on a Apple II microcomputer, afforded the following numerical values for the A and B parameters, which are reported in the given order for the various cations: Li^+, 21, 5.2×10^3; Ba^{2+}, 75, 4.6×10^3; Sr^{2+}, 65, 2.1×10^4; Ca^{2+}, 13, 1.2×10^5; Mg^{2+}, 354, 2.1×10^7. For Na^+, $B = 25$, but A is so small that it is devoid of physical significance. The A and B values were translated by means of eq 2 and 3 into the rate and equilibrium constants listed in Table I. It should be noted that the figures reported for Mg^{2+} are not meaningful as such, as in this case the products Ax and Bx are greater than one in the whole concentration range. As a consequence, the quantity y is very close to the limiting value A/B approached at high cation concentrations. The ratio $A/B = k_{ip}/k_i$ is highly significant, however. It is determined in this case with an inherent precision which is higher than those obtained with the other salts.

Product Analyses. These were carried out on scaled-up kinetic runs. GLC analyses[8] were carried out at 125 °C, using hexadecane as the internal standard. The yield of 1-acetyl-1-(ethoxycarbonyl)cyclohexane was 75% in the absence of added salt, 88% in the presence of 0.1 M LiBr, and 75% in the presence of 1.7×10^{-2} M $Mg(ClO_4)_2$.

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Amino Acid Containing Macrocycles. Synthesis, Complexation of Water, and Transport and Binding of Metal Cations

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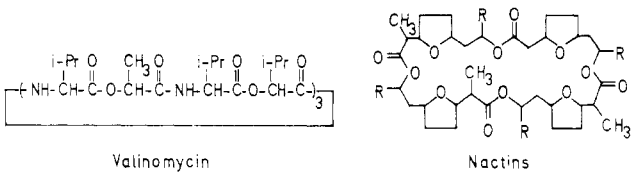
A series of macrocycles incorporating two α-phenylglycine and a variable number of ethyleneoxy units have been prepared as new ionophore models. Transport studies (U-cell, chloroform liquid membrane) showed that only 24-membered macrocycles 8 mimic naturally occurring cyclic ionophores (valinomycin, 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^{2+} (Ba^{2+}, Sr^{2+}, Mg^{2+}, Ca^{2+}) picrates. *meso*-8 and (±)-8 exhibited poor extraction equilibrium constants (K_{ex} = 164 and 83 M^{-2}, respectively) for K^+ picrate in a chloroform–water system. ^1H and ^{13}C NMR studies of complexation with (±)- and *meso*-8 and K^+, Na^+, Ba^{2+}, and Mg^{2+} salts in $CDCl_3/CD_3CN$ solvent mixture showed that ligands 8 bind metal cations by the mutual assistance of amide carbonyl or ester carbonyl and ether oxygen donors. In this work the first crystalline complex with a macrocycle of this type and a metal cation was obtained, from *meso*-8 and KSCN. 24-Membered ligands (±)-8 and *meso*-8 form considerably more stable water complexes in chloroform than the equally large crown ethers.

Naturally occurring macrocyclic ionophores such as valinomycin and nactins exhibit highly selective transport of K^+ ions across biological and artificial membranes.[1] This property is the cause of their antibiotic activity.[2] Both kinds of natural ionophores bind metal cations in the central cavity of the macroring by ion–dipole interactions with ester carbonyls (valinomycin[3,4]) or with ester carbonyls and ether oxygens (nactins[5]). 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.[3,6] These unique properties of valinomycin and nactins present a challenge from the synthetic as well as the biological point of view.

Chart I



Several attempts have been made to mimic valinomycin and nonactin activities by using synthetic polyether macrocycles. In one approach, 18- and 19-membered dilactone analogues of 18-crown-6 were studied as valinomycin models.[7] However, the ring size of the model dilactones 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 cyclopolyethers 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

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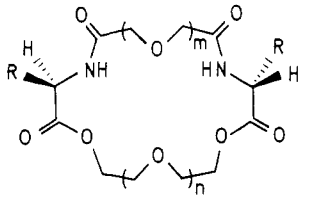
lariat ethers with side arms bearing ester groups were considered in valinomycin modeling,[10] too. Binding studies showed that flexible N-pivot lariat ethers were directed by the cation to envelop in complexation, thus acting similarly to valinomycin. The structure of the crystalline Na^+ complex showed 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[9] and benzo[12] 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.[13] 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 macroring should be capable of adopting solution conformations having the ester and/or the amide carbonyls directed inward and therefore mimicking the natural ionophores. The presence of three different ligating functions in I raises the interesting question of whether they cooperate in complexation of cationic guests. 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;



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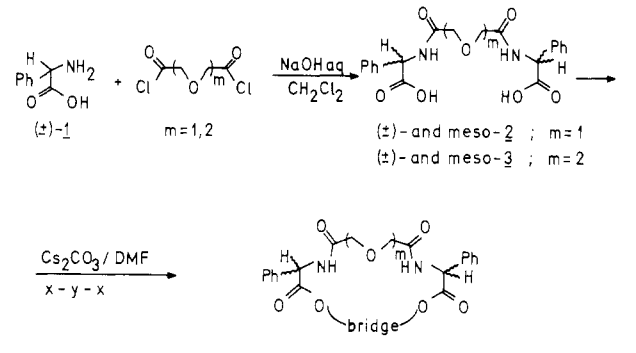
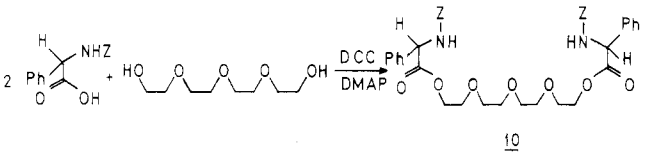
n = 0, 1, 2, 3) and describe their properties relevant to ionophoresis, e.g., their readiness to form complexes with metal cations to transport them across the chloroform layer as well as to facilitate extraction of their salts from the aqueous phase into the lipophilic phase.

