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# SYNTHESIS AND IONOPHORIC PROPERTIES OF A NEW SERIES OF POLYESTER HETEROCYCLOPHANES OF 3,5-DISUBSTITUTED 1-METHYLPYRAZOLE AND 2,6-BIS(METHYLENE)PYRIDINE

**Pilar Navarro[a*], Encarnación Pueyo[a], María Isabel Rodríguez Franco[a] and André Samat[b]**
[a]Instituto de Química Médica (CSIC), Juan de la Cierva, 3.
28006 Madrid, Spain
[b]Université d'Aix-Marseille III. LA 126 du CNRS.
Avenue Escadrille Normandie Niemen-C12, 13397 Marseille,
Cédex 13, France

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**Abstract.**- A new series of polyester pyrazolopyridophanes of cyclic 5-7 and acyclic structure **8** has been synthesized. The larger cyclic receptors **6** (36-membered) and **7** (48-membered) show efficient transport of $Na^+$, $K^+$, $NH_4^+$ and $Ca^{2+}$ ions. Their acyclic analogue **8** is, comparatively a worse carrier of all the above cations. Compound **6** is an excellent complexing agent that selectively transports $NH_4^+$ ions.

## INTRODUCTION

Naturally-occurring ionophores are able to take up or release essential metals ($Na^+$, $K^+$, $Ca^{2+}$), ammonium ions and organic cations of biogenic amines by highly specific transport processes across the membrane. All of them function by similar principles, although they may vary widely in chemical composition, geometry and molecular size.[1,2] Thus, Valinomycin **1** and nonactin **2** are cyclic neutral ionophores that exhibit good cation selectivities in the binding of potassium and ammonium ions respectively.[3] Valinomycin is a cyclic depsipeptide, while nonactin may be described as a polyether antibiotic. (Fig 1). Much can be learned from nature in the design of artificial ionophores.

In previous works, we have studied the synthesis and ionophoric behaviour of 3,5-pyrazolo polyether crowns having different sizes, donor sites, symmetry and steric hindrance. In general, we have found that flexible receptors **3** and **4** of 36 members (Fig 1) are more efficient and selective carriers of $K^+$ and $NH_4^+$ ions than their smaller analogues having half the size (18-membered).[4-5]

