237. Lipophilic Amides of EDTA, NTA and Iminodiacetic Acid as Ionophores for Alkaline Earth Metal Cations

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(9.IX.80)

Summary

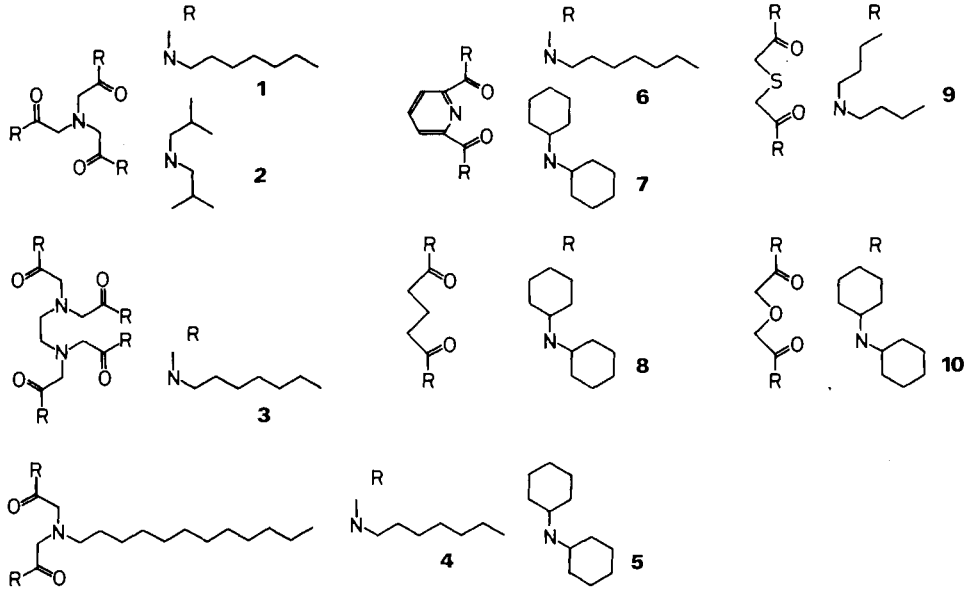
A series of electrically neutral lipophilic di-, tri-, and tetra-amides containing tertiary-amine N-atoms were prepared in order to investigate their selectivity for alkali and alkaline earth metal cations in solvent polymeric membranes. Considerable selectivity changes were observed for membranes incorporating certain of these ligands as compared with ligand-free membranes. A 1:1 cation/ligand complex was isolated from *N,N',N''*-triheptyl-*N,N',N''*-trimethyl-nitrilotriacetamid and $Mg(SCN)_2$ whereas with $Ca(SCN)_2$ the corresponding 2:3 cation/ligand complex was formed. *N,N',N'',N'''*-Tetraheptyl-*N,N',N'',N'''*-tetramethyl-ethylenediaminetetraacetamide yields a 1:1 cation/ligand complex with $Mg(SCN)_2$.

Introduction. – Electrically neutral lipophilic ligands containing the appropriate number of binding sites of high dipole moment and/or of high polarizability could behave as ionophores for alkaline earth cations [1–4]. The complexing agents EDTA and NTA have the ability to form cavities suitable for the uptake of alkaline earth cations [5] [6]. Complexing occurs between the cations and O- and N-atoms of the complexing agent. The resulting complexes possess a high stability [7]. It might be expected, therefore, that the corresponding lipophilic amides should behave as ionophores leading to membranes with selectivity for alkaline earth metal cations. Compounds **1–7** were prepared *(Scheme)* to test this hypothesis. A molecular model [8] of the hexadentate ligand **3** can be constructed in which octahedral coordination sphere is almost optimal. This is of special interest in view of achieving selectivity for Mg^{2+} [1] [3].

