5. Lipophilic Synthetic Monoamides of Dicarboxylic Acids as Ionophores for Alkaline Earth Metal Cations

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(15.X.81)

Summary

N, N-Dioctadecyl-substituted lipophilic monoamides of certain dicarboxylic acids have been prepared. It is shown that they induce a transport of alkaline earth metal cations through solvent polymeric membranes coupled to a counter transport of hydrogen ions or K^+. They proved to be suitable components for ion-selective electrodes.

Introduction. – Certain lipophilic, electrically neutral, *N, N*-disubstituted amides exhibit highly selective transport properties for alkali and alkaline earth metal cations in membranes [1–6]. Under zero-current conditions these neutral ionophores allow an efficient transport only in the presence of a counter transport system in the membrane phase [7]. Antibiotics of the monensin/nigericin group [8] undergo deprotonation in ethanol/H_2O 9:1 at pH-values around 7 and therefore constitute electrically charged ligands in such organic media. Metal ions having been complexed can easily be carried across membranes by a direct coupling of their flux to a counterflux of protons induced by a transmembrane pH gradient [9]. This behaviour has been confirmed by synthetic ionophores [10]. Here we report on lipophilic *N, N*-dioctadecyl-monoamides of certain dicarboxylic acids which induce a selective and efficient ion transport through membranes under zero-current conditions. These compounds are suitable as components in solvent polymeric membranes for the potentiometric measurement of ion activities.

Results and Discussion. – The potentiometrically determined ion selectivities of the compounds synthesized (see *Scheme*) are presented in *Figure 1*. The selectivity factor K^{Pot}_{MgX} indicates the preference of the membrane system of the ion X relative to Mg^{2+}. The ligands **1–4** induce changes in the ion selectivity as compared to the ligand-free membrane (columns 2–5 relative to column 1 in *Fig. 1*). Stearic acid also induces some selectivity changes (*Fig. 1*, column 6). The selectivity

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0018-019X/82/1/0055-08$01.00/0

