A series of macrocycles incorporating two α-phenylglycine and a variable number of ethylenedioxy units have been prepared as new ionophore models. Transport studies (U-cell, chloroform liquid membrane) showed that only 24-membered macrocycles mimic naturally occurring cyclic ionophores (valinomycin, nonactin) in their ability to transport K⁺ and Na⁺ ions across the lipophilic membrane. meso-8 was found to be a more efficient ion carrier than (±)-8 for M⁺ picrates (K⁺ > Na⁺ > Rb⁺ > Cs⁺). However, both ligands exhibited negligible transport of M⁺ (Ba²⁺, Sr²⁺, Mg²⁺, Ca²⁺) picrates. meso-8 and (±)-8 exhibited poor extraction equilibrium constants (Kₑₓ = 164 and 83 M⁻², respectively) for K⁺ picate in a chloroform-water system.¹¹²¹³¹⁴¹⁵¹⁶¹⁷¹⁸¹⁹¹⁰¹¹¹²¹³¹⁴¹⁵¹⁶¹⁷¹⁸¹⁹¹⁰ Natural occurring macrocyclic ionophores such as valinomycin and nactins exhibit highly selective transport of K⁺ ions across biological and artificial membranes.¹ The property is the cause of their antibiotic activity.² Both kinds of natural ionophores bind metal cations in the central cavity of the macrocyclic ring by ion–dipole interactions with ester carbonyls (valinomycin),³ with ester carbonyls and ether oxygens (nactins).⁴ High selectivities exhibited in the transport of metal cations are a consequence of the specific, rigid conformations of valinomycin and nactins in their cationic complexes.⁵,⁶ These unique properties of valinomycin and nactins present a challenge from the synthetic as well as the biological point of view. Several attempts have been made to mimic valinomycin and nonactin activities by using synthetic polyether macrocycles. In one approach, 18- and 19-membered dialactone analogues of 18-crown-6 were studied as valinomycin models.⁷ However, the ring size of the model dialactones studied was too small to permit the ester carbonyls to turn inward and take part in the complexation of cations.⁸ On the other hand, 32-membered tetralactone cyclodiplothers were studied as nactin models.⁹ These tetralactones achieved only slow transport and poor K⁺/Na⁺ selectivity in comparison to nonactin due to the greater flexibility of model macrocycles. Nitrogen-pivot

Chart 1

<table>
<thead>
<tr>
<th>Valinomycin</th>
<th>Nonactin</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="link" alt="Diagram" /></td>
<td><img src="link" alt="Diagram" /></td>
</tr>
</tbody>
</table>

lariat ethers with side arms bearing ester groups were considered in valinomycin modeling.14 too. Binding studies showed that flexible N-pivot lariat ethers were directed by the cation to envelop in complexation, thus acting similarly to valinomycin. The structure of the crystalline Na+ complex showed that the ester carbonyl from the side arm participates in binding of the cation.11 Recent studies on large-size pyrido and benzo crown ethers (27–33 membered) showed that 30-membered crowns had appreciable K+/Na+ selectivity.12 This fact is probably due to the tennis-ball-like conformation that a ring of that size can adopt.

Modeling studies of the kind described showed that the large-ring or side-arm synthetic polyether macrocycles exhibit some properties common to the natural cyclic ionophores. However, such model compounds are much less selective in complexation of cations than the naturally occurring compounds, presumably due to the much greater flexibility of their polyether backbones. It was shown that incorporation of different heterocyclic and benzo12 units into the polyether ring restricts the flexibility of such models, which resulted in increased selectivities. Our attempt was to study the effects of ester and amide units incorporated in the polyether ring on the complexation and transport properties of new ionophore models of the general type I.15 The ester and the amide units should also restrict the conformational freedom of the polyether macrocycle because of their planar geometries and the well-known tendencies of amide groups to form intramolecular hydrogen bonds. Since compounds of type I contain two amino acid residues, incorporation of chiral amino acids with bulky substituents on the chiral center presents the further possibility to obtain rigid structures. On the other hand, compounds of type I having a certain size of the macrocyclic ring may seem promising for designing ion carriers or complexing agents. Studies of this question may open new possibilities for designing ion carriers or complexing agents.