Scheme I



x	y		bridge	m
Br	CH_2CH_2	4	CH_2CH_2	1
OMs	$CH_2CH_2OCH_2CH_2$	5	$CH_2CH_2OCH_2CH_2$	1
Br	$(CH_2)_4$	6	$(CH_2)_4$	1
Br	$CH_2(CH_2OCH_2)_2CH_2$	7	$CH_2(CH_2OCH_2)_2CH_2$	1
Br	$CH_2(CH_2OCH_2)_3CH_2$	8	$CH_2(CH_2OCH_2)_3CH_2$	1
		9	$CH_2(CH_2OCH_2)_2CH_2$	2

Scheme II



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Results and Discussion

Synthesis. The desired macrocycles of type I were obtained by the synthetic route in Scheme I. *rac*-α-Phenylglycine (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 ^{13}C NMR spectra. The macrocyclization by Kellogg's procedure[13b] using dicesium 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**, $[\alpha]_D$ −0.64°; **8**, $[\alpha]_D$ −0.41° (*c* 1, $CHCl_3$)), 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*-carbobenzoxy-**1** and tetraethylene glycol, using 4-(dimethylamino)pyridine (DMAP) as a catalyst[13a] (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-

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Table I. Chemical Shifts of Amide NH's, Chemical Shifts of Water Protons, and NH Temperature Coefficients ($\Delta\delta_{NH}/\Delta T$) for 0.005 M $CDCl_3$ Solutions of 4–9

compd[a]	δ_{NH}	δ_{H_2O}	$\Delta\delta/\Delta T \times 10^3$, ppm/°C
4	7.62	1.54	2.28
5	7.56	1.56	2.35
6	7.48	1.57	1.71
(±)-7	7.73	1.67	6.28
meso-7	7.73	1.70	5.97
(±)-8	8.14	1.99	14.50
meso-8	7.73	1.71	6.50
9	8.07	1.58	4.22

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

pounds 4–9 to evaluate their tendency toward intra- or intermolecular hydrogen bonding.

High NH temperature coefficients ($\Delta\delta/\Delta T$) were measured for macrocycles 7–9 in $CDCl_3$[15] (Table I), indicating strong involvement of their amide NH's in hydrogen bonding. On the other hand, the resonance of water normally present in $CDCl_3$ was considerably shifted downfield from its position in the solute-free $CDCl_3$ ($\delta_{H_2O} \sim 1.53$) 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 NH's and water oxygen.

In one experiment, a 0.1 M solution of (±)-8 in $CDCl_3$ was titrated with water (0.2-μL portions) till no further downfield shift of the amide NH's 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 δ_{H_2O} together with the smaller δ_{NH}'s 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 NH's and the ether oxygens from the amide bridge,[16] without involving the water molecules (Table I).

Complexation of water by crown ethers is well documented.[17] In such complexes a water molecule donates two hydrogen bonds to ether oxygens. Macrocycles 7 and 8 bind water molecules additionally via two amide NH's acting as hydrogen-bond donors, which should make those complexes more stable. To check this, equilibrium constants (K_w) of their water complexes in $CDCl_3$, as well as those of compounds 6 and 9, and the amount of water solubilized in $CDCl_3$ per mole of macrocycle were determined by ^1H NMR spectroscopy, relying on eq 1[18] (Table II).

$$[H_2O]_0 + [Mc]_0 \rightleftharpoons [Mc{\cdot}H_2O]_0 \quad (1)$$

Solutions of macrocycles 6–9 in $CDCl_3$ were equilibrated with water, and the concentrations of water in the organic phase relative to that of the macrocycle, $R_w = [H_2O]_0/[Mc]_0$, were determined from the ^1H NMR spectra. From

Table II. Complexation of Water by 6–9 in $CDCl_3$ at 22 ± 1 °C

compd	R_w	K_w	$R_w - S_w/[Mc]_0$
6	0.93	20	0.47
(±)-7	1.34	172	0.88
meso-7	0.74	65	0.74
(±)-8[a]	1.46[a]	*b*	1.01[a]
meso-8	1.43	1565	0.98
9	0.97	23	0.51
m-xyleno-21-crown-6[c]	0.83	14	0.38
m-xyleno-24-crown-7[c]	0.92	20	0.47

[a] Mean value of four determinations with $[Mc]_0$ = 0.10, 0.15, 0.20, and 0.25 M. [b] Too large to be determined by this method. [c] All values taken from ref 18.