Results and Discussion. – The potentiometrically determined [9] selectivity factors induced in solvent polymeric membranes by some of the ligands studied are presented in *Figures 1* and *2*. The selectivity factors given as K^{Pot}_{MgX} represent the membrane's preference of the ion X relative to Mg^{2+} [9]. Columns 2 and 3 in *Figure 1* show clearly that ligands **1** and **3** induce a selectivity change relative to the membrane without ionophore (column 1). The same holds for ligand **2**. Of the alkali and alkaline earth metal cations tested, Ca^{2+} is the preferred ion for ligand **1**

0018-019X/80/8/2264-07$01.00/0

Scheme



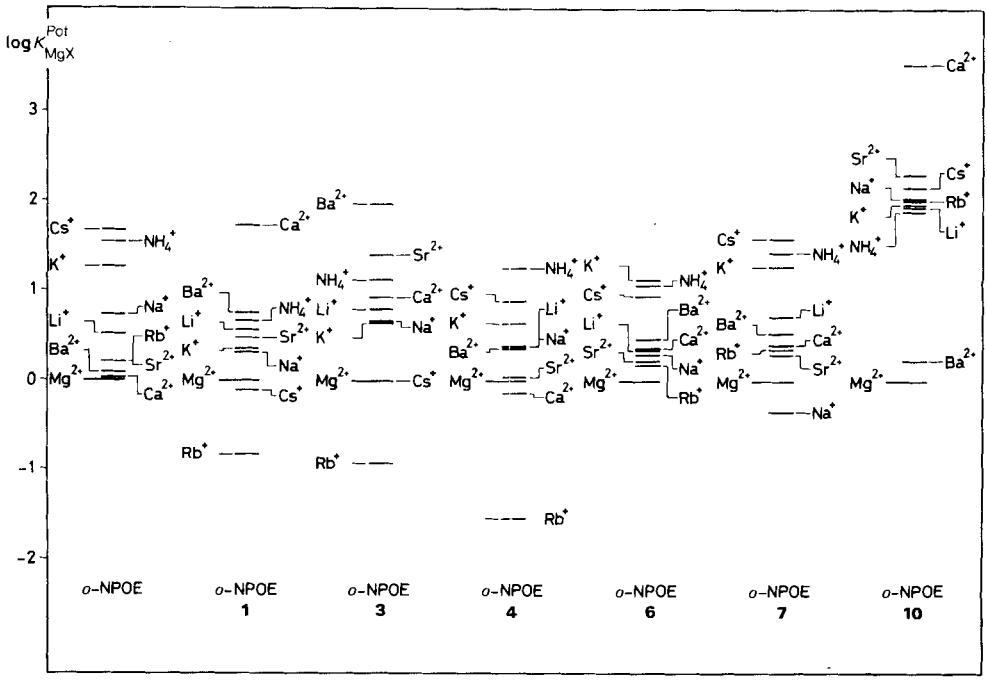


Fig. 1. *Selectivity factors, log* K^{Pot}_{MgX}, *for solvent polymeric membranes with* o-*nitrophenyl octyl ether (*o-*NPOE) as membrane solvent.* Ligand-free membranes (column 1) are compared with membranes containing different ligands (separate solution method, 0.1 M solutions of the chlorides, 20–22°).

