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SYNTHESIS AND IONOPHORE PROPERTIES OF A SERIES OF NEW TETRAPYRAZOLIC MACROCYCLES

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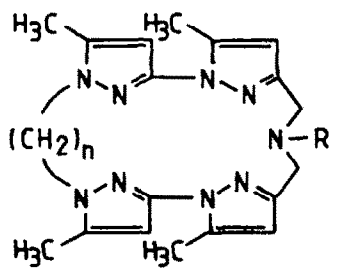
Abstract: The synthesis of several macrocycles containing two bipyrazolic subunits, with different cavity sizes and with donor-group-bearing side arms attached, is reported. Their alkali cation binding ability has been studied from two aspects : extraction and transport through an artificial liquid membrane. Macrocycles described here show a high selectivity towards Li^+ and Na^+ cations; furthermore one of them is remarkably well adapted to extract selectively and to transport efficiently the lithium cation in competitive conditions.

Oxygen donor macrocycles such as crown ethers are well known to give strong complexes almost exclusively with alkali and alkaline earth ions. By contrast, saturated and unsaturated polyazamacrocycles show a high affinity for transition metal ions.[1,2] Macrocycles containing nitrogen heterocyclic units concern mainly porphyrins and phthalocyanines[2] but some of them incorporating pyridine units have also been described.[1a,b,f,g] These all complex transition metal cations but lately macropolycyclic ligands containing 2,2'-bipyridine and 1,10-phenanthroline subunits have been reported to give stable sodium[3a,c] or lithium[3b,c] ion complexes. Some studies have been done on mixed O and N containing macrocycles[1a,b,f,4] but none of these has high affinity for alkali and transition metal ions.

For some time we have been interested in polypyrazolic macrocycles: the novelty of these structures containing nitrogen donor sites is that they can complex alkali ions[5-8] as well as transition metal ions such as ruthenium(II).[9,10]

In this paper we describe the synthesis and behaviour of a series of new macrocycles containing two bidentate bipyrazolic entities towards alkali cations (their complexation with transition metal ions will be reported elsewhere).

The following molecules have been obtained (Py= Pyridine, Pz= Pyrazine):



	n	R
1	1	CH_2CH_2Py
2a	2	CH_3
2b	2	CH_2CH_2Py
2c	2	CH_2CH_2OPy
2d	2	CH_2CH_2OPz
3a	3	CH_3
3b	3	CH_2CH_2Py

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These macrocyles have been prepared with two ideas in mind:

- to obtain a series of macrocycles with different cavity sizes in order to obtain the best stability and selectivity properties.

- to allow introduction of a mobile chain containing a donor heteroatom which could participate in the complexation of metal ions. It has been found that a donor atom in a side chain of lariat ethers increases the binding ability of the macrocycle.[11] Furthermore, structures with side arms attached at a nitrogen (N-pivot lariat ethers) instead of a carbon (C-pivot lariat ethers) have stronger binding properties[11b] because of a greater flexibility, allowing the donor site to have the best binding position. The authors have shown that the notion of cavity size is not absolute in these flexible systems, but rather the nature and total number of donor atoms as well as the potential for optimal organization of the macrocycle aroud the metal ion.[12]

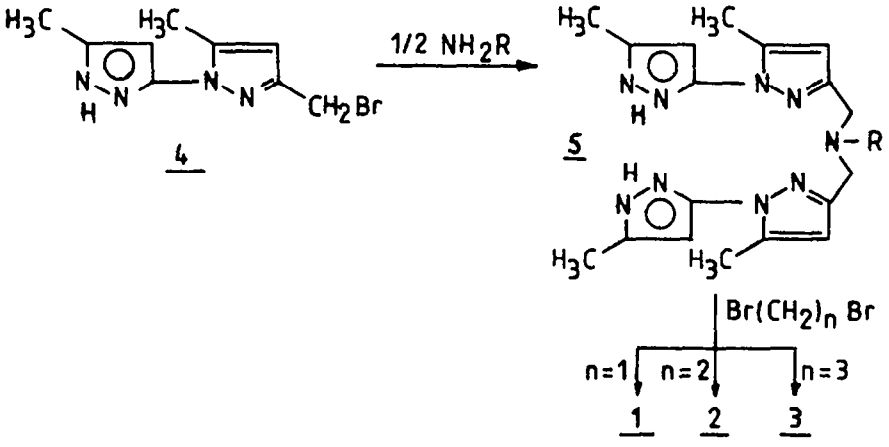
The new macrocycles we have obtained, have been studied from two aspects: extraction and transport of alkali cations through an artificial membrane both individually and in competitive conditions as this last case represents the real use of ionophores.[13]