the known solubility of water in $CDCl_3$, $S_w = 0.045 \pm 0.005$ M at 22 ± 1 °C,[18] 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.[18]

$$R_w[Mc]_0 = S_w + \frac{[Mc]_0 K_w S_w}{1 + K_w S_w} \quad (2)$$

Macrocycles 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's 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's 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,[16] 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 ^{13}C NMR Study of Metal Cation Complexation. Determination of Complexation Sites. ^1H and ^{13}C NMR spectroscopy proved to be extremely useful for recognizing complexation at certain sites of a ligand.[19] Resonances of methylene protons in a crown ether were shifted downfield in ^1H NMR spectra of crown–cation complexes,[19a,b] while involvement of the ester and the amide carbonyls in complexation of cations caused downfield shifts of the ^{13}C NMR resonances assignable to these carbons.[4c,13b,20] Macrocycles 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 ^{13}C 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 III. Shifts ($\Delta\delta$) of Methylene Proton Signals and Variations of $^3J_{NHCH}$ in the ^1H NMR Spectra of (±)-7, (±)-8, and *meso*-8 Induced by Addition of Metal Cations

compd[b]	salt[c]	$\Delta\delta$,[a] ppm α-CH_2	β-CH_2	γ-CH_2	δ-CH_2	CH_{2Am}	$^3J_{NHCH}$, Hz
(±)-7	$NaClO_4$	0.00	0.08	0.04		0.00	7.03
	$Mg(ClO_4)_2$	0.05	0.09	0.09		0.11	6.70
(±)-8	KSCN	0.10	−0.04	0.05	0.05	0.01	7.6
	$Ba(ClO_4)_2$	0.00	0.11	0.20	0.20	0.19	4.9
meso-8	$Ba(ClO_4)_2$	0.00	−0.09	0.17	0.17	0.19	4.9

[a] This notation differentiates methylene groups from the ester bridge (α, β, γ, δ) and from the amide bridge (CH_{2Am}). [b] 0.2 M solutions in 1:1 (v/v) $CDCl_3/CD_3CN$. [c] Each salt (0.1 mmol, previously dried for 24 h over P_2O_5 under high vacuum) was added to 0.5 mL of $CDCl_3$/CDCN solutions of 7 and 8. A minus sign denotes an upfield shift.

Table IV. Shifts ($\Delta\delta$) of Amide Carbonyl, Ester Carbonyl, and CH_{2Am} Carbon Resonances in the ^{13}C NMR Spectra of (±)-7 and (±)-8 Induced by Addition of Metal Cations

compd[a]	salt[b]	$\Delta\delta$, ppm COOR[c]	CONH	CH_{2Am}
(±)-7	$NaClO_4$	1.70	1.28	0.00
	$Mg(ClO_4)_2$	−0.04	2.75	−0.70
(±)-8	KSCN	1.70	0.11	−0.48
	$Ba(ClO_4)_2$	1.55	2.40	−0.70

[a] 0.2 M in 1:1 (v/v) $CDCl_3/CD_3CN$. [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 $^3J_{NHCH}$ 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_{2Am}) 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 ^1H NMR shifts of the CH_{2Am} 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 spectrum 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 ^1H and ^{13}C NMR spectra of (±)-8.

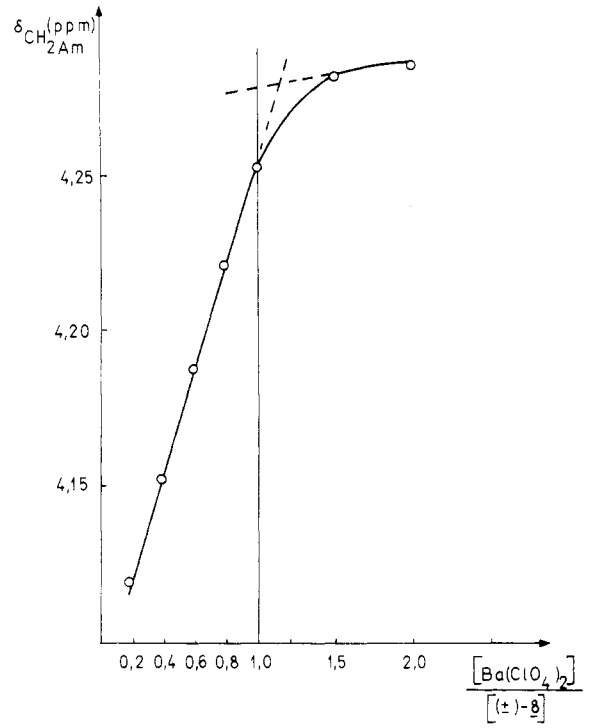

Figure 1. ^1H NMR chemical shift variation of the CH_{2Am} resonance in (±)-8 vs [$Ba(ClO_4)_2$]/[(±)-8] ratios in $CDCl_3/CD_3CN$ (1:1) solvent mixture.

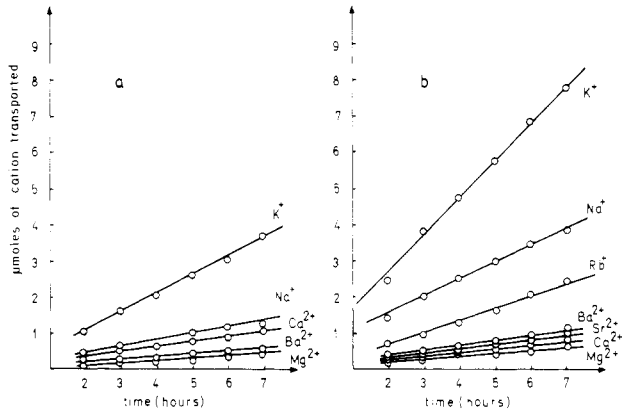

Figure 2. Cation transport across a chloroform boundary layer by (a) (±)-8 and (b) *meso*-8. Concentration of each ion carrier in the chloroform phase, 2.00×10^{-4} M.

