188. Cation Transport across Bulk Liquid Organic Membranes with Oligomers of (*R*)-3-Hydroxybutanoic Acid

by **H. Michael Bürger**[1]) and **Dieter Seebach***

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, ETH-Zentrum, Universitätstrasse 16, CH–8092 Zürich

(28.VII.93)

Several oligomeric derivatives **1**–**5** of (*R*)-3-hydroxybutanoic acid and a cyclic trimer of (*R*)-3-hydroxypentanoic acid (**6**) were used as ionophores to transport potassium picrate across a bulk liquid CH_2Cl_2 membrane. Using the cyclic trimer **1** and an oligomer mixture of (*R*)-3-hydroxybutanoic acid, **5** (*ca.* 28-mer), for the transport experiments, the alkali-metal ions from Li^+ to Cs^+ and the alkaline-earth-metal ions from Mg^{2+} to Ba^{2+} were also shown to be transported through the organic phase. Although a pronounced enhancement of the transport rates was observed in the presence of 3-hydroxyalkanoate oligomers, no special selectivity for one ion was detected. The ionophore properties of the investigated oligomers and oligolides derived from 3-hydroxybutanoic acid are compatible with the alleged role of oligo(3-hydroxybutanoate) (*c*-PHB; *ca.* 120-mer) as component of ion channels through cell membranes.

Introduction. – The biopolymer poly[(*R*)-3-hydroxybutanoic acid] (P(3-HB)) is the most important member of the family of polyhydroxyalkanoates [1] [2]. These compounds are accumulated by several microorganisms as storage materials [3]. Depending upon the growth conditions, very high levels of accumulation may be reached[2]). Since polyhydroxyalkanoates are fully biodegradable, and biocompatible as well, they are subject to many expectations in the field of medicine and of material science [4] [5]. Especially the copolymer of (*R*)-3-hydroxybutanoic acid with (*R*)-3-hydroxypentanoic acid (P(3-HB/3-HV)), produced by fermentation with *Alicaligenes eutrophus*, is of some commercial interest, because its physical properties are somehow similar to those of polypropylene; it can be molded, blown to bottles, processed to films, and drawn to fibres [4]. It is sold under the trade name '*BIOPOL*' and is currently used for the manufacture of biodegradable bottles. The homopolymer P(3-HB), also produced by fermentation, is commercially available as well [6]; its use as a food additive has recently been patented [7]. Due to the stereo regular (all-*R*)-configuration of P(3-HB), it is a useful and versatile starting material for the preparation of chiral building blocks in organic synthesis [1] [8].

Besides its occurrence as microbial storage material (*s*-PHB)[3]) of high molecular weight (from *A. eutrophus ca.* 750000 g/mol), P(3-HB) is known to be present in a variety of biological samples, especially in cell membranes [9]. Samples from these sources have a comparatively low molecular weight (*ca.* 10000 g/mol or 100 to 150 units of 3-HB) [9]. Although it was speculated that this P(3-HB) is involved in the transport of ions across cell membranes [9], the biological function of these oligomers (*c*-PHB)[4]) has yet to be

[1]) Part of the Ph. D. thesis work of *H. M. B.*, ETH-Zürich, 1993.

[2]) Up to 96% of the dry weight in the case of the strain *Alcaligenes eutrophus N9a.*

[3]) This abbreviation was proposed for storage PHB [1].

proved [1]. During our investigations on the structure and synthesis of the proposed non-proteinogenic P(3-HB) Ca-polyphosphate-ion channel [9], we have synthesized 3-HB derivatives that formed complexes with alkali-metal salts, characterized by X-ray crystal-structure analysis [10] [11]. Encouraged by these results, we set out to investigate a possible ionophoric activity of P(3-HB) and its derivatives. We, therefore, examined the ion-transport rates for alkali and alkaline-earth metal ions mediated by cyclic and open-chain 3-HB derivatives across bulk liquid membranes. To the best of our knowledge, this is the first example of ion transport through bulk liquid membranes by ionophores that carry exclusively ester carbonyl O-atoms as complexing sites for the cations[5]).

Results and Discussion. – *Transport of Potassium Picrate across a CH_2Cl_2 Bulk Liquid Membrane Mediated by Various 3-HB Oligomers.* A simple device to test compounds for ionophoric activity is a U-shaped tube in which a more dense organic phase containing the carrier is overlayered with aqueous solutions in the two legs. The metal-ion solution is in one leg (donor solution) and an aqueous receiver solution in the other one (*Fig. 1*). As this apparatus allows for stirring of the organic phase, diffusion processes across the liquid membrane are minimized, and the overall transport rate is mainly determined by the rates of complex formation or dissociation and diffusion in the unstirred layers at the phase boundaries [14].