RESULTS and DISCUSSION

- Ligand syntheses

Ligands 1 to 3 were prepared as described in scheme 1: the tetrapyrazolic opened structure 5 was obtained by reaction of the bipyrazole 4[5] with the appropriate primary amine. Condensation of compound 5 with a dibromoalkane $Br(CH_2)_nBr$ was carried out at infinite dilution to favour cyclisation over linear condensation and by transfer catalysis in order to favour substitution on the nitrogen atoms α to the methyl group.

Scheme 1



The first reaction was done in one step (R= CH_2CH_2Py, CH_2CH_2OPy, CH_2CH_2OPz) or two steps (R =CH_3) depending on the nature of R (see experimental part). In the second reaction, the expected macrocycle 1-3 was obtained; however when dibromoethane was used, a linear derivative 8 was also produced. Its formation can be explained by the very basic conditions of the phase transfer catalysis reaction (see scheme 2) leading to the dianion 6 which undergoes a first N-alkylation by $Br(CH_2)_2Br$ to give 7. At this stage two competitive reactions may occur: an intramolecular substitution (full arrows) or an elimination (dotted arrows) leading respectively to the macrocycle 2 or to the divinylic compound 8. Yields obtained for compounds 2 and 8 are given in table I. These results may be discussed in terms of the nature of the amine and dibromoalkane: for a given value of n, macrocycle yields are higher when R is different from CH_3, that is to say when R is bulkier. For cyclisation to occur easily, the two bipyrazolic units must be as close as possible; when R is a methyl group this conformation must be disfavoured in order to avoid interactions between these two bulky bipyrazolic arms. In the case of R =CH_2CH_2Py or CH_2CH_2OPy the chain is too bulky and the configuration in which the two bipyrazolic arms are close is more favoured. In the

case of the ethano-bridged structure, these same steric hindrance problems explain why the intramolecular cyclisation leading to the macrocycle 2 is favoured over the elimination reaction giving the divinylic compound 8, when R is bulkier.

Scheme 2

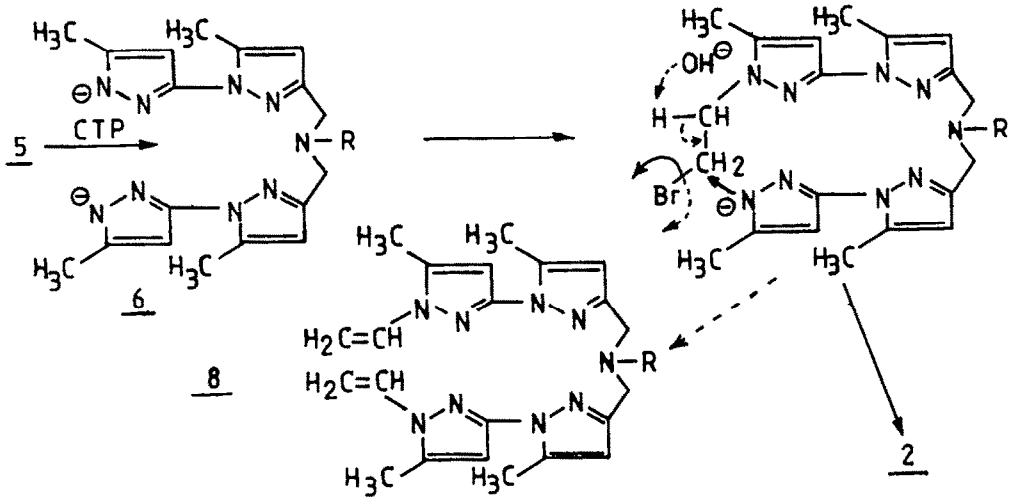


Table I: Compounds obtained by reaction of the opened tetrapyrazole 5 with a dibromoalkane.