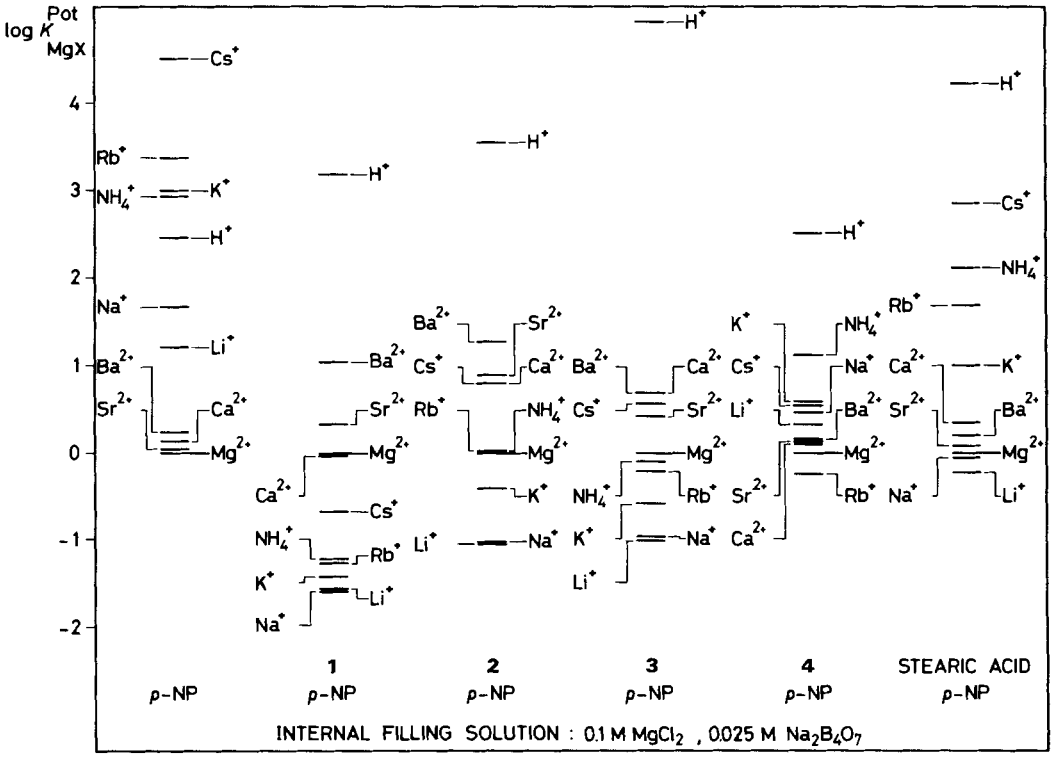


Fig. 1. *Selectivity factors, log K^{Pot}_{MgX}, of solvent polymeric membranes based on various synthetic ligands with* p-*nonylphenol (*p-*NP) as membrane solvent.* Ligand-free membranes (column 1) are compared with membranes containing the dicarboxylic acid monoamides **1**–**4** and stearic acid (separate solution method, 0.1 M solutions of the chlorides). Throughout, internal filling solutions of 0.1 M $MgCl_2$ and 0.025 M $Na_2B_4O_7$ (pH ≃ 8.8) were used.

sequence observed, however, is the one expected for classical cation exchangers such as tetraphenylborate [11]. Obviously the amide group is to a large extent responsible for the selectivity behaviour of the membrane. Although these ligands contain charged binding sites which should increase the interaction energy, especially with small divalent cations such as Mg^{2+} [12], they do not induce a pronounced selectivity for these ions in membranes. Surprisingly, the selectivity sequence observed for the most selective ligand **1** ($Ba^{2+} > Ca^{2+} \approx Mg^{2+}$) is similar to the one observed for the antibiotics A 23187 [13] and nigericin [14] [15][2]). These antibiotics contain carboxyl groups.

As indicated in *Figure 2* for **1**, **1**–**4** indeed behave as ionophores in membranes. The slope of the electrode response above 10^{-4} M is 29.4±0.8 mV (s.d., n=3) and 30.0±0.4 mV (s.d., n=4) for Mg^{2+} and Ba^{2+}, respectively (theoretical: 29.1 mV at 20°). Such a behaviour is observed only at a rather high pH (≥8) of the internal

[2]) Membrane composition: 16 wt.-% Na-salt of nigericin, 33 wt.-% PVC, 51 wt.-% *p*-NP (*p*-nonylphenol); unpublished results.

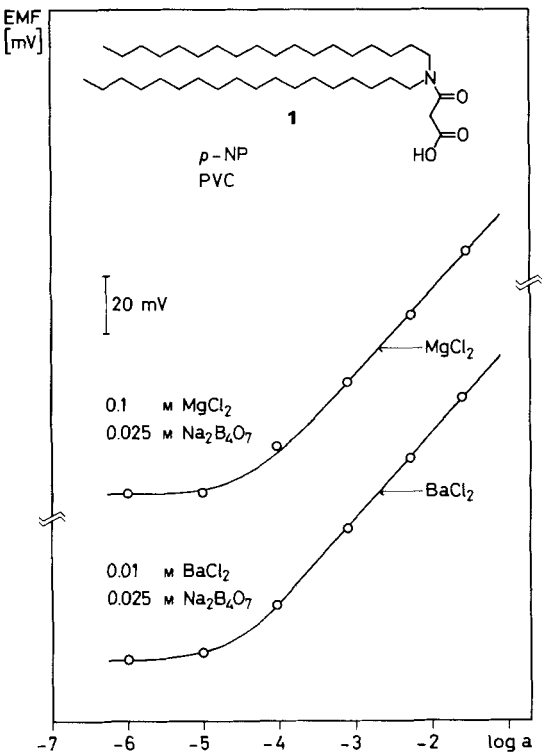
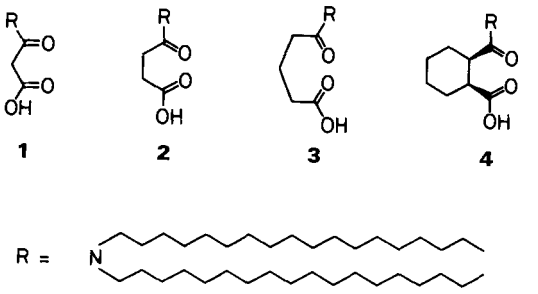


