

# An Artificial Channel Type Ionophore

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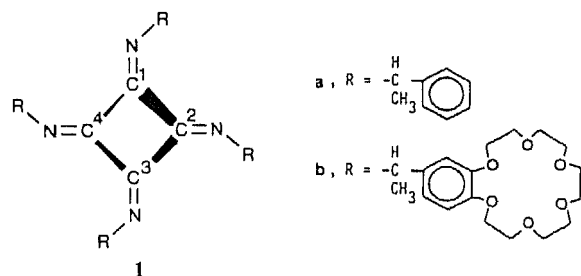
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**Abstract.** A polymer of an isocyanide ( $R-N=C$ )<sub>n</sub> has been synthesized in which R contains a benzo-18-crown-6 group. The crown ether rings are on top of each other and form channels which bind metal ions. The channel compound can be incorporated in vesicles and is able to transport ions across the bilayer membrane.

## INTRODUCTION

Ion transport across the membrane of the living cell is a biologically important process. Generally, two different modes of transmembrane transport have been established: the carrier and the channel mode.<sup>1</sup> The first type of transport is displayed by depsipeptide and macrotetrolide antibiotics like Valinomycin and Nonactin.<sup>2</sup> These ionophores form lipophilic complexes with cations at one interface of the membrane which then migrate across the membrane to the other interface where the cation is released. The second type of transport is found with linear peptides, e.g. Gramicidin A, and transport proteins,<sup>1</sup> which create selective pores. These pores may be solvent-filled channels, or more likely, may be a series of ion binding sites which span the membrane. Ion transport would then consist of a series of hops between these sites.

Numerous models of carrier-type ionophores have been synthesized and studied in natural and model membrane systems.<sup>3</sup> Synthetic models of channel-type ionophores are very scarce.<sup>4</sup> In the present paper we report the first synthesis of a channel type ionophore.<sup>5</sup> The compound is a polymer of an isocyanide, ( $R-N=C$ )<sub>n</sub>, **1b** which contains a benzo-18-crown-6 group in its side chain. Furthermore, we would like to demonstrate that channel compound **1b** can be incorporated into vesicles and is able to transport ions across the membrane.



## RESULTS AND DISCUSSION

### Synthetic Approach

A model of a channel-type ionophore should display the following features: a series of ion binding sites, pores with a polar interior and an apolar exterior, a hydrophilic top and bottom which may face the two aqueous sides of a membrane, and a chain of sufficient length to span the membrane.

The problem of how to construct such a model may be attacked in several ways. An obvious and straightforward one is the stacking of a number of ringlike segments. We have chosen this approach as versatile building blocks, i.e. macrocyclic rings, are available. Crown ether rings, e.g. 18-crown-6, fit our purpose as they bind ions and possess a polar interior and an apolar exterior.<sup>6,7</sup> The stepwise connection of these rings via lateral appendages is synthetically difficult and has not gone far beyond two rings.<sup>7</sup> We have found a way of building up the stack of rings by using a polymer of an isocyanide as central anchorage.

Polymers of isocyanides, called poly(iminomethylenes) or poly(carbonimidoyls), are prepared from isocyanides by the catalytic action of nickel(II) salts.<sup>8</sup> Their structure is very regular and rigid. In particular this is true for poly( $\alpha$ -phenylethyliminomethylene), **1a**.<sup>8,9</sup> This polymer is a tightly coiled helix with four repeating units per helical turn. Its side chains form four stacks which run parallel to the polymer helix axis. In these stacks the phenyl groups are situated on top of each other at  $\approx 0.4$  nm distance and are locked in this position by the tight packing of the polymer chain. If the phenyl groups are made part of a crown ether ring system, like in **1b**, these crown ether rings are on top of each other and form four channels (Fig. 1). The core, top and bottom of these channels are polar, whereas the mantle is apolar.