R	Dibromoalkane	Macrocycle		Divinylic compound	
CH_3	$Br(CH_2)_2Br$	2a	26%	8(R=CH_3)	40%
CH_3	$Br(CH_2)_3Br$	3a	40%		
CH_2CH_2Py	$Br(CH_2)Br$	1	20%		
CH_2CH_2Py	$Br(CH_2)_2Br$	2b	42%	8(R=CH_2CH_2Py)	30%
CH_2CH_2Py	$Br(CH_2)_3Br$	3b	70%		
CH_2CH_2Py	$Br(CH_2)_2Br$	2c	40%	8(R=CH_2CH_2OPy)	28%
CH_2CH_2OPz	$Br(CH_2)_2Br$	2d	40%	8(R=CH_2CH_2OPz)	32%

Complexing studies

- *Liquid-liquid extraction of individual alkali cations*

We have used this method in order to compare the relative abilities of macrocycles 1 to 3 towards extraction of the alkali cations Li^+, Na^+, K^+, Cs^+. Metal picrates were extracted into the organic phase by complex formation with the macrocycle; the decrease in absorbance of the picrate in the aqueous phase was followed by UV spectroscopy. The percentage limits of extraction are given in table II.

Table II: Alkali extracted percentages

M^+	2a	2b	2c	2d	3a	3b
Li^+	18	45	33	18	43	50
Na^+	4	9	18	6	25	34
K^+	0	1	0	0	1	1
Cs^+	0	0	0	0	0	1

In order to show that the macrocycle protonation does not occur in the presence of metal picrates , we have detrmined the extracted cation percentage in the case of macrocycle 2b by atomic absorption measurements: the same results as those reported in table II were found.

All the experiments done on macrocyle 1 and on the opened structure 5 show no detectable extraction with any of the alkali cations. These observations show that the complexation observed for the macrocyclic structures 2 and 3 is due to the presence of an electronegative cavity and not to chelating behaviour, and that the cavity is too small to incorporate the metal in the case of macrocycle 1.

Results in table II show the lack of affinity of macrocycles 2 and 3 for potassium and cesium ions, undoubtably because of their oversized ionic radii. A second result is that better extraction percentages are obtained with Li^+ than with Na^+ for all the macrocycles though the difference is less obvious in the case of the larger, more flexible macrocycles 3a and 3b which can accomodate both metal ions.

- *Extractibility of Li^+*

In the case of structures 3a and 3b, the Li^+ extraction values are very close, whereas for 2a and 2b they are quite different. This implies the participation of the pyridinic side arm in the binding of structure 2 but not in the case of macrocycles 3. This behaviour and the smaller extraction percentage observed for 3a than for 2a, can both be explained by the difference in cavity sizes. Macrocycles 3 have a cavity size and a flexibility such that they easily bind the lithium ion which is enclosed by the ring donors (and to a smaller extent, Na^+) with a low contribution from the side arm. Another factor which may diminish the influence of the arm is the necessary deformation of the macrocycle if pyridine binds the cation. In such a situation the two central protons of the propane chain of the macrocycle are oriented towards the inside of the cavity causing severe steric hindrance. In the case of macrocycles 2, their smaller cavity size and their reduced flexibility do not allow strong binding with the sodium cation and also do not favour a complete enclosure of the lithium ion inside the cavity, and thus the complex is strongly stabilized by side arm pyridine binding. Such a structure, if it produces a macrocycle deformation, does not cause any steric hindrance inside the cavity as was the case for 3. An increase of the side arm length as in 2c and 2d does not seem to favour Li^+ complexation in comparison with 2b. In the case of 2d the binding ability is even lower, undoubtably because of the weaker donor character of the bound nitrogen in pyrazine.

