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TETRAHEDRON

New Podands and Macrocycles containing "Dioxazaphosphocane" moieties. Synthesis, Structural Determination and Study of their Binding and Ionophoric Properties with Ca^{2+} and Mg^{2+} cations

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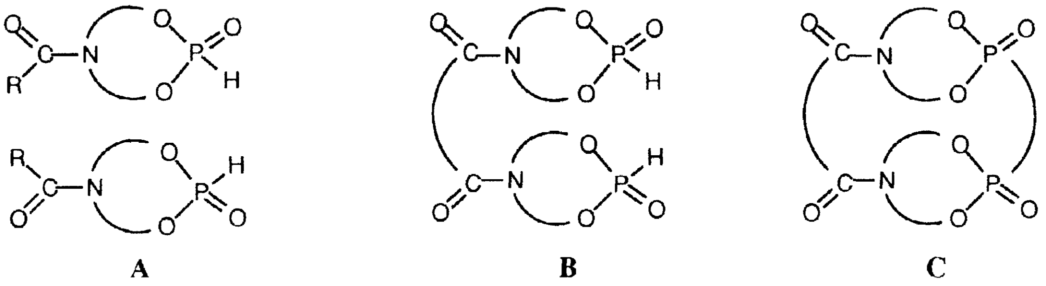
Abstract: The reactions of diacids with the bicyclophosphane **1** lead to podands **3a-f** in which two dioxazaphosphocane moieties are linked by a more or less rigid spacer owing to the starting diacid. Macrocycles **4a-b** are obtained by cyclization of podands **3a-b** by way of Michaelis-Becker reaction. The formation of Ca^{2+} and Mg^{2+} complexes with **3a-f** and **4a-b** has been investigated by UV, IR and NMR spectroscopies. Liquid-liquid extraction studies show for macrocycles efficient extracting properties and good selectivities of Ca^{2+} towards Mg^{2+}. The calcium transport across a chloroformic membrane agrees better with stability constants than with extraction data. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

We have recently shown that eight membered cyclic hydrogenophosphonates named "dioxazaphosphocanes" bearing a lipophilic moiety exhibit phospholipid properties.[1] These compounds are phospholipase A2 inhibitors and act on blood platelet aggregation and on cellular proliferation. Their reactivity towards calcium dependent systems and the presence of amide and phosphoryl groups in the same molecule prompted us to study the complexing ability of these heterocycles. In a previous paper, we have shown that these compounds display interesting complexing properties towards alkaline-earth cations.[2] We demonstrated that the calcium ion is located between two dioxazaphosphocane units either independent as in model **A** or linked by a tetramethylenic spacer as in model **B** (scheme 1).



Scheme 1

In this paper we describe the synthesis and the characterization of new podands **B** and macrocycles **C** containing two dioxazaphosphocane subunits. A more extensive study has been performed in view of analyzing their complexing properties in relation with rigidity and lipophilicity of the spacers, and their ionophoric properties.

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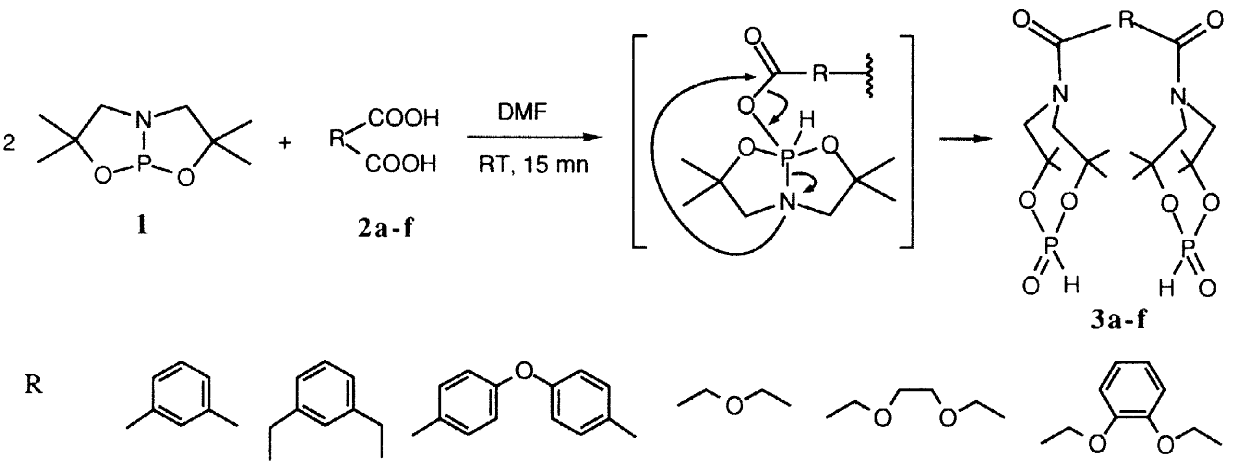
RESULTS AND DISCUSSION

Synthesis and characterization

The different podands **3a-f** described in this paper are prepared by the same approach, outlined in scheme 2. The key step of this method is based on the reactivity of the constrained bicyclophosphane **1** towards carboxylic acids according to a literature procedure of Houalla and coll.[3] These authors studied in detail the oxidative addition of benzoïc acid onto bicyclophosphane **1**. Low temperature ^{31}P NMR (-80 °C) showed the formation of a pentacoordinated bicyclic intermediate. Rearrangement by phosphorus-nitrogen bond cleavage and acyl migration leads to the dioxazaphosphocane. We have extended this reaction to the diacids **2a-f**. Each function of the diacid reacts with a bicyclophosphane to give podands **3a-f** in which two dioxazaphosphocane cycles are linked by a more or less rigid spacer owing to the starting diacid (scheme 2).



Diacids	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**
Podands	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**

Scheme 2. Synthetic scheme and podands **3a-f** described in this study

The structures proposed for the podands **3a-f** are consistent with data derived from infrared, phosphorus, carbon and proton nuclear magnetic resonance spectra. In addition, satisfactory elemental analyses and molecular weights determined by mass spectrometry were obtained (see experimental section).