To avoid the formation of a pH gradient, we used a similar set-up as *Okada* and coworkers did for their transport experiments with nonactin [15]: buffered aqueous donor or receiver solutions were employed, and CH_2Cl_2 was the bulk liquid membrane. In

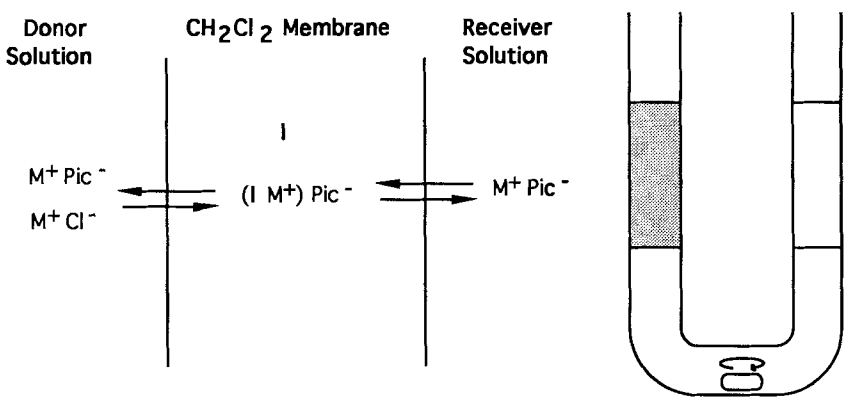

Fig. 1. *Experimental setup and membrane scheme for the cation-transport experiments.* One of the aqueous solutions above the denser CH_2Cl_2 phase contains 1 mM alkali-metal picrate and 100 mM alkali-metal chloride in a 100 mM *Tris* ('tris(hydroxymethyl)aminomethane') buffer, the other one contains only the *Tris* buffer. M^+ = metal ion, Pic^- = picrate, I = ionophore.

[4]) This abbreviation was proposed [9b] for the low-molecular-weight P(3-HB) (100–200 3-HB units), because it appears to be always complexed with other molecules (for instance Ca polyphosphate or proteins).

[5]) Many crystal structures are known in which keto or amide carbonyl O-atoms act as ligands for alkali-metal cations, or in which ether and ester carbonyl O-atoms cooperate in the coordination [12] [13]; but only few complexes of alkali-metal ions with ligands carrying only ester groups which may participate in complexation are known so far [1] [10] [11].

addition to a metal-ion picrate, the donor solutions contained a hundred-fold equimolar amount of the corresponding metal chloride. This increases the chemical potential of the cation and leads to the desired linear correlation of %-transport with time in the diagrams. The choice of the counterion is important, because it has to accompany the cation on its migration through the organic phase. We chose the picrate anion for two reasons: picrates show higher transport rates than salts of other anions, at least with crown ethers [16], and the progress of the transport is easily monitored by UV spectrophotometry.

Using the set-up described above, we first compared the transport of potassium picrate with several cyclic (*R*)-3-hydroxybutanoic-acid derivatives **1**–**4**, with a cyclic trimer **6** of (*R*)-3-hydroxypentanoic acid (3-HV), and with a mixture **5** of open-chain oligomers having an average chain length of 28 3-HB units[6]) (see *Figs. 2* and *3*). For the sake of comparison, we kept the molar equivalents of C=O groups per ml constant in all experiments, *i.e.* equal masses of the 3-HB derivatives **1**–**5**; only for the triolide **6**, derived from 3-HV, a correspondingly larger amount was employed.

The differences in the transport rates betweeen the triolide **1** and its epimer **2** (*Fig. 3, a*) are nicely compatible with the different conformations of the two compounds in the crystal and in solution [19]: the three unidirectional C=O groups of **1** (as shown in *Fig. 1*) are certainly better suited for a cooperative complexation than the two in the epimer **2**.

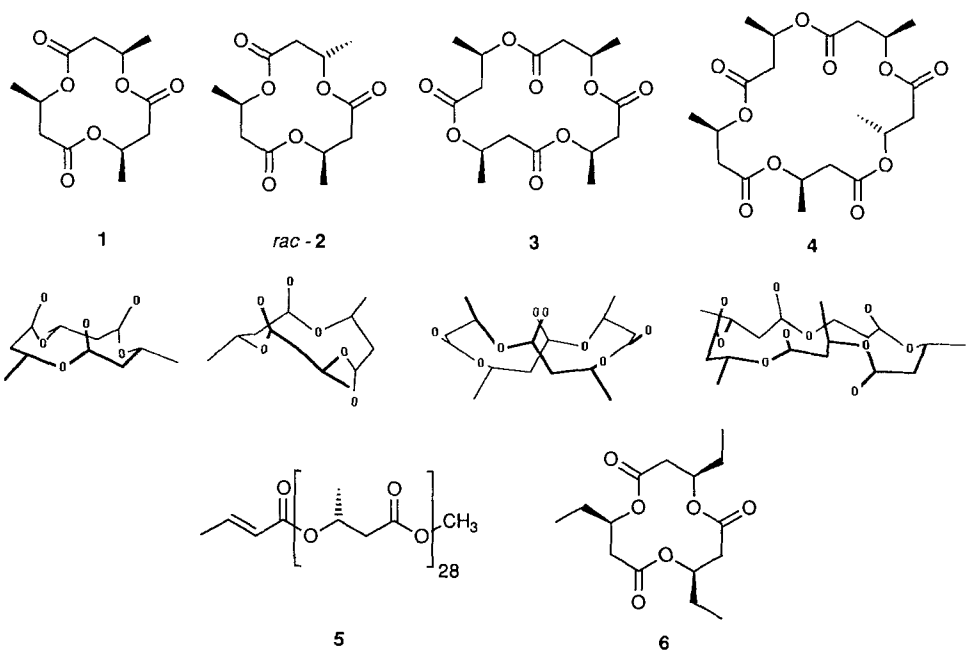

Fig. 2. *Formulae of the oligo(3-HB) and oligo(3-HV)* [17] *derivatives used in this study*. The MacMoMo presentations [18] of the corresponding crystal structures of **1**–**4** are also shown [19].