In this paper we report the synthesis of several compounds of type I derived from α-phenylglycine (m = 1; 2; 3; n = 0; 1; 2; 3) and describe their properties relevant to ionophoresis, e.g., their readiness to form complexes with metal cations to transport them across the chloroform phase as well as to facilitate extraction of their salts from the aqueous phase into the lipophilic phase.

**Results and Discussion**

**Synthesis.** The desired macrocycles of type I were obtained by the synthetic route in Scheme I. rac-α-Phenyglycine (1) and diglycoloyl or triglycoloyl chloride gave the mixture of racemates and meso diastereoisomers 2 and 3, which could not be differentiated either by TLC analysis or by 1H NMR or 13C NMR spectra. The macrocyclization by Kellogg’s procedure13 using ciceium salts of 2 or 3 and the appropriate ω,ω'-dibromides or -dimesylates yielded diastereoisomeric mixtures of macrocycles 4–9. When 21- (7) and 24-membered (8) macrocycles were produced, diastereomeric products were easily detected by TLC and separated by column chromatography on silica gel.

Diastereoisomeric mixtures of 7 and 8 obtained from (R)-(−)-α-phenylglycine (1) implied racemization. These mixtures were separated chromatographically. The chromatographically more mobile diastereoisomers showed low optical rotations (7, [α]D −0.64°; 8, [α]D −0.41° (c 1, CHCl3)), and the chromatographically less mobile diastereoisomers were optically inactive. Thus, the latter were identified as the meso diastereoisomers of 7 and 8. Smaller ring compounds 4–6, as well as one of the larger, namely the 24-membered 9, were obtained as inseparable diastereoisomeric mixtures.

Compound 10 was prepared as the open-chain analogue of 8. The analogue was obtained by DCC condensation of (±)-N-carboxybenzoy-1 and tetaathylen glycol, using 4-(dimethylaminopyridine (DMAP) as a catalyst12a (Scheme II).

**1H NMR Study of Hydrogen Bonding in Solution.** Complexation of Water. It is well-known that amide protons are readily involved in hydrogen bonding, which is responsible for the secondary structures in linear and cyclic peptides.14 We made a 1H NMR study of com-
pounds 4–9 to evaluate their tendency toward intramolecular hydrogen bonding. High NH temperature coefficients (ΔΔ/ΔT) were measured for macrocycles 4–9 in CDCl₃ (Table I), indicating strong involvement of their amide NHs in hydrogen bonding. On the other hand, the resonance of water normally present in CDCl₃ was considerably shifted downfield from its position in the solute-free CDCl₃ (δH₂O ≈ 1.53) in the ¹H NMR spectra of 7 and 8. These observations strongly suggest complexation of water by 7 and 8 via hydrogen bonding between amide NHs and water oxygen.

In one experiment, a 0.1 M solution of (±)-8 in CDCl₃ was titrated with water (0.2 μL portions) till no further downfield shift of the amide NHs could be observed. This experiment showed that the ratio of (±)-8 and water in the hydrogen-bonded complex is 1:1.

In the ¹H NMR spectra of 4–6, higher field positions of δH₂O together with the smaller ⁵¹N coefficients and low NH temperature coefficients show the lack of water complexation. The results for 9 would tend to indicate a predominant intramolecular hydrogen bonding between the amide NHs and the ether oxygens from the amide bridge, without involving the water molecules (Table I).