The ^{1}H and ^{13}C NMR spectra of podands **3a-f** show that the hydrogen and carbon atoms of the dioxazaphosphocane rings are non equivalent. The ^{13}C NMR spectrum of the podand **3b** is represented on figure 1 and reveals that each carbon of a cycle is equivalent to its homologue in the other cycle. Thus, the four singlets at $\delta = 27.9$, 26.8, 25.9 and 22.9 ppm can be assigned to the four methyl groups. Moreover two singlets at $\delta =$ 59.5 and 57.3 were observed for the methylenic carbons α to the nitrogen atom and two doublets arising from a coupling with the phosphorus atom at $\delta = 85.3$ and 84.0 for the methylenic carbons α to the oxygen atom. This behaviour was described earlier in the case of separated dioxazaphosphocanes.[3] It indicates that each dioxazaphosphocane unit exists at room temperature in an averaged asymmetric conformation. The extracyclic carbon atoms of the same type are also equivalent : only one signal at $\delta = 173,6$ was observed for the two carbon atoms of the carbonyl groups and at $\delta = 41,3$ for the methylenic carbon atoms. The two quaternary aromatic carbon atoms appear as a singlet at $\delta = 136$.

Moreover, only one singlet was observed in $^{31}P\{^1H\}$ NMR ($-5.8 \leq \delta \leq -5.6$) for the two phosphorus atoms of the podands. These observations agree with podands possessing an element of symmetry passing through the middle of the spacer.

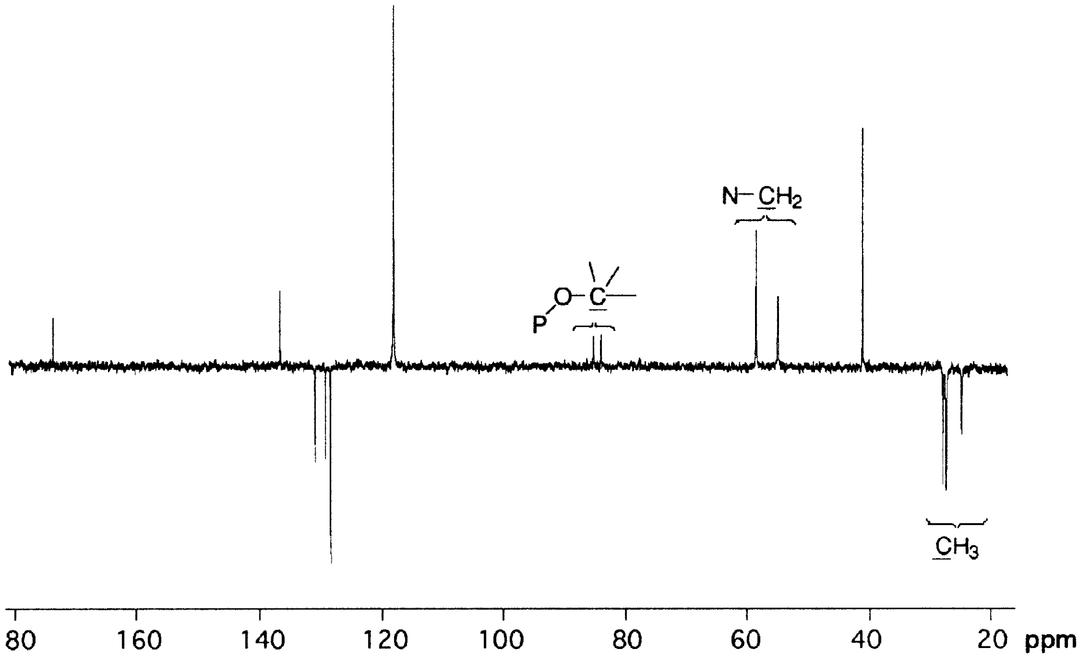
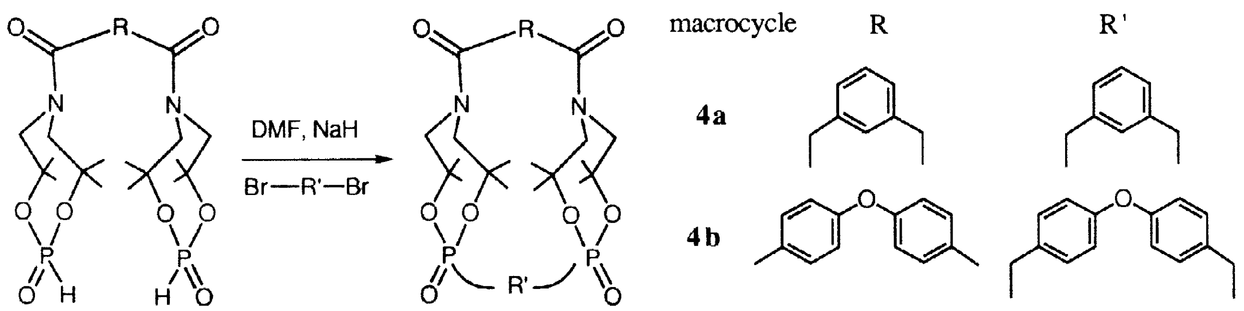


Figure 1: ^{1}H-Decoupled and J-Modulated ^{13}C NMR (62.9 MHz) spectra of podand **3b** in CD_3CN

Macrocycles **4a** and **4b** were synthesized by reacting the two phosphonate functions of the podands with a dibromide, by way of the well-known Michaelis-Becker reaction,[4] according to scheme 3. We chose the podands leading to complexes with the best stability constants and showing the best extraction properties (see Tables 3 and 5)



Scheme 3

To avoid the use of high dilution techniques, the macrocyclization reactions were conducted with the podands **3a** and **3b** bearing rigid spacers. They were reacted with dibromides with the same kinds of spacer.
As for compounds **3a-f** the macrocycles **4a** and **4b** behave, at room temperature, as mirror-symmetry compounds.