Ba^{2+}, which has the higher charge density (3.17×10^{20} C/Å^3),[1] prefers stronger carbonyl donors such as the amide carbonyls[22] in combination with ether oxygens, whereas K^+ (charge density 1.62×10^{20} C/Å^3) preferably binds to

(21) Stoichiometries of [(±)-7,Na^+] and [(±)-8,K^+] complexes could not be determined by ^1H NMR as in the case of [(±)-8,Ba^{2+}] since effects on CH_{2Am} and other methylene resonances were too small. However, the stoichiometry of [*meso*-8,K^+] in chloroform was determined to be 1:1 by extraction experiments (next section).

(22) Day, M. C.; Medley, J. H.; Ahmad, N. *Can. J. Chem.* **1983**, *61*, 1719.

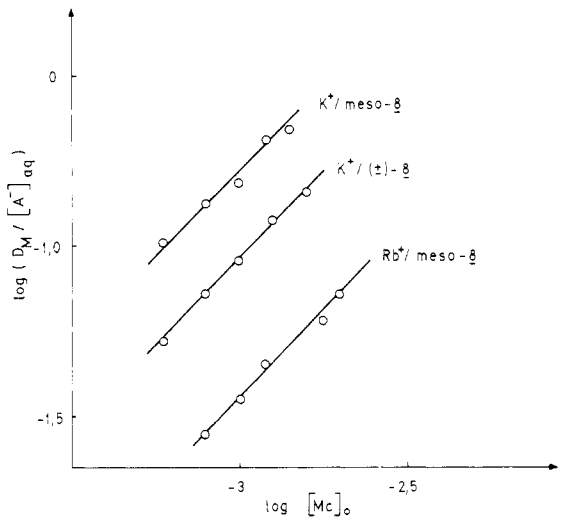

Figure 3. Plots of log $(D_M/[A^-]_{aq})$ vs log $[Mc]_0$ for the extraction equilibria with (±)- and *meso*-8 and K^+ and Rb^+ picrates in the chloroform–water system at 25 ± 1 °C.

ester carbonyls as a weaker carbonyl donor and ether oxygens.

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 M^{2+} cations, and *meso*-8 was a more efficient carrier than (±)-8. Of the alkali-metal cations, K^+ (ionic radius 1.33 Å) was preferably transported. For the large Cs^+ ion (ionic radius 1.69 Å) very slight transport (under 1 μmol of salt/7 h) was measured, and Rb^+ (ionic radius 1.48 Å) and Na^+ (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 H_2O and $CHCl_3$ if the complex formed in $CHCl_3$ is of relatively low stability.[24,25] In that case, *meso*-8 should afford a higher extraction equilibrium constant (K_{ex}) for potassium picrate than (±)-8. The K_{ex} values were determined in the presence of either diastereoisomer of 8. Plots of log $D_M/[A^-]_{aq}$ vs log $[Mc]_0$ were used for determination based on eq 3, which

$$\log (D_M/[A^-]_{aq}) = \log [Mc]_0 + \log K_{ex} \qquad (3)$$

was derived for a similar extraction system, assuming 1:1 cation:ligand stoichiometry.[23,26] D_M denotes the distribution ratio of the metal cation, and $[A^-]_{aq}$ 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). Extrapolation of each line to log $[Mc]_0 = 0$ gave K_{ex} values of 164 and 83 M^{-2} for *meso*-8 and (±)-8, respectively. The fact that the K_{ex} found for *meso*-8 is greater than that found for (±)-8 shows that the overall transport rate largely depends on the rather low extraction equilibria of K^+ picrate complexes with these ligands.

Table V. Comparison of the Association Constants (K_a) in $CHCl_3$ for (±)- and *meso*-8 and K^+ and Rb^+ Picrates with K_a's Exhibited by a Cyclooctapeptide and Two Common Crown Ethers

compd	$K_a \times 10^{-3}$, M^{-1}	
	K^+	Rb^+
meso-8	64	7
(±)-8	32	
$(CGLSP)_2$[a]	185	79
dicyclohexyl-18-crown-6[b]	200000	5050
2,3-naphtho-18-crown-6[b]	85900	11300

[a] *cyclo*(Gly-L-Lys(Z)-Sar-L-Pro)$_2$.[23] [b] Reference 31.

For purposes of comparison, the association constants (K_a) for (±)- and *meso*-8 and K^+ and Rb^+ picrates were evaluated in the customary manner[27,28] and are presented in Table V, together with K_a's for two common crown ethers and a 24-membered cyclopeptide. K_a's for (±)- and *meso*-8 complexes with K^+ and Rb^+ picrates in chloroform are very low in comparison to K_a's of the crown complexes. However, they are closer to K_a's of 24-membered cyclooctapeptide complexes with the same salts.

Preparation of a Crystalline Complex of *meso*-8 and KSCN. The first crystalline complex with a macrocyclic of type I and a metal cation to be obtained was formed by mixing equimolar solutions of *meso*-8 in $CDCl_3$ and KSCN in CD_3CN. A crystalline precipitate formed, mp 198–199 °C. The substance was identified from its IR spectrum and elemental analysis as the 1:1 *meso*-8:KSCN complex.