Polymer **1b** was prepared as shown in Scheme 1. Starting material is 4'-acetyl-benzo-18-crown-6 which can be prepared by acetylation of benzo-18-crown-6<sup>10</sup> or by ring closure of 1-acetyl-3,4-dihydroxybenzene with pentaethyleneglycol dichloride.<sup>11</sup> The keto function of the macrocycle was converted (88%) into a formamide group by means of a Leuckart reaction.<sup>12</sup> Formamide **3** was dehydrated with phosphorus oxychloride and base. After purification by column chromatography isocyanide **4** was obtained in 80% yield as a colourless oil. The infrared absorption spectrum showed a characteristic isocyanide stretching vibration at  $2138\text{ cm}^{-1}$ . Polymerization of **4** was performed by heating the monomer neat at  $90^\circ\text{C}$  for 5 days with 3 mol % of  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ . Polymer **1b** was isolated in 75% yield as a pale yellow solid. Its molecular weight amounted to  $M_n = 15,000$  which corresponds to 40 repeating units or 10 helical turns. Since the

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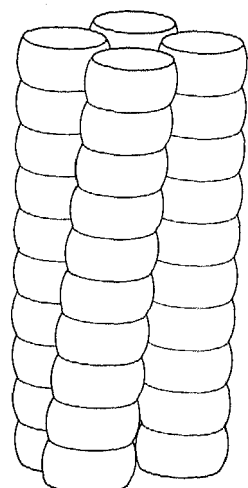
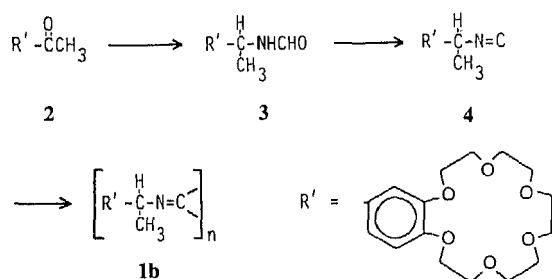


Fig. 1. Schematic picture of the channels of **1b**.



Scheme 1.

distance between neighbouring turns is 0.4 nm,<sup>8</sup> the average length of the channels will be 4 nm. This length is of the same order of magnitude as the thickness of the bilayer of most vesicle systems (4–5 nm<sup>19</sup>).

The binding properties of the channels of **1b** towards metal ions and ammonium ions were measured by the picrate extraction technique described by Cram et al.<sup>13</sup>

Association constants and free energies of binding are given in Table 1. As reference compound 4'-acetylbenzo-18-crown-6 (**2**) was used. Compound **1b** displays free energies of binding ranging from 35.5 to 42.7 kJ/mol. These binding energies are roughly 5 kJ/mol higher than the binding energies of the reference compound. The difference in binding profile between **1b** and **2** may be

Table 1. Association Constants,  $K_a$ , and Free Energies of Complexation of Picrate Salts by Ionophore **1b** and 4'-acetylbenzo-18-crown-6, **2**<sup>a</sup>

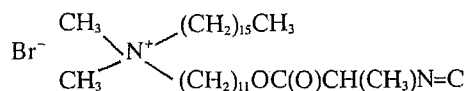
Guest	$K_a \times 10^{-5}/(\text{l. mol}^{-1})$		$-\Delta G^\circ/(\text{kJ. mol}^{-1})$	
	<b>1b</b>	<b>2</b>	<b>1b</b>	<b>2</b>
Li <sup>+</sup>	17	2.8	35.6	31.0
Na <sup>+</sup>	20	3.8	36.0	31.8
K <sup>+</sup>	300	130	42.7	40.6
Rb <sup>+</sup>	120	28	40.6	36.8
Cs <sup>+</sup>	90	7.4	39.7	33.5
NH <sub>4</sub> <sup>+</sup>	55	20	38.5	36.0
Co <sup>2+</sup>	< 0.05		< 20	

a. Compare Ref. 13.

explained from the fact that in the former compound the metal ions can be sandwiched between consecutive crown ether rings, which favours binding, and in the latter compound they cannot.