Complexation

Complexation sites – Calcium complexes were prepared by mixing equal quantities of podands **3a-f** (or macrocycles **4a-b**) solutions (1.5 10^{-2} mol.dm^{-3}) and perchlorate salts solutions (1.5 10^{-2} mol.dm^{-3}) of the studied cation in acetonitrile. Sites of complexation were located by IR spectroscopy in the solid state (KBr pellets) and by ^{31}P NMR spectroscopy in CH_3CN. Table 1 summarizes the IR spectral data of the carbonyl, phosphoryl and P-H groups of ligands **3a-f** and **4a-b** in their free forms and in their complexes obtained with calcium perchlorate.

Table 1. IR spectral data (KBr, cm^{-1}) of the free ligands and of their complexes with calcium perchlorate.

compd	vibration	Ligand	Complex	Δν $^{a)}$	compd	vibration	Ligand	Complex	Δν $^{a)}$
3a	νC=O	1647	1627	-20	**3e**	νC=O	1660	1635	-25
	νP=O	1269	1239	-30		νP=O	1264	1242	-22
	νP-H	2436	2463	+27		νP-H	2431	2463	+32
3b	νC=O	1654	1629	-25	**3f**	νC=O	1683	1646	-37
	νP=O	1263	1236	-27		νP=O	1262	1232	-30
	νP-H	2437	2462	+25		νP-H	2432	2466	+34
3c	νC=O	1646	1625	-21	**4a**	νC=O	1651	1618	-33
	νP=O	1261	1243	-18		νP=O	1258	1244	-14
	νP-H	2436	2463	+27					
3d	νC=O	1667	1651	-16	**4b**	νC=O	1640	1611	-29
	νP=O	1263	1241	-22		νP=O	1260	1241	-19
	νP-H	2440	2468	+28					

$^{a)}$ Δν = ν(complex) -ν(free ligand)

Complexation with podands and macrocycles shifts to lower frequencies the carbonyl (16-37 cm^{-1}) and the phosphoryl (14-30 cm^{-1}) stretching vibrations. These results may be related to the decrease of the double bond character of the C=O and P=O bonds by coordination of the oxygen donor atoms. A variation of the same magnitude has been observed for alkaline-earth complexes with linear amides by Simon,[5] with macrocyclic polyether tetralactams by Tisnes [6] and with phosphorylated macrocycles by Chaikovskaya.[7] In the case of the PH vibrator, the complexation leads to a displacement towards higher frequencies. This may be explained by a reinforcement of this bond.

Table 2. ^{31}P NMR (CH_3CN) shifts δ (ppm) and coupling constants J (Hz) of the free ligands and of their calcium perchlorate complexes

compd	Ligand		Complex		Δδ $^{a)}$	ΔJ $^{b)}$	compd	Ligand		Complex		Δδ $^{a)}$	ΔJ $^{b)}$
	δ ^{31}P	$^1J_{PH}$	δ ^{31}P	$^1J_{PH}$				δ ^{31}P	$^1J_{PH}$	δ ^{31}P	$^1J_{PH}$		
3a	-5.7	706	-4.5	737	1.2	31	**3e**	-5.8	708	N.D.$^{c)}$			
3b	-5.8	706	-4.8	740	1.0	34	**3f**	-5.8	706	-4.7	745	1.1	39
			-5.3	736	0.5	30							
3c	-5.7	705	-4.9	729	0.8	24	**4a**	16.4		17.1		0.7	
3d	-5.9	707	N.D. ^{c}				**4b**	16.5		16.9		0.4	

$^{a)}$ Δδ = δ(complex) - δ(free ligand); $^{b)}$ ΔJ = $^1J_{PH}$(complex) - $^1J_{PH}$(free ligand); $^{c)}$ N.D. = Not determined (Insolubility of complexes).

The ^{31}P NMR spectra of the complexes were compared to those of the free ligands. As shown in Table 2, we observed for all complexes a deshielding of the signal ($0.4 \leq \Delta\delta \leq 1.2$) and for the complexes issued from the podands a strong increase of the coupling constant $^{1}J_{PH}$ ($24 < \Delta J < 39$ Hz). Analogous observations were made for complexes obtained with other phosphonates and BF_3[8] and with some Ca^{2+} and Mg^{2+} phosphinate complexes.[9]

Stability constants – The stability constants were measured in THF solutions by U.V. spectrophotometry for podands or macrocycle /metallic picrate complexes. This technique is particularly suitable for the measurement of stability constants ranging from 10^2 to 10^5 $l.mol^{-1}$. Furthermore, in a solvent of low polarity (THF), absorption of the metallic picrate shows a bathochromic shift (11 nm $\leq \Delta\lambda \leq$ 25 nm) in the presence of a ligand with Ca^{2+} and Mg^{2+}, resulting from the change of a tight ion pair to a looser ion pair.[10,11] This bathochromic shift is explained by the complexation phenomenon and is not observed with alkaline picrates (Na^+ and K^+).
The computational treatment of the electronic spectra modifications of metal picrates / THF solutions in presence of increasing ligand amounts showed the formation of one (ML) or two (ML and ML_2) complexes with podands **3a-f** and a main ML complex for macrocycles **4a-b**. The so determined constants are gathered in table 3.

In contrast with podands **3a-b** with aromatic spacers, podands **3d-f**, bearing an ether or diether bridge show a good selectivity for calcium as compared to magnesium (the complexes of calcium are about 26 times more stable). Introduction of oxygen atoms in the spacers with an ether bridge increases the stability of the complexes only in the case of the Ca^{2+} cation. This can be explained by the fact that the magnesium ion is small and its coordination with additional oxygen atoms of the ligand would increase steric crowding of the molecule more than the coordination of the larger calcium ion. In the case of **3d-f**, ML_2 complexes were found to be less stable than the ML ones (with $\log K_{ML}/K_{ML2} \sim 2.5$). On the other hand, in the case of **3b**, the stability of the two kinds of complexes (ML and ML_2) are comparable ($\log K_{ML}/K_{ML2} = 1.1$). Finally, the increase of the stability constants going from podands **3b-c** to the corresponding macrocycles **4a-b** is in accord with the well-known macrocyclic effect.[12]

Table 3. Stability constants in THF at 25 °C for 1:1 (K_{ML}) and 1:2 (K_{ML_2}) complexes of Ca^{2+} and Mg^{2+} picrate with ligands **3a-f** and **4a-b**.

compd	Ca^{2+}		Mg^{2+}	
	$\log K_{ML}$ [a)]	$\log K_{ML_2}$ [b)]	$\log K_{ML}$	$\log K_{ML_2}$
3a	2.8	-	2.6	
3b	3.3	2.9	3.1	3.3
3c	3.0	-	2.8	-
3d	5.0	1.9	2.7	-
3e	5.6	2.4	3.0	-
3f	5.1	-	2.7	-
4a	4.6	-	4.3	-
4b	5.1	-	U.C.[c)]	U.C.