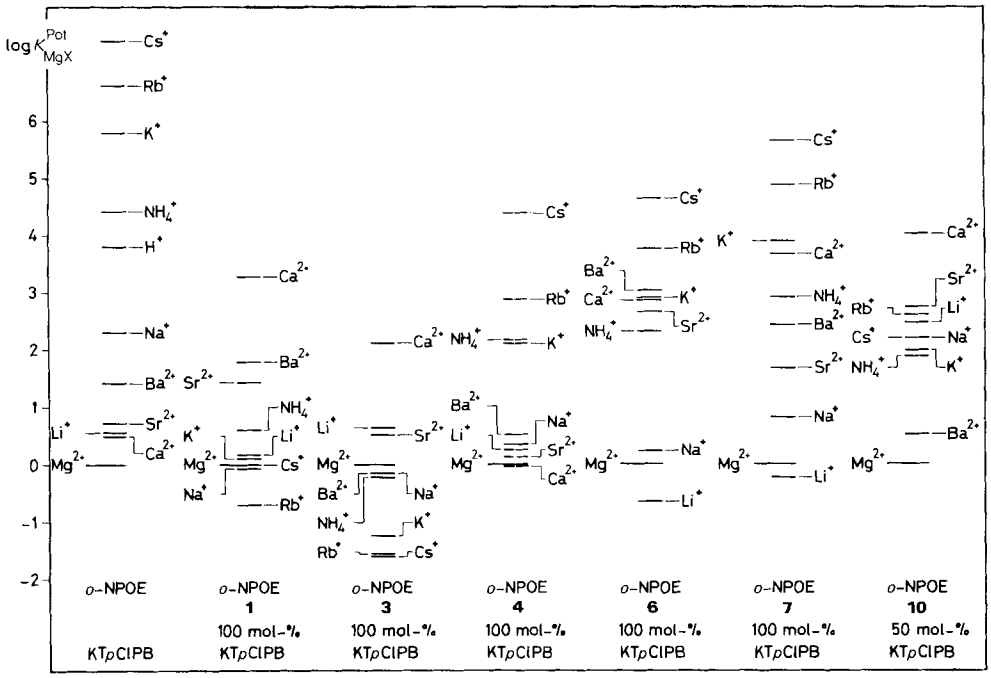


Fig. 2. *Selectivity factors, log* K^{Pot}_{MgX}, *for solvent polymeric membranes with* o-*nitrophenyl octyl ether (*o-*NPOE) as membrane solvent and incorporated lipophilic anionic sites (potassium-tetra-(*p-*chlorophenyl)borate (KTpClPB)).* Ligand-free membranes (column 1) are compared with membranes containing different ligands (separate solution method, 0.1M solutions of the chlorides, 20–22°).

whereas ligand **3** has a greater selectivity for Ba^{2+} ions. Under the same conditions ligands **4** to **9** *(Scheme)* do not induce selectivity changes as compared with solvent polymeric membranes without ligand. In the absence of ion-selective ligands the incorporation of lipophilic anions (potassium salt of tetra-(*p*-chlorophenyl)borate (KT*p*ClPB)) into membranes of the type discussed leads to a heavy preference for large cations over small ones of the same charge (see column 1 in *Fig. 2*). A comparison of columns 2 and 3 with column 1 in *Figure 2* makes clear that ionophores **1** and **3** induce strong selectivity changes, which amount to a factor of 10^9 for Cs^+ relative to Mg^{2+} in the case of **3**. As described earlier [10] 3-oxapentane diamides (*e.g.* **10**; see columns 7 in *Fig. 1* and *2*) are extremely efficient carriers for Ca^{2+}. A replacement of the ether O-atom by an aromatic N-atom leads to some preference for alkaline earth relative to alkali metals cations (**6** and **7**, see columns 5 and 6 in *Fig. 2*), whereas a replacement by a tertiary amine N-atom (**4** and **5**) nearly abolishes the ion-selectivity as observed in membranes (see columns 4 in *Fig. 1* and *2*). No selectivities are induced when the ether O-atom of **10** is replaced by a S-atom (**9**) or a methylene group (**8**).

The interaction of ligand **1** with Mg^{2+} and Ca^{2+} is corroborated by the isolation of lipophilic 1:1 and 2:3 cation/ligand complexes for magnesium and calcium

thiocyanates, respectively. Similarly, with magnesium thiocyanate ligand **3** yields a 1:1 Mg^{2+}/ligand complex. This is in agreement with the existence of 1:1 Mg^{2+}/EDTA complexes [6].

This work was partly supported by the *Swiss National Science Foundation.*

Experimental Part

EMF.-Measurements. – The solvent polymeric membranes were prepared using 1–2 wt.-% ligand, 33 wt.-% polyvinylchloride (SDP, hochmolekular, *Lonza AG*, CH-3930 Visp) and 65–66 wt.-% *o*-nitrophenyl octyl ether (synthesized according to [11]). The membrane preparation and the measuring technique have been described in detail elsewhere [12]. Throughout, cell assemblies of the type Hg; Hg_2Cl_2, KCl (satd.)/3M KCl/sample solution//solvent polymeric membrane//0.1M $MgCl_2$, AgCl; Ag have been used. The selectivity factors, log K^{Pot}_{MgX}, were obtained by the separate solution method (SSM, 0.1M metal chloride solutions) [9]. The activity coefficients used are described in detail in [13] [14]. The measurements were performed at a temperature of 20–22°.