[6]) In a similarly performed experiment, in which the buffer was omitted from the receiver phase, the picrate was still transported, but no Cl^- ions were detectable in the receiver solution by addition of $AgNO_3$.

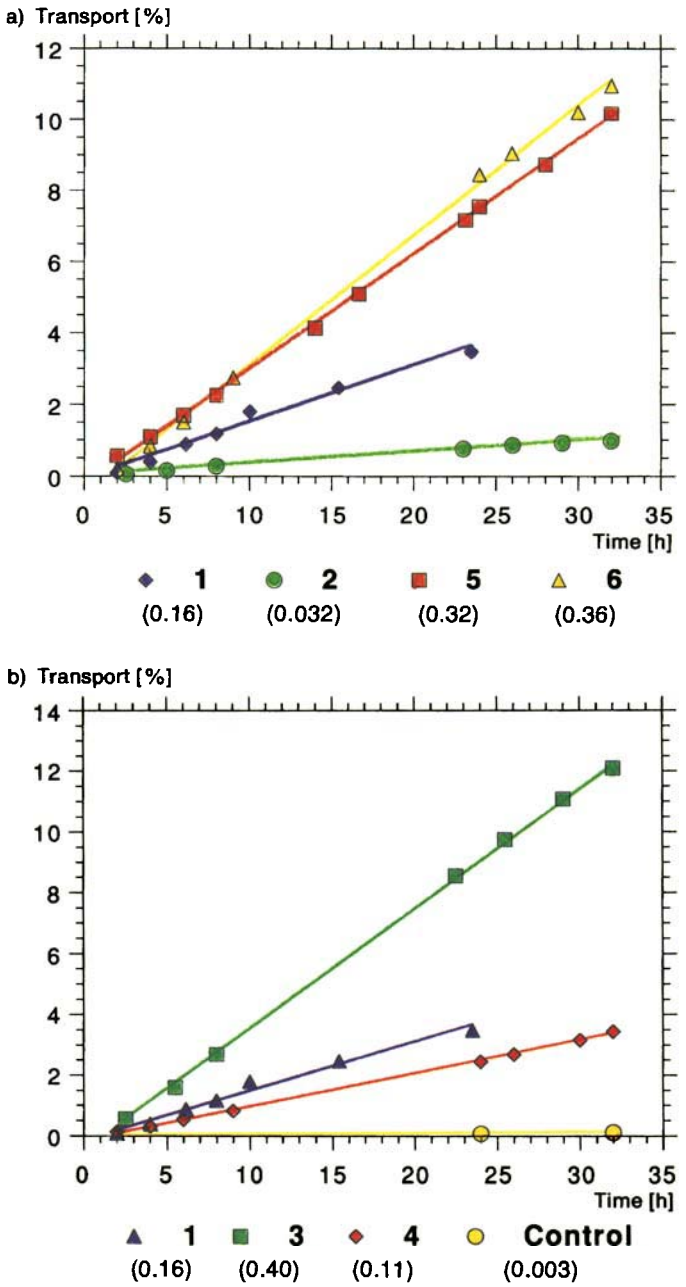

Fig. 3. *Comparison of the potassium-ion transport with different derivatives of 3-HB and 3-HV.* The values on the ordinate correspond to the percentage of the initial amount of picrate from the donor phase. The numbers given in brackets underneath the color codes denote % picrate migrating per hour. *a*) Transport with the triolide **1**, its epimer **2**, the 'tris-homologous' triolide **6**, and the open-chain oligo(3-HB) derivative **5**. *b*) Transport with the cyclic 3-HB oligomers **1**, **3**, and **4** of increasing ring size. No ionophor was added in the control experiment.

The enhancement of transport rate with the homologous triolide **6** (*Fig. 3, a*) is understandable as well: the solubility of **6** in H_2O is much lower[7]) than that of **1**, and it is known that, as long as the addition of hydrophobic groups, resulting in a solubility decrease in H_2O, does not alter the complexing abilities of a ligand, an increase in the transport rate is expected [16]. We were surprised to see that the tetrolide **3** (*Fig. 3, b*) is a better carrier than the triolide, because its conformation in the crystal does not at all look as attractive for simultaneous multiple complexation of an ion, as does the 'tripole' of **1** (see the extensive discussion in the preceding paper on the structure and bonding in complexes of **1** [11]). We must conclude that the conformation of the tetrolide **3** in solution is quite flexible[8]), like that of all the higher cyclic oligo(3-HB) derivatives [19]. On the other hand, the pentolide **4**, which has an average C_5 symmetry in solution [19], and the conformation of which in the crystal (*Fig. 2*) does not look favorable for complexation either, transports K^+ ions less efficiently than the triolide **1**.