Complexation of water by crown ethers is well documented. In such complexes a water molecule donates two hydrogen bonds to ether oxygens. Macrocycles 7 and 8 bind water molecules additionally via two amide NHs forming a ring of the same size (24-membered) as in their corresponding complexes. These interactions should reflect the importance of the structural arrangement of the amide and the ether functions in rings of equal size. The greater distance between amide groups, the possibility of intramolecular hydrogen bonding to ether oxygens from the amide bridge, and the smaller ester bridge in 9, and the amount of water solubilized in CDCl₃ per mole of macrocycle were determined by ¹H NMR spectroscopy, relying on eq 1.28 (Table II).

\[
[H₂O]₀ + [Mc]₀ = [Mc·H₂O]₀
\]

Solutions of macrocycles 6–9 in CDCl₃ were equilibrated with water, and the concentrations of water in the organic phase relative to that of the macrocycle, \( R_w = [H₂O]₀ / [Mc]₀ \), were determined from the ¹H NMR spectra. From the known solubility of water in CDCl₃, \( S_w = 0.045 ± 0.005 \) M at 22 ± 1 °C, the amount of solubilized water per mole of macrocycle \( R_w = S_w / [Mc]₀ \) was calculated. Equilibrium constants \( K_w \) were then obtained from eq 2.

\[
R_w/[Mc]₀ = S_w + [Mc]₀K_wS_w / 1 + [Mc]₀S_w
\]

Macroycles 7 and 8 form considerably more stable water complexes than crown ethers with equally sized rings (Table II). This is especially true for both diastereoisomers of 8; in the case of (±)-8, \( K_w \) was too large to be determined from the ¹H NMR spectra. These results clearly demonstrate that hydrogen bonding involving the amide protons contributes an additional stabilizing effect to such complexes. Comparison of \( K_w \) for compounds 6–8 shows that their complexing power toward water strongly depends on their ring sizes. Even for the large 21-membered ring of 7 and 24-membered ring of 8, a considerable difference in \( K_w \) was established, which can be attributed to the greater flexibility of, and hence better encapsulation of, a water molecule by the larger ring in 8. However, a diastereoisomeric mixture of (±)- and meso-9, a compound possessing a ring of the same size (24-membered) as in 8, showed a small overall equilibrium constant equaling 23 (Table II). This result reflects the importance of the structural arrangement of the amide and the ether functions in rings of equal size. The greater distance between amide groups, the possibility of intramolecular hydrogen bonding to ether oxygens from the amide bridge, and the smaller ester bridge in 9 had the consequence of yielding a \( K_w \) approximately 70 times lower than that for 8.

¹H and ¹³C NMR Study of Metal Cation Complexation. Determination of Complexation Sites. ¹H and ¹³C NMR spectroscopy proved to be extremely useful for recognizing complexation at certain sites of a ligand. Resonances of methylene protons in a crown ether were shifted downfield in ¹H NMR spectra of crown-cation complexes, while involvement of the ester and the amide carbonyls in complexation of cations caused downfield shifts of the ¹³C NMR resonances assignable to these carbons. Macroycles 6–9, which contain amide, ester, and ether donor functions within the same ring, may complex cationic guests by different combinations of available ligating sites. These interactions should be differentiated by the ¹H and ¹³C NMR spectra of their corresponding complexes.

Addition of Na⁺ and K⁺ to solutions of 21- and 24-membered (±)- and meso-8 caused small downfield shifts

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**Table I. Chemical Shifts of Amide NHs, Chemical Shifts of Water Protons, and NH Temperature Coefficients (ΔΔ/ΔT) for 0.005 M CDCl₃ Solutions of 4–9**

<table>
<thead>
<tr>
<th>compd</th>
<th>δH₂O</th>
<th>δH₂O</th>
<th>ΔΔ/ΔT × 10³ ppm/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.54</td>
<td>2.25</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.56</td>
<td>2.35</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.57</td>
<td>1.71</td>
<td></td>
</tr>
<tr>
<td>(±)-7</td>
<td>1.67</td>
<td>6.28</td>
<td></td>
</tr>
<tr>
<td>meso-7</td>
<td>1.70</td>
<td>5.97</td>
<td></td>
</tr>
<tr>
<td>(±)-8</td>
<td>1.99</td>
<td>14.50</td>
<td></td>
</tr>
<tr>
<td>meso-8</td>
<td>1.71</td>
<td>6.50</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.58</td>
<td>4.22</td>
<td></td>
</tr>
</tbody>
</table>

*Compounds 4–6 and 9 are diastereoisomeric mixtures of the (±) and meso forms. In each case a single resonance appeared from the two diastereoisomers.