Syntheses. – *General remarks.* IR. spectra were recorded on a *Perkin-Elmer* Infracord 157G spectrophotometer. Absorptions are given in cm^{-1}. ^{1}H-NMR. spectra were measured on a *Varian* T-60 at 60 MHz and on a *Varian* HA100 at 100 MHz using, unless otherwise stated, $CDCl_3$ as solvent. The chemical shifts are reported in δ (ppm) using tetramethylsilane (TMS) as internal standard. For each signal the multiplicity (with the following abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *m* = multiplet, br. = broad), the relative intensity, and the assignment is given in parenthesis. ^{13}C-NMR. spectra were recorded on a *Varian* XL-100 spectrometer at 25.2 MHz. Chemical shifts are reported in δ (ppm) relative to TMS as internal reference. Mass spectra (MS.) were taken on a *Hitachi*-RMU-6M mass spectrometer (Prof. Dr. *J. Seibl*, ETHZ). The most important ions are reported as *m/z* values and relative intensities (% base peak in parenthesis). Microanalyses were performed by *D. Manser* (ETHZ). Note that such ion carriers of rather high molar mass may tenaciously retain solvent molecules (see ligands **1**, **2** and **4**). Melting points (m.p.) were determined on a *Culatti* apparatus and are uncorrected. Thin layer chromatography was carried out on 0.25 mm precoated silica gel plates (*E. Merck*, Kieselgel 60 F_{254}) using UV. light (254 and 366 nm), and/or iodine, and/or 3.5% phosphormolybdic acid (*E. Merck*) for visualisation. Preparative thin layer chromatography (TLC.) was performed on 2 mm precoated silica gel plates (*E. Merck*, Kieselgel 60 F_{254}). Unless indicated otherwise, compounds were eluted from the adsorbents with ethyl acetate. Column chromatography was performed using silica gel (*E. Merck*, Kieselgel 60, 0.040–0.063 mm). Yields are not optimized.

Preparation of the ligands. The synthesis of ligands **8**, **10** [10] and **9** [15] were described earlier.

N,N′,N″-*Triheptyl*-N,N′,N″-*trimethyl-nitrilo-triacetamide* (**1**). – *Nitrilo-triacetic acid tris*(p-*nitrophenyl)ester.* To a solution of 5 g (26.2 mmol) nitrilo-triacetic acid *(Fluka, puriss. p.a.)* and 10.9 g (78 mmol) *p*-nitrophenol *(Fluka, puriss. p.a.)* in 150 ml ethyl acetate was added 16.2 g (78 mmol) *N,N′*-dicyclohexylcarbodiimide *(Fluka, puriss.)* dissolved in 30 ml ethyl acetate. The reaction was completed by stirring overnight at room temperature. The solution was filtered and the filtrate concentrated *in vacuo*. The residue was triturated with chloroform/acetone 1:1 in order to dissolve the unreacted *p*-nitrophenol. The undissolved crystalline part was filtered off to obtain 1.1 g (2.0 mmol) triester (8%). – IR. (nujol): 1775, 1760. – To a solution of 1.1 g (2.0 mmol) nitrilo-triacetic acid-tris(*p*-nitrophenyl)ester in 20 ml chloroform was added dropwise 0.77 g (6.0 mmol) *N*-heptyl-*N*-methyl-amine *(Fluka, purum)* in 10 ml chloroform. The resulting solution was stirred overnight at 50°. The chloroform was evaporated and the reaction mixture redissolved in diethyl ether. This ether solution was washed twice with 0.02M NaOH and three times with water. The solvent was evaporated and the crude product distilled under vacuum (0.2 Torr, 150°) to yield 0.79 g (1.5 mmol) **1** (75%). – IR. ($CHCl_3$): 1640. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 9 H, 3 CH_3CH_2); 1.1–1.6 (br., 30 H, 3$(CH_2)_5$); 2.85 and 3.0 (2 *s*, 9 H, 3 CH_3N); 3.3 (*t*, 6 H, 3 CH_2N); 3.6 (*s*, 6 H, 3 NCH_2CO). – ^{13}C-NMR. ($CDCl_3$): 14.1 (*qa*, CH_3CH_2); 22.6 (*t*, CH_3CH_2); 26.7, 26.9, 27.2, 28.5, 29.1 and 31.8 (6 *t*, CH_2); 33.3 and 34.8

(2 *qa*, CH_3N); 47.9 and 49.4 (2 *t*, CH_2N); 55.4 and 56.2 (2 *t*, NCH_2CO); 169.8 and 170.1 (2 *s*, CO). – MS.: 524 (8, M^+), 395 (45), 368 (100), 354 (27), 239 (5), 225 (5), 156 (3), 142 (44).