Fig. 2. *EMF. response of liquid membrane electrodes based on ligand* **1** *to aqueous solutions of* $MgCl_2$ *and* $BaCl_2$. Internal filling solutions were: 0.1 M $MgCl_2$, 0.025 M $Na_2B_4O_7$ and 0.01 M $BaCl_2$, 0.025 M $Na_2B_4O_7$ for the Mg^{2+} and Ba^{2+} electrode function respectively.

filling solution. This is in agreement with the assumption that the deprotonated ionophore predominantly transports the divalent cations. *Figure 3* indeed shows that ionophore **2** in a PVC-membrane is completely deprotonated at a pH of the sample solution above 8. The same figure corroborates the interaction of the carboxyl group with Ba^{2+}. A study of the membrane by IR. spectroscopy *(Fig. 3)*

Scheme



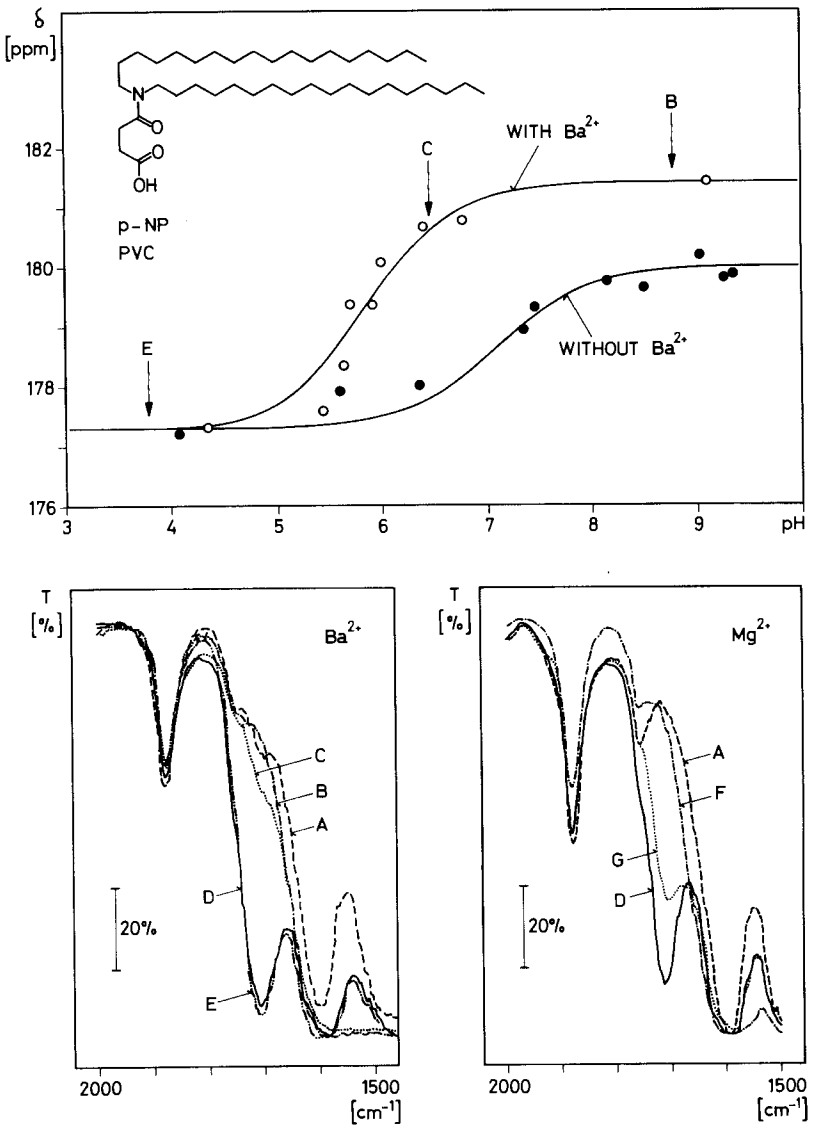


Fig. 3. *^{13}C-NMR.- and IR.-studies of acid-base equilibria of ligand* **2** *in solvent polymeric membranes equilibrated with aqueous solutions.* Upper part: Dependence of the chemical shift of the carboxyl C-atom on the pH of the aqueous solutions. Full circles indicate experiments in the absence of Ba^{2+}. The curve was calculated using a pH for 50% protonation