Intrigued by the strong transporting effect of the compounds **1**–**6** – compared to the control experiment with no 3-HB derivative added – we also performed a test with AcOBu[9]), 'offering the same concentration of ester groups' as in the 3-HB experiments. The effect on the transport rates was very small, only 0.007% of the picrate migrated per hour, which is *ca.* twice the rate of the control experiment (with no ester at all in the organic phase). Thus, the effects of the 3-HB derivatives **1**–**6** are clearly due to a chelating or crown ester effect rather than to a simple increase of the polarity of the CH_2Cl_2 liquid membrane by the presence of ester groups!

The high transport activity of the open chain 3-HB derivative **5** is most astonishing to us, as this ligand is not expected to possess a preformed geometry which is suitable for complexation [13]. However, the flexible conformation of the chain may allow it to adopt conformational geometries required for complexation of cations [20]. It is also worthwhile at this point to mention in passing that the addition of $Ba(SCN)_2 \cdot 3H_2O$ to a solution of microbial high-molecular-weight P(3-HB) in CF_3CH_2OH/H_2O causes a change in its specific rotation[10]), which may indicate that a conformational change of the polymer structure has taken place, and that conformers capable of varying cavity dimensions to adjust to the size of the different cations may be formed [21].

For the examination of the transport behavior with different alkali and alkaline-earth metal ions, we limited our studies to the readily available triolide **1** and the open-chain oligomer mixture **5**.

Transport of Alkali and Alkaline-Earth Metal Salts across a CH_2Cl_2 Bulk Liquid Membrane Mediated by the Triolide **1**. Under conditions similar to those outlined above, the transport ability of the cyclic trimer **1** of 3-HB was examined with all alkali-metal cations from Li to Cs and with the alkaline-earth metal cations from Mg to Ba (*Fig. 4*)[11]).

---

[7]) The solubility of **1** in H_2O (*ca.* 0.9%) [19] is *ca.* ten times larger than that of **6**.

[8]) The ^{1}H-NMR spectrum of **3** indicates an average C_4 symmetry in $CDCl_3$ solutions at ambient temperature [19].

[9]) The solubility of AcOBu in H_2O is 1%, which is in the same range as that of **1**.

[10]) Specific rotation of P(3-HB) in CF_3CH_2OH/H_2O (80:20): $[\alpha]_{436} = +3.0$, $[\alpha]_D = -1.69$, after the addition of 10 mol-% $Ba(SCN)_2$: $[\alpha]_{436} = +4.1$, $[\alpha]_D = -0.88$.

[11]) No hydrolysis of the compound **1** was observed during the experiments; recovered and initially used material showed identical ^{1}H-NMR spectra. This was also true for compound **5**.