$C_{30}H_{60}N_4O_3 \cdot \frac{1}{3} H_2O$	Calc.	C 67.88	H 11.52	N 10.55%
(524.83 + 6.01)	Found	„ 67.96	„ 11.87	„ 10.01%

N,N,N′,N′,N″,N″-*Hexaisobutyl-nitrilo-triacetamide* (**2**). – Following the procedure given above 0.8 g (1.4 mmol) nitrilo-triacetic acid tris(*p*-nitrophenyl)ester was reacted with 2.6 g (20 mmol) diisobutylamine *(Fluka, purum)* in 20 ml chloroform and 2 ml triethylamine to obtain 0.4 g (0.8 mmol) of crude **2** (57%). A part (120 mg, 0.23 mmol) of the product was purified by TLC. (ethyl acetate): 68 mg (0.13 mmol) **2**. – IR. ($CHCl_3$): 1640. – ^{1}H-NMR. ($CDCl_3$): 0.85 (2 *d*, 36 H, 12 CH_3CH); 1.95 (*m*, 6 H, 6 CH); 3.15 (2 *d*, 12 H, 6 NCH_2CH); 3.7 (*s*, 6 H, 3 NCH_2CO). – MS.: 524 (13, M^+), 395 (15), 368 (100), 354 (17), 312 (4), 298 (1), 194 (14).

$C_{30}H_{60}N_4O_3 \cdot \frac{1}{2} H_2O$	Calc.	C 67.50	H 11.52	N 10.50%
(524.83 + 9.01)	Found	„ 67.61	„ 11.57	„ 10.64%

N,N′,N″,N‴-*Tetraheptyl*-N,N′,N″,N‴-*tetramethyl-ethylenediamine-tetraacetamide* (**3**). – N-*Heptyl*-N-*methyl-chloroacetamide*. To a solution of 13 g (100 mmol) *N*-heptyl-*N*-methyl-amine *(Fluka, purum)* in 60 ml diethyl ether 5.6 g (50 mmol) chloroacetylchloride *(Fluka, purum)* was added dropwise at −5°. The solution was stirred overnight at room temperature, then filtered and evaporated. The residue (10.1 g, 49.1 mmol, 98%) was distilled *in vacuo* (0.08 Torr, 97–105°) to yield 8.6 g (41.8 mmol, 84%) product. – IR. (liq.): 1655. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 3 H, CH_2CH_3); 1.2–1.7 (br., 10 H, $(CH_2)_5$); 2.9 and 3.0 (2 *s*, 3 H, NCH_3); 3.35 (*t*, 2 H, NCH_2); 4.05 (*s*, 2 H, $ClCH_2CO$).

A solution of 0.34 g (5.6 mmol) anhydrous 1,2-diamino ethane *(Fluka, puriss p.a.)*, 4.6 g (22.6 mmol) of *N*-heptyl-*N*-methyl-chloroacetamide and 2.3 g (22.6 mmol) of triethylamine *(Fluka, puriss. p.a.)* in 30 ml of dry *m*-xylene was heated at 100–105° under N_2 for 28 h. The cooled reaction mixture was filtered and the precipitate washed with *m*-xylene. Evaporation of the solvent *in vacuo* (50°) afforded quantitatively a crude product which was portionwise (100–300 mg) chromatographed on *Merckogel* (100 g OR-PVA 2000, *E. Merck* No. 9375, column: 1.4 cm × 1 m, flow rate: 9–10 ml/h, eluent THF (distilled over $LiAlH_4$)). The total recovery of pure **3** was 42–45%. – IR. ($CHCl_3$): 1645. – ^{1}H-NMR. ($CDCl_3$): 0.9 (*t*, 12 H, 4 CH_2CH_3); 1.1–1.7 (br., 40 H, 4 $(CH_2)_5$); 2.85 and 3.0 (2 *s*, 12 H, 4 NCH_3); 2.9 (*s*, 4 H, NCH_2CH_2N); 3.3 (*t*, 8 H, 4 NCH_2); 3.6 (*s*, 8 H, 4 NCH_2CO). – MS.: 736 (15, M^+), 607 (8), 580 (68), 566 (11), 425 (6), 411 (8), 382 (65), 368 (54), 225 (26), 211 (25), 199 (100).