Conclusions

On the basis of the results presented it can be concluded that only the 24-membered macrocycles (±)- and *meso*-8 mimic naturally occurring cyclic ionophores in their ability to transport metal cations. ^1H and ^{13}C NMR studies showed that both diastereoisomers of 8 bind K^+ and Ba^{2+} ions by the mutual assistance of either ester or amide carbonyls and available ether oxygens.

The fact that open-chain (**10**) and cyclic (**9**) analogues of 8 were unable to transprt K^+ and Ba^{2+} ions shows the importance of both cyclic structure and disposition of binding functions. Furthermore, a different length of ester and amide bridges as in 8 and **9** seems to be responsible for their different abilities to bind water molecules and cationic guests.

Both diastereoisomers of 8 exhibit a rather low ability to extract and transport K^+ in comparison with crown ethers and nonactin.[9]

One of the factors that may reduce the cation extraction abilities of (±)- and *meso*-8 is their preference to complex water instead. The [*meso*-8,H_2O] complexes are approximately 80 times more stable than the corresponding complexes of equally large crown ethers. The enhanced water complexation of 8 is the consequence of the favorable combination of hydrogen bond donating (amide NH's) and hydrogen bond accepting (ether oxygens) functions located at opposite sides of a flexible macroring.

(23) For comparison purposes with cyclic peptides as ionophores we have chosen the experimental conditions used by: Shimizu, T.; Tanaka, Y.; Tsuda, K. *Int. J. Pept. Protein Res.* **1986**, *27*, 344.
(24) Behr, J.-P.; Kirch, M.; Lehn, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 241.
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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 297 spectrophotometer. Spectral bands are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 100 MHz on a JEOL FX 100Q instrument. Chemical shifts (parts per million (δ) downfield from internal Me_4Si) 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 ^{13}C NMR spectra were recorded at 25.2 MHz on a JEOL FX 100Q; chemical shifts (δ, ppm downfield from Me_4Si) followed by the spin multiplicities (in parentheses) in broad-band decoupled spectra are reported. UV measurements were made with a Beckman DU-2 spectrophotometer. The mass spectra (MS) of macrocycles 4–9 were recorded on a Shimadzu GCMS-QP 1000 spectrometer. Masses (m/z) of the molecular ion (M^+), the base peak, and their intensities (percent) are reported. pH values were determined with a pHM 64 Radiometer Copenhagen instrument, using a GK 2401 C combination electrode. Optical rotations were determined with an AA-10 automatic polarimeter (Optical Activity Ltd., England).

All reagents were the best grade commercially available. Solvents were purified and dried in the usual manner before use. Chromatographic columns were filled with Merck silica gel 60 (70–230 mesh). Merck Fertigplatten F-254 was used for TLC.

1,3-Bis(((carboxyphenylmethyl)amino)carbonyl)-2-oxapropane (2). To a cold (0–5 °C, ice bath) solution of *rac*-1 (2.0 g, 13.2 mmol) in potassium hydroxide (2 M, 10 mL) were simultaneously added a solution of diglycoloyl chloride (1.1 g, 6.6 mmol) in dry dichloromethane (10 mL) and potassium hydroxide (4 M, 5 mL) such that the temperature of the reaction mixture did not exceed +5 °C. The resulting mixture was stirred at +5 °C for 30 min and then at room temperature for 20 min. The aqueous layer was diluted with water (to 200 mL) and acidified to pH 2 with concentrated hydrochloric acid. The product precipitated as a white solid (2.4 g, 70%); mp 185–187 °C. The product recrystallized from MeOH/water melted partially at 111 °C and completely at 207–208 °C. ^1H NMR (DMSO-d_6): 4.08, s, 4 H; 5.61, d (J = 7.6 Hz), 2 H; 7.36, m, 10 H; 8.61, d (J = 7.6 Hz), 2 H. ^{13}C NMR (DMSO-d_6): 55.66 (d), 69.78 (t), 127.20 (d), 127.55 (d), 128.14 (d), 136.64 (s), 168.20 (s), 171.09 (s). IR: 3445, 3400, 1725, 1635, 1540. Anal. Calcd for $C_{20}H_{20}N_2O_7$: C, 59.77; H, 5.03; N, 7.00. Found: C, 59.77; H, 5.26; N, 7.26.

1,6-Bis(((carboxyphenylmethyl)amino)carbonyl)-2,5-dioxahexane (3). The procedure was the same as for **2**. After acidification of the aqueous layer, **3** separated as an oil, which was extracted with EtOAc. Partial solvent removal caused separation of **3** in a crystalline form (1.0 g, 34%); mp 170–176 °C. ^1H NMR (DMSO-d_6): 3.64, s, 4 H; 3.95, s, 4 H; 5.35, d (J = 7.3 Hz), 2 H; 7.34, s, 10 H; 8.31, d (J = 7.3 Hz), 2 H. ^{13}C NMR (DMSO-d_6): 56.15 (d), 69.86 (t), 70.48 (t), 127.76 (d), 128.33 (d), 128.89 (d), 137.47 (s), 169.30 (s), 171.89 (s). IR: 3300–2500 br, 1740, 1608, 1575, 1485, 1462, 1413, 1365, 1220, 1180, 1118. Anal. Calcd for $C_{22}H_{24}N_2O_8$: C, 59.46; H, 5.44; N, 6.30. Found: C, 59.20; H, 5.66; N, 6.36.