[a)] K_{ML} in $l.\ mol^{-1}$ [b)] K_{ML_2} in $l^2.\ mol^{-2}$ is determined by supposing that ML_2 is obtained from ML. [c)] U.C. = uncomputable.

We tried to characterize ML and ML_2 complexes , analyzing by mass spectrometry (ES positive mode) an equimolecular solution of **3b** and calcium picrate in THF. For comparison, we also studied the ES mass spectrum of an equimolecular solution of **3b** and hexahydrated calcium perchlorate in acetonitrile. Table 4 summarizes the results obtained. It must be noticed that the species are the same as detected by UV spectrophotometry or by ES mass spectrometry. Moreover, the results are identical whatever the counterion or the solvent may be.

Table 4. m/z and relative abundance of positive ions observed for THF solutions of **3b** complexes with calcium picrate or perchlorate

$Ca(Pic)_2$/**3b**			$Ca(ClO_4)_2$, 6 H_2O/**3b**		
principal ions	m/z	relative abundance	principal ions	m/z	relative abundance
L[a] H^+	573.3	10	LH^+	573.1	90
L Na^+	595.3	100			
LK^+ (or L-1 Ca^+)	611	12	LK^+ (or L-1 Ca^+)	611	100
Pic[b], LCa^+	840.1	16	ClO_4, LCa^+	711	65
L Ca^{++}	306.1	43			
Pic, L_2Ca^+	1412.6	2	ClO_4, L_2Ca^+	1283.3	36
L_2Ca^{++}	592.2	15	L_2Ca^{++}	592.2	50

[a] L = **3b**; [b] Pic = picrate

Liquid - liquid extraction – Calcium and magnesium picrate salts were extracted from an aqueous phase to a chloroformic one by formation of complexes with podands **3b-f** and macrocycles **4a-b.**

Whereas the metallic picrate is, in absence of ligands only in the aqueous phase , in presence of ligands it is contained both in the organic and in the aqueous phase. The decrease in absorbance of the picrate ion in the aqueous phase was monitored by UV-VIS spectrophotometry. The extraction percentages (E%) and the lipophilicities, as log P,[13] of the five podands, the two macrocycles and two reference compounds are reported in table 5.

Table 5. Extraction percentage (E%) of Ca^{2+} and Mg^{2+} picrates by podands **3b-f** and macrocycles **4a-b**[a].

compound	Ca^{2+}	Mg^{2+}	log P [b]
3b	5	3	1.45
3c	3.5	3	1.5
3d	3	2	0.5
3e	4	2	0.5
3f	3.5	0	1.2
4a	16	2	2.3
4b	32.5	5	2.7
ETH 1001 [c]	38	3	6.2
18-C-6 [d]	26.2	2.5	0

[a] Extraction conditions: temperature 25.0±0.2°C; aqueous phase (0.25 mL): [picrate] = 1.5 10^{-2}M; organic phase ($CHCl_3$, 0.25 mL): [ligand] = 1.5 10^{-2} M. E% = 100 (1 - AD/ε.l. C_0) with A = absorbance; D = dilution factor for the different aliquots; ε molar extinction coefficient; l: width of the cell; C_0: initial picrate concentration.

[b] Lipophilicity measured by RPTLC technique. [c] $[picrate]_{aq}$ = 6.5 10^{-4}M; $[ligand]_{CH_2Cl_2}$ = 1.5 10^{-3} M according to ref 14. [d] $[picrate]_{aq}$ = $[ligand]_{CH_2Cl_2}$ = 3 10^{-3} M according to 15.

It can be noticed that the podands **3b-f** with low lipophilicity are poor extractants. Although their stability constants are higher, podands **3d-f** show extracting properties of the same order of magnitude as podands **3b-c**. On the other hand, macrocycles **4a-b** with stability constants of the same order as the **3d-f** podands, show extracting properties which can be compared to those of ETH 1001[14] and 18-C-6[15] As in the case of these last compounds, a good selectivity of Ca^{2+} towards Mg^{2+} was observed. This selectivity may be partly attributed to a much higher hydration energy in the case of magnesium ($\Delta G^0 = 1897$ kJ mole $^{-1}$)[16] as compared to calcium ($\Delta G^0 = 1584$ kJ mole $^{-1}$).[16] Extraction of magnesium requires therefore a ligand possessing a great affinity towards this ion , which is not the case for our type of compounds.

The main conclusion of this extraction study is the significant increase of calcium extraction by the macrocycles compared to the podands.

Cation transport through a liquid membrane - The pronounced interaction of our compounds with Ca^{2+} ions prompted us to study their possible activity as ionophores. We investigated the Ca^{2+} migration through a $CHCl_3$ liquid membrane system , under the influence of two podands and one macrocycle.

The cell used for this study is divided into three parts separated by two fluoropore membranes. A schematic mechanism of the process is given in figure 2.