$C_{42}H_{84}N_6O_4$ (737.16) Calc. C 68.43 H 11.49 N 11.40% Found C 68.41 H 11.36 N 11.31%

N,N′-*Diheptyl*-N,N′-*dimethyl-3-dodecyl-3-aza-glutaramide* (**4**). – A solution of 2.06 g (10 mmol) *N*-heptyl-*N*-methyl-chloroacetic amide (see procedure above) in 10 ml toluene was added slowly at room temperature to a stirred solution of 0.93 g (5 mmol) dodecylamine *(Fluka, puriss.)* and 1 g (10 mmol) triethylamine *(Fluka, puriss. p.a.)* in 30 ml toluene. After stirring for 3 days at room temperature and 1 h at 50° the reaction was shown to be complete. The solvent was removed under vacuum, the residue redissolved in chloroform and the solution washed with water. Evaporation of the organic phase gave 1.9 g of crude product, which was purified by column chromatography (chloroform/acetone 3:1) to yield 1.0 g (1.9 mmol, 38%) diamide **4**. – IR. ($CHCl_3$): 1640. – ^{1}H-NMR. ($CDCl_3$): 0.8 (*t*, 9 H, 3 CH_2CH_3); 1.0 to 1.6 (br., 40 H, $(CH_2)_{20}$); 2.6 (*t*, 2 H, NCH_2); 2.85 and 3.0 (2 *s*, 6 H, 2 NCH_3); 3.25 (*t*, 4 H, 2 $CONCH_2$); 3.4 (*s*, 4 H, 2 NCH_2CO). – MS.: 523 (4, M^+), 394 (14), 367 (100), 353 (18).

$C_{32}H_{65}N_3O_2 \cdot \frac{1}{3} H_2O$	Calc.	C 72.54	H 12.49	N 7.93%
(523.88 + 6.01)	Found	„ 72.76	„ 12.39	„ 7.79%

N,N,N′,N′-*Tetracyclohexyl-3-dodecyl-3-aza-glutaramide* (**5**). – N,N-*Dicyclohexyl-chloro-acetamide*. To a solution of 18.1 g (100 mmol) dicyclohexylamine *(Fluka, puriss. p.a.)* in 100 ml diethyl ether was added dropwise at −5° 5.6 g (50 mmol) chloroacetylchloride *(Fluka, purum)*. The mixture was stirred over night at room temperature, filtered and the solvent diethyl ether evaporated. The residue (11 g, 43 mmol, 85%) was distilled *in vacuo* (0.05 Torr, 140–144°) to yield 1.5 g (5.8 mmol, 12%) of the chloro-amide. – IR. (liq.): 1640. Reaction of *N,N*-dicyclohexyl-chloro-acetamide with dodecylamine under the same experimental conditions, given above for the preparation of compound **4**, yielded the diamide **5** (40%). – IR. ($CHCl_3$): 1635. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 3 H,

CH_2CH_3); 1–3.8 (br., 66 H, 4 C_6H_{11} and $(CH_2)_{11}$); 3.4 (*s*, 4 H, 2 NCH_2CO). – MS.: 627 (16, M^+), 544 (1), 446 (7), 419 (100), 405 (10), 337 (14). – M.p.: 93–95°.