Preparation of Macrocycles 4–9. Compounds **4–9** were prepared from the dicesium salts of **2** or **3** (used as diastereoisomeric mixtures of the (±) and meso forms) and the appropriate ω,ω'-dibromides or ω,ω'-dimesylates using the method developed by Kellogg,[13b] whose procedure was strictly followed.

The mass spectra (MS) of macrocyclic products **4–9** were recorded with ionization energies of 20 and 70 eV and mass ranges covering the 2:2 cycloadducts. In each case no masses larger than the molecular ion (M^+) of **4–9** could be detected.

3,11-Diphenyl-1,7,13-trioxa-4,10-diazacyclopentadecane-2,5,9,12-tetrone (4). Compound **4** was prepared as the diastereoisomeric mixture of the (±) and meso forms, starting with **2** (1.0 g, 2.5 mmol), Cs_2CO_3 (0.79 g, 1.68 mmol), and 1,2-dibromoethane (0.21 mL, 2.5 mmol). Obtained after column chromatography (EtOAc) and recrystallization from the same solvent: 0.21 g (19.8%); mp 225–260 °C. ^1H NMR ($CDCl_3$): 4.17, s, 4 H; 4.40, s, 4 H; 5.83, d (J = 7.6 Hz), 2 H; 7.39, s, 10 H; 7.62, d (J = 7.6 Hz), 2 H. ^{13}C NMR ($CDCl_3$/DMSO-d_6): 56.71 (d), 62.46 (t), 70.70 (t), 128.02 (d), 127.32 (d), 128.25 (d), 135.40 (s), 168.91 (s), 169.27 (s). IR: 3390, 3330, 1750, 1730, 1675, 1665, 1535. Anal. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.96; H, 5.20; N, 6.57. Found: C, 62.05; H, 5.47; N, 6.35. MS: M^+ 426 (calcd 426) (11.8), 106 (100).

3,11-Diphenyl-1,7,13,16-tetraoxa-4,10-diazacyclooctadecane-2,5,9,12-tetrone (5). Compound **5** (mixture of the (±) and meso forms) was prepared from **2** (0.85 g, 2.1 mmol), Cs_2CO_3 (0.67 g, 1.42 mmol), and diethylene glycol dimesylate (0.55 g, 2.5 mmol). After column chromatography (6:1 chloroform/acetone) and recrystallization from EtOAc, 0.324 g (32.3%) of **5** was obtained; mp 134–135 °C. ^1H NMR ($CDCl_3$): 3.70, m, 4 H; 4.14, s, 4 H; 4.39, m, 4 H; 5.81, d (J = 8.0 Hz), 2 H; 7.39, s (10 H); 7.56, d (J = 8.0 Hz), 2 H. ^{13}C NMR ($CDCl_3$): 56.54 (d) 64.78 (t), 69.07 (t), 71.16 (t), 127.09 (d), 128.67 (d), 129.01 (d), 136.23 (s), 168.00 (s), 169.07 (s). IR: 3295, 1700, 1670, 1658, 1540, 1130. Anal. Calcd for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.40; H, 5.83; N, 6.04. MS: M^+ 470 (calcd 470) (14.1), 106 (100).

3,11-Diphenyl-1,7,13-trioxa-4,10-diazacycloheptadecane-2,5,9,12-tetrone (6). Compound **6** (mixture of the (±) and meso forms) was prepared from **2** (1.0 g, 2.5 mmol), Cs_2CO_3 (0.79 g, 1.68 mmol), and 1,4-dibromobutane (0.5 g, 2.5 mmol). After column chromatography (EtOAc), 0.60 g (52.8%) of **6** was obtained: mp 216–222 °C (recrystallized from EtOAc). ^1H NMR ($CDCl_3$): 1.80, m, 4 H; 3.99, s, 4 H; 4.18, m, 4 H; 5.60, d (J = 7.3 Hz), 2 H; 7.35, m, 10 H; 7.81, d (J = 7.3 Hz), 1 H; 8.00, d (J = 7.3 Hz), ^1H. ^{13}C NMR ($CDCl_3$): 25.22 (t), 25.26 (t), 56.99 (d), 65.40 (t), 65.06 (t), 70.65 (t), 71.05 (t), 127.09 (d), 128.72 (d), 129.01 (d), 135.9 (s), 168.05 (s), 168.45 (s), 169.01 (s), 169.18 (s). All ^{13}C resonances except the signal from the phenyl and asymmetric carbons were doubled, which differentiates (±)-**6** from *meso*-**6**. Of each pair of resonances in the proton-decoupled spectra the higher field signals were more intense. When **6** was prepared from (*R*)-**1**, the lower field ^{13}C resonances were more intense. It was concluded that the lower field signals in each pair are due to the (±)-**6** diastereoisomer. IR: 3380, 3290, 1730, 1700, 1675, 1650, 1535. Anal. Calcd for $C_{24}H_{26}N_2O_7$: C, 63.43; H, 5.76; N, 6.16. Found: C, 63.21; H, 6.01; N, 6.33. MS: M^+ 454 (calcd 454) (43), 106 (100).