#### Incorporation and Ion Transport

As shown above, compound **1b** displays the main features which are thought to be required for channel mediated ion transport. Therefore, it is tempting to investigate whether **1b** can be incorporated in the bilayer membrane of vesicles and favour such an ion transport. Experiments were performed with the synthetic surfactant **5**.<sup>14</sup>



**5**

On dispersal in water **5** forms closed aggregates. The bilayers of these aggregates can be polymerized through their isocyanato functions by addition of nickel capronate. The polymerized aggregates show enhanced stability.

Surfactant **5** and channel compound **1b** were mixed in water in a molar ratio of 250 and dispersed by vortexing for 2 min. In separate experiments nickel capronate was added to achieve cross-linking of the bilayers. Freeze fracture electron micrographs revealed the presence of small, closed aggregates (Fig. 2). From the size distribution histograms the average diameters of the unpolymerized and polymerized vesicles were calculated to be 17 and 23 nm, respectively (Fig. 3a,b). Electron micrographs of vesicles and polymerized vesicles prepared under the same conditions as mentioned above, however without **1b**, show diameters of 60 and 165 nm (Fig. 3c,d). The decrease in vesicle size when **1b** is added and the concomitant narrower size distribution strongly suggests that this compound is incorporated. A similar effect is observed when proteins are built in liposome, e.g. the incorporation of glycoporphin in phosphatidylethanolamine vesicles.<sup>15</sup>

Evidence of incorporation also comes from gel filtration experiments on Sephadex columns. These experiments reveal that channel compound **1b** and the unpolymerized or polymerized vesicles are present in the same peak in the void volume of the column. Blank gel filtration experiments with dispersions of the separate components show peaks at different elution volumina, i.e. vesicles in the void volume and compound **1b** in a broad band at a relative elution volume of  $\approx 4$ .

The phase-transition temperature of the vesicles was determined by observing changes in line widths of the CH<sub>2</sub>-protons in the <sup>1</sup>H NMR spectra as a function of temperature. The unpolymerized vesicle dispersions containing compound **1b** showed a phase transition at  $\approx 24$  °C. Dispersions without **1b** had this transition at 30 °C. The lowering of the transition temperature suggests incorporation of **1b**, although not conclusively, as phase transition temperatures also depend on vesicle size.<sup>16</sup> The polymerized vesicles with and without **1b** do not show phase transitions anymore. Clearly, the presence of cross-links leads to restricted mobility of the hydrocarbon core.<sup>14</sup>

Ion transport across the bilayer membrane of the vesicles was studied using cobalt(II) ions. The latter ion was selected as ample dyes are available that form coloured complexes with this ion, e.g. 4,5-

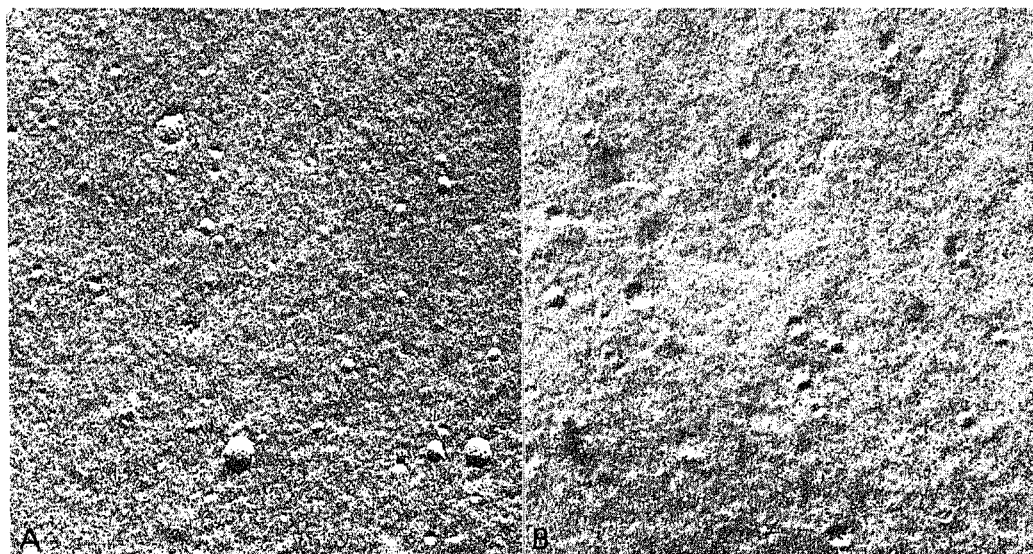


Fig. 2. Freeze fracture electron micrographs of unpolymersed (A) and polymerized (B) vesicles containing **1b**. Magnification,  $\times 100,000$ .