- *Extractibility of Na^+*

Obviously macrocycles 2 and 3 are not good complexing agents for Na^+ for reasons of cavity size.

- *Competitive liquid-liquid extraction measurements*

We have chosen macrocycle 2b which seems to have good selective properties towards Li^+. By competitive extraction from aqueous solutions of Li^+, Na^+, K^+ and Cs^+ nitrates with a CH_2Cl_2 solution of macrocycle 2b, we have obtained the following percentages of extraction using atomic absorption technique: Li^+ 6.67%, Na^+ 0.23%, K^+ and Cs^+ 0%. These low values compared to those measured by separate cation extraction may be explained in terms of the use of nitrate salts which are less lipophilic than picrates. The Li^+/Na^+ selectivity ratio of 15.5 obtained in these competitive conditions, shows the good lithium selectivity of 2b. Several structures have been described as extracting Li^+ selectively from aqueous solutions: crown-ethers[14-18], cryptands[19], quadridentate amido-ethers[20] and a diazaphosphacycloundecane[21]. The best of them, a crown-ether bearing carboxylic substituents[17], has a selectivity ratio close to the one found for 2b. The advantage of our structure is that the extraction percentage does not depend on the pH, at least at pH > 7 : for instance Li^+ extraction is not modified in absence of metal hydroxide (replacement of alkali hydroxide by alkali nitrate in the aqueous phase).

- *Proton NMR studies*

Three kinds of information may be obtained if this method is used in alkali complexation studies: complex stoichiometry, complexing power of ligands, and ligand conformation within the complex.[22, 23] Because of the affinity of macrocycles 2 and 3 for Li^+,

as previously observed, we have chosen to study these types of complexes using proton NMR spectroscopy. In table III the proton chemical shifts are given for macrocycles 2 and 3, both free and complexed with LiBr. In the case of crown-ethers and cryptands, complexation shifts have been attributed to electric-field effects of the cation, anion and to conformational contributions.[22] These same effects must operate in the case of the macrocycle complexes here. Most of the observed shifts are downfield; the protons undergoing the highest shifts are those of the ethane chain in 2a-d demonstrating the macrocycle deformation as complexation occurs, especially when the side arm participates in the complexation. These results corroborate those deduced from liquid-liquid extraction experiments.

Table III: ^1H Chemical shifts of macrocycles 1 to 3 both free and complexed with LiBr in $CDCl_3$. Complexation shifts are given in parentheses.

Compound	H pyr	CH_3 pyr	$CH_2N_{sp^3}$	$CH_2N_{sp^2}$	CH_2 arm	Pyridine
1	5.87 6.10	2.30 2.40	3.60	6.12	2.93	8.45(α), 7.00(β) 7.48(γ), 7.20(δ)
2a	5.89 6.09	2.15 2.26	3.62s	4.16s	2.59s	
+LiBr excess	6.05(+0.16) 6.08(-0.01)	2.45(+0.30) 2.45(+0.19)	3.60s (-0.02)	4.73s (+0.57)	~2.40(-0.19)	
2b	5.87 6.10	2.17 2.23	3.70s	4.11s	3.15s	8.50(α), 7.06(β) 7.53(γ), 7.23(δ)
+LiBr excess	5.88(+0.01) 5.97(-0.13)	2.36(+0.19) 2.47(+0.24)	3.73s (+0.03)	4.94s (+0.83)	3.13m (-0.02)	8.40(α), 7.10(β) 7.47(γ), 7.10(δ)
2c	5.87 6.11	2.23 2.30	3.80s	4.13s	3.20(CH_2N) 4.63(CH_2O)	8.12(α), 7.05(β) 7.53(γ), 6.75(δ)
+LiBr excess	5.84(-0.03) 5.88(-0.23)	2.27(+0.04) 2.36(+0.06)	3.76s (-0.04)	4.74s (+0.61)	3.05(-0.15) 4.25(-0.38)	8.05(α), 6.80(β) 7.53(γ), 6.62(δ)
2d	5.85 6.08	2.17 2.23	3.77s	4.10s	3.20(CH_2N) 4.67(CH_2O)	7.98(2H) 8.20(1H)
+LiBr excess	5.94(+0.09) 5.97(-0.11)	2.33(+0.16) 2.36(+0.13)	3.85b (+0.08)	4.74s (+0.64)	3.13(-0.07) 4.39(-0.28)	8.00(3H)
3a	5.89 5.97	2.20 2.87	3.63s	4.07t	2.65s	
+LiBr excess	6.16(+0.27) 6.20(+0.23)	2.47(+0.27) 2.51(+0.14)	3.58s (-0.05)	4.28t (+0.21)	2.47(-0.18)	
3b	5.80 5.95	2.09 2.30	3.77s	4.02t	3.17s	8.57(α), 7.12(β) 7.58(γ), 7.28(δ)
+LiBr excess	5.83(+0.03) 5.83(-0.12)	2.36(+0.27) 2.36(+0.06)	3.64s (-0.13)	4.13t (+0.11)	2.94m (-0.23)	8.10(α), 6.85(β) 7.25(γ), 6.85(δ)