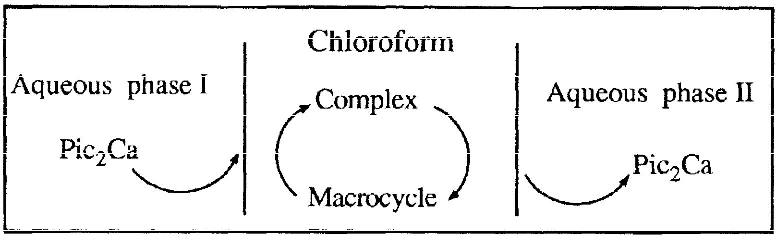


Figure 2 : Schematic mechanism of the transport phenomenon

At the first interface, cation complexation leads to a neutral complex which can diffuse across the membrane. At the second interface the reverse process occurs the metal ion loss regenerating the carrying ligand. The transport of Ca^{2+} was followed by the analysis of aliquots withdrawn from the aqueous phases. Table 6 summarizes the results obtained.

Table 6. Transport percentages (T%) and Transport rates of Ca^{2+} with podands **3b-c** and macrocycle **4b**

compound	$[Pic_2Ca]$ [a) aq. phase I	$[Pic_2Ca]$ [b) aq.phase II	T% [c)	Transport rate [d) (10^{-7} mol.h^{-1})
3b	12.3 mM	0.10 mM	0.8	0.45
3c	13.0 mM	0.09 mM	0.7	0.41
4b	14.3 mM	0.8 mM	5.7	3.7

Transport condition : Temperature 25.0 ± 0.2 °C; aqueous phase I and II and $CHCl_3$ phase: 11 mL. [a) initial concentration ; [b) concentration after 24h ; [c) T% = $[Pic_2Ca]_{II}$ / $[Pic_2Ca]_{I}$. 100; [d) Transport rate = $[Pic_2Ca]_{II}$. v / 24h (v = 11 mL)

The weak extraction percentages (E%) observed in the case of the podands (Table 5) explain their poor performances as carriers. However, the rather high extraction value of **4b** (E% = 32) allowed us to expect better carrying properties than those observed (T% = 5.7). The high formation constant ($\log K_{ML} = 5.1$) observed in

THF for the complex **4b/Pic$_2$Ca** probably explains this result, the complex formed remaining in the chloroformic membrane.

In conclusion , it is difficult to predict the ionophoric efficiency of our compounds , but it seems that the correlation is better using the stability constants than the extraction percentages as previously observed. [17,18]

EXPERIMENTAL SECTION

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrophotometer in KBr disks. NMR spectra were recorded in the case of ^{31}P (32.44 MHz) on a Bruker AC 80 spectrometer, ^{1}H (250 MHz) and ^{13}C (62.89 MHz) unless otherwise indicated on a Bruker AC 250 spectrometer and are reported in parts per million from internal H_3PO_4 85% for ^{31}P and Me_4Si for ^{1}H and ^{13}C on the δ scale. Data are reported in the following order: chemical shift, spin multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant, integration and assignment. UV-Vis spectra were monitored on a Perkin-Elmer Lambda 17 spectrophotometer coupled with an Epson PC AX Elmer computer. Mass spectra (MS) were performed with a NERMAG R10-10C spectrometer using the Fast Atom Bombardment (FAB, GLY matrix) or Electro Spray (ES) techniques. Elemental analyses were carried out by the "Service Commun de Microanalyse-Ecole de Chimie" in Toulouse. Commercially available chemicals were used without further purification: isophtalic acid **2a**; 1,3-phenylene diacetic acid **2b**; 4,4'-oxybis(benzoïc acid) **2c**; 2,2'-oxydiacetic acid **2d**; 1,2-phenylene dioxydiacetic acid **2f** and calcium perchlorate. The following compounds were prepared as described in the literature: 4,4,8,8-tetramethyl-1,3-dioxa-6-aza-2-phosphabicyclo[3.3.0] octane **1**[19,20] , 4,4'-di(bromomethyl)diphenyl oxide [21] 1,2-ethylenedioxydiacetic acid **2e**[22] , calcium and magnesium picrates [23]. Solvents were purified prior to use by standard methods.

Preparation of podands 3(a-f)

To a stirred solution of the bicyclophosphane **1** (5 mmol) in dry DMF (10 mL) was added under argon a solution of diacid (2.5 mmol). The mixture was stirred for 1 hour. The solution was then flash evaporated.

Compound **3a**: **3a** was recrystallized from toluene in 72% yield; white crystals, m.p. = 173 °C. IR cm^{-1} (KBr): $\nu_{C=O}$ = 1647 ; $\nu_{P=O}$ = 1262 ; $\nu_{P\text{-}H}$ = 2436. ^{31}P NMR (DMF) δ: -5.4 (d,$^1J_{PH}$ = 706 Hz); ^{1}H NMR($CDCl_3$) δ: 1.39, 1.46, 1.59 (s, 24H, CH_3); 3.6-4.2 (m, 8H, NCH_2); 6.87 (d, $^1J_{HP}$ = 708,6Hz, 2H, PH); 7.3 (s, 1H, H_{ar}); 7.4 (d, $^3J_{HH}$ = 7.1 Hz,2H, H_{ar}); 7.5 (d, $^3J_{HH}$ = 7.1 Hz, 1H,H_{ar}); ^{13}C NMR ($CDCl_3$) δ: 27.97, 27.45, 27.20, 25.80 (CH_3); 53.08 and 59 (NCH_2); 84.74 (d, $^2J_{COP}$ = 9.5 Hz, $(CH_3)_2\underline{C}$-O); 83.26 (d, $^2J_{COP}$ = 9.5 Hz, $(CH_3)_2\underline{C}$-O); 124.89, 127.71, 129.29, 137.03 (C_{ar}); 172.80 (C=O). Anal. calcd for $C_{24}H_{38}N_2O_8P_2$: C, 52.94; H, 7.03; N, 5.14. Found: C, 52.12; H, 7.28; N, 5.13.