---

**Table II. Complexation of Water by 6–9 in CDCl₃ at 22 ± 1 °C**

<table>
<thead>
<tr>
<th>compd</th>
<th>( R_w )</th>
<th>( K_w )</th>
<th>( R_w - S_w / [Mc]₀ )</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.95</td>
<td>0.47</td>
<td>0.47</td>
</tr>
<tr>
<td>(±)-7</td>
<td>1.34</td>
<td>0.88</td>
<td>0.88</td>
</tr>
<tr>
<td>meso-7</td>
<td>0.74</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>(±)-8</td>
<td>1.46</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>meso-8</td>
<td>1.43</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>meso-9</td>
<td>0.97</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>m-xylene-21-crown-6</td>
<td>0.83</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>m-xylene-24-crown-7</td>
<td>0.92</td>
<td>0.47</td>
<td>0.47</td>
</tr>
</tbody>
</table>

---

Table III. Shifts ($\Delta \delta$) of Methylene Proton Signals and Variations of $3J_{\text{NHCH}}$ in the $^1$H NMR Spectra of (±)-7, (±)-8, and meso-8 Induced by Addition of Metal Cations

<table>
<thead>
<tr>
<th>compd$^b$</th>
<th>salt$^c$</th>
<th>$\alpha$-CH$_2$</th>
<th>$\beta$-CH$_2$</th>
<th>$\gamma$-CH$_2$</th>
<th>$\delta$-CH$_2$</th>
<th>CH$_{\text{Am}}$</th>
<th>$3J_{\text{NHCH}},$ Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-7</td>
<td>NaClO$_4$</td>
<td>0.00</td>
<td>0.08</td>
<td>0.04</td>
<td>0.00</td>
<td>7.03</td>
<td></td>
</tr>
<tr>
<td>(±)-8</td>
<td>Mg(ClO$_4$)$_2$</td>
<td>0.05</td>
<td>0.09</td>
<td>0.09</td>
<td>0.11</td>
<td>6.70</td>
<td></td>
</tr>
<tr>
<td>meso-8</td>
<td>KSCN</td>
<td>0.10</td>
<td>-0.04</td>
<td>0.05</td>
<td>0.05</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ba(ClO$_4$)$_2$</td>
<td>0.00</td>
<td>0.11</td>
<td>0.20</td>
<td>0.20</td>
<td>19.4</td>
<td></td>
</tr>
</tbody>
</table>

$^a$This notation differentiates methylene groups from the ester bridge ($\alpha, \beta, \gamma, \delta$) and from the amide bridge (CH$_2$Am). $^b$0.2 M solutions in 1:1 (v/v) CDCl$_3$/CD$_3$CN. $^c$Each salt (0.1 mmol, previously dried for 24 h over P$_2$O$_5$ under high vacuum) was added to 0.5 mL of CDCl$_3$/CD$_3$CN solutions of 7 and 8. A minus sign denotes an upfield shift.