of 7.1. Open circles denote results obtained in the presence of Ba^{2+} in the aqueous solution. The curve was calculated assuming a 1:1 and 1:2 metal/ligand-complex formation ($\log\beta_1 = 1$, $\log\beta_2 = 5$), the total Ba^{2+} concentration in the membrane being half the ligand concentration ($c_L = 0.24$ mol kg^{-1}). Lower part: Carbonyl region of the IR. spectra of membranes equilibrated with aqueous solutions of Ba^{2+} and Mg^{2+} at different pH-values. A: ligand-*free membrane*; D: membrane before equilibration; membrane equilibrated with; B: 0.01M $BaCl_2$ and 0.025M $Na_2B_4O_7$; C: 0.01M $BaCl_2$; E: 0.01M $BaCl_2$ at pH = 3.8 (adjusted with HCl); F: 0.1M $MgCl_2$ and 0.025M $Na_2B_4O_7$; G: 0.1M $MgCl_2$.

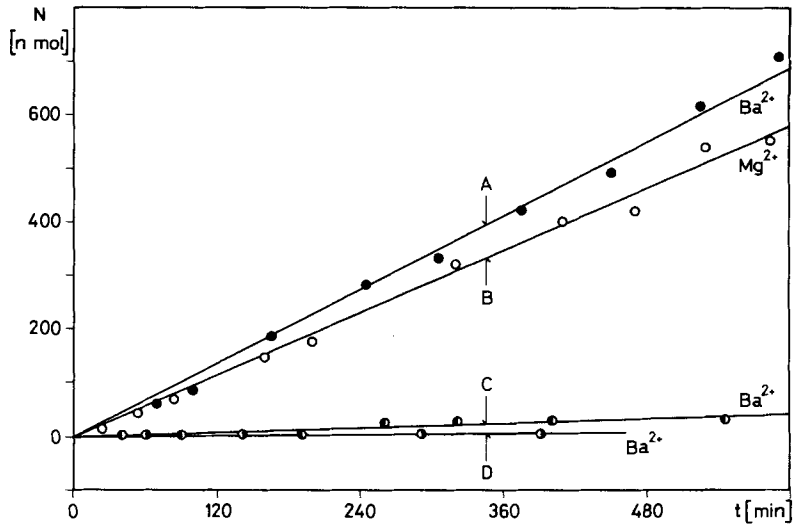


Fig. 4. *Ba^{2+}- and Mg^{2+}-transport through a solvent polymeric membrane.* Curve A and B: Ba^{2+}- and Mg^{2+}-transport in a pH gradient through the membrane containing ligand **1**, C: Ba^{2+}-transport with a pH gradient through the ligand-free membrane, D: Ba^{2+}-transport without pH gradient through the membrane containing ligand **1**.