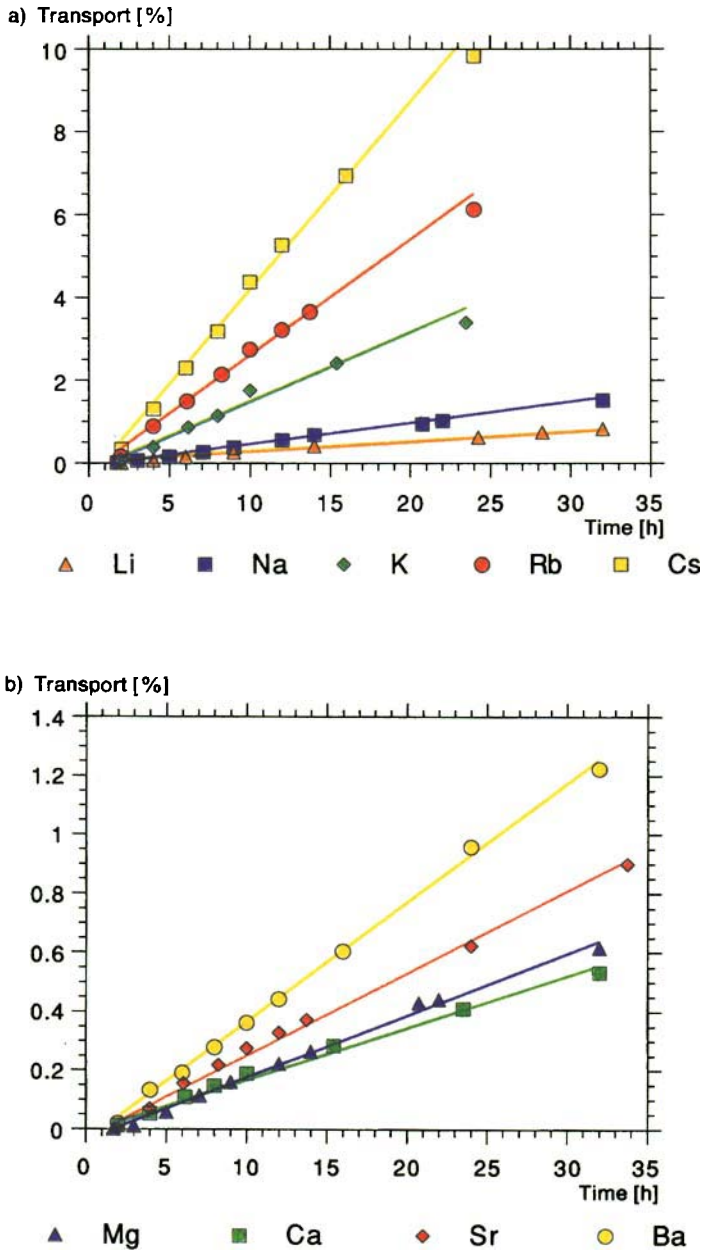

Fig. 4. *Relative rate of transport of the alkali and alkaline-earth metal ions through a CH_2Cl_2 bulk liquid membrane mediated by the triolide* **1**. The values are corrected, *i.e.* the rates obtained without any carrier have been substracted. *a*) Transport rate for Li^+, Na^+, K^+, Rb^+, and Cs^+. *b*) Transport rate for Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}.

The transport rates ($Li < Na < K < Rb < Cs$ and $Mg \approx Ca < Sr < Ba$) increase in the lyotrophic order [22], *i.e.* the transport efficiency becomes larger with increasing ionic diameter and smaller heat of hydration in both series. No exceptional selectivity for one of the ions is detected. The remarkable initiation period of *ca.* 2 h is probably due to the prior saturation of the organic phase with the cations. We then performed another control experiment, in which we used the same ionophore solution and examined the transport of solely picrate, *i.e.* no metal ions were added to the donor solution. The rates obtained (see the *Table*) are in the same range as the rates for Li, Mg, and Ca. Therefore, it is impossible to decide whether these anions were transported or not.

Table. *Comparison of the Transport Rates Using the Triolide* **1** *and the Oligomer* **5** *as Carriers for Alkali and Alkaline-Earth Metal Ions.* The rates are given in % picrate migrated/hour.

Compound	Transport Metal Ion									
	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}	no M^{X+}
1	0.03	0.05	0.16	0.27	0.45	0.02	0.02	0.03	0.04	0.03
5	0.04	0.10	0.32[a])	0.31[a])	0.34[a])	0.02	0.04	0.07	0.20	0.02
Control	0.001	0.002	0.003	0.004	0.016	0.001	0.001	0.003	0.002	–

[a]) With one tenth of the amount of ionophore the values for **5**, and K^+, Rb^+, and Cs^+ were 0.11, 0.14, 0.19.

Transport of Alkali and Alkaline-Earth Metal Cations across a Bulk Liquid CH_2Cl_2 Membrane Mediated by Open-Chain 3-HB Oligomers. Oligomers of P(3-HB) are easily accessible by three different methods: pyrolysis, degradation with bases, and partial transesterification [23–25]. Pyrolysis of P(3-HB) at temperatures exceeding 175° leads to statistical chain scissions by the mechanism of an ester pyrolysis [25]. The average molecular weight obtained is a function of temperature and duration of pyrolysis.

A sample of oligo(3-HB) **5** prepared by this method, with a number average degree of polymerization (X_n) of 28 monomer units, was used for the transport experiments with alkali and alkaline-earth metal salts. Before performing the experiments, the free COOH groups of the oligomers were esterified with CH_2N_2 to avoid an ion-exchange-type transport by the carboxylate anion[11]). The results of the transport experiments with **5** are collected in *Fig. 5*. The fact that the transport rates for K^+, Rb^+, and Cs^+ are approximately equal (*Fig. 5, a*) puzzled us initially. When we repeated the experiment with one tenth of the ionophore concentration (data not shown), a decrease in the rates following the sequence $Cs > Rb > K$ was established again. The solutions of the oligomers **5** show a higher viscosity than those of the other compounds, so that another step in the overall transport process may become rate-limiting and determine the maximum rate. Again the control experiment with the buffered picrate donor solution (containing no metal ions) gave a rate comparable to the Mg^{2+} ion transport (see the *Table*); therefore, no transport of Mg may have taken place.

Conclusions. – The experiments demonstrate that several oligomers of 3-HB and 3-HV are well suited for the ion transport across bulk liquid CH_2Cl_2 membranes (*Fig. 6*). Probably the most surprising finding is the high transport ability of the open-chain oligomer **5**, which – *a priori* – does not possess a geometry suitable for complexation. The linear oligomer transports all cations – with the exception of Cs^{2+} and Mg^{2+} – with considerably higher velocities than does the triolide (see the *Table*).