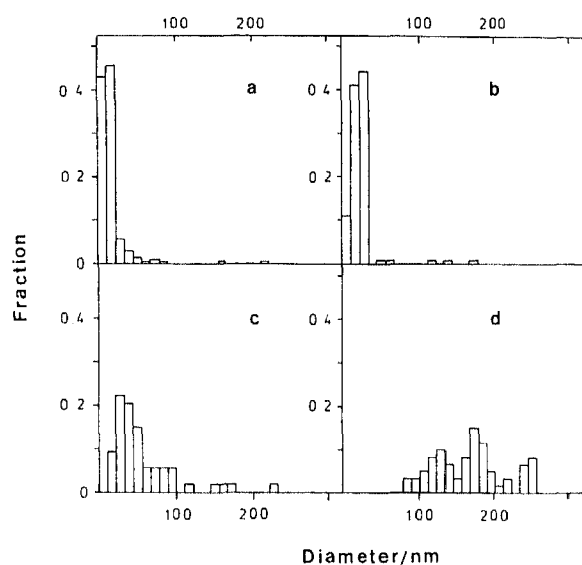
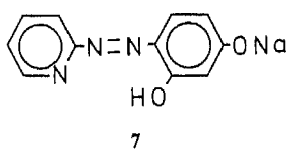
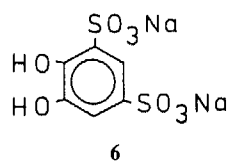


Fig. 3. Size distribution histograms: (a) unpolymersed vesicles containing **1b**; (b) polymerized vesicles containing **1b**; (c) unpolymersed vesicles without **1b**; (d) polymerized vesicles without **1b**.

dihydroxybenzenedisulphonic acid disodium salt (Tiron, **6**) and 4-(2-pyridylazo)resorcinol mono sodium salt (PAR, **7**).



Extraction experiments showed that Co(II) ions are bound to the channels of **1b**, although to a lesser extent than the alkali metal ions (Table 1).

In a first series of experiments surfactant **5** and channel compound **1b** were vortexed in water and subsequently

mixed with an aqueous solution of  $\text{Co}(\text{NO}_3)_2$  and Tiron. The change in absorption of the  $\text{Co}^{2+}$ -Tiron complex was measured at 314 nm. Blank experiments were performed with vesicles without **1b**. The results are given in Fig. 4. Decrease in absorption, suggestive of cobalt ion transport, is clearly visible for vesicles containing **1b** but not for those without this compound. As these experiments are not conclusive — they only show that cobalt ions disappear from the exterior aqueous solution — a second series of experiments was carried out with vesicles containing PAR in their aqueous interior. To this end vesicle dispersions were prepared by vortexing surfactant **5**, compound **1b** and PAR in water. Polymerized vesicle dispersions were prepared in a similar way by adding nickel capronate. The exo vesicular dye was removed by dialysis with diluted aqueous HCl. After neutralization

