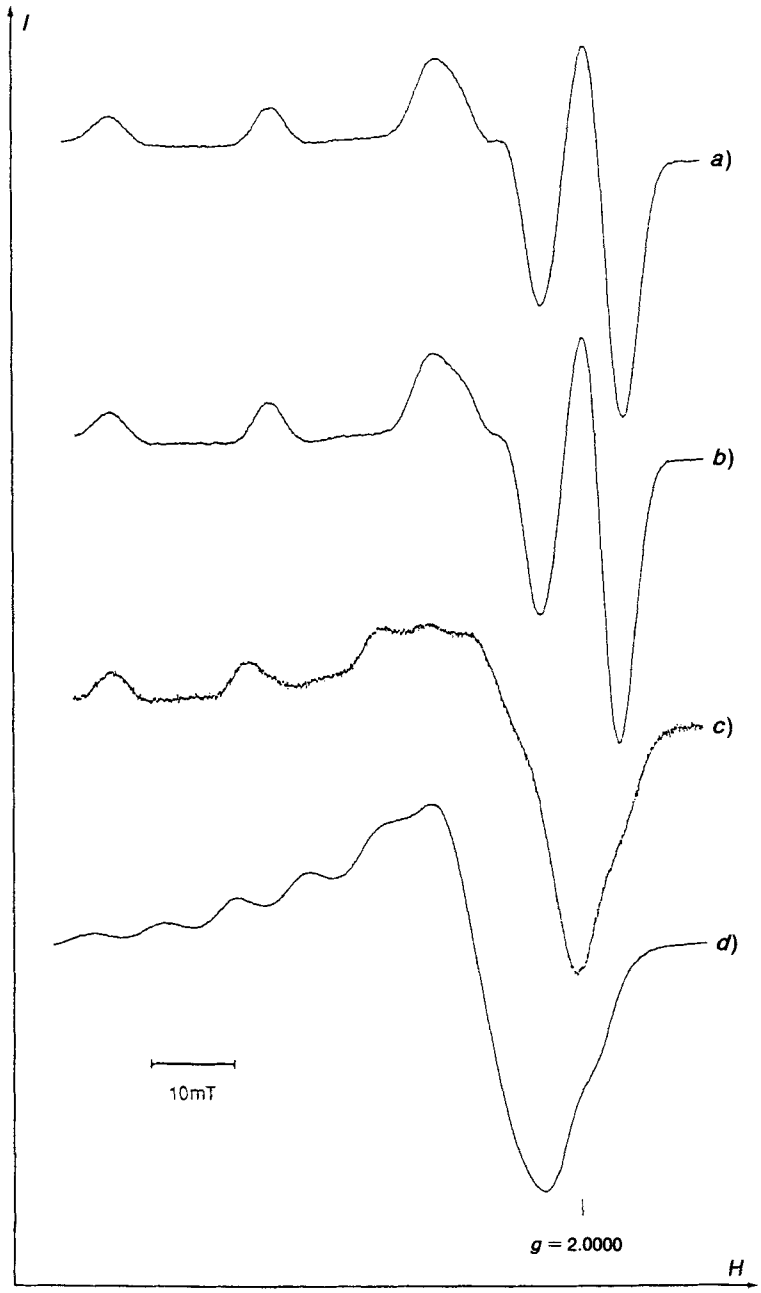


Fig. 10. *EPR Spectra of the* Cu^{2-} *complexes with* $L = \mathbf{13}$ *in* DMF/H_2O *glass at* $-120°$: a) $[Cu^{2-}L]$, b) $[(Cu^{2+},Zn^{2+})L]$, c) $[(Zn^{2+},Cu^{2+})L]$, *and* d) $[(Cu^{2+},Cu^{2+})L]$

The EPR spectrum of [(Cu^{2+},Cu^{2+})(**13**)] clearly shows the Cu^{2+}-Cu^{2+} interaction by the smaller value of $a_{\|}$, which is typical when dipole-dipole interaction is present in such binuclear Cu^{2+} complexes [27].

In summary, we can state that the synthetic approach chosen here opens up the possibility to prepare a series of heteroditopic ligands. However, as shown by compound **8**, this is not always a guarantee for the easy preparation of heterobinuclear complexes by sequential addition of two metal ions. With compound **13**, the preparation of heterobinuclear complexes, however, is possible due to the different nature of the binding site and of their complexation rates.

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