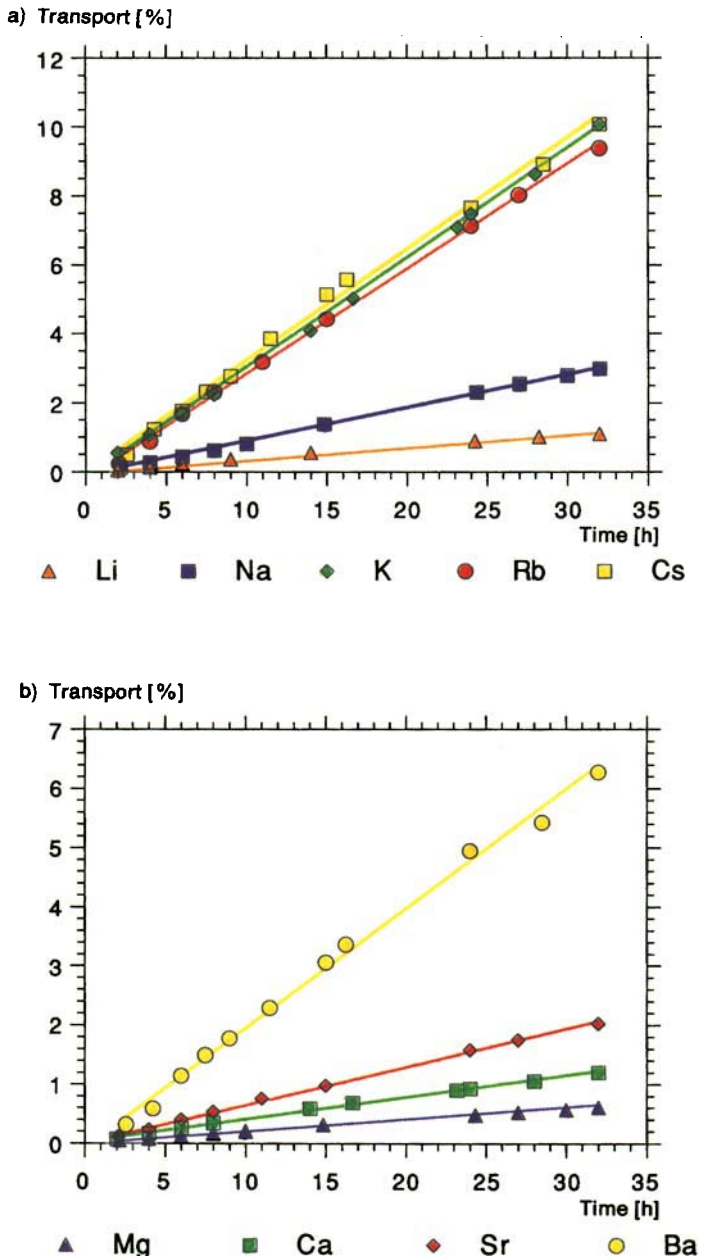

Fig. 5. *Relative rate of transport of the alkali and alkaline-earth metal ions through a bulk liquid membrane mediated by the oligomer mixture* **5**. The values are corrected, *i.e.* the rates obtained without any carrier are substracted. The values are, however, not corrected for viscosity differences between the solution of **5** and that of the low-molecular-weight 3-HB derivatives. *a*) Rates for Li^+, Na^+, K^+, Rb^+, and Cs^+. *b*) Rates for Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}.

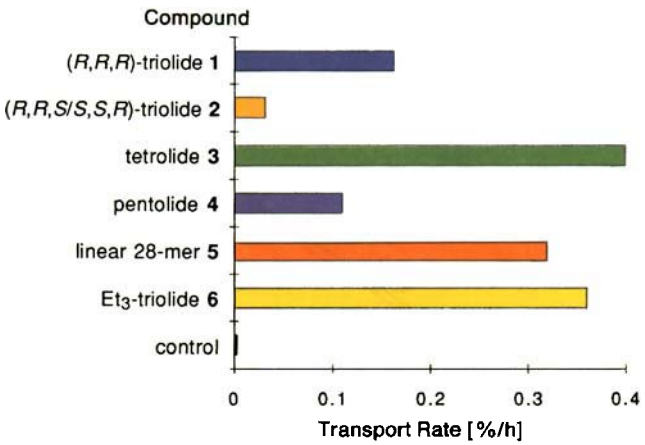

Fig. 6. *Comparison of the potassium-ion transport rates with the 3-HB and 3-HV derivatives* **1**–**6**. In the control experiment, no ionophor was added to the CH_2Cl_2 phase.

This results is in support of the proposal by *Reusch* [9], according to which linear oligo(3-HB) of 100 to 150 3-HB units forms an ion-channel complex with Ca-polyphosphate embedded in cell membranes. A discussion of the P(3-HB) structure, lamellae formation, and possible structures of an ion channel involving P(3-HB) will be reported separately [24].

The transport efficiency for Ca^{2+} ions is low with the compounds studied herein. This fact does not support the proposed function of P(3-HB) in biological systems [9]. Also, in collaboration with *Riddell*'s group, we tested the influence of several derivatives of 3-HB on ion transport across vesicle bilayers – a model biological membrane system –, to find that the effect was very small. The transport of Na^+ through a vesicle wall was accelerated at most by a factor of 2 by adding CF_3CH_2OH solutions of rather large amounts of various 3-HB derivatives [26]. For the technique, see a review article [27] and references cited therein. We thank Prof. *Riddell* for allowing us to mention these results here.

We gratefully acknowledge generous supply of P(3-HB) and '*BIOPOL*' from *ZENECA Bio Products*, a company of the *ICI* group, Billingham, England [6].