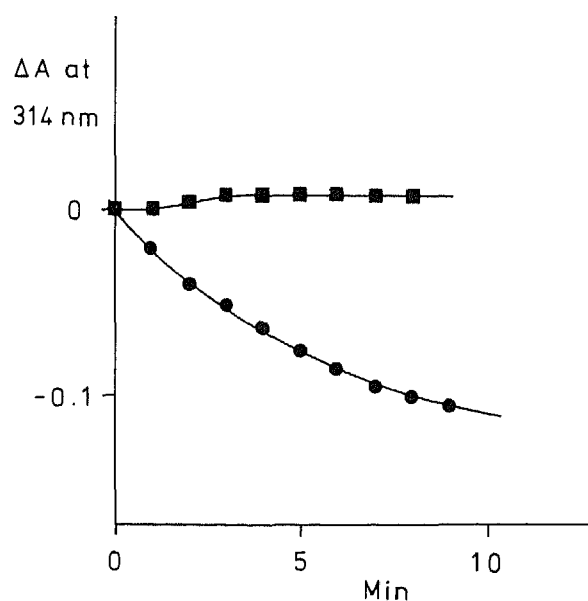


Fig. 4. Change in absorption at 314 nm vs. time. (●) Vesicles containing **1b**; (■) vesicles without **1b**.

the dispersions were mixed with an aqueous solution of  $\text{Co}(\text{NO}_3)_2$ . The increase in absorption by the cobalt-PAR complex was measured at 510 nm at 20 °C. Blank experiments were performed with unpolymerized and polymerized vesicles without **1b**. In Fig. 5 the results of a typical experiment with unpolymerized vesicles are presented. Apparently, transport of cobalt ions across the bilayer occurs when channel compound **1b** is present. Pseudo-first-order kinetics are obeyed. The transport rate constants are in the order of  $10^{-4} \text{ s}^{-1}$ . Without **1b** no ion transport takes place. Only after destruction of the vesicles by the neutral surfactant Triton-X-100 increase in absorption at 510 nm is visible.

Leakage of the unpolymerized vesicles and thus a measurable blank rate was observed when the experiments were carried out at temperatures above the phase transition temperature. Leakage also occurred when the dye was not or incompletely removed from the exterior aqueous solution. Apparently, under these conditions the vesicles are destabilized.

All polymerized vesicle dispersions showed the same cobalt ion transport rate whether channel compound **1b** was present or not. Rate constants are in the range of  $10^{-5}$  to  $10^{-4} \text{ s}^{-1}$ . This suggests that in these systems **1b** does not contribute to transmembrane transport. The reason might be that the ionophore is not able to span the membrane, e.g. because of the cross-links in the bilayers. In this context it is of interest to mention that after standing for a week or longer compound **1b** slowly precipitated from the polymerized vesicle dispersions. A similar effect was not observed with the unpolymerized samples. Apparently, polymerized vesicles of **5** and **1b** are not completely compatible. The observed ion transport rate in case of the polymerized vesicles is probably due to leakage or due to a process in which the capronate ions from the polymerization catalyst act as carrier molecules.

### Conclusion

This investigation has shown that a realistic model of a channel-type ionophore can be designed and constructed on the basis of polymers of isocyanides which contain macrocyclic rings. As macrocyclic rings of different size are easily accessible nowadays, this opens the possibility

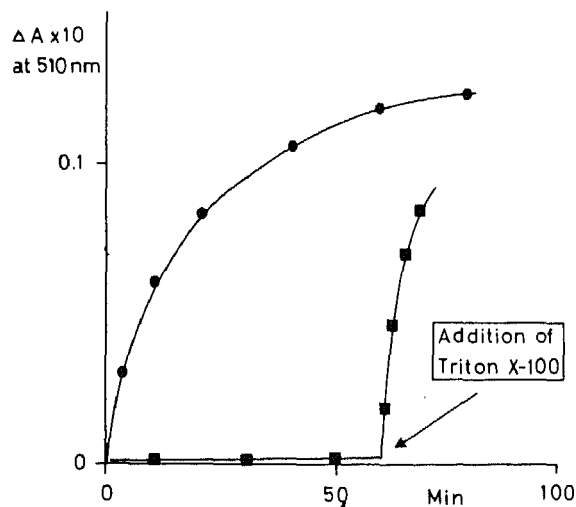


Fig. 5. Change in absorption at 510 nm vs. time. (●) Vesicles containing **1b**; (■) vesicles without **1b**.

of synthesizing ionophores which display ion selectivity. Work along these lines is currently in progress.