Table IV. Shifts ($\Delta \delta$) of Amide Carbonyl, Ester Carbonyl, and CH$_{\text{Am}}$ Carbon Resonances in the $^{13}$C NMR Spectra of (±)-7 and (±)-8 Induced by Addition of Metal Cations

<table>
<thead>
<tr>
<th>compd$^a$</th>
<th>salt$^b$</th>
<th>COOR$^c$</th>
<th>CONH</th>
<th>CH$_{\text{Am}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-7</td>
<td>NaClO$_4$</td>
<td>1.70</td>
<td>1.28</td>
<td>0.00</td>
</tr>
<tr>
<td>(±)-8</td>
<td>Mg(ClO$_4$)$_2$</td>
<td>-0.04</td>
<td>2.75</td>
<td>-0.70</td>
</tr>
<tr>
<td>meso-8</td>
<td>KSCN</td>
<td>1.70</td>
<td>0.11</td>
<td>-0.48</td>
</tr>
<tr>
<td></td>
<td>Ba(ClO$_4$)$_2$</td>
<td>1.55</td>
<td>2.40</td>
<td>-0.70</td>
</tr>
</tbody>
</table>

$^a$0.2 M in 1:1 (v/v) CDCl$_3$/CD$_3$CN. $^b$The same as $c$ in Table III. A minus sign denotes an upfield shift. $^c$Amide and ester carbonyl assignments based on the analysis of coupled spectra before and after addition of metal salt.

of methylene protons from the amide and the ester bridge, which could indicate a rather poor complexing power of the corresponding macrocycles (Table III). However, Ba$^{2+}$ and Mg$^{2+}$ induced more significant downfield shifts of methylene proton resonances together with the considerable decrease of the vicinal $3J_{\text{NHCH}}$ coupling constant. The latter effect would indicate the involvement of donors from the amide bridges in 7 and 8 in the complexation of Ba$^{2+}$ and Mg$^{2+}$ ions.

With Ba$^{2+}$ and Mg$^{2+}$ the amide carbonyl resonances in the $^{13}$C NMR spectra of (±)-7 and (±)-8 were shifted more downfield than those of ester carbonyls whereas Na$^+$ and K$^+$ caused further shifts of the ester carbonyls (Table IV). According to the literature, binding of metal cations by crown ethers is reflected by $^{13}$C NMR spectroscopy in upfield shifts of the methylene carbons.$^{19}$ Effects of added cations on resonances of the amide methylene carbons (CH$_2$Am) of (±)-7 and (±)-8 were observed and are shown in Table IV. The effects on carbons adjacent to ether oxygens in the ester bridge caused complete overlap so that interpretation was impossible.

The stoichiometry of the [(±)-8,Ba$^{2+}$] complex was 1:1 (Figure 1) as determined by plotting $^1$H NMR shifts of the CH$_{\text{Am}}$ protons vs the [Ba$^{2+}$]/[(±)-8] molar ratio.$^{21}$

The observation that Ba$^{2+}$ induced a considerably larger downfield shift of the amide carbonyls than the ester carbonyls in the $^{13}$C NMR spectra of the [(±)-8,Ba$^{2+}$] complex could be explained by a stronger binding of the cation to the amide carbonyls. On the other hand, the shifts in the $^{13}$C NMR spectra of [(±)-7,Na$^+$] and [(±)-8,K$^+$] are consistent with a predominant formation of complexes with ester carbonyls and ether oxygens serving as ligating sites.

It is interesting to compare the effects of the almost equally sized K$^+$ and Ba$^{2+}$ ions (ionic radii 1.33 and 1.44 Å, respectively) on the $^1$H and $^{13}$C NMR spectra of (±)-8.$^{22}$

Figure 1. $^1$H NMR chemical shift variation of the CH$_{\text{Am}}$ resonance in (±)-8 vs [Ba(ClO$_4$)$_2$]/[(±)-8] ratios in CDCl$_3$/CD$_3$CN (1:1) solvent mixture.

Figure 2. Cation transport across a chloroform boundary layer by (a) (±)-8 and (b) meso-8. Concentration of each ion carrier in the chloroform phase, 2.00 $\times$ 10$^{-4}$ M.