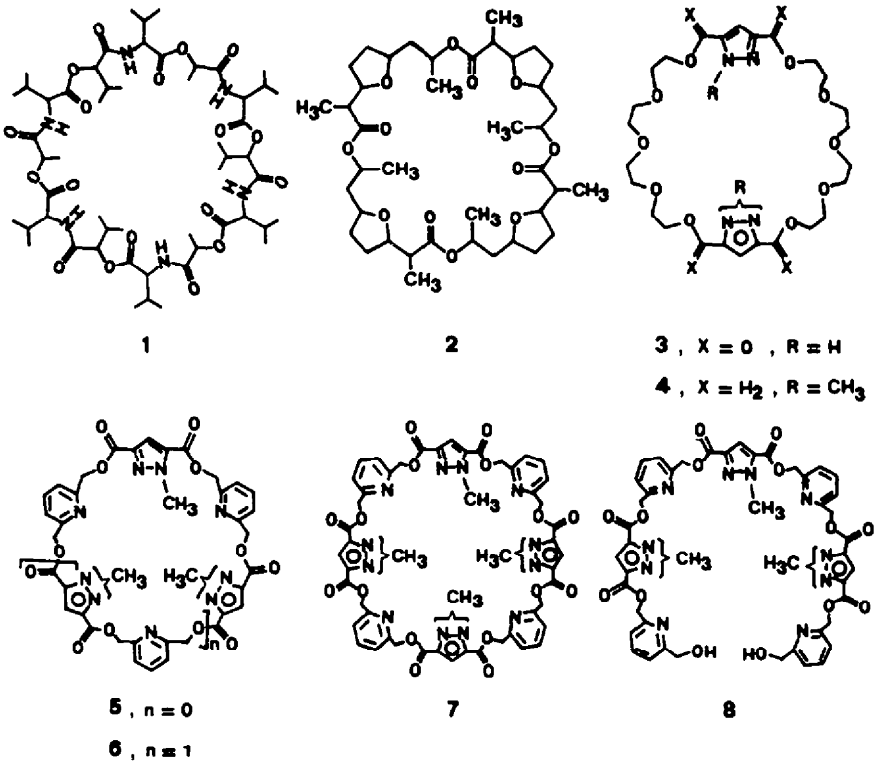



Fig. 1

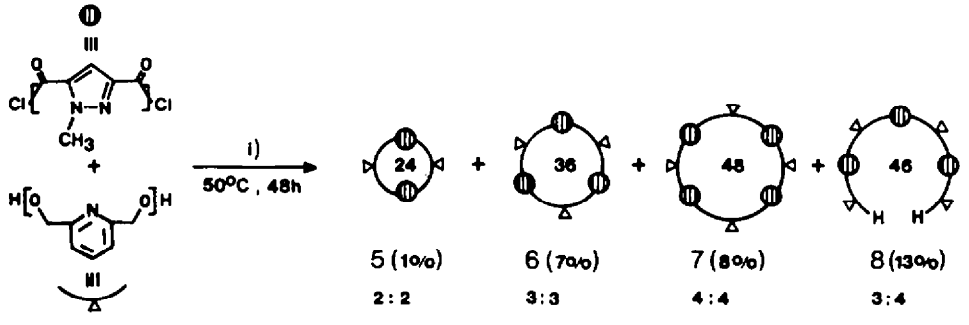
In relation to the size, the above behaviour mimics that exhibited by natural cyclic ionophores. Thus, valinomycin (36-membered) is an efficient carrier showing higher selectivity ($K^+$ over $Na^+$ and $NH_4^+$) than enniatins, which are also depsipeptides with half the ring size of Valinomycin. Enniatins are known to activate the permeability of membrane cations but they rather indiscriminately form 1:1 complexes with alkali, alkaline earth metals and ammonium cations.[6] Valinomycin and nonactin (32-membered) are rigid receptors which have in common a neutral macrocyclic cavity of large size built by alternative subunits interlinked by lactam or lactone bonds. Both of them are capable of folding giving rise to selective interactions with $K^+$ or $NH_4^+$ ions. On the basis of the above observations and taking into account that symmetry is not an essential requirement for ionophoricity,[7] we now wish to report the synthesis of a new series of pyrazolopyridophanes of rigid polycarbonyl structure 5-8 (Fig 1).

In these new receptors the $sp^2$ nitrogens of both 3,5-disubstituted 1-methylpyrazole[4,5] and 2,6-bis(methylene)pyridine[8,9] may contribute to the selective transport of $NH_4^+$ (over $Na^+$ and $K^+$). Since complexing properties toward $Ca^{2+}$ of heteroaromatic crowns containing 2,6-bis(pyrazol-5-yl) pyridine units[10] have previously been described, in this work, we have studied the complexing and transport properties toward $Na^+$, $K^+$, $NH_4^+$ and $Ca^{2+}$ of ligands **6-8** having cyclic and acyclic cavities of 36, 48 and 46 members, respectively.

## RESULTS AND DISCUSSION

**Synthesis.-** We have previously reported, in detail, the cyclization behaviour of 1-methyl-3,5-pyrazolyldicarbonyl chloride with flexible chains of tetraethylene glycole (TEG). Using high dilution and triethylamine (TEA) as acceptor of hydrochloric acid, both di- and tetraester crowns of 18 and 36 members were formed by 1:1 and 2:2 cyclization in 54% and 24% yields, respectively.[11] Considering the ability of the $Cs^+$ cation to promote intramolecular cyclization of large ring systems the above mentioned reaction, in the presence of caesium chloride (molar ratio 1:1), afforded a mixture of 1:1, 2:2, 3:3 and 4:4 cyclic adducts of 18, 36, 54 and 72 members in 48%, 22%, 6% and 4% yields, respectively.[12]