We have chosen to examine the behaviour of the protons belonging to the ethane chain in 2a-d more closely. Their chemical shifts undergo downfield shifts until one equivalent of LiBr has been added; further addition of LiBr does not cause any significative shift. Such a result shows that macrocycles 2a-d form 1/1 complexes with Li^+.[21,23b]

Spectra of the same macrocycles at room temperature show a broadening of some peaks mainly those arising from the CH_2 protons of the ethane chain. We have studied their behaviour as a function of the temperature for macrocycles 2a, 2b and 2d in $CDCl_3$ solutions, after addition of 0.5 equivalent LiBr in order to form solutions containing the ligand and its Li^+ complex in a 1/1 ratio. In the case of macrocycle 2a, decreasing the temperature to -55°C does not modify the spectrum except for a slight broadening of the CH_2 ethanic signals. For macrocycle 2b, all the signals are broadened as temperature decreases, then they split into two peaks which become sharp at low temperature. This dynamic phenomenon may be easily followed by observing the signals given by the CH_2 protons in the ethane chain and the CH pyrazolic ones. It is possible to calculate the activation energy of the process at the coalescence temperature, $\Delta G_c^{\neq}$=13.8 kcal/mole.

In the case of 2d the same phenomenon occurs but it is more difficult to calculate ΔG_C^* because of the proximity or the overlapping of several signals; however the activation energy may be estimated to be 12 kcal/mole. The behaviour observed for macrocycles 2, shows that two entities are present, whose exchange is slowed down as the temperature decreases. This phenomenon may have four possible causes:

- a cation exchange $[Li^+Mac] \rightleftharpoons Li^+ + [Mac]$
- a side arm dissociation
- a macrocyclic conformational change
- an inversion of the macrocyclic sp^3 nitrogen

The two last hypotheses may be ruled out as the dynamic process does not occur in the case of macrocycle 2a, at least in the same energy field as for 2b and 2d. A complexation-decomplexation mechanism of the side arm only (second hypothesis), cannot be considered as a slight broadening has been observed for macrocycle 2a. Thus the observed phenomenon corresponding to the first hypothesis, is a slowing down of the Li^+ exchange, allowing observation of separate signals belonging to both free and 1/1 complexed ligand at low temperature. We have verified that the differences in chemical shifts observed for macrocyclic protons in the free or 1/1 complexed macrocycle are only due to temperature effects when determined in the molecule alone at ambient temperature or in the case of the frozen exchange at low temperature.

- *Transport of alkali cations through a liquid membrane*

For transport experiments we have chosen to use artificial liquid membranes, first to allow comparison with our previous experiments,[5-8] and secondly because literature transport studies are reported under conditions which are too different to be comparable.