3,11-Diphenyl-1,7,13,16,19-pentaoxa-4,10-diazacycloheneicosane-2,5,9,12-tetrone (7). This compound was prepared from **2** (1.45 g, 3.6 mmol), Cs_2CO_3 (1.16 g, 2.4 mmol), and 1,8-dibromo-3,6-dioxaoctane (1.0 g, 3.6 mmol). (±)-**7** and *meso*-**7** isomers were separated by column chromatography (EtOAc) and recrystallized from the same solvent. (±)-**7**: 0.896 g (48.4%); mp 172–173 °C; R_f 0.30. ^1H NMR ($CDCl_3$): 3.62–3.54, m, 8 H; 4.66–4.20, m, 4 H; 4.05, s, 4 H; 5.73, d (J = 8.3 Hz), 2 H; 7.40, m, 10 H; 7.81, d (J = 8.3 Hz), 2 H. ^{13}C NMR ($CDCl_3$): 56.19 (d), 64.10 (t), 69.14 (t), 70.31 (t), 70.42 (t), 127.55 (d), 128.35 (d), 128.67 (d), 135.99 (s), 167.45 (s), 169.45 (s). IR: 3375, 1750, 1734, 1685, 1655, 1530. Anal. Calcd for $C_{26}H_{30}N_2O_9$: C, 60.69; H, 5.88; N, 5.44. Found: C, 60.92; H, 6.12; N, 5.34. *meso*-**7**: 0.574 g (31.0%); mp 171–172 °C; R_f 0.20. ^1H NMR ($CDCl_3$): 3.61–3.52, m, 8 H; 4.57–4.13, m, 2 H; 4.05, s, 4 H; 5.72, d (J = 7.8 Hz), 2 H; 7.36, m, 10 H; 7.78, d (J = 7.8 Hz), 2 H. ^{13}C NMR ($CDCl_3$): 56.37 (d), 64.39 (t), 69.01 (t), 70.54 (t), 70.65 (t), 127.82 (d), 128.50 (d), 128.89 (d), 136.29 (s), 167.83 (s), 169.91 (s). IR: 3300, 1740–1750, 1650–1660, 1530. Anal. Calcd for $C_{26}H_{30}N_2O_9$: C, 60.69; H, 5.88; N, 5.44. Found: C, 60.96; H, 6.03; N, 5.63. MS: M^+ 514 (calcd 514) (17.2), 106 (100). When the synthesis was started with (*R*)-**1**, the product with R_f 0.3 (50%) was optically active ($[\alpha]^{25}_D$ −0.64° (±0.01°) (*c* 1.0, $CHCl_3$)), whereas the product with R_f 0.2 (11%) was optically inactive *meso*-**7**.

3,11-Diphenyl-1,7,13,16,19,22-hexaoxa-4,10-diazacyclotetracosane-2,5,9,12-tetrone (8). This compound was prepared from **2** (1.0 g, 2.5 mmol), Cs_2CO_3 (0.795 g, 1.68 mmol), and 1,12-dibromo-3,6,9-trioxaundecane (0.80 g, 2.5 mmol). The diastereoisomers, (±)-**8** (R_f 0.28) and *meso*-**8** (R_f 0.18), were separated by column chromatography (EtOAc) and recrystallized from the same solvent. (±)-**8**: 0.388 g (27.8%); mp 102–103 °C. ^1H NMR ($CDCl_3$): 3.53, m, 6 H; 4.09, s, 4 H; 5.82, d (J = 8.3 Hz), 2 H; 7.30–7.45, m, 10 H; 8.19, d (J = 8.3 Hz), 2 H. ^{13}C NMR ($CDCl_3$): 55.89 (d), 64.10 (t), 68.61 (t), 70.19 (t), 70.37 (t), 70.48 (t), 128.08 (d), 128.55 (d), 136.05 (s), 167.51 (s), 169.56 (s). IR: 3320, 3270,

1745, 1650, 1540, 1130. Anal. Calcd for $C_{28}H_{34}N_2O_{10}$: C, 60.20; H, 6.13; N, 5.01. Found: C, 60.18; H, 6.37; N, 5.07. *meso*-**8**: 0.279 g (20%); mp 130–132 °C. ^{1}H NMR ($CDCl_3$): 3.57, m 12 H; 4.11, s, 4 H; 4.35, m, 4 H; 5.73, d (J = 7.8 Hz), 2 H; 7.37, m, 10 H; 7.68, d (J = 7.8 Hz), 2 H. ^{13}C NMR ($CDCl_3$): 55.89 (d), 64.57 (t), 68.67 (t), 70.48 (t), 127.08 (d), 128.20 (d), 128.61 (d), 125.94 (s), 167.34 (s), 169.51 (s). IR: 3330, 3285, 1740, 1650, 1540, 1100–1130. Anal. Calcd for $C_{28}H_{34}N_2O_{10}$: C, 60.20; H, 6.13; N, 5.01. Found: C, 59.94; H, 6.34; N, 5.01. MS: M^+ 558 (calcd 558) (20.5), 106 (100). When the synthesis was started with (*R*)-**1**, the product with R_f 0.28 (28%) was optically active ($[\alpha]^{25}_D$ −0.41° (±0.01°) (*c* 1 in $CHCl_3$)), whereas the product with R_f 0.18 (20%) was optically inactive *meso*-**8**.