$C_{40}H_{73}N_3O_2$ (628.04) Calc. C 76.50 H 11.72 N 6.69% Found C 76.83 H 11.85 N 6.60%

N,N'-*Diheptyl*-N,N'-*dimethyl-2,6-pyridine-dicarboxamide* (**6**). – *2,6-Pyridine-dicarbonyl dichloride.* A solution of 3.3 g (20 mmol) 2,6-pyridine-dicarboxylic acid *(Fluka, purum)* and 9.5 g (80 mmol) thionylchloride *(Fluka, puriss. p.a.)* was heated overnight in 50 ml refluxing benzene. The benzene was then evaporated under reduced pressure to give the dicarbonyl dichloride. – IR. (liq.): 1760. A solution of 1.3 g (6.4 mmol) 2,6-pyridine-dicarbonyl dichloride in 10 ml toluene was added slowly at 0° to a stirred solution of 1.65 g (12.8 mmol) *N*-heptyl-*N*-methyl-amine *(Fluka, purum)* and 1.3 g (12.8 mmol) triethylamine *(Fluka, puriss. p.a.)* in 30 ml toluene. The mixture was stirred overnight at room temperature. The solvent was evaporated under vacuum and the residue dissolved in diethyl ether. The organic phase was consecutively washed with 0.1M HCl, 0.1M NaOH and with water to give 1.9 g of crude product. Purification by column chromatography (chloroform/acetone 4:1) yielded 0.62 g (1.6 mmol) of the diamide **6** (25%). – IR. ($CHCl_3$): 1630. – ^{1}H-NMR. ($CDCl_3$): 0.8 and 0.9 (2 *t*, 6 H, 2 CH_2CH_3); 1.0–1.8 (br., 20 H, $(CH_2)_{10}$); 3.0 and 3.05 (2 *s*, 6 H, 2 NCH_3); 3.3 and 3.5 (2 *t*, 4 H, 2 NCH_2); 7.5–7.9 (*m*, 3 H, aryl). – MS.: 389 (7, M^+), 332 (4), 304 (7), 235 (15), 128 (100).

$C_{23}H_{39}N_3O_2$ (389.58) Calc. C 70.91 H 10.09 N 10.79% Found C 70.82 H 10.14 N 10.74%

N,N,N',N'-*Tetracyclohexyl-2,6-pyridine-dicarboxamide* (**7**). – The diamide **7** was prepared following the same procedure as for the synthesis of compound **6**. The product was further purified by recrystallization from diethyl ether/hexane (yield: 50%). – IR. ($CHCl_3$): 1625. – ^{1}H-NMR. ($CDCl_3$): 1.0–3.5 (br., 44 H, 4 C_6H_{11}); 7.2–7.9 (*m*, 3 H, aryl). – MS.: 493 (8, M^+), 410 (5), 368 (7), 328 (20), 312 (7), 286 (11), 180 (100). – M.p.: 177–180°.

$C_{31}H_{47}N_3O_2$ (493.73) Calc. C 75.41 H 9.59 N 8.51% Found C 75.25 H 9.45 N 8.45%

Mg^{2+}-*Complex of* **1**. After mixing 100 mg (0.19 mmol, 1 mol-equiv.) **1** in acetone and 27 mg (0.19 mmol, 1 mol-equiv.) anhydrous $Mg(SCN)_2$ in acetone, petroleum ether was added to precipitate the crude complex which was purified by crystallization from acetone/petroleum ether, m.p. 202–203°. Another batch using 2 mol-equiv. of **1** and 1 mol-equiv. of $Mg(SCN)_2$ gave the same result (m.p.: 203–204°).

$C_{30}H_{60}N_4O_3 \cdot Mg(SCN)_2$	Calc.	C 57.77	H 9.09	N 12.63	S 9.64%
(665.29)	Found	„ 57.23	„ 8.97	„ 12.36	„ 9,67%

Ca^{2+}-*Complex of* **1**. After mixing 131 mg (0.25 mmol, 1 mol-equiv.) **1** in acetone and 40 mg (0.25 mmol, 1 mol-equiv.) anhydrous $Ca(SCN)_2$ in acetone at room temperature, diethyl ether was added to precipitate the crude complex which was purified by crystallization from acetone/diethyl ether, m.p. 263–265°. Other experiments using 1 mol-equiv. of $Ca(SCN)_2$ together with 2 and 3 mol-equiv. of **1** gave the same product (m.p. 263–265°, resp. 266–268°).