Compound **3**: **3b** was recrystallized from toluene affording white crystals in 72% yield; m.p. = 98 °C; IR cm^{-1} (KBr): $\nu_{C=O}$ = 1654 ; $\nu_{P=O}$ = 1263 ; $\nu_{P\text{-}H}$ = 2436. ^{31}P NMR δ: (DMF) -5.6 (d,$^1J_{PH}$ = 705 Hz) ; ^{1}H NMR ($CDCl_3$) δ: 1.50,1.44,1.38,1.34 (s, 24H, CH_3); 3.71 (s, 4H, $C(O)C\underline{H_2}Ph$); 3.62-4.01 (m, 8H, NCH_2); 6.80 (d, $^1J_{HP}$ = 712 Hz,2H, HP); 7.08 (s, 1H, H_{ar}); 7.09 (d, $^3J_{HH}$ = 6.9 Hz, 2H, H_{ar}); 7.27 (d, $^3J_{HH}$ = 6.4 Hz, 1H,H_{ar}). ^{13}C NMR ($CDCl_3$) δ: 25.30, 27.40, 27.59, 28.00 (CH_3); 41.52($Ph\text{-}\underline{C}H_2C(O)$)); 54.79 and 58.36 ($NCH_2$); 83.10 (d, $^2J_{COP}$ = 9.4 Hz, $(CH_3)_2\underline{C}$-O); 85.20 (d, $^2J_{COP}$ = 9.3 Hz, $(CH_3)_2\underline{C}$-O); 127.70, 129.40, 129.48, 135.10(C_{ar}); 172.50 (C=O). Anal. calcd for $C_{26}H_{42}N_2O_8P_2$. 0.3 H_2O: C,54.03; H, 7.43; N, 4.85. Found: C, 53.98; H, 7.41; N, 4.87.

Compound **3c**: **3c** was recrystallized from toluene/ petroleum ether mixture (- 30°C) affording white crystals in 77% yield; m.p. = 108-109 °C; IR cm^{-1} (KBr): $\nu_{C=O}$ = 1646 ; $\nu_{P=O}$ = 1261 ; $\nu_{P\text{-}H}$ = 2436. ^{31}P NMR (DMF) δ: -5.6 (d, $^1J_{PH}$ = 705 Hz; ^{1}H NMR ($CDCl_3$) δ: 1.25, 1.30, 1.46, 1.60 (s, 24H, CH_3); 3.65-4.18 (m, 8H, NCH_2); 6.89 (d, $^1J_{HP}$ = 707 Hz, 2H, HP); 7.04 (d, $^3J_{HH}$ = 8.2 Hz, 4H, H_{ar}); 7.36(d, $^3J_{HH}$ = 8.7 Hz, 4H, H_{ar}); ^{13}C NMR (75MHz) ($CDCl_3$) δ: 26.12, 26.88, 27.58, 27.88 (CH_3); 52.86 and 58.66 (NCH_2); 83.62 (d,$^2J_{COP}$ = 9.5 Hz, $(CH_3)_2\underline{C}$-O); 84.74 (d,$^2J_{COP}$ = 9.4 Hz, $(CH_3)_2\underline{C}$-O); 119.19, 128.81, 131.49, 157.70(C_{ar}); 173.33 (C=O). Anal.cald for $C_{30}H_{42}N_2O_9P_2$: C, 56.60; H, 6.65; N, 4.40. Found: C, 56.40; H, 6.91; N, 4.07

Compound **3d**: **3d** was precipitated in petroleum ether as a white powder with 77% yield ; m.p. = 132 °C; IR cm^{-1} (KBr): $\nu_{C=O}$ = 1667 ; $\nu_{P=O}$ = 1264 ; $\nu_{P\text{-}H}$ = 2436.^{31}P NMR (DMF) δ: -5.6 (d, $^1J_{PH}$ = 706 Hz); ^{1}H NMR ($CDCl_3$) δ: 1.28, 1.34, 1.48, 1.50 (s, 24H, CH_3); 3.60-4.09(m, 8H, NCH_2); 4.26 (s, 4H, $C(O)CH_2O$); 6.81

(d, $^1J_{HP}$ = 712 Hz, 2H, HP);^{13}C NMR ($CDCl_3$) δ: 25.14, 27.46, 27.57, 27.99 (CH_3); 55.18 and 57.45 (NCH_2); 70.10 ($C(O)\underline{C}H_2O$); 83.20 (d, $^2J_{COP}$ = 9.3 Hz, $(CH_3)_2\underline{C}$-O); 84.75 (d, $^2J_{COP}$ = 9.2 Hz, $(CH_3)_2\underline{C}$-O); 170.47 (C=O). Anal. calcd for $C_{20}H_{38}N_2O_9P_2$: C, 46.87; H, 7.47; N, 5.47.Found: C, 46.64; H, 7.99; N, 5.50.

Compound **3e**: **3e** was precipitated in petroleum ether as a yellow powder in 77% yield, m.p. = 148 °C; IR cm^{-1} (KBr): $\nu_{C=O}$ = 1660 ; $\nu_{P=O}$ = 1264 ; $\nu_{P\text{-}H}$ = 2431. ^{31}P NMR (DMF) δ: -5.6 (d, $^1J_{PH}$ = 706 Hz); ^{1}H NMR ($CDCl_3$) δ: 1.27, 1.34, 1.46, 1.49 (s, 24H, CH_3); 3.63-4.07 (m, 8H, NCH_2); 3.70 (s, 4H, O-$C\underline{H_2}$-$C\underline{H_2}$-O); 4.21 (s, 4H, $C(O)CH_2O$); 6.80 (d, $^1J_{HP}$ = 711.5 Hz, 2H, HP); ^{13}C NMR ($CDCl_3$) δ: 25.28, 27.36, 27.47, 27.96 (CH_3); 54.59 and 57.14 (NCH_2); 68.44 (O-$\underline{C}H_2$-C=O); 70.48 (s, O-$\underline{C}H_2$-CH_2-O); 83.26 (d, $^2J_{COP}$ = 9.3 Hz, $(CH_3)_2\underline{C}$-O); 84.86 (d, $^2J_{COP}$ = 9.4 Hz, $CH_3)_2\underline{C}$-O); 170.80 (C=O).