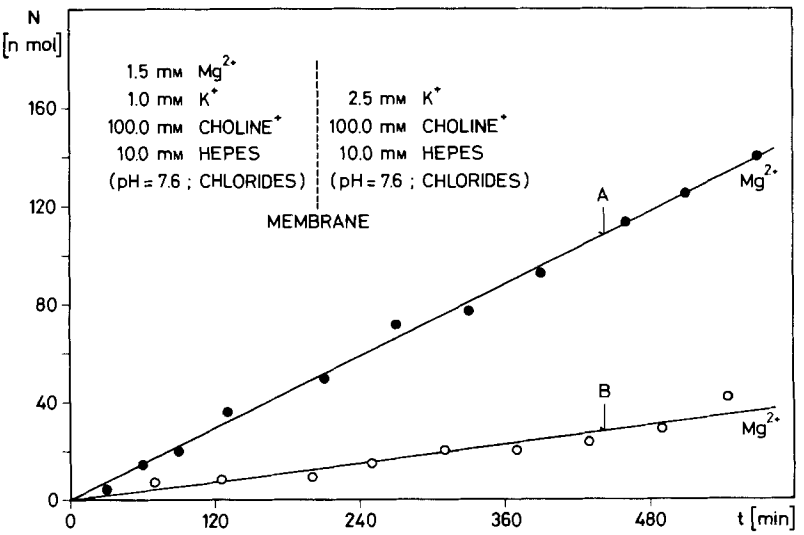


Fig. 5. *Mg^{2+}-transport in a K^{+}-concentration gradient through a solvent polymeric membrane.* A: Mg^{2+}-transport through the membrane containing ligand **1**. B: Mg^{2+}-transport through a ligand-free membrane.

demonstrates the reversibility of the protonation and deprotonation of the carboxyl group. *Figure 3* further shows that relative to Mg^{2+}, Ba^{2+} preferably deprotonates the ionophore in the membrane (C and G in *Fig. 3*).

As expected, a pH-gradient across the above studied solvent polymeric membranes leads to an efficient transport of Ba^{2+} and Mg^{2+} *(Fig. 4)*. Almost no transport is observed if there is no pH-gradient and/or in the absence of ionophore (C, D in *Fig. 4*). *Figure 5* further shows that under physiological conditions [16] ionophore **1** is capable of transporting Mg^{2+} through a coupled counter transport of K^+ across solvent polymeric membranes.

This work was partly supported by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung. Magdalena Maj-Żurawska* thanks the *Scientific Exchange Agreement* for financial support.

Experimental Part

EMF.-Measurements. – The solvent polymeric membranes were prepared using: 15 wt.-% ligand **1**, **2** or **3**, 33 wt.-% polyvinylchloride (PVC S 704, *hochmolekular, Lonza AG*, CH-3930 Visp) and 52 wt.-% *p*-nonylphenol (*p*-NP) (*Fluka AG*, CH-9470 Buchs, techn.); 7 wt.-% ligand **4**, 33 wt.-% PVC and 60 wt.-% *p*-NP; 1.5 wt.-% stearic acid, 33 wt.-% PVC and 65.5 wt.-% *p*-NP; 50 wt.-% PVC and 50 wt.-% *p*-NP.

The membrane preparation and the measuring technique have been described in detail elsewhere [10] [17]. Cell assemblies of the type Hg; Hg_2Cl_2, KCl (satd.)/3 M KCl/sample solution//solvent polymeric membrane//internal filling solution, AgCl; Ag were used. The selectivity factors $\log K^{Pot}_{MgX}$ were obtained by the separate solution method (SSM, 0.1 M metal chloride solutions) [18]. The activity coefficients are described in detail in [16] [19]. The measurements were performed at a temperature of 20–22°.