Ba$^{2+}$, which has the higher charge density (3.17 $\times$ 10$^{26}$ C/Å$^3$),$^1$ prefers stronger carbonyl donors such as the amide carbonyls$^{22}$ in combination with ether oxygens, whereas K$^+$ (charge density 1.62 $\times$ 10$^{26}$ C/Å$^3$) preferably binds to...


estery carbanoyl as a weaker carbanoyl donor and ether oxy-
gens.

**Transport and Extraction of Metal Cations.** The ability of compounds 4–9 to act as ionophores was tested by standard "U-cell" experiments in which chloroform was used as a lipophilic barrier and the metal cations transported were derived from their picrate salts.23 Significant transport was achieved only with the 24-membered (±) and meso-8 macrocycles (Figure 2).

Both diastereoisomers of 8 exhibited somewhat better transport ability for M+ than for M2+ cations, and meso-8 was a more efficient carrier than (±)-8. For the alkali-metal cations, K+ (ionic radius 1.33 Å) was preferably transported. For the large Cs+ ion (ionic radius 1.69 Å) A was measured, and Na+ (ionic radius 1.48 Å) and Rb+ (ionic radius 0.95 Å) were transported more readily, but still less efficiently than K+.

Meso-8 was found to be more efficient than (±)-8 in transporting K+ and Na+ ions. Recently, it was shown that the overall transport rate may be controlled by the salt extraction equilibrium between H2O and CHCl3 if the complex formed in CHCl3 is of relatively low stability.24,25 In that case, meso-8 should afford a higher extraction equilibrium constant (Kex) for potassium picrate than (±)-8. The Kex values were determined in the presence of either diastereoisomer of 8. Plots of log (DM/[A]-eq) vs log [Mc]0 were used for determination based on eq 3, which

$$\log (D_M/[A]_{eq}) = \log [Mc]_0 + \log K_{ex}$$

was derived for a similar extraction system, assuming 1:1 cation:ligand stoichiometry.26 DM denotes the distribution ratio of the metal cation, and [A]-eq and [Mc]0 represent the concentration of picrate anion in the aqueous phase and that of the macrocycle 8 in the organic phase. Straight lines with unit slope were obtained for both diastereoisomers of 8, which confirms 1:1 stoichiometries in complexes [(±)-8,K+] and [meso-8,K+] (Figure 3). Ex-

![Figure 3](image_url)
We believe that macrocycles of type I open new possibilities in designing more efficient organic water binders. In addition, properly designed macrocycles of that type could accommodate other neutral guests depending on their ability to hydrogen bond the host in a certain way.

Experimental Section

Melting points (Kofler stage) are uncorrected. Infrared (IR) spectra of KBr samples were recorded on a Perkin-Elmer 689 spectrophotometer. Spectral bands are reported in cm⁻¹. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded at 100 MHz on a JEOL FX 100 Q instrument. Chemical shifts (parts per million (δ)) downfield from internal Me₄Si are reported in the following order: chemical shift, spin multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and integration. Proton-decoupled ¹³C NMR spectra were recorded at 25.2 MHz on a JEOL FX 100Q; chemical shifts (ppm downfield from Me₄Si) followed by the spin multiplicities (in parentheses) in broad-band decoupled spectra are reported. UV measurements were made with a Beckman Amino Acid Containing Macrocycles

The molecular ion (M⁺) of 4-9 were reported in the parentheses). In the UV spectrum in the visible region (< 230 nm) and the UV spectrum in the UV region (230 nm). The absorption coefficient of the molecular ion (M⁺) is 20 and 70 eV, and mass ranges covering the 2-2 cycloadducts. In each case no masses larger than the molecular ion (M⁺) could be detected.

The molecular ion (M⁺), the base peak, and their intensities were recorded with ionization energies of 20 and 70 eV and mass ranges covering the 22 cycloadducts. In each case no masses larger than the molecular ion (M⁺) could be detected.