Compound **3f**: **3f** was recrystallized in toluene affording white crystals in 85% yield ; m.p. = 161 °C; IR cm^{-1} (KBr): $\nu_{C=O}$ = 1683 ; $\nu_{P=O}$ = 1262 ; $\nu_{P\text{-}H}$ = 2432.5 ; ^{31}P NMR ($CDCl_3$) δ: -4.5 (d, $^1J_{PH}$ = 728 Hz); ^{1}H NMR ($CDCl_3$) δ: 1.34, 1.48, 1.50,1.54 (s, 24H, CH_3); 3.70-4.09 (m, 8H, NCH_2); 6.90 (d, $^3J_{HH}$ = 7 Hz, 2H, H_{ar}); 6.92 (d, $^3J_{HH}$ = 5.3 Hz, 2H, H_{ar}) ; 4.80 (s, 4H, $C(O)CH_2O$); 6.84 (d, $^1J_{HP}$ = 711.2 Hz, 2H,HP); ^{13}C NMR ($CDCl_3$) δ: 25.35, 27.38, 28.05 (CH_3); 54.67 and 57.27 (NCH_2); 83.33 (d, $^2J_{COP}$ = 9.3 Hz, $(CH_3)_2\underline{C}$-O); 84.84 (d, $^2J_{COP}$ = 9.3 Hz, $CH_3)_2\underline{C}$-O);88.59 (O-$\underline{C}H_2C(O)$) 115.08, 122.81, 147.82 (C_{ar}); 169.78 (C=O). Anal. calcd for $C_{26}H_{42}N_2O_{10}P_2$. 0.1 toluene: C, 52.25; H, 7.03; N, 4.56. Found: C, 52.17; H, 7.01; N, 4.53.

Preparation of macrocycles 4(a-b)

To a stirred suspension of NaH (2.4 eq.) in 6 mL of dry DMF was added a solution of 1 equivalent of the podand in 6 mL of dry DMF. The reaction mixture was stirred under argon protection at -10 °C during one hour. The dibromide solution (1 eq. in 12 mL of dry DMF) was then introduced dropwise. After completion of the reaction, the DMF was evaporated. The residue was extracted three times with $H_2O/CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and concentrated to 10 mL. Compound **4a** was recristallized at -30° from $CHCl_3$/ petroleum ether and **4b** from $CHCl_3$/isopropylic ether

Compound **4a**: Yield : 40%; m.p. = 172 °C; IR cm^{-1} (KBr): $\nu_{C=O}$ = 1654 ; $\nu_{P=O}$ = 1259 ; ^{31}P NMR (CH_3CN) δ: 17.1 (t, $^2J_{PH}$ = 20,4 Hz); ^{1}H NMR ($CDCl_3$) δ: 1.37-1.28 (s large, 24H, CH_3); 3.01 (d, $^2J_{HP}$ = 20.8 Hz, 4H, $P(O)CH_2Ph$); 3.68 (s, 4H, $C(O)C\underline{H_2}Ph$); 3.71-4.22 (m, 8H, NCH_2); 7.25-7.08 (m, 8H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ: 22.86, 25.90, 26.85, 27.87 (CH_3); 36.15 (d, J_{PC} = 144.3 Hz, $P(O)CH_2Ph$); 40.92 (s, Ph-CH_2-C(O)); 57.35 and 59.55 (NCH_2); 82.26 (d, $^2J_{COP}$ = 10.4 Hz, $(CH_3)_2\underline{C}$-O); 84.44 (d, $^2J_{COP}$ = 9.8 Hz, $(CH_3)_2\underline{C}$-O); 127.70, 128.33, 129.21, 129.63, 131.51, 135.12 (C_{ar}); 172.90 (C=O). MS (FAB, GLY) m/e 675 [MH^+] (10%). Anal. calcd for $C_{34}H_{48}N_2O_8P_2$: C, 60.52; H, 7.17; N, 4.15. Found: C, 60.44; H, 7.09; N, 4.14.

Compound **4b**: Yield : 40%; m.p. = 190 °C. ^{31}P NMR ($CHCl_3$) δ: 18.1 (t, $^2J_{PH}$ = 19.8 Hz); ^{1}H NMR ($CDCl_3$) δ: 1.26-1.47 (s large, 24H, CH_3); 3.06 (d, $^2J_{HP}$ = 21.5 Hz, 4H, $P(O)C\underline{H_2}Ph$); 3.50-4.45 (m, 12H, NCH_2) + $C(O)C\underline{H_2}Ph$); 6.90-7.33 (m, 16H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ: 26.67, 27.01, 27.82, 27.88 (CH_3); 35.59 (d, J_{PC} = 142.9 Hz, $P(O)\underline{C}H_2Ph$); 57.35 and 59.55 (NCH_2); 82.26(d, $^2J_{COP}$ = 10.4 Hz, $(CH_3)_2\underline{C}$-O); 84.44 (d, $^2J_{COP}$ = 9.8 Hz, $(CH_3)_2\underline{C}$-O); 118.83, 119.02, 126.55, 128.79, 131.07, 131.75, 156.15, 157.38 (C_{ar}) 173.25 (C=O). MS (FAB, GLY) m/e 831[MH^+] (15%). Anal. calcd for $C_{44}H_{52}N_2O_{10}P_2$: C, 63.61; H, 6.31; N, 3.37. Found: C, 63.38; H, 6.29; N, 3.40.

Determination of formation constants. The formation constants for ion-ligand complexes were determined by UV spectrophotometry in tetrahydrofuran solutions following Smid.[10] The sequential addition of aliquots of a ligand to a 3 x 10^{-5} M solution of calcium picrate in THF (ρ = ligand/salt = 0 → 10-17) induces large spectral changes in the 280-450 nm wavelength range. The calculation method uses the STAR/FA and the STAR programs developped by Beltran[24] for studying ionic equilibria from spectrophotometric data. STAR is a non-linear regression program for the refinement of complex formation constants. The mass balance equations of the system were solved from the given model and the total concentration of the components. STAR gives several statistical characteristic parameters to test the reliability of the regression process. The most important parameter is the standard deviation of the absorbances (A) which must be compared to the instrumental error of the spectrophotometer 0.002; an acceptable fit is S(A) < 0.005. Other parameter: the distribution of residuals is examined by the Skewness, Kurtosis and Pearson's χ^2 tests; for a Gaussian distribution these values should be equal to 0.3 and < 12.6 (for six degrees of freedom at the 95% confidence level) respectively. The Hamilton R factor (%) indicates the relative fit (≤1%). The STAR/FA program is used to determine the number of absorbing species in solution by factor analysis of the absorbance data matrix. In all cases the characteristic parameters were very good. In THF, the maxima of the main optical absorption band of alkaline-earth picrates are found at λ_{max} = 322.5 nm (ε_M = 24 700 $cm^{-1}.M^{-1}$) for $MgPic_2$ and 333.1 nm (ε_M = 29700 $cm^{-1}.M^{-1}$) for $CaPic_2$.