3,14-Diphenyl-1,7,10,16,19,22-hexaoxa-4,13-diazacyclotetracosane-2,5,12,15-tetrone (9). Compound **9** was obtained as a mixture of the (±) and meso forms from **3** (0.43 g, 0.97 mmol), Cs_2CO_3 (0.31 g, 0.65 mmol), and 1,8-dibromo-3,6-dioxaoctane (0.27 g, 0.97 mmol). After column chromatography (EtOAc) and recrystallization from the same solvent, 0.23 g (42.2%) of **9** was obtained; mp 128–129 °C. ^{1}H NMR ($CDCl_3$): 3.44, s, 4 H; 3.56, m, 4 H; 3.72, s, 4 H; 4.02, s, 4 H; 4.31, m, 4 H; 5.69, d (J = 7.3 Hz), 2 H; 7.37, m, 10 H; 8.09, d (J = 7.3 Hz), 2 H. IR: 3365, 3330, 3100–2900, 1740, 1730, 1650, 1533, 1415, 1115. Anal. Calcd for $C_{28}H_{34}N_2O_{10}$: C, 60.20; H, 6.13; N, 5.01. Found: C, 60.37; H, 6.35; N, 5.12. MS: M^+ 558 (calcd 558) (71.8), 118 (100).

1,11-Bis(((benzyloxycarbonyl)amino)phenylacetoxy)-3,6,9-trioxaundecane (10). To a cold (ice bath) solution of tetraethylene glycol (0.22 mL, 1.3 mmol) and 4-(dimethylamino)pyridine (DMAP) (31 mg, 0.13 mmol) in dry dichloromethane (4 mL) was added a cold solution of DCC (0.57 g, 0.13 mmol) in dry dichloromethane (3 mL) dropwise. The resulting mixture was stirred at 0–5 °C for 1 h and then at room temperature for 16 h. Dicyclohexylurea was filtered off (Celite), the filtrate was evaporated, and the crude product was purified by column chromatography (12:1 $CHCl_3$/EtOAc). Yield 0.3 g (31%) as an oil. ^{1}H NMR ($CDCl_3$): 3.47, s, 8 H; 3.57, t, 4 H; 4.26, m, 4 H; 5.08, s, 4 H; 5.38, d (J = 7.3 Hz), 2 H; 7.33, s, 20 H. IR (film): 3340, 1700–1750 br, 1490–1530 br, 1455, 1320, 1180. Anal. Calcd for $C_{40}H_{44}N_2O_{11}\cdot 2H_2O$: C, 62.82; H, 6.32; N, 3.66. Found: C, 63.24; H, 6.11; N, 3.50.

Preparation of [*meso*-8,KSCN] Complex. The crystalline complex of *meso*-**8** and KSCN was obtained by mixing a solution of *meso*-**8** (27.7 mg, 0.05 mmol in $CDCl_3$ (0.25 mL) and KSCN (4.85 mg, 0.05 mmol) in CD_3CN (0.25 mL). Precipitation occurred immediately, and 12.8 mg of [*meso*-**8**,KSCN] complex was obtained; mp 198–199 °C. IR: 3305, 2060 (SCN^-), 1730, 1674, 1530, 1145, 1170, 1090. Anal. Calcd for $C_{28}H_{34}N_2O_{10}\cdot$KSCN: C, 53.11; H, 5.22; N, 6.40. Found: C, 52.97; H, 5.43; N, 6.36.

Determination of Equilibrium Constants (K_w) of Complexes Formed by Macrocycles 6–9 and Water in $CDCl_3$. Half-milliliter portions of deuteriochloroformic solutions of macrocycles **6** [(±) and meso forms], (±)-**7**, *meso*-**7**, (±)-**8**, *meso*-**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 Köttermann shaker for 1 h at constant speed. After standing for another hour, the cuvettes were centrifuged. From each cuvette 0.3 mL of the $CDCl_3$ layer was transferred to an NMR tube and ^{1}H NMR spectra were recorded. Concentrations of water relative to those of macrocycles ($R_w = [H_2O]_0/[Mc]_0$) were determined by signal integration of macrocyclic and water resonances. The amount of solubilized water per mole of macrocycle ($R_w - S_w/[Mc]_0$) and K_w's were calculated by using eq 2. The solubility of water in $CDCl_3$ (S_w = 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,[23] so as to obtain results comparable to the ones reported.[23] 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 mM 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 mM 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 mM HEPES solution adjusted to pH 7.20–7.25 with LiOH. Macrocyclic compound (0.02 mmol) was weihged 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 organic phase. 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 reported molar extinction coefficients (ϵ) of picrate anion at 355 nm (1.64×10^4).[23] 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 (±)- and *meso*-8. 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 marks with chloroform. These solutions were transferred to centrifuge cuvettes containing 5 mL of aqueous KCl (10 mM) and picric acid (25 mM), the solution having been adjusted to pH 7.20–7.25 with HEPES and LiOH. All cuvettes were stoppered and agitated on a Köttermann shaker for 0.5 h at constant speed. After standing for another hour, the cuvettes were centrifuged, and 3 mL of the chloroform layers was transferred to UV optical cells. Concentrations of metal ions extracted into chloroform were determined indirectly by measuring the absorbance of picrate anion in chloroform at 410 nm; the molar extinction coefficient (ϵ) of 9100[29,30] was used in calculation. Extraction equilibrium constants (K_{ex}) were calculated from plots of log ($D_m/[A^-]_{aq}$) vs log $[Mc]_0$ by applying eq 3.[23,26]

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