^{13}C-NMR.-Measurements. – ^{13}C-NMR. spectra were recorded on a *Bruker* HFX-90/B-SC-FFT-12 spectrometer at 22.63 MHz. D_{12}-Cyclohexane was used for stabilization of the magnetic field. Chemical shifts are reported in δ (ppm) relative to TMS as an internal standard. The solvent polymeric membranes were prepared using 20 wt.-% ligand, 33 wt.-% PVC and 47 wt.-% *p*-NP. The membrane was equilibrated during 48 h before measurements with aq. solutions of varying pH and in some cases containing 0.05 M $BaCl_2$. 0.1 M KOH and 0.1 M HCl were used to adjust the pH.

IR.-Measurements. – IR. spectra of solvent polymeric membranes were recorded on a *Perkin-Elmer* 157G IR spectrophotometer. The membranes were the same as those used in the potentiometric measurements.

Transport-Measurements. – Two cylindrical compartments (diameter: 2.5 cm, height: 5 cm) were contacted *via* a solvent polymeric membrane (same composition as in the potentiometric measurements, diameter: 0.5 cm, thickness: 0.01 mm). The cell is described in detail in [20]. The concentrations of the transported cations were measured using flameless atomic absorption (*Perkin-Elmer* 300 spectrometer, graphite cuvette HGA/72). The pH was measured using a pH-minielectrode (*Philips* C 71/02) and a pH-meter (*Beckman*, pH Asar I). The compositions of the solutions used were: a) in experiments with pH gradient: compartment I: $5 \cdot 10^{-4}$ M KOH, 0.01 M of the chloride of the cation transported; compartment II: $5 \cdot 10^{-4}$ M HCl, 0.01 M KCl, b) without pH gradient: compartment I *(Fig. 4)*: $5 \cdot 10^{-4}$ M HCl, 0.01 M $BaCl_2$, compartment II: $5 \cdot 10^{-4}$ M HCl, 0.01 M KCl. Compartment I *(Fig. 5)*: $1.5 \cdot 10^{-3}$ M Mg^{2+}, $1 \cdot 10^{-3}$ M K^+, 0.1 M choline$^+$, 0.01 M HEPES (pH = 7.6; chlorides); compartment II: $2.5 \cdot 10^{-3}$ M K^+, 0.1 M choline$^+$, 0.01 M HEPES (pH = 7.6; chlorides). The pH was adjusted with 0.1 M KOH.

Preparation of the ligands. – *General remarks.* For recording procedures and abbreviations see [21].

Preparation of N,N-*dioctadecylmalonamide* (**1**). *Methyl* N,N-*dioctadecylmalonamate.* To a solution of 10.4 g (20 mmol) dioctadecylamine *(Fluka, pract.)* and 2.0 g (20 mmol) triethylamine *(Fluka, purum)*

in 40 ml toluene 2.7 g (20 mmol) methyl chloroformylacetate *(Fluka, purum)* in 40 ml toluene were added at 5° under stirring. The reaction was completed over night at RT. The precipitated triethylamine hydrochloride was filtered off and the solvent evaporated i.V. The residue was dissolved in diethyl ether and the organic phase was washed with water. The crude product (6.3 g, 10 mmol, 50%) was purified by flash chromatography (35 kPa) on silicagel with ethyl acetate/hexane 1:4 as eluent. – IR. ($CHCl_3$): 1740, 1638. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 6 H, 2 CH_2CH_3); 1.1–1.65 (br., 64 H, 2 $(CH_2)_{16}CH_3$); 3.15 and 3.3 (2 *t*, 4 H, 2 NCH_2); 3.4 (*s*, 2 H, $COCH_2$); 3.7 (*s*, 3 H, OCH_3). – ^{13}C-NMR. ($CDCl_3$): 14.2 (*qa*, CH_3); 22.8, 26.9, 27.0, 27.6, 29.1, 29.5, 29.8 and 32.1 (8 *t*, CH_2); 41.1, 46.1 and 48.6 (3 *t*, $COCH_2CO$ and $CONCH_2$); 52.2 (*qa*, OCH_3); 165.4 and 168.2 (2 *s*, COO and CON). – MS.: 621 (0.8, M^+), 606 (0.3), 548 (7), 520 (23), 492 (23), 478 (3), 464 (9), 396 (3), 382 (8), 368 (4), 354 (10), 310 (4), 296 (3), 282 (16), 254 (21), 85 (39), 71 (53), 57 (100), 43 (56).