Now, using high dilution, in the absence of any catalyst, the cyclic and acyclic ligands **5-7** and **8** were simultaneously formed by reaction of 1-methyl-3,5-pyrazolyldicarbonyl chloride and 2,6-bis(hydroxymethyl)pyridine




i) High dilution/$N_2$, benzene, dimethoxyethane (84 : 16), Triethylamine in molar ratio 3:1

Scheme 1

(see Scheme 1). In contrast with the results obtained with flexible chains, the new pyridinic units act as rigid spacers, preventing the

formation of the 1:1 adduct, and strongly hindering the 2:2 cyclization which affords receptor **5** of 24 members in only 1% yield. However, they favour the formation of both 3:3 and 4:4 adducts which lead to two larger cyclic analogues **6** and **7**, of 36 and 48 members, in 7% and 8% yields respectively. Diol **8** is obtained in higher amount (13%) corresponding to an acyclic intermediate of 46 members formed by alternative condensations of three pyrazole and four pyridine subunits.

Purification of the above ligands was effected on silica gel using chromatographic techniques as it is indicated in the Experimental Part. In each of the mass spectra of **5-8** registered by fast atomic bombardement (FAB) techniques, both molecular ions $MH^+$ and $(MH+1)^+$ clearly appear in accordance with the molecular weight expected for each ligand (see Experimental Part). All of them showed 300-$MH_2$ $^1H$ NMR spectra in agreement with their structures (see Table 1).

Table 1. $^1H$ NMR Spectral Data (300 MHz, $CDCl_3$, δ) of Ligands 5-8 (Figure 1)

| | Pyrazole ring | | Pyridine ring | | | |
|---|---|---|---|---|---|---|
| Ligand | 4-H | 1-$CH_3$ | Hp | Hm | Py-$\underline{CH_2}$-OCO | Py-$\underline{CH_2}$-OH |
| 5 | 7.25(s, 1H)<br>7.26(s, 1H) | 4.27(s, 3H)<br>4.28(s, 3H) | 7.78(m, 2H) | 7.47(m, 4H) | 5.43(m, 8H) | - |
| 6 | 7.39(s, 3H) | 4.27(s, 3H)<br>4.28(s, 3H)<br>4.29(s, 3H) | 7.75(m, 3H) | 7.37(m, 6H) | 5.46(m, 12H) | - |
| 7 | 7.48(s, 4H) | 4.26(s, 6H)<br>4.28(s, 6H) | 7.79(m, 4H) | 7.36(m, 8H) | 5.54(m, 16H) | - |
| 8[a] | 7.47(s, 1H)<br>7.48(s, 1H)<br>7.49(s, 1H) | 4.28(s, 3H)<br>4.29(s, 3H)<br>4.30(s, 3H) | 7.79(m, 4H) | 7.36(m, 8H) | 5.49(m, 12H) | 4.78(m, 4H) |

[a]At δ 2.88 (m, 2H), disappear by treatment with $D_2O$

The chemical shifts corresponding to all the $\underline{CH_2}OCO$ groups adjacent to the pyridine ring are very close in cyclic and acyclic ligands. Furthermore, in the $^1H$ NMR of podand **8** the two Py-$\underline{CH_2}OH$ groups can be clearly distinguished since they appear 0.7 ppm shielded in relation to all the Py-$\underline{CH_2}OCO$ protons. The above mentioned spectrum, also showed a broad signal belonging to two hydroxy groups which disappear by treatment with $D_2O$.

Owning to their particular complexing ability, the above ligands are very difficult to isolate free from water and neutral molecules of solvents (acetone and chloroform) which were employed in their

chromatographic purification. Only after prolonged drying by heating under vacuum, satisfactory elemental analyses (C.H.N.) were obtained.