Lipophilicity determination. Lipophilicities of the ligands were determined by their TLC retention R_F. The TLC system is calibrated with a set of reference compounds of known lipophilicities with detection at 254 nm. TLC was performed with Macherey-Nagel Sil RP8W reversed-phase plates and the solvent system used consisted of methanol-water (8-2 by volume).

Extraction experiments. The method used was essentially that of Frensdorff[25] and Cram.[26] They were carried out by adding a $CHCl_3$ solution of the ligand (0.015 M, 0.25 mL) to an aqueous solution of metal picrate (0.015 M, 0.25 mL). After stirring the mixture for 15 h, the aqueous phase was separated and the percent of picrate salt extracted (E%) was determined by UV spectrophotometry as previously related. The aqueous extinction coefficient were used : 28000 $cm^{-1}.M^{-1}$ for $CaPic_2$ and 24700 $cm^{-1}.M^{-1}$ for $MgPic_2$ at λ_{max} = 354 nm.

Transport experiments. They were performed at 25 °C in a new apparatus which will be described later in a full paper. The cell used is divided into three parts of 11 mL each separated by two Fluoropore membranes of 175 μm thickness and stirred independently and synchronously at 550 rpm. The ionophore, dissolved in $CHCl_3$, was placed in the middle compartment and the two aqueous phases were placed in the other parts. The transport rates gathered in Table 3 were calculated from the quantity of ion transported after 24 h in the aqueous phase II.

REFERENCES

1. Bellan, J.; Chap, H.; Gaigé, B.; Grevy, J.M.; Lamandé, L.; Manechez, D.; Renard, P.; Simon, M.F. Brevet I.N.P.I. **1995**, n° 95-04667.
2. Lamandé, L.; Grévy, J.M.; Houalla, D.; Cazaux, L.; Bellan, J. *Tetrahedron Lett.* **1995**, *36,* 8201.
3. Houalla, D.; El Abed, K.; Bounja, Z.; Wolf, R.; Jaud, J. *Phosphorus, Sulfur and Silicon* **1992**, *69*, 13.
4. Michaelis, A.; Becker,T. *Ber. Dtsch. Chem. Ges.* **1897**, *30,* 1003.
5. Kirsch, N.M.L.; Simon, W. *Helv. Chimica Acta* **1976**, *59*, 357.
6. Pigot, T.; Duriez, M.C.; Cazaux, L.; Picard, C.; Tisnès, P. *J. Chem. Soc Perkin Trans.* **1993**, 221.
7. Raevskii, O.A.; Zubareva, V.E.; Solotnov, A.F.; Kudra, T.N.; Tochilkina, L.N.; Chaikovskaya, A.A. *J.Gen. Chem. USSR*, **1986**, *56*, 925.
8. Elegant, L.; Wolf, R.; Azzaro, M. *Bull. Soc. Chim. Françe*, **1969**, *12*, 4269.
9. Spitz, F.R.; Cabral, J.; Haake, P. *J. Am. Chem. Soc.* **1986**, *108,* 2802.
10. a) Wong, K.H.; Bourgoin, M.; Smid, J. J. Chem. Soc., Chem. Commun. **1974**, 715. b) Bourgoin, M.; Wong, K.H.; Hui, J.Y.; Smid, J. *J. Am. Chem. Soc.* **1975**, *97*, 3462.
11. Wada, F.; Wada, Y.; Goto, T.; Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1980**, 1189 and references therein.
12. Cabbiness, D.K.; Margerum, D.W. *J. Am. Chem. Soc.* **1969**, *91*, 6540.
13. a) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525.b) Ellgehausen, H.; D'Hondt, C.; Fuerer, R. *Pestic. Sci.* **1981**, *12*, 219.
14. Inoue, Y.; Ouchi, M.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 525.
15. Kirsch, N.N.L.; Funck, R.J.J.; Simon, W. *Helv. Chim. Acta* **1978**, *61*, 2019.
16. Dietrich, B. *J. Chem. Educ.* **1985**, *57*, 954.
17. Lamb, J.D.; Christensen, J.J.; Oscarson, J.L.; Nielsen, B.L.; Asay, B.W.; Izatt, R.M. *J. Am. Chem. Soc.* **1980**, *102*, 6820.
18. Hernandez, J.C.; Traflon, J.E.; Gokel, G.W. *Tetrahedron Lett.* **1991**, *32,* 6269.
19. Bonningue, C.; Houalla, D.; Wolf, R.; Jaud, J. *J. Chem. Soc. Perkin Trans. II* , **1983**, 773.
20. Huang, Y.; Sopchik, A.E.; Arif, A.M.; Bentrude, W.G. *Heteroatom Chem.* **1993**, *4(2/3)* , 271.
21. Doedens , J.D.; Rosenbrock, E.H. US Patent **1961**, n° 3004072 (*Chem. Abstr.* **1962**, *57*,3363a).
22. Dietrich, B.; Lehn, J.M.; Sauvage, J.P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629.
23. Silberrad, O.; Phillips, H.A. *J. Chem. Soc.* **1908**, *93*, 474.
24. Beltran, J.L.; Codony, R.; Prat, M.D. *Anal. Chim. Acta* **1993**, *276*, 441.
25. Frensdorf, H.K. *J. Am. Chem. Soc.* **1971**, *93*, 4684.
26. Moore, S.S.; Tarnowski, T.L.; Newcomb, M.; Cram, D.J. *J. Am. Chem. Soc.* **1977**, *99*, 6398.