The procedure was the same as for the preparation of 3,11-Diphenyl-2,5,9,12-tetraene (6). Compound 6 (mixture of the (α) and (meso) forms) was prepared from 2 (1.2 g, 2.5 mmol), Cs₂CO₃ (0.79 g, 1.68 mmol), and 1,4-dibromobutane (0.5 g, 2.5 mmol). After column chromatography (6:l chloroform/acetone). In each case no masses larger than the molecular ion (M⁺) could be detected.

The molecular ion (M⁺) of 3,11-Diphenyl-2,5,9,12-tetraene (6). Compound 6 (mixture of the (α) and (meso) forms) was prepared from 2 (1.2 g, 2.5 mmol), Cs₂CO₃ (0.79 g, 1.68 mmol), and 1,4-dibromobutane (0.5 g, 2.5 mmol). After column chromatography (6:l chloroform/acetone). In each case no masses larger than the molecular ion (M⁺) could be detected.

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The molecular ion (M⁺) of 3,11-Diphenyl-2,5,9,12-tetraene (6). Compound 6 (mixture of the (α) and (meso) forms) was prepared from 2 (1.2 g, 2.5 mmol), Cs₂CO₃ (0.79 g, 1.68 mmol), and 1,4-dibromobutane (0.5 g, 2.5 mmol). After column chromatography (6:l chloroform/acetone). In each case no masses larger than the molecular ion (M⁺) could be detected.

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and 9 cuvettes and equilibrated with 1-mL portions of water by mixing on a Kottermann shaker for 1 h at constant speed. After standing for another hour, the cuvettes were centrifuged. From each cuvette 0.3 mL of the CDCl₃ layer was transferred to an NMR tube and the filtrate was evaporated, and the crude product was purified by column chromatography (12:1 CHCl₃/EtOAc). Yield 0.3 g (31%) as an oil. 'H NMR (CDCl₃): 3.47, s, 8 H; 3.57, t, 4 H; 4.26, m, 4 H; 3.72, s, 4 H; 3.58, d (J = 7.3 Hz), 2 H; 7.33, s, 20 H.

Determination of Equilibrium Constants

The crystalline complex of meso-8 and KSCN was obtained by mixing a solution of meso-8 (27.7 mg, 0.05 mmol in CDCl₃ (0.25 mL) and KSCN (0.31 g, 0.65 mmol), and Cs₂CO₃ (0.31 g, 0.65 mmol), and 1,8-dibromo-3,6-dioxoactane (0.27 g, 0.97 mmol). After column chromatography (EtOAc) and recrystallization from the same solvent, 0.23 g (42.2%) of Cs₂C₄O₇N₁₄C₂₁H₂₂O₁₆ was obtained as white crystals; mp 128-129 °C. 'H NMR (CDCl₃): 3.44, s, 4 H; 3.56, H, 6.13; N, 5.01. MS: M⁺ 558 (calcd 558) (71.8), 118 (100).

Transport Experiments.

The dimensions of a U-cell and the general experimental conditions applied were the same as those used in a transport study with some cyclic peptides, so as to obtain results comparable to the ones reported. In a typical experiment, 0.25 mmol of metal chloride and 0.625 mmol of picric acid were admixed to 20 mL of aqueous 0.1 M 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) solution. To the resulting suspension aqueous LiOH solution was added dropwise until the picric acid dissolved. Thereupon the pH was adjusted to 7.20-7.25 with a few drops of either aqueous LiOH or 0.1 M HEPES solution. The solution was transferred to a 25-mL volumetric flask and made up to the mark with distilled water; 10 mL of this solution was used as the source phase. The receiving phase was 10 mL of 0.1 M HEPES solution adjusted to pH 7.20-7.25 with LiOH. Macroyclic compound (0.02 mmol) was weighed into a 10-mL volumetric flask, dissolved in chloroform, and made up to the mark with the same solvent. One milliliter of this solution was transferred to another 10-mL volumetric flask and made up to the mark with chloroform; this solution was used as the receiving phase at 1-h intervals. Calculation used the reported molar extinction coefficients (ε) of picrate anion at 355 nm (1.64 × 10⁴). In each experiment the chloroform phase was stirred with the same small stirring bar, keeping the same constant speed.