**Transport and Complexing Properties of Cyclic and Acyclic Ligands 6-8.-** We have previously reported that asymmetric di- and tetraester crowns of 3,5-disubstituted 1-methylpyrazole are more selective for $NH_4^+$ than for alkali cation transport. However, after removal of the N-methyl groups the resulting symmetrical ligands of 3,5-disubstituted 1H-pyrazole showed the opposite selectivity. Thus, crown **3** of 36 members (Fig. 1) is an efficient carrier of $K^+$ ions which showed a high selectivity $K^+/Na^+$ = 6.8 and a lower $K^+/NH_4^+$ = 1.4 very close to that exhibited by dibenzo-18-crown 6 ($K^+/Na^+$ = 8.8 and $K^+/NH_4^+$ = 1.5).[4] In agreement with the above results, other polyether crowns of asymmetrical structure such as crown **4** (Fig. 1), also turned out to be efficient and selective carriers of $NH_4^+$ in relation to $Na^+$ and $K^+$ ions.[5] The above results have now encouraged us to evaluate the ionophore properties of the new asymmetric heterocyclophanes of 3,5-disubstituted 1-methylpyrazole **6-8**.

**Table 2.** Transport rates (x $10^{-6}$ mol $l^{-1}$ $h^{-1}$) across a $CHCl_3$ phase and liquid-liquid extraction percentage in $CHCl_3$ (%)

| | | $Na^+$ | $K^+$ | $NH_4^+$ | $Ca^{2+}$ |
|---|---|---|---|---|---|
| **Transport rates** | 6 | 42.16 | 35.86 | 67.45 | 21.65 |
| | 7 | 34.75 | 55.48 | 42.63 | 26.37 |
| | 8 | 1.61 | 2.84 | 2.97 | 1.04 |
| | DB18C6 | 22.54 | 390.25 | 201.48 | 1.83 |
| **Extracted picrates** | 6 | 30 | 29 | 29 | 33 |
| | 7 | 2 | 3 | 3 | 2 |
| | 8 | 4 | 3 | 3 | 1 |
| | DB18C6 | 4 | 25 | 19 | 3 |

All these compounds contain six or more $sp^2$ nitrogens as potential donor sites of ammonium ions. Besides, as occurs with Valinomicyn, their backbone incorporates six or more ester type carbonyl groups. We have measured the transport rates of sodium, potassium, calcium and ammonium picrates through a chloroform liquid membrane which contains one of the carriers and which separates two aqueous phases. The guest cation salts are complexed with the carrier from the first aqueous phase and are transported to the second one by using a classical experimental apparatus previously reported (see Experimental Section). The transport process

occurs by carrier-mediated facilitated diffusion along the concentration gradient of the guest salts. The results are gathered in Table 2.

The transport rates of both cyclic receptors **6** and **7** are in general much higher than those corresponding to the diol **8** of acyclic structure. According to our principal aim, the hexaester **6** of 36 members whose electrostatic cavity has three pyridinic and three pyrazolic $sp^2$ nitrogens is a selective carrier of $NH_4^+$ in relation to $K^+$ ($NH_4^+/K^+$ = 1.9), $Na^+$ ($NH_4^+/Na^+$ = 1.6) and $Ca^{2+}$ ($NH_4^+/Ca^{2+}$ = 3.1) ions. However, the octaester **7** of larger size (48 members) which has four pyridinic and four pyrazolic $sp^2$ nitrogens as potential donor sites, shows a moderate transport selectivity toward $K^+$ in relation to the other cations ($K^+/NH_4^+$ = 1.3; $K^+/Na^+$ = 1.6; $K^+/Ca^{2+}$ = 2.1). As could be expected, in **6** and **7** the presence of six and eight $sp^2$ nitrogens may highly favour the transport of $Ca^{2+}$ in relation to the polyether crown taken as reference (DB18C6)[13]