### EXPERIMENTAL

Infrared and UV-Vis spectra were recorded on Perkin-Elmer 283 and 555 spectrometers, respectively.  $^1\text{H}$  NMR spectra were obtained on Varian EM 390 and Bruker WP 200 instruments. Chemical shifts are given downfield from internal  $\text{Me}_4\text{Si}$ . Abbreviations used are s = singlet, m = multiplet, d = doublet and b = broad. Electron microscopy was carried out with a Philips EM 301 instrument. Samples were frozen in a splash of liquid and solid nitrogen, fractured with a Denton freeze etch apparatus, and replicated with Pt/C according to standard procedures.<sup>17</sup> Glycerol was added up to 25% to prevent freeze damage.

4,5-Dihydroxybenzene-1,3-disulphonic acid disodium salt (Tiron) and 4-(2-pyridylazo)resorcinol monosodium salt (PAR) were purchased from Merck and UCB, respectively. Triton-X-100 was obtained from Schuchardt. Nickel capronate was prepared from capronic acid and  $\text{NiCO}_3 \cdot \text{Ni}(\text{OH})_2$ .

**4'-(1-N-Acetylbenzo-18-crown-6 (2)).** This compound was prepared by ring closure of 3,4-dihydroxyacetophenone with 1,14-dichloro-3,6,9,12-tetraoxatetradecane (yield 48%)<sup>11</sup> or by acetylation of benzo-18-crown-6 (yield 84%).<sup>10</sup>

**4'-(1-N-Formylaminoethyl)benzo-18-crown-6 (3).** Compound **2** (17.5 g, 49.4 mmol) and ammonium formate (50 g) were heated in a  $\text{N}_2$  atmosphere for 7 h. During this period the temperature was slowly raised to 190 °C while water and ammonium carbonate were distilled off. After cooling to room temperature the mixture was diluted with water (100 ml) and chloroform (100 ml). The organic layer was separated and the aqueous layer was extracted twice with chloroform (100 ml). The combined extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ,  $\text{MgSO}_4$ ) and concentrated under vacuum. The resulting orange-red oil was purified by chromatography using a short column of neutral alumina (eluent EtOAc-EtOH, 9:1 v/v) and recrystallization from EtOAc-diethyl ether. Yield 16 g (44 mmol, 88%) of **3**; IR (KBr) 1675 (CO), 1100 and 1250 (ether)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.43 (d, 3H,  $\text{CH}_3$ ), 3.67–4.10 (m, 20 H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 5.1 (m, 1H, CH), 7.0 (b, 1H, NH), 6.8 (m, 3H, ArH), 8.13 (s, 1H, CHO).

**4'-(1-isocyanoethyl)benzo-18-crown-6 (4).** To a solution of **3** (9.57 g, 25 mmol) and triethylamine (8.1 g, 80 mmol) in methylene chloride (50 ml) was added dropwise at 0 °C over a 1 h period phosphorus oxychloride (4.9 g, 32 mmol) in methylene chloride (15 ml). The mixture was stirred at 0 °C for 1 h. Subsequently, the temperature was slowly (0.5 h) raised to 25 °C. Aqueous  $\text{Na}_2\text{CO}_3$  was added and the organic layer was separated, dried ( $\text{Na}_2\text{SO}_4$ ,  $\text{Mg}_2\text{SO}_4$ ), and concentrated under vacuum. The product (11 g) was purified by column chromatography (neutral  $\text{Al}_2\text{O}_3$ , eluent EtOAc-Et<sub>2</sub>O 1:1 v/v). Yield 7.3 g (20 mmol, 80%) of **4** as an almost colourless oil. IR (neat) 2138 (NC), 1100 and 1260 (ether)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.62 (m, 3H,  $\text{CH}_3$ ), 3.65–4.15 (m, 20 H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 4.74 (m, 1H, CH), 6.90 (s, 3H, ArH).