We have studied the carrier abilities of macrocycles 2 and 3 towards Li^+ and Na^+ as their extraction percentages have been found to be high enough to undertake such experiments. The transport was carried out through a CH_2Cl_2 membrane separating two aqueous solutions as described previously.[5] In a first series of experiments we studied the transport of the Li^+ and Na^+ cations individually from an aqueous solution which contained a mixture of metal picrate and nitrate; the transported coanion will be the picrate because of its lipophilic properties.[26] This allows a good incorporation in the organic phase containing the macrocycle studied. Transport rates and selectivity ratios are given in table IV.

Table IV: Transport rate values in 10^{-6} mole/h and selectivity ratios in non-competitive conditions.

	2a	2b	2c	2d	3a	3b
V_{Li^+}	0.62	0.54	0.62	0.33	0.58	0.62
V_{Na^+}	0.38	0.32	0.43	0.50	0.25	0.60
Selectivity transport $S=V_{Li^+}/V_{Na^+}$	1.6	1.7	1.4	0.7	2.3	1.0

All the macrocycles 2 and 3 show high rates of transport for Li^+ and Na^+ cations but with no real selectivity between them: in the best case the selectivity ratio does not exceed 2. In order to develop a better approach to the ionophore properties of these same macrocycles, we examined their transport in competitive conditions. For these experiments we used the atomic absorption technique to evaluate the effective transport of a Li^+ and Na^+ cation mixture, whether as picrate or nitrate salts. All the observed transport rates and selectivity ratios are given in table V. When picrates are used, these values are higher than those determinated in non-competitive conditions: selectivity ratios vary between 1 and 3 for all the macrocycles, except for 2b which shows a higher selectivity ratio of 8 in favour of Li^+. In measurements made with nitrates as counterions, transport rates through the membrane are lower but selectivity ratios are

higher especially that belonging to structure 2b which reaches 22. Structures described as good Li^+ ionophores may be classified in several categories: crown-ethers[16,17,27-30] with or without ionisable substituents; cryptands;[31] acyclic polyether carboxylic acids;[32] acyclic diamides[20,33] and organometallic ligands.[34] It is difficult to compare the efficiency of macrocycle 2b as lithium carrier with these literature results because of differing experimental conditions: transport experiments have been carried out through liquid membranes, planar or vesicular lipid bilayers and polymeric PVC membranes. As far as liquid membranes are concerned, our result is comparable to the best described.[17] The design of new synthetic ionophores with lithium ion selectivity is of great interest because of important potential applications such as neutral carriers for ion-selective electrodes.[15,16,28,33]

Table V: Transport rate values and selectivity ratios in competitive conditions.

	Alkali picrates		Alkali nitrates	
	Transport rate 10^{-6} mole/h	Selectivity $S=V_{Li^+}/V_{Na^+}$	Transport rate 10^{-6} mole/h	Selectivity $S=V_{Li^+}/V_{Na^+}$
2a	$Li^+ \rightarrow 2.2$ $Na^+ \rightarrow 0.78$	2.8	$Li^+ \rightarrow 0.1$ $Na^+ \rightarrow 0.01$	10.0
2b	$Li^+ \rightarrow 4.5$ $Na^+ \rightarrow 0.54$	8.3	$Li^+ \rightarrow 1.08$ $Na^+ \rightarrow 0.05$	21.6
2c	$Li^+ \rightarrow 2.5$ $Na^+ \rightarrow 1.13$	2.2	$Li^+ \rightarrow 0.53$ $Na^+ \rightarrow 0.09$	5.9
2d	$Li^+ \rightarrow 1.29$ $Na^+ \rightarrow 0.64$	2.0	$Li^+ \rightarrow 0.4$ $Na^+ \rightarrow 0.08$	5.0
3a	$Li^+ \rightarrow 2.2$ $Na^+ \rightarrow 1.36$	1.6	$Li^+ \rightarrow 0.66$ $Na^+ \rightarrow 0.19$	3.5
3b	$Li^+ \rightarrow 1.93$ $Na^+ \rightarrow 1.48$	1.3	$Li^+ \rightarrow 1.65$ $Na^+ \rightarrow 0.84$	2.0

CONCLUSIONS

We have prepared a series of tetrapyrazolic macrocycles which have the unsual aptitude for formation of complexes with alkali and transition metal cations, due to the presence of four donor sp^2 nitrogen atoms in the cavity. We have reported the influence of the cavity size and of a pyridine-bearing side arm on their ability to complex alkali cations. Most of the macrocycles clearly show a better aptitude to complex Li^+ and Na^+ ions than K^+ or Cs^+: one of the macrocycles, 2b, is especially well adapted to complex the Li^+ ion: it shows high Li^+/Na^+ selectivity ratios in competitive extraction and transport experiments and a slow Li^+ exchange rate in the dissociation process.