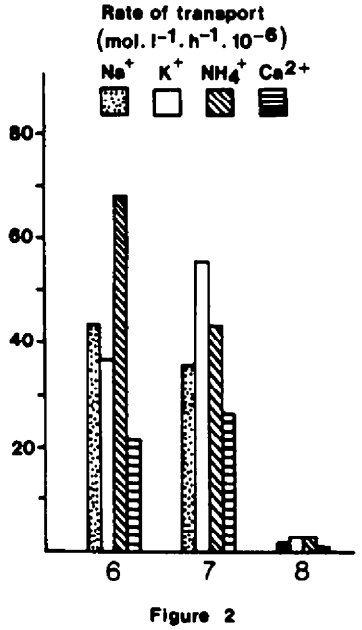


Figure 2

In figure 2, the significantly higher $Na^+$, $K^+$, $NH_4^+$ and $Ca^{2+}$ transport rates of both cyclic receptors **6** and **7** are graphically compared with those corresponding to their acyclic analogue **8** which, in spite of being a worse carrier, also shows an interesting selectivity toward $NH_4^+$ in relation to $Na^+$ ($NH_4^+/Na^+$ = 1.8) and $Ca^{2+}$($NH_4^+/Ca^{2+}$ = 2.8) ions. In contrast with the above results, we had previously found that flexible podands of 3,5-disubstituted 1-methylpyrazole of polyether structure bearing terminal hydroxyl groups were not selective but very efficient carriers of $Na^+$, $K^+$ and $NH_4^+$ ions.[5] In this new series, the aromatic structure of podand **8** may be responsible for its inefficiency as carrier since its rigid backbone may hinder the correct orientation of its terminal hydroxyl groups in order to form a pseudocyclic cavity by hydrogen bond interactions.

In order to evaluate the relative complexing power of ligands **6-8** toward the same cations, the liquid-liquid extraction technique was used following Cram's method.[14] Solutions of picrates in $H_2O$ were extracted with $CHCl_3$ (in the absence and in the presence of each receptor), and the increase in UV absorbance of the picrate in the organic phase measured. For monovalent cations we have applied identical distribution constants ($K_d$) and extinction coefficients ($\varepsilon$) as those determined by the authors

mentioned above. However, for divalent $Ca^{2+}$ both $K_d$ and $\varepsilon$ have been determined by us (See experimental part). The resulting extraction percentages are also gathered in table 2. The trimeric pyrazolopyridocyclophane **6** has shown to be, in general, a much better complexing agent than the rest of the cyclic and acyclic ligands evaluated including DB18C6. The above difference is extreme by comparing the extraction percentages for $Na^+$ and $Ca^{2+}$ (7.5 and 11.0 higher for **6** than from DB18C6).

The larger tetrameric analogue **7**, in spite of being an efficient carrier of $Na^+$, $K^+$, $NH_4^+$ and $Ca^{2+}$ ions, under liquid-liquid extraction conditions behaves as a poor complexing agent of the above cations. Its large rigid cavity may be responsible for the above fact, since it requires more severe deformation for contact binding than that corresponding to its smaller cyclic analogue **6**. It is known that such deformation implies increased conformational energy with, consequently, decreased complex stability.[15] The relatively high transport rates of **7** could "a priori" be due to an increase in exchange rates. In any case, extensive numerical analysis of carrier diffusion has shown that transport rates display a bell-shaped dependence on extraction constants.[16]

## EXPERIMENTAL SECTION

Melting points were determined with a Köfler apparatus and are uncorrected. Elemental analyses were carried out by the Organic Chemistry Department of Centro Nacional de Química Orgánica (CSIC), Madrid, Spain. The IR spectra were recorded with a Perkin-Elmer 257 spectrometer and the $^1H$ NMR ones with a Varian XL-300 using $Me_4Si$ as an internal standard. All the mass spectra (MS) were registered using the fast atomic bombardment (FAB) technique in a FAB-HF apparatus. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel $60F_{254}$ (Merck). Chromatographic separations were performed either on columns, using the flash chromatography technique[17] on silica gel (Merck), 200-400 mesh, or by preparative layer chromatography on 20 x 20 cm glass plates coated with a 2 mm layer of silica gel $PF_{254}$ (Merck). Compounds were detected with UV light (254 nm) and/or iodine chamber. 1-Methylpyrazole-3,5-dicarbonyl chloride was obtained from 1-methylpyrazole-3,5-dicarboxylic acid following a procedure previously described by us.[18]