$(C_{30}H_{60}N_4O_3)_3 \cdot 2\,Ca(SCN)_2 \cdot 2\,H_2O$	Calc.	C 58.71	H 9.64	N 11.65	S 6.67%
(1922.99)	Found	„ 58.51	„ 9.39	„ 11.71	„ 7.45%

Mg^{2+}-*Complex of* **3**. After mixing 147 mg (0.20 mmol, 2 mol-equiv.) **3** in acetone and 14 mg (0.10 mmol, 1 mol-equiv.) anhydrous $Mg(SCN)_2$ in acetone at room temperature, petroleum ether was added to precipitate the crystallized complex.

$C_{42}H_{84}N_6O_4 \cdot Mg(SCN)_2 \cdot 1\,H_2O$	Calc.	C 59.01	H 9.68	N 12.51%
(895.64)	Found	„ 58.32	„ 9.41	„ 12.14%
$C_{42}H_{84}N_6O_4 \cdot Mg(SCN)_2 \cdot 2\,H_2O$	Calc.	C 57.84	H 9.71	N 12.26%
(913.65)	Found	„ 58.32	„ 9.41	„ 12.14%

REFERENCES

[1] *W. Simon, W.E. Morf & D. Ammann,* in 'Proceedings of the International Symposium on Calcium-Binding Proteins and Calcium Function in Health and Disease', Cornell University, Ithaca, N.Y., USA, June 5–9, 1977, in 'Calcium-Binding Proteins and Calcium Function' (R.H. Wasserman, R.A. Corradino, E. Carafoli, R.H. Kretsinger, D.H. MacLennan and F.L. Siegel (Eds.)), North Holland, New York, Amsterdam, Oxford 1977, p. 50.

[2] *D. Ammann, R. Bissig, M. Güggi, E. Pretsch, W. Simon, I.J. Borowitz & L. Weiss,* Helv. *58,* 1535 (1975).

[3] *R.J.P. Williams,* in 'The Regulation of Intracellular Calcium' (C.J. Duncan (Ed.)), Cambridge University Press, England 1976, p. 1.

[4] *W.E. Morf & W. Simon,* Helv. *54,* 2683 (1971).

[5] *G. Schwarzenbach & H. Flaschka,* in 'Die komplexometrische Titration', Enke, Stuttgart 1965.

[6] *J.J. Stezowski, R. Countryman & J.L. Hoard,* Inorg. Chem. *12,* 1749 (1973).

[7] *L.G. Sillen & A.E. Martell,* in 'Stability Constants of Metal-Ion Complexes', The Chemical Society Spec. Publ. No. 17, London 1964.

[8] *Corey-Pauling-Koltun,* Ealing Scientific Limited, London.

[9] *G.G. Guilbault, R.A. Durst, M.S. Frant, H. Freiser, E.H. Hansen, T.S. Light, E. Pungor, G. Rechnitz, N.M. Rice, T.J. Rohm, W. Simon & J.D.R. Thomas,* Pure Appl. Chem. *48,* 127 (1976).

[10] *E. Pretsch, D. Ammann, H.F. Osswald, M. Güggi & W. Simon,* Helv. *63,* 191 (1980).

[11] *E.C. Horning,* in 'Organic Syntheses', Vol. III, J. Wiley & Sons, Inc., New York 1955, p. 140.

[12] *D. Erne, W.E. Morf, S. Arvanitis, Z. Cimerman, D. Ammann & W. Simon,* Helv. *62,* 994 (1979).

[13] *P.C. Meier, D. Ammann, H.F. Osswald & W. Simon,* Med. Progr. Technol. *5,* 1 (1977).

[14] *P.C. Meier, D. Ammann, W.E. Morf & W. Simon,* in 'Medical and Biological Applications of Electrochemical Devices' (J. Koryta (Ed.)), J. Wiley & Sons, Chichester, New York, Brisbane, Toronto 1980, p. 13.

[15] *J.K. Schneider, P. Hofstetter, E. Pretsch, D. Ammann & W. Simon,* Helv. *63,* 217 (1980).