EXPERIMENTAL

^1H NMR spectra have been obtained in $CDCl_3$ with Varian EM390 or HA100 spectrometers using Me_4Si as internal reference; chemical shifts are given in ppm; the following abbreviations are used: s (singlet), d (doublet), t (triplet and b (broad). Mass spectra have been recorded on a Jeol JMS DX-333 mass spectrometer. Melting points are uncorrected. Elemental analyses have been performed by the Central Microanalytical Service of the CNRS; all compounds described give analytical results with a maximum error of 0.3%.

- Extraction and transport experiments in non-competitive conditions

- *Extraction:* The cyclindric reaction cell (50mm in diameter) contained a spectroscopic grade CH_2Cl_2 solution (30ml) of the ligand ($7x10^{-5}$M) and an aqueous solution (30ml) of metal picrate ($7x10^{-5}$M) and hydroxide (0.1M). The organic phase was magnetically stirred (a 25mm long magnetic bar, 5mm in diameter, was rotated at one turn/s); the complexation was followed by measuring the picrate anion concentration in the aqueous phase by UV spectroscopy at 355 nm.

- *Transport:* The apparatus described by Ramdani[5] has been used (a= 8mm, b= 28mm, c= 50mm). Source phase: aqueous solution (10ml) of metal picrate (10^{-3}M) and nitrate (10^{-1}M). Membrane phase: 50 ml of a CH_2Cl_2 solution of the macrocycle ($7x10^{-5}$M). Receiving phase: bidistilled water

(20ml). The appearance of picrate anion in the third phase was followed by UV spectroscopy.

- Extraction and transport in competitive conditions

They were performed using the atomic absorption technique on a Varian 1275 spectrophotometer.

- *Extraction:* each alkali salt had a concentration of 10^{-1}M in the aqueous phase and the macrocycle a concentration of $7x10^{-4}$M in the CH_2Cl_2 solution.

- *Transport:* experiments were carried out from aqueous solutions of Li^+ and Na^+ picrate mixture ($5x10^{-3}$M in each) or nitrate mixture (10^{-1}M in each). The macrocycle had a concentration of $7x10^{-4}$M in CH_2Cl_2.

- Syntheses

The 3-bromomethyl 3'(5'),5-dimethyl 1,5'(3')-pyrazolylpyrazole 4 has been prepared as described in the literature.[5,35]

- *(2-aminoethoxy) 2-pyridine*

A mixture of 2-hydroxyethylamine (0.1 mole) and of sodium hydride (0.1 mole) in anhydrous dioxane was refluxed for 30 mn. After cooling of the solution down to room temperature, the 2-chloropyridine (0.1 mole) was added and the mixture refluxed for 18 hours and then concentrated. The residue was suspended in water and extracted with CH_2Cl_2. Organic extracts were dried over Na_2SO_4 and concentrated to obtain an oil; distillation gives the pure compound (83% yield), b.p. 70-72°C/0.6mm Hg; ^{1}H NMR ($CDCl_3$) δ 2.93 (N-CH_2), 4.20 (O-CH_2), 8.00 (pyridine H-α), 6.70 (pyridine H-β), 7.44 (pyridine H-γ), 6.63 (pyridine H-δ).

- *(2-aminoethoxy) 2-pyrazine*

This compound was prepared in the same way as the (2-aminoethoxy) 2-pyridine (80% yield) b.p. 66-68°C/0.6mm Hg; ^{1}H NMR ($CDCl_3$) δ 3.00 (N-CH_2), 4.29 (O-CH_2), 7.98 and 8.15 