**Synthesis of Ligands 5-8.-** Following the high dilution technique described by Lehn and co-workers[19], to a solution of anhydrous benzene (110 mL) vigorously stirred under nitrogen and heated at 50°C, the following

independent solutions were simultaneously added: a) 3.9 mmol of 1-methylpyrazole-3,5-dicarbonyl chloride in anhydrous benzene (70 ml) and b) 3.9 mmol of 2,6-bis(hydroxymethyl)pyridine and triethylamine (3 x 3.9 mmol) both dissolved in a mixture of anhydrous benzene (30 mL) and dimethoxyethane (40 mL). After the addition was complete (40 minutes) the reaction was kept along a period of 48 h and then cooled to room temperature. The triethylamine hydrochloride formed along the reaction was filtered off and the filtrate evaporated to dryness under vacuum to give a syrup which was dried under vacuum. Its analytical (TLC) control showed a mixture of by-products which was purified by flash chromatography on a silica gel column using first a mixture of chloroform, acetone (v/v 2:1), second acetone and third ethanol. The first fractions (45 x 10cc) afforded a mixture which controlled by TLC using chloroform, acetone (v/v, 3:1) indicated the presence of macrocycles **5** (Rf = 0.75) and **6** (Rf = 0.62) which were definitely separated by preparative chromatography using the above mentioned mixture. In a similar way, the fraction obtained by elution with acetone and ethanol (75 x 10 cc) yielded a residual solid which controlled by TLC using a more polar mixture of chloroform, acetone (v/v, 1:1) indicated the presence of two additional products **7** (Rf = 0.71) and **8** (Rf = 0.42) which were later isolated and purified by preparative chromatography on silica gel using the same eluent. After the purification was concluded, ligands **5-8** were obtained as pure solids which were dried under vacuum at 50°C for 12 h. **5**: yield 1%. Mp. 171-173°C. Anal. Calcd for $C_{26}H_{22}N_6O_8$: C = 57.14; H = 4.02; N = 15.38. Found: C = 56.90; H = 4.05; N = 15.20; IR(KBr) $\nu_{max}$, 1740, 1720, 1618, 1600, 1520, 1445, 1260, 1200, 1130, 1090, 760 $cm^{-1}$; UV ($Cl_3CH$) $\lambda_{max}$ (log $\varepsilon$), 240 (4.07), 249 sh (3.79), 260 sh (3.64), 266 sh (3.60); MS (m/z) 547 ($MH^+$, 5), 548 [$(MH + 1)^+$, 2].

**6**: Yield 8%. Mp 138-140°C; Anal. Calcd. for $C_{39}H_{33}N_9O_{12}$: C = 57.14; H = 4.02; N = 15.38. Found: C = 56.85; H = 4.12; N = 15.02; IR (KBr) $\nu_{max}$, 1730, 1590, 1440, 1250, 1200, 1130, 980, 760 $cm^{-1}$; UV ($Cl_3CH$) $\lambda_{max}$ (log $\varepsilon$), 242 (4.27), 250 sh (3.86), 257 sh (3.63), 267 sh (3.93); MS (m/z) 820 ($MH^+$, 12), 821 [$(MH + 1)^+$, 6], 822 [$(MH+2)^+$,2]

**7**: Yield 7%. Mp. 68-70°C. Anal. Calcd. for $C_{52}H_{44}N_{12}O_{16}$: C = 57.14; H = 4.02; N = 15.38. Found: C = 56.74; H = 4.21; N = 14.96; IR (KBr) $\nu_{max}$ 1720, 1590, 1520, 1450, 1250, 1200, 1120, 1080, 760 $cm^{-1}$. UV ($Cl_3CH$) $\lambda_{max}$ (log $\varepsilon$), 247 (4.34), 255 sh (3.84), 260 sh (3.78), 267 sh (4.06). MS (m/z), 1093 ($MH^+$, 1), 1094 [$(MH + 1)^+$, 0.2].