Extraction of Potassium Picrate by Macrocyclic Isomers

Determination of Equilibrium Constants (Kₑ) of Complexes Formed by Macrocycles 6-9 and Water in CDCl₃.

Half-milliliter portions of deuterochloroformic solutions of macrocycles 6 [(±) and meso forms], (±)-7, meso-7, (±)-8, and 9 [(±) and meso forms] were placed into 10-mL centrifuge cuvettes and equilibrated with 1-mL portions of water by mixing on a Köttnerm shaker for 1 h at constant speed. After standing for another hour, the cuvettes were centrifuged. From each cuvette 0.3 mL of the CDCl₃ layer was transferred to an NMR tube and 1H NMR spectra were recorded. Concentrations of water relative to those of macrocycles (Rₑ = [H₂O]₀/[Mc]₀) were determined by signal integration of macrocyclic and water resonances. The amount of solubilized water per mole of macrocycle (Rₑ = Sₛ/[Mc]₀) and Kₑ's were calculated by using eq 2. The solubility of water in CDCl₃ (Sₛ = 0.045 ± 0.005 M at 22 ± 1 °C) was the value reported in ref 18.

Transport Experiments. The dimensions of a U-cell and the general experimental conditions applied were the same as those used in a transport study with some cyclic peptides, so as to obtain results comparable to the ones reported. In a typical experiment, 0.25 mmol of metal chloride and 0.625 mmol of picric acid were admixed to 20 mL of aqueous 0.1 M 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) solution. To the resulting suspension aqueous LiOH solution was added dropwise until the picric acid dissolved. Thereupon the pH was adjusted to 7.20-7.25 with a few drops of either aqueous LiOH or 0.1 M HEPES solution. The solution was transferred to a 25-mL volumetric flask and made up to the mark with distilled water; 10 mL of this solution was used as the source phase. The receiving phase was 10 mL of 0.1 M HEPES solution adjusted to pH 7.20-7.25 with LiOH. Macroyclic compound (0.02 mmol) was weighed into a 10-mL volumetric flask, dissolved in chloroform, and made up to the mark with the same solvent. One milliliter of this solution was transferred to another 10-mL volumetric flask and made up to the mark with chloroform; this solution was used as the receiving phase at 1-h intervals. Calculation used the reported molar extinction coefficients (ε) of picrate anion at 355 nm (1.64 × 10⁴). In each experiment the chloroform phase was stirred with the same small stirring bar, keeping the same constant speed.

Extraction of Potassium Picrate by Macrocyclic Isomers

About 0.03 mmol (exactly weighed) of (±)-8 and meso-8, respectively, was dissolved in 15 mL of chloroform in a 15-mL volumetric flask and made up to the mark with chloroform. Portions (1.5, 2.0, 2.5, 3.0, and 3.5 mL) of this solution were pipetted into five 5-mL volumetric flasks and made up to the mark with the same solvent. One milliliter of this solution was transferred to another 10-mL volumetric flask and made up to the mark with chloroform; this solution was used as the receiving phase. The transport of the metal cation was measured indirectly, determining the UV absorbance due to picrate anion in the receiving phase at 1-h intervals. Calculation used the following equation for the transport of picrate anion: 

\[ \frac{D_{aq}}{[A^-]_{aq}} = \text{constant} \]

where [A⁻]ₐq is the concentration of picrate anion in the aqueous phase. The experiments were performed at pH 7.20-7.25 with HEPES and LiOH. Macrocylic compound (0.02 mmol) was weighed into a 10-mL volumetric flask, dissolved in chloroform, and made up to the mark with the same solvent. One milliliter of this solution was transferred to another 10-mL volumetric flask and made up to the mark with chloroform; this solution was used as the source phase.