Experimental Part

General. All solvents were *puriss. p.a.* quality or distilled over suitable drying agents. The aq. solns. for the transport experiments were prepared with double-distilled H_2O in polypropylene containers to avoid interferences of ions extracted from the glassware. M.p.: *Büchi/Tottolli* melting point apparteous, not corrected. ^{1}H-NMR: *Varian Gemini 200*, 200 MHz with $CDCl_3$ as solvent. *Reagents.* P(3-HB) was from *Marlboro Biopolymers Ltd.*, today *Zeneca Bio Products* (GB); Lot No. MBL 100/703. LiCl, NaCl, KCl, $MgCl_2 \cdot 6H_2O$, $CaCl_2 \cdot 2H_2O$, $BaCl_2 \cdot 2H_2O$, and HCl were from *Baker*, RbCl and 'tris(hydroxymethyl)aminomethane' (*Tris*) from *Sigma* $SrCl_2 \cdot 6H_2O$ and picric acid (1% aq. soln.) from *Aldrich* and CsCl from *USB*. $Ba(SCN)_2 \cdot 3H_2O$ was from *Alpha* and 99% pure.

*(4*R,*8*R,*12*R*)-4,8,12-Trimethyl-1,5,9-trioxacyclododecane-2,6,10-trione* (**1**) was prepared as described in [10]. rac-*(*l,u*)-4,8,12-Trimethyl-1,5,9-trioxacyclododecane-2,6,10-trione* (**2**), *(4*R,*8*R,*12*R,*16*R*)-4,8,12,16-Tetramethyl-1,5,9,13-tetraoxacyclohexadecane-2,6,10,14-tetrone* (**3**), *(4*R,*8*R,*12*R,*16*R,*20*R*)-4,8,12,16,20-pentamethyl-

1,5,9,13,17-pentaoxacycloicosane-2,6,10,14,18-pentone (**4**) were prepared as described in [19] and **6** analogously as **1** [17].

α-Methyl-ω-(but-2-enoyloxy)oligo{(R)-[oxy(3-methyl-1-oxopropylene)]} (**5**) P(3-HB) (50 g, 0.58 mol monomeric units) was heated neat under Ar to 210° for 140 min, the melt cooled to r.t., dissolved in $CHCl_3$, and treated with activated charcoal. After evaporation of the solvent, the residue was suspended in Et_2O and stirred vigorously, until a fine suspension formed, the insoluble residue was collected on a *Büchner* funnel, and washed with Et_2O. Drying under high vacuum yielded 38.2 g of a white powder. This oligomer mixture (5 g) was dissolved in CH_2Cl_2 and CH_2N_2 in Et_2O was added in excess. After ceasing of the N_2 evolution, the solvent was removed and the residue dried under high vacuum to yield 5.0 g (76%) of **5** with a number average degree of polymerization of 28 (calculated from the ratio CH_3/CH_3O in the ^{1}H-NMR). M.p. 146.5–150°. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.02–6.85 (*m*, H–C(3) ω-end group); 5.82–5.74 (*m*, H–C(2) ω-end group); 5.32–5.16 (*m*, H–C(3)); 3.67 (*s*, CH_3O, α-end group); 2.66–2.38 (*m*, CH_2(2)); 1.87–1.83 (*m*, CH_3(4) ω-end group); 1.31–1.22 (*m*, CH_3(2)).

Transport Experiments. The transport experiments were performed in a conventional U-tube (i.d. = 15 mm) made of quartz glass. The donor solns. were prepared the following way: 5.05 mmol alkali-metal chloride were mixed with 5 mmol *Tris* and 50 μmol picric acid, the pH adjusted to 8.1 and brought to a final volume of 50 ml. Alkaline-earth metal chloride (5.05 mmol) was mixed with 5 mmol *Tris* and 100 μmol picric acid, the pH adjusted to 8.1, and brought to a final volume of 50 ml. The solns. of the ionophores **1**–**6** were 300 mM in terms of monomeric units in CH_2Cl_2. A *Tris*/HCl buffer (100 mM, pH 8.1) served as receiving phase. Both the donor and receiving solns. (7.5 ml) were carefully overlayered over 15 ml of the denser org. ionophore soln. and magnetically stirred (200 rpm) at 22° for extended time. The amounts of migrated ions were determined photometrically at 356 nm in 1-cm quartz kuvettes with a *Perkin Elmer Lambda 3A* UV/VIS spectrophotometer or a *Kontron Uvikon 860* by comparing the initial absorption of the donor soln. with the absorption of the receiving phase as a function of time.

REFERENCES

[1] H.-M. Müller, D. Seebach, *Angew. Chem.* **1993,** *105,* 483; *ibid. Int. Ed.* **1993,** *32,* 477.

[2] *FEMS Microbiol. Rev.* **1992,** *103,* 91–490.

[3] H. Brandl, R. A. Gross, R. W. Lenz, R. C. Fuller, *Adv. Biochem. Eng. Biotechnol.* **1990,** *41,* 77.

[4] 'MBL Biopol Natural Thermoplastics. A Guide for Processors', ICI Biological Products, PO Box 1, Billingham, Cleveland TS23 1LB, England.

[5] Y. Doi, 'Microbial Polyesters', VCH, Weinheim, 1990.

[6] *ZENECA Bio Products*, PO Box 2, Belasis Avenue, Billingham, Cleveland TS23 1YN, England.