$C_{40}H_{79}NO_3$ (622.07) Calc. C 77.23 H 12.80 N 2.25% Found C 77.28 H 12.80 N 2.30%

A solution of 1.0 g (1.6 mmol) *methyl* N,N-*dioctadecylmalonamate* and 0.26 g (6.4 mmol) NaOH in 20 ml CH_3OH and 7 ml water was stirred at RT. over night and neutralized with 0.1M HCl. The precipitate was filtered off and washed with water. The crude product was purified by flash chromatography to give 0.16 g (0.26 mmol, 16%) acid **1**, m.p. 55–57°. – IR. ($CHCl_3$): 1738, 1607. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 6 H, 2 CH_2CH_3); 1.1–1.7 (br., 64 H, 2 $(CH_2)_{16}CH_3$); 3.2 and 3.35 (2 *t*, 4 H, 2 NCH_2); 3.3 (*s*, 2 H, $COCH_2$). – ^{13}C-NMR. ($CDCl_3$): 14.1 (*qa*, CH_3); 22.8, 26.9, 27.0, 27.4, 28.7, 29.0, 29.4, 29.8, 32.0 and 35.4 (10 *t*, CH_2); 46.8 and 48.1 (2 *t*, $COCH_2CO$ and $CONCH_2$); 168.4 and 169.3 (2 *s*, CON and COOH). – MS.: 607 (0.1, M^+), 606 (0.3), 590 (0.3), 562 (10), 548 (32), 520 (70), 506 (16), 492 (34), 478 (9), 464 (12), 450 (6), 436 (6), 422 (6), 408 (6), 394 (6), 380 (6), 366 (6), 352 (7), 338 (7), 324 (58), 310 (18), 308 (1), 296 (55), 282 (59), 280 (2), 268 (21), 266 (4), 254 (52), 252 (2), 240 (5), 238 (1), 226 (12), 224 (2), 212 (2), 210 (2), 198 (2), 196 (2), 184 (2), 182 (2), 170 (2), 168 (2), 156 (2), 154 (2), 142 (3), 140 (2), 128 (5), 126 (2), 71 (5), 57 (10), 44 (100).

$C_{39}H_{77}NO_3$ (608.04) Calc. C 77.04 H 12.76 N 2.30% Found C 76.92 H 12.70 N 2.39%

General procedure for the preparation of the ligands **2–4**. The diacid anhydride (20 mmol) was reacted with dioctadecylamine (20 mmol) *(Fluka, pract.)* in toluene (100 ml) at RT. over night. The solvent was then evaporated i.V. The crude product was purified by flash chromatography (35 kPa, eluent in brackets) on silica gel and recrystallized if indicated.

Data of N,N-*dioctadecylglutaramide* (**2**). Yield after chromatography (ethyl acetate): 65%. A portion was recrystallized from ethyl acetate, m.p. 59–61°. – IR. ($CHCl_3$): 1738, 1712, 1630, 1590. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 6 H, 2 CH_2CH_3); 1.1–1.6 (br., 64 H, 2 $(CH_2)_{16}CH_3$); 2.65 (*s*, 4 H, $COCH_2CH_2CO$); 3.2 and 3.3 (2 *t*, 4 H, 2 NCH_2). – ^{13}C-NMR. ($CDCl_3$): 14.1 (*qa*, CH_3); 22.8, 27.1, 27.8, 28.0, 28.9, 29.5, 29.8 and 32.0 (8 *t*, CH_2); 75.9 and 77.2 (2 *t*, $COCH_2CO$ and $CONCH_2$); 171.4 (*s*, CON); 176.9 (*s*, COOH). – MS.: 622 (0.7, $M^+ + 1$), 621 (0.4, M^+), 548 (8), 534 (1), 520 (10), 506 (1), 492 (4), 478 (0.8), 464 (1), 450 (1), 436 (1), 422 (1), 408 (1), 394 (1), 382 (3), 366 (1), 252 (2), 338 (2), 324 (3), 310 (7), 296 (5), 282 (100), 268 (9), 254 (46), 240 (3), 226 (2), 210 (1), 196 (2), 182 (2), 168 (2), 154 (2), 140 (2), 126 (2), 112 (3), 71 (9), 57 (17), 44 (24).