**Poly[1-(4'-benzo-18-crown-6)ethyliminomethylene] (1b).** Compound **4** (0.60 g, 1.64 mmol) and  $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$  (12 mg, 0.05 mmol) were heated neat at 90 °C for 5 days. The reddish glassy polymerization product was dissolved in chloroform (25 ml). The latter solution was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated to a smaller volume (5 ml) and added dropwise to a well stirred mixture of diethylether-*n*-hexane (1:1 v/v). The flocky precipitate was filtered, washed with diethylether-*n*-hexane (1:1 v/v) and dried to give pale-yellow **1b**. Yield 0.45 g (75%);  $[\eta]$  0.031 (toluene, 30.00 °C);  $M_n = 15,000$ ; IR (KBr) 1625 (N=C), 1260 and 1100 (ether)  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.4 (b, 3H,  $\text{CH}_3$ ), 3.6–4.3 (b,  $\approx$  20H,  $\text{CH}_2\text{CH}_2\text{O}$ ), 6.8 (b, 3H, ArH), the methine H is probably (see Ref. 18) masked by the crown ether protons. Anal. Calcd. for  $\text{C}_{19}\text{H}_{27}\text{NO}_6$ : C, 62.45; H, 7.45; N, 3.83; O, 26.27. Found: C, 62.13; H, 7.19; N, 3.96; O, 26.72.

Dimethylhexadecyl[11-((1-isocyanoethyl)carboxyloxy)undecyl]ammonium bromide (**5**). This compound was prepared as described previously.<sup>14</sup>

**Determination of association constants.** Association constants of metal picrates by **1b** and **2** were determined as described in the literature.<sup>13</sup>

**Incorporation experiments.** Compound **1b** (2.0 mg, 0.14  $\mu\text{mol}$ ) and surfactant **5** (20 mg, 32  $\mu\text{mol}$ ) were dispersed in water (1 ml) by vortexing for 2 min at 20 °C. To separate samples nickel capronate (1.8 mg, 6.2  $\mu\text{mol}$ ) was added to achieve polymerization of the bilayers (reaction time 12 h). The dispersions were used for electron microscopy, gel filtration (Sephadex G-100, sample size 0.1 ml, eluent water) and <sup>1</sup>H NMR experiments. In the latter case D<sub>2</sub>O was used as solvent.

**Ion transport.** Surfactant **5** (10 mg, 16  $\mu\text{mol}$ ), compound **1b** (1 mg, 0.07  $\mu\text{mol}$ ), and an aqueous solution containing PAR (1 ml, 8.2  $\mu\text{mol}$ , pH 7.5) were vortexed for 2 min at 20 °C. Polymerized vesicle dispersions containing PAR were prepared in a similar way by adding nickel capronate (1 mg, 3.5  $\mu\text{mol}$ , polymerization time 12 h). The exo vesicular PAR was removed by dialysis (Amicon Diaflo UM or YM 2 filter) with diluted aqueous HCl (4 × 40 ml, pH 3). The pH of the resulting dispersions was raised to 7.8 with diluted NaOH and the volume was adjusted to 25 ml. The latter dispersion (0.5 ml) was mixed with an aqueous solution of Co(NO<sub>3</sub>)<sub>2</sub> (20  $\mu\text{l}$ , 1.19 mol/l) and after 3 min the increase in absorption at 510 nm was measured. Blank experiments were performed with unpolymerized and polymerized vesicles without **1b**. Destruction of the vesicles occurred with 0.1 ml of a 2% aqueous solution of Triton-X-100.

For the experiments with indicator Tiron a vesicle dispersion was prepared from **5** (20 mg, 32  $\mu\text{mol}$ ), **1b** (2 mg, 0.14  $\mu\text{mol}$ ) and 2 ml of water as indicated above. This dispersion (0.6 ml) was mixed with an aqueous solution (10  $\mu\text{l}$ ) of Co(NO<sub>3</sub>)<sub>2</sub> and Tiron (both reagents 5 × 10<sup>-3</sup> mol/l, pH 7.3) and after osmotic equilibration (3 min) the decrease in absorption was measured at 314 nm.

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