[7] M. Yalpani, PCT Int. Appl. WO 9209210, 1992, *Nutrasweet Co.* (*CA*: **1992,** *117,* 149843u); M. Yalpani, PCT Int. Appl. WO 9209211, 1992, *Nutrasweet Co.* (*CA*: **1992,** *117,* 190663y).

[8] D. Seebach, R. Imwinkelried, T. Weber, in 'Modern Synthetic Methods', Ed. R. Scheffold, Springer-Verlag, Berlin, 1986, p. 125–260; D. Seebach, S. Roggo, J. Zimmermann, in 'Stereochemistry of Organic and Bioorganic Transformations', Eds. W. Bartmann and K. B. Sharpless, VCH, Weinheim, 1987, p. 85–126; D. Seebach, *Angew. Chem.* **1990,** *102,* 1363; *ibid. Int. Ed.* **1990,** *29,* 1320.

[9] a) R. N. Reusch, H. L. Sadoff, *Proc. Natl. Acad. Sci. U.S.A.* **1988,** *85,* 4176; R. Reusch *Proc. Soc. Exp. Biol. Med.* **1989,** *191,* 377; b) R. N. Reusch, *FEMS Microbiol. Rev.* **1992,** *103,* 119.

[10] D. Seebach, H.-M. Müller, H. M. Bürger, D. A. Plattner, *Angew. Chem.* **1992,** *104,* 443; *ibid. Int. Ed.* **1992,** *31,* 434.

[11] D. Seebach, H. M. Bürger, D. A. Plattner, R. Nesper, T. Fässler, *Helv. Chim. Acta* **1993,** *76,* 2581.

[12] M. Dobler, 'Ionophores and Their Structures', Wiley & Sons, New York, 1981; J. P. Michael, G. Pattenden, *Angew. Chem.* **1993,** *105,* 1; *ibid. Int. Ed.* **1993,** *32,* 1.

[13] B. Dietrich, P. Viout, J.-M. Lehn, 'Macrocyclic Chemistry', VCH, Weinheim, 1993.

[14] B. G. Cox, H. Schneider, 'Studies in Physical and Theoretical Chemistry', Elsevier Science Publishers, Amsterdam, 1992, Vol. 76, 'Coordination and Transport Properties of Macrocyclic Compounds in Solution', Chapt. 5.

[15] I. Tajima, M. Okada, H. Sumitomo, *J. Am. Chem. Soc.* **1981,** *103,* 4096.

[16] R. M. Izatt, G. A. Clark, J. S. Bradshaw, J. D. Lamb, J. J. Christensen, *Sep. Purif. Meth.* **1986,** *15,* 21.

[17] Part of Ph. D. thesis work of T. Hoffmann, ETH-Zürich, 1993.

[18] M. Dobler, 'MacMoMo II – Molecular Modelling Program', Laboratory of Organic Chemistry, ETH-Zürich, 1992.

[19] D. A. Plattner, A. Brunner, M. Dobler, H.-M. Müller, W. Petter, P. Zbinden, D. Seebach, *Helv. Chim. Acta* **1993,** *76,* 2004; D. Seebach, U.Brändli, H.-M. Müller, M. Dobler, M. Egli, M. Przybylski, K. Schneider, *ibid.* **1989,** *72,* 1704.

[20] W. J. Schultz, M. C. Etter, A. V. Pocius, S. Smith, *J. Am. Chem. Soc.* **1980,** *102,* 7982; B. M. Novak, R. H. Grubbs, *ibid.* **1988,** *110,* 960.

[21] H. Hashimoto, T. Kakuchi, K. Yokota, *J. Org. Chem.* **1991,** *56,* 6470.

[22] S. G. A. McLaughlin, G. Szabo, S. Ciani, G. Eisenman, *J. Membrane Biol.* **1972,** *9,* 3.

[23] F. E. Küng, US-Patent 2361036, 1944, *B. F. Goodridge Co.* (*CA*: **1944,** *38,* 6301); H. Morikawa, R. H. Marchessault, *Can. J. Chem.* **1981,** *59,* 2306; M. Kunioka, Y. Doi, *Macromolecules* **1990,** *23,* 1933; D. Seebach, A. K. Beck, U. Brändli, D. Müller, M. Przybylski, K. Schneider, *Chimia* **1990,** *44,* 112; N. Vanlautem, J. Gilain, Eur. Pat. Appl. EP 43620 Al, 1982, *Solvay et Cie* (*CA*: **1982,** *96,* 163397f); E. L. Welland, J. Stejny, A. Halter, A. Keller, *Polym. Commun.* **1989,** *30,* 303.

[24] D. Seebach, H. M. Bürger, H.-M. Müller, U. Lengweiler, A. K. Beck, P. J. Barham, P. A. Barker, K. E. Sykes, *Helv. Chim. Acta,* in preparation.

[25] N. Grassie, E. J. Murray, P. A. Holmes, *Polym. Degrad. Stabil.* **1984,** *6,* 47, 95, 127.

[26] H. M. Bürger, D. Seebach, F. G. Riddell, Z. Zhou, unpublished results.

[27] F. G. Riddell, *Chem. Br.* **1992,** *28,* 533.