**8**: Yield 13%. Mp 85-88°C; Anal. Calcd. for $C_{46}H_{42}N_{10}O_{14}$: C = 57.62; H = 4.38; N = 14.61. Found: C = 57.33; H = 4.40; N = 14.37; IR (KBr) $\nu_{max}$ 3400 (broad), 1720, 1600, 1440, 1260, 1200, 800, 760 $cm^{-1}$; UV ($Cl_3CH$) $\lambda_{max}$

(log ε), 240 (3.65), 242 (3.65), 244 (3.64), 250 sh (3.61); 268 sh (3.43); MS (m/z) 959 ($MH^+$, 6), 960 [$(MH+1)^+$, 3].

**Transport Rate Measurements.**- The transport experiments were performed in a similar apparatus as described before[20,21] (a = 8 mm, b = 9 mm, c = 20 mm). The first aqueous phase (1.5 mL) contains $5.10^{-5}$ M of LiOH, $10^{-1}$ of metal or ammonium nitrate and 2 x $10^{-3}$ M of metal or ammonium picrate. The second aqueous phase contains 5 mL of deionized water. The membrane phase (5 mL of chloroform, Merck), in which the carrier is dissolved ($7.10^{-4}$ M) lies below two aqueous phases and bridges them. This membrane phase is stirred slowly and constantly by a magnetic stirrer. A similar experiment was carried out in the absence of carrier. The picrate concentration in the second aqueous phase, monitored spectroscopically, was confirmed to increase linearly with running time (< 6 h) and the initial transport rates were calculated. The values indicated in Table 2 were estimated from the differences in the transport rates of carrier-containing systems and blank systems (no carrier present). Dibenzo-18-crown-6 was taken as reference ligand.

**Liquid-liquid Extraction Measurements.**- All ultraviolet (UV) measurements were made on a Perkin Elmer 550 SE UV/VIS spectrometer at 380 nm at room temperature following Cram's Method[14]. Picrates salts in distilled water in volumetric flasks (50 mL) were prepared that involved the following cations $Na^+$, $K^+$, $NH_4^+$ and $Ca^{2+}$ all of them in concentration $1.5.10^{-2}$M. Solutions of the ligands **6-8** ($7.5.10^{-2}$M in $Cl_3CD$) were also prepared in 10 mL volumetric flasks. A picrate solution, 1 mL was introduced into a 5 mL centrifuge tube. To one tube 1.0 mL $H_2O$ was added to be used as a blank. To each of the tubes, including the one containing $H_2O$, 1.0 mL of the ligand solution was added. The tubes were stoppered to prevent evaporation. The contents of each tube were then vigorously shaken for ca. 3 min, and separated into clear layers by centrifugation. With each cation two independent experiments were carried out. In each case, four aliquots of the $Cl_3CH$ were measured ( = 50, 75, 100 and 125 µL) and transferred by a microsyringe into a 5 mL volumetric flask and diluted to the mark with $CH_3CN$.

For each size aliquot, a blank was also made by measuring the desired volume from the $Cl_3CH$ layer of the $H_2O$ blank and diluting to the mark with $CH_3CN$ in a 5 mL volumetric flask. The UV absortion of each 5 mL solution was measured against the appropriate blank solution at 380 nm and the resulting data processed by linear regression in order to obtain the number of extracted picrates moles in $CHCl_3$. The extraction percentages

calculated by the above procedure for each ligand (**6-8**) are given in Table 2. For monovalent cations we have applied identical distribution constants (Kd) and extinction coefficients as those determined by Cram and coworkers.[14] However, for divalent $Ca^{2+}$ cations the ε value (15.500 at 380 nm) has experimentally been determined by us in acetonitrile solution using a concentration range of $10^{-6}$ to $10^{-4}$ M of pure calcium picrate. The corresponding Kd value was also obtained shaking vigorously an aqueous calcium picrate solution ($1.15.10^{-2}$M) with pure $Cl_3CH$. The experimental Kd ($26.61M^{-2}$) was found applying the following equation: $Kd = [Ca(Pic)_2]_{CHCl_3}/[Ca^{2+}]_{H_2O}[Pic^-]^2_{H_2O}$.

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