

Binding and Transport of Alkali and Alkaline Earth Metal Ions by Synthetic Macrolides Containing Tetrahydropyran Rings

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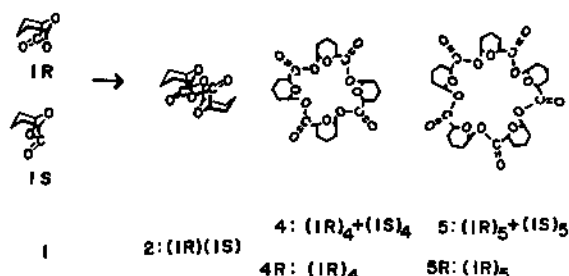
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Abstract: Ion binding and transport abilities of 10-, 20-, and 25-membered macrolides (2, 4, and 5, respectively) consisting of alternating tetrahydropyran and ester moieties were evaluated mainly by extraction equilibrium and transport experiments of various metal picrates. The macrolide 2 was totally ineffective in ion binding and transport. The ion extraction constants of the macrotetrolide 4 and the macropentalide 5 were found to be in the order of $\sim 10^{-10}$, and their ion selectivity sequences were $\text{Cs}^+ > \text{Rb}^+ > \text{K}^+ > \text{Na}^+ > \text{Li}^+$ and $\text{Ba}^{2+} > \text{Ca}^{2+}$. The transport rate of metal picrates mediated by 4 and 5 through organic liquid membranes decreased in the order, $\text{Cs}^+ > \text{Rb}^+ > \text{K}^+ > \text{Ba}^{2+} > \text{Ca}^{2+} \approx \text{Na}^+ > \text{Li}^+$, the selectivity of K^+ over Na^+ being ~ 2 –3. Separated measurements of ion uptake and ion release, along with the selectivity sequences above, suggested that the ion uptake step was rate determining in the transport of metal picrates by 4 and 5. These ion binding properties and transport behaviors are discussed in comparison with those of some natural and synthetic ionophores.

Introduction

There have been found in nature a variety of macrocyclic antibiotics which show a high degree of cation selectivity and act as ionophores to permeate specific ions through biological membranes.¹ Such elaborate functions displayed by these antibiotics have been elucidated to a considerable extent, particularly with recent advances in crystallographical and spectroscopical techniques. On the other hand, since the epoch-making discovery of crown ethers by Pedersen,² numerous multidentate macrocyclic ligands aiming at specific ion and substrate selectivities have been designed and their characteristic binding behaviors have been quantitatively investigated.³ Some of these synthetic macrocyclic ligands have been studied as model carriers for transport of cations across cell membranes by naturally occurring ionophores.⁴

Recently, the authors succeeded in the highly selective synthesis of 10-, 20-, and 25-membered macrocyclic oligoesters (macrolide 2, macrotetrolide 4, macropentalide 5, respectively) by cationic ring-opening polymerization of (\pm)-6,8-dioxabicyclo[3.2.1]octan-7-one (1) at -40°C .⁵⁻⁷ In addition, optically active macrotetrolide (4R) and macropentalide (5R) were prepared in a similar manner from (+)-(1R,5R)-6,8-dioxabicyclo[3.2.1]octan-



7-one (1R).⁸⁻¹⁰ These macrolides are composed of alternating tetrahydropyran ring and ester moieties, and they bear structural resemblance to nonactin which is a 32-membered naturally occurring macrotetrolide. Nonactin has been shown to be influential in the regulation of metabolic behavior and is thought to act by selectively enhancing the transport of potassium ion through cell

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(10) All the macrolides used in this work are sufficiently pure; elemental analysis ($\text{C}_6\text{H}_{10}\text{O}_5$)_n (n = 2, 4, and 5), C, H; no impurity was detected by GPC, IR, or ^1H and ^{13}C NMR techniques. Their structures were established by X-ray analysis. Previously, it was reported erroneously that a 30-membered cyclic hexamer was produced from both racemic and optically active 6,8-dioxabicyclo[3.2.1]octan-7-one, on the basis of the molecular weight determination by vapor pressure osmometry. Recent X-ray analysis has disclosed that it is actually a 25-membered cyclic pentamer. The error was due to the formation of a molecular complex of the cyclic pentamer with chloroform, whose molecular weight was close to that of the cyclic hexamer.

membranes.¹¹ Therefore, it would be of considerable interest to investigate ion binding and transport behaviors of these novel synthetic macrolides. The present paper is concerned with ion extraction and transport abilities of 2, 4, and 5 as evaluated by extraction equilibrium and carrier-mediated transport of alkali and alkaline earth picrates. The optically active macrolides 4R and 5R are structurally identical with the racemic macrolides 4 and 5, respectively, and therefore the ion binding and transport behaviors of the former ligands are expected not to differ from those of the latter ligands.