$C_{40}H_{79}NO_3$ (622.07) Calc. C 77.23 H 12.80 N 2.25% Found C 77.11 H 12.83 N 2.33%

Data of N,N-*dioctadecylglutaramide* (**3**). Yield after chromatography (ethyl acetate): 67%. A portion was recrystallized from ethyl acetate, m.p. 52–55°. – IR. ($CHCl_3$): 1710, 1625. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 6 H, 2 CH_2CH_3); 1.1–1.7 (br., 64 H, 2 $(CH_2)_{16}CH_3$); 2.0 (*m*, 2 H, $COCH_2CH_2$); 2.30 and 2.32 (2 *t*, 4 H, 2 $COCH_2$); 3.20 and 3.27 (2 *t*, 4 H, 2 NCH_2). – MS.: 635 (3, M^+), 548 (21), 534 (3), 520 (31), 506 (4), 492 (15), 478 (3), 464 (4), 338 (4), 324 (4), 310 (9), 296 (6), 282 (100), 268 (9), 254 (53), 240 (3), 226 (4), 71 (6), 57 (15), 44 (19).

$C_{41}H_{81}NO_3$ (636.10) Calc. C 77.42 H 12.83 N 2.20% Found C 76.95 H 12.56 N 2.26%

Data of cis-2-(N,N-*dioctadecylcarbamoyl*)-1-*cyclohexanecarboxylic acid* (**4**). Yield after chromatography (ethyl acetate/hexane 7:3): 71%, m.p. 30–32°. – IR. ($CHCl_3$): 1716, 1630, 1572. – ^{1}H-NMR. ($CDCl_3$): 0.85 (*t*, 6 H, 2 CH_2CH_3); 1.1–1.9 (br., 72 H, 2 $(CH_2)_{16}CH_3$ and $(CH_2)_4$-ring); 2.4–3.6 (br., 6 H, 2 NCH_2 and COCHCHCO); 8.6 (br., 1 H, COOH). – ^{13}C-NMR. ($CDCl_3$): 14.2 (*qa*, CH_3); 22.8, 23.8, 25.9, 27.1, 27.3, 27.7, 28.0, 29.2, 29.5, 29.8, 30.8 and 32.0 (12 *t*, CH_2); 40.0 and 43.8 (2 *d*, CHCON and CHCOOH); 46.2, 47.5 and 48.4 (3 *t*, CH_2N and CH_2-ring); 175.5 and 177.1 (2 *s*, CON

and COOH). – MS.: 675 (< 0.1, M^+), 548 (0.2), 520 (3), 506 (0.8), 492 (4), 478 (1), 464 (2), 450 (1), 436 (1), 422 (1), 408 (1), 394 (1), 380 (1), 366 (1), 352 (1), 338 (2), 324 (2), 310 (3), 296 (4), 282 (100), 268 (17), 254 (82), 240 (7), 226 (9), 210 (0.4), 196 (0.4), 182 (0.4), 168 (0.6), 154 (0.6), 140 (0.6), 126 (0.6), 112 (0.6), 98 (0.6), 57 (4), 43 (7).

$C_{44}H_{85}NO_3$ (676.16) Calc. C 78.16 H 12.67 N 2.07% Found C 78.13 H 12.77 N 2.20%

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