Experimental Section

Preparation of (±)-6,8-Dioxabicyclo[3.2.1]octan-7-one (1). An aqueous solution (122 mL) of racemic sodium 3,4-dihydro-2H-pyran-2-carboxylate (50 g) was slightly acidified with 6 N hydrochloric acid (64 mL), and after a sufficient amount of sodium chloride was added to saturate the solution, the liberated racemic carboxylic acid was extracted several times with ethyl ether (500 mL). The ethyl ether extract was washed three times with a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and distilled under reduced pressure to give racemic monomer 1 in 78% yield, bp 68–70 °C (4 mm) (lit.¹² bp 62–64 °C (3 mm)). It was purified by drying over calcium hydride and repeated fractional distillation before use.

Polymerization. Freshly distilled monomer and solvent were charged into a glass ampule, and an initiator solution was added to the monomer solution at –78 °C. All these manipulations were carried out under a nitrogen atmosphere. The ampule was chilled in liquid nitrogen, evacuated, sealed off, and allowed to stand in a constant-temperature bath. After the addition of a small volume of pyridine to terminate the polymerization, the composition of the reaction products was determined by a Jasco Trirotar gel permeation chromatograph using chloroform as eluent (column, Jasco JSP101, 20 i.d. × 500 mm). Cyclic dimer (2), racemic cyclic tetramer (4), and racemic cyclic pentamer (5) were selectively prepared in acetonitrile, chloroform, and 1-nitropropane, respectively, by the oligomerization of racemic monomer (1). 2 and 4 were purified by crystallization in acetonitrile and chloroform, respectively, while 5 was separated by a preparative gel permeation chromatograph.

Extraction Measurement. The ion extraction efficiencies of the cyclic oligomers were evaluated from distribution equilibria of the respective metal picrate complexes between an aqueous phase and an immiscible organic phase (methylene chloride). A Tris buffer solution (tris(hydroxymethyl)aminomethane, pH 8.3, 5 mL) containing 1×10^{-4} mol/L of metal picrate and 1×10^{-1} mol/L of metal chloride was vigorously shaken in a small flask with an equal volume of a methylene chloride solution containing 1×10^{-2} mol/L of cyclic oligomer. The binary system was allowed to stand overnight to give clear aqueous and organic phases. The metal picrate concentration of the aqueous phase was measured by UV spectroscopy (λ_{max} 357 nm, ϵ 1.45×10^4). By assuming a 1:1 stoichiometry for the complexation between metal picrate and cyclic oligomer, the ion extraction constants of cyclic oligomers were evaluated from the eq 1 for alkali metal picrates and from the eq 2 for alkaline earth metal picrates.¹³

$$K_e = \frac{[\text{LM}^+\text{Pi}^-]_{\text{org}}}{[\text{M}^+]_{\text{aq}}[\text{Pi}^-]_{\text{aq}}[\text{L}]_{\text{org}}} \quad (1)$$

$$K_e = \frac{[\text{LM}^{2+}(\text{Pi}^-)_2]_{\text{org}}}{[\text{M}^{2+}]_{\text{aq}}[\text{Pi}^-]_{\text{aq}}^2[\text{L}]_{\text{org}}} \quad (2)$$

L = oligomer; M^+ and M^{2+} = metal cations; Pi^- = picrate anion. Initial concentrations: [oligomer] = 1×10^{-2} mol/L, [metal chloride] = 1×10^{-1} mol/L, and [metal picrate] = 1×10^{-4} mol/L.

Cation Transport through Liquid Membranes. Cation transport experiments were conducted using a double cylindrical glass cell (diameter, inner cylinder 22 mm, outer cylinder 35 mm) in which the inner cylinder had small channels connecting inner and outer areas at its bottom. A methylene chloride solution (7 mL) containing 1×10^{-2} mol/L of cyclic oligoester was placed at the bottom. Atop the methylene chloride solution inside the inner cylinder was carefully placed a Tris buffer solution (7 mL) containing 1×10^{-4} mol/L of metal picrate and 0.1 mol/L of metal chloride (aqueous phase I, surface area 380 mm²). Simultaneously, atop the outer ring of the methylene chloride solution was placed a Tris buffer

Table I. Ion Extraction Constants of Synthetic Macrolides^a

ion	diameter, Å	–ΔH ^b kJ/mol	K _e ^c (L/mol) ²		
			dilide	tetrolide	pentalide
Li ⁺	1.20	559	0	15 ± 5	20 ± 10
Na ⁺	1.90	444	0	15 ± 5	20 ± 10
K ⁺	2.66	360	0	45 ± 5	75 ± 5
Rb ⁺	2.96	339	0	65 ± 15	110 ± 10
Cs ⁺	3.38	315	0	110 ± 30	155 ± 35
Ca ²⁺	1.98	1669	0	30 ± 10 ^d	45 ± 15 ^d
Ba ²⁺	2.70	1379	0	50 ± 10 ^d	60 ± 20 ^d

^a Aqueous phase: [metal picrate] = 1×10^{-4} mol/L, [metal chloride] = 1×10^{-1} mol/L; methylene chloride phase: [macrolide] = 1×10^{-2} mol/L. ^b Heat of hydration.¹⁴ ^c K_e values are given by an average value of three measurements. ^d K_e × 10⁴ (L/mol)³.

solution (10 mL, aqueous phase II, surface area 470 mm²). These three phases were gently stirred at ca. 200 rpm without mixing at 25 ± 1 °C using a magnetic stirrer. At specified time intervals, the concentrations of metal picrate in both aqueous phases were determined by UV spectroscopy. It was confirmed by the silver nitrate titration method using 5% potassium chromate as indicator that no chloride ion was transported from aqueous phase I to aqueous phase II.

Separated Measurements of Ion Uptake and Ion Release. A methylene chloride solution (7 mL) containing 5 (1×10^{-2} mol/L) was placed at the bottom of a glass cell (35 mm i.d.) and a Tris buffer solution (10 mL) of cesium chloride (1×10^{-1} mol/L) and cesium picrate (1×10^{-4} mol/L) was placed on the organic phase. The two phases were slowly agitated without mixing at 25 ± 1 °C. At prescribed intervals, the concentration of cesium picrate remaining in the aqueous phase was determined, from which the rate of ion uptake into the organic phase was estimated. The ion release from a methylene chloride solution containing cesium picrate (7.1×10^{-5} mol/L) and 5 (1×10^{-2} mol/L) into a Tris buffer solution was examined in a similar manner.

Results and Discussion

Ion Extraction. The ion extraction properties of the novel synthetic macrolides (2, 4, and 5) were examined by the extraction equilibria of metal picrates between an aqueous phase (a Tris buffer solution) and an immiscible organic phase (methylene chloride) containing these macroligands. The extraction equilibrium constants K_e's determined by using eq 1 and 2 in the experimental section are listed in Table I, along with the reported data of ion diameter and heat of hydration.¹⁴ The K_e values are a composite of several equilibria which taken together define the amount of picrate ion extracted from an aqueous phase to an organic phase.

The 10-membered macrolide 2 did not extract alkali and alkaline earth metal picrates above a detectable limit. This is understandable in view of its structure determined by X-ray analysis.¹⁵ 2 is composed of a pair of different enantiomeric units and all the substituents attached to the two tetrahydropyran rings are axially oriented. A molecular model shows that there is virtually no cavity in this molecule and that flipping of the tetrahydropyran rings is impossible because of its extremely rigid structure. On the other hand, the 20-membered macrotetrolide 4 and the 25-membered macropentalide 5 possess a cavity with a diameter of ca. 3.5 and 4.5 Å, respectively, in the center of the molecule, and they extracted alkali and alkaline earth metal picrates to some extent into a methylene chloride phase. The ion extraction strength of 4 and 5 as evaluated from the K_e values is much weaker than that of structurally related nonactin.¹⁶ Rather, it is comparable to that of beauvericin,¹³ an 18-membered depsipeptide belonging to enniatins. The ion selectivity sequences for both 4 and 5, although not remarkable, are Cs⁺ > Rb⁺ > K⁺ > Na⁺ > Li⁺, and Ba²⁺ > Ca²⁺. Namely, an ion having a larger diameter and smaller heat of hydration in the alkali and alkaline earth metal series is apt to be extracted more favorably with these

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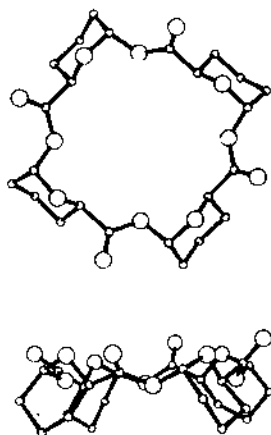


Figure 1. Energy minimized conformation of macroretrolide 4 calculated by MMI method.

synthetic macrocyclics from an aqueous phase into an organic phase. The ion selectivity sequence above belongs to the Eisenman's sequence I which was classified on the basis of theoretical electromechanical analysis.¹⁷ The ion selectivity sequence of nonactin determined by a similar extraction equilibrium method is reportedly $K^+ \approx Rb^+ > Cs^+ > Na^+$,¹⁸ and also in this respect, 4 and 5 differ from nonactin.

The characteristic ion binding properties of the synthetic macrocyclics described above can be interpreted in relation to their relatively rigid structures. These macrocyclics are composed of alternating bulky tetrahydropyran ring and ester moieties, and, unlike nactins, there is no aliphatic chain between them. Therefore, these macrocyclics, especially 4, are conformationally strained. X-ray analysis disclosed that 4 in the form of a molecular complex with acetonitrile takes a conformation in which its four carbonyl groups are oriented nearly perpendicular to the plane of its 20-membered ring and moreover they are on the same side of the macro-ring plane.¹⁵ X-ray analysis of the macroretrolide itself has not yet been accomplished, but conformational energy calculation by the molecular mechanics I method¹⁹ using the X-ray structural data of the macroretrolide-acetonitrile complex predicted that 4 in its uncomplexed state would take a conformation with all the four carbonyl groups oriented considerably outward from their positions in the acetonitrile complex (Figure 1). Molecular model inspection also suggested that a conformation with all the four carbonyl groups directed toward the center of the macro-ring would be extremely strained and therefore improbable. Recent X-ray analysis of a 5-acetonitrile molecular complex revealed that 5 also takes a conformation analogous to that of 4. In view of such a rather less flexible conformation, it would appear that these synthetic macrocyclics capture a metal cation with their carbonyl oxygens situated outside their macro-rings.

The hypothesis above was, at least partly, substantiated by NMR and IR spectroscopy. Thus, the addition of excess metal thiocyanates to solutions of the macrocyclics in chloroform or acetonitrile did not cause significant changes in the chemical shifts of their ¹H and ¹³C NMR spectra, except those of the carbonyl carbon and of the methine proton on the carbon adjacent to the carbonyl group (e.g., $\Delta\delta(C=O) = 1.95$ ppm at $[KSCN]/[macroretrolide] = 1$; $\Delta\delta(CH-CO) = 0.17$ ppm at $[NaSCN]/[macroretrolide] = 1$ (both in deuteriochloroform)). Furthermore, the addition of metal thiocyanates to solutions of the macrocyclics in acetonitrile shifted the carbonyl absorption in IR spectra to a lower wavenumber and increased the intensity of the $\nu(C-O-C)$ band at 1200 cm^{-1} ($\Delta\delta = -20\text{ cm}^{-1}$ at $[NaSCN]/[macroretrolide] = 10$). These spectroscopical data are compatible with the direct participation of the carbonyl oxygens of the macrocyclics in the

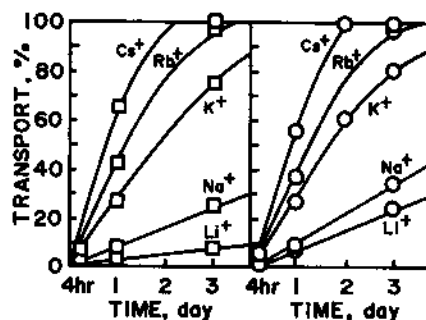


Figure 2. Transport of alkali metal picrates by macroretrolide 4 and macropentalide 5: \square , 4; \circ , 5. $[macroretrolide]_{CH_2Cl_2} = 1 \times 10^{-2}$ mol/L; $[metal\ picrate]_{aq} = 1 \times 10^{-4}$ mol/L; $[metal\ chloride]_{aq} = 1 \times 10^{-1}$ mol/L.

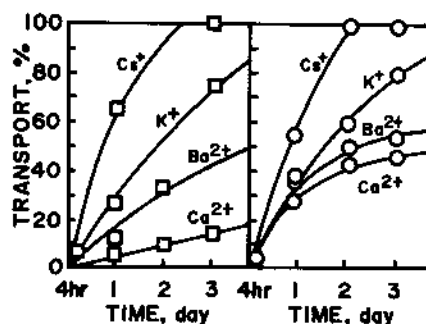


Figure 3. Transport of alkali and alkaline earth metal picrates by macroretrolide 4 and macropentalide 5: \square , 4; \circ , 5. $[macroretrolide]_{CH_2Cl_2} = 1 \times 10^{-2}$ mol/L; $[metal\ picrate]_{aq} = 1 \times 10^{-4}$ mol/L; $[metal\ chloride]_{aq} = 1 \times 10^{-1}$ mol/L.

complexation with alkali and alkaline earth metal cations. The somewhat stronger ion extraction ability of 5 in comparison with that of 4 (Table I) is presumably due to the increased number of available binding sites in the former. This effect, however, is partially compensated by the increased cavity size of 5. Its size is too large to fit any metal ions examined, but still the molecule is not sufficiently flexible, so that it is incapable of folding into a three-dimensional spherical cage about cations, as in a nonactin-potassium ion complex.

Cation Transport through Organic Liquid Membranes. Cation transport mediated by the synthetic macrocyclics through organic liquid membranes was investigated by using a double cylindrical glass cell in which inner and outer aqueous phases were bridged by a methylene chloride solution containing macrocyclics. Practically no ion transport occurred in the absence of macrocyclics or in the presence of 2.

Figure 2 represents the transport curves of alkali metal picrates by 4 (left half) and 5 (right half). In both series, the transport rate decreased in the order, $Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$, and the preference of K^+ over Na^+ in the transport was in the range from 2 to 3. The ion selectivity sequence is in agreement with the decreasing order of the K_e values given in Table I. The difference in the transport rate between 4 and 5 seems to be insignificant. Furthermore, it was confirmed that no detectable amount of chloride ion was transported through liquid membranes, irrespective of the presence of a 10^3 times larger amount of chloride ion than that of picrate ion in the aqueous phase I. This is understandable in view of the reported data that the rate of potassium ion transport with chloride counteranion was approximately seven orders of magnitude lower than that with picrate anion.²⁰

Figure 3 presents the comparison of the transport of alkali and alkaline earth metal picrates by 4 (left half) and 5 (right half). Also in these cases, both macrocyclic ligands showed a similar trend. These ion carriers transported Ba^{2+} faster than Ca^{2+} , but their rates were appreciably lower than the rates for monovalent

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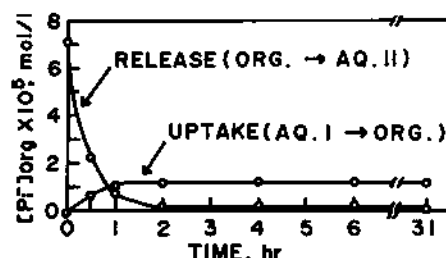


Figure 4. Uptake and release of cesium picrate by macropentalide 5. Uptake: AQ I (Tris buffer, 10 mL), $[CsCl] = 1 \times 10^{-1}$ mol/L, $[CsPi] = 1.1 \times 10^{-4}$ mol/L; ORG (CH_2Cl_2 , 7 mL), $[5] = 1 \times 10^{-2}$ mol/L. Release: ORG (CH_2Cl_2 , 7 mL), $[CsPi] = 7.1 \times 10^{-5}$ mol/L, $[5] = 1 \times 10^{-2}$ mol/L; AQ II (Tris buffer, 10 mL). $[Pi]_{org} = [metal\ picrate]_{CH_2Cl_2}$.

cations Cs^+ and K^+ in the corresponding periods. Furthermore, the rate for Ba^{2+} is smaller than that for K^+ of a similar ion size. Therefore, the lower transport rates for Ba^{2+} and Ca^{2+} compared with those for Cs^+ and K^+ are primarily ascribable to the much higher dehydration energies required for the uptake of the former ions into an organic phase. It is noticeable that the transport rate for Ca^{2+} by 4 is smaller than that by 5, thus resulting in a distinct difference in the transport rate between Ba^{2+} and Ca^{2+} by the former carrier. Presumably, the less flexible structure of 4 compared with that of 5 is responsible for the enhanced discriminating ability toward metal ions. This is also observed, although not so markedly, in the transport of Na^+ and Li^+ (Figure 2).

There are three kinetic processes of importance: uptake, release, and diffusion in ion transport from an aqueous phase to another aqueous phase through an intervening organic liquid membrane. The last process may well be rate determining for liquid membranes which have unstirred Nernst layers. In the present transport system, however, the organic layer was stirred at about 200 rpm using a magnetic stirrer, and hence the diffusion process can safely be regarded as a non-rate-determining step. The foregoing observation that the sequence of transport rate is in parallel with the sequence of ion extraction ability strongly suggests that the uptake process is rate determining in the present transport system. In order to confirm this, the uptake of cesium picrate from an aqueous phase to a methylene chloride phase containing 5 (AQ I \rightarrow ORG) and its release from an organic phase to an aqueous phase (ORG \rightarrow AQ II) were separately examined. The time-concentration profiles are shown in Figure 4. Although the time needed for the attainment of equilibrium between the aqueous and organic phases is nearly the same in both uptake and release processes, the initial slope of the release curve is larger than the uptake curve, indicating that the uptake of cesium picrate is the rate-determining step. A similar, but more remarkable, phenomenon was reported for the uptake and release of sodium picrate by a macrocyclic polyether containing tetrahydrofuran rings.²¹

Among a variety of synthetic macrocycles, 18-crown-6 is one of the most familiar macrocyclic polyethers having a specifically strong affinity toward a potassium ion. Table II presents the comparison of the extraction of potassium picrate between 18-crown-6 and 5 under identical conditions. The organic phase containing 18-crown-6 extracted potassium picrate from the aqueous phase quantitatively, while the organic phase containing 5 extracted only 7% of the salt. However, the much weaker ion extraction strength of the latter ligand does not necessarily mean that it is also less effective in ion transport.

The transport behaviors of potassium picrate by 18-crown-6 and 5 are compared in Figure 5. The uptake of potassium picrate from the source phase (AQ I) into the organic phase (ORG) by 18-crown-6 was, as expected, overwhelmingly rapid compared with that by 5. On the other hand, the increase in the concentration of potassium picrate in the receiving phase (AQ II) was slightly slower for 18-crown-6 than that for 5 in the initial stage, although

Table II. Extraction of Potassium Picrate from Aqueous Phase to Organic Phase by 18-Crown-6 and Macropentalide 5^a

ligand	potassium picrate, %	
	AQ	ORG
18-C-6	0	100
5	93	7

^a AQ: Tris buffer solution, $[KCl] = 1 \times 10^{-1}$ mol/L, [potassium picrate] = 1×10^{-4} mol/L; ORG: methylene chloride, [ligand] = 1×10^{-2} mol/L; time, 1 day; a single measurement.

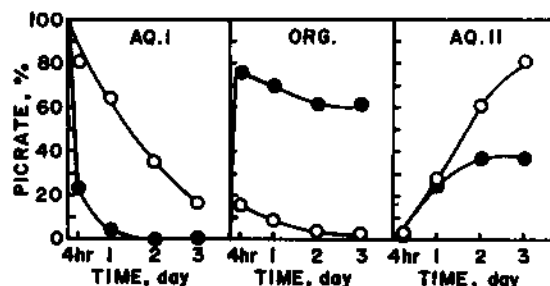


Figure 5. Comparison of potassium picrate transport between 18-crown-6 and macropentalide 5: ●, 18-crown-6; ○, 5. AQ I: Tris buffer, $[KCl] = 1 \times 10^{-1}$ mol/L; $[KPi] = 1 \times 10^{-4}$ mol/L; ORG: CH_2Cl_2 , [ligand] = 1×10^{-2} mol/L; AQ II: Tris buffer.

the concentration of potassium picrate in the organic phase was much higher in the former system. Furthermore, in the 18-crown-6 system, the concentration of potassium picrate in the receiving phase leveled off after about 35% of the picrate initially contained in the source phase had been transported to the receiving phase, while in the macrolide system, it steadily increased with time. Such a distinct difference in the transport behavior between 18-crown-6 and 5 can be interpreted as follows. In the transport of potassium picrate by 18-crown-6, the ion release is undoubtedly rate determining, and the specifically high binding strength for potassium ion prevents the transport of potassium picrate through its organic liquid membrane. On the contrary, the uptake of potassium picrate in the macrolide system is much slower because of its much lower extraction ability for potassium ion than that of 18-crown-6, but for this reason, potassium picrate once extracted into the organic phase is readily released to the receiving phase, thus making its concentration in the organic phase very low throughout transport. This is another way of saying that 5 acts as a more efficient ion carrier than 18-crown-6 at least in the present transport system, although the ion extraction strength of the former is much weaker than that of the latter.

Finally, it would be of interest to compare the aforementioned ion extraction and ion transport behaviors of the synthetic macrolides with those of naturally occurring ionophores. Natural ionophores are classified by transport modes into three categories, namely, neutral ionophores, carboxylic ionophores, and channel-forming ionophores.¹ Ion selectivity patterns of these ionophores have been found in most cases to agree with those predicted by Eisenman.¹⁷ Figure 6 shows the comparison of ion selectivity sequences of some natural ionophores (beauvericin¹³ and nonactin¹⁸) and the synthetic macrolides (4 and 5) which were determined by extraction equilibrium methods.

An 18-membered cyclic depsipeptide, beauvericin ($R = -CH_2C_6H_5$), having a relatively low complexation ability for alkali and alkaline earth metal ions shows a lyotropic sequence,¹³ $Rb^+ \approx Cs^+ > K^+ \gg Na^+ > Li^+$, which is very similar to that observed for the synthetic macrolides as described before. Recently, it has been disclosed crystallographically that in its complex with barium picrate, beauvericin interacts with a barium ion by its three amide carbonyl oxygens which are situated outside the ring; in other words, the barium ion is not located in the cavity of the 18-membered ring.²² In comparison with a nonactin-potassium ion

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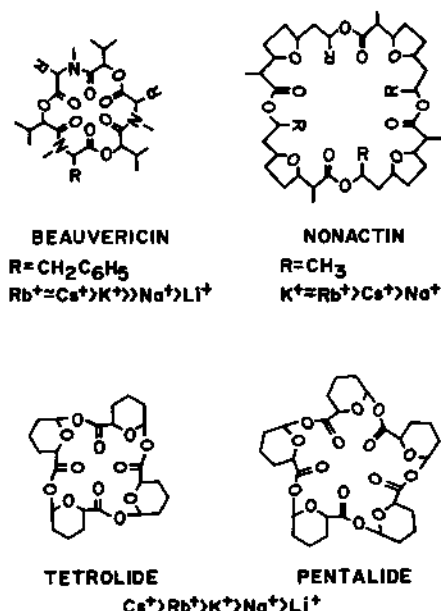


Figure 6. Metal ion selectivity sequences of natural antibiotics (beauvericin¹⁵ and nonactin¹⁸) and synthetic macrolides (4 and 5).

complex in which the liganding oxygens, both the heterocyclic ether oxygens and the ester carbonyl oxygens, are deployed to form the apices of a cube,²³ the complexation of beauvericin is more planar, which tends to limit its ion selectivity (K^+/Na^+ is less than 10).¹³ Therefore, as described in the foregoing section, the complexation mode of 4 or 5 with a metal ion bears a striking re-

semblance to that of beauvericin. In addition, nonactin is a meso macrotetrolide in contrast to the synthetic macrolides 4 and 5 which are racemic compounds; in other words, the latter are chiral but not asymmetric molecules (gyrochiral molecules according to the definition by Nakazaki et al.).²⁴ In 4 and 5, all the carbonyl groups are on the same side of the plane involving the macro-ring, thus making the molecule as a whole more polar than its meso counterpart having their carbonyl groups alternately oriented above and below the macro-ring. Therefore, these synthetic macrolides are expected to interact not only with metal cations but also with polar neutral molecules. In fact, it has recently been revealed that 4 readily forms a 1:1 molecular complex with acetonitrile, in which the acetonitrile molecule is located in the center of an approximate C_4 symmetry.¹⁵

In summary, the 20-membered macrotetrolide 4 and 25-membered macropentalide 5 consisting of alternating tetrahydropyran and ester moieties showed relatively low ion extraction abilities and a lyotropic sequence for alkali metal ion selectivity. They transported alkali and alkaline earth metal ions efficiently through their organic liquid membranes. In these respects, these synthetic macrolides can be regarded as model compounds for naturally occurring neutral ionophores having relatively low ion binding strength such as beauvericin. The 10-membered macrodilide 2 was totally ineffective in ion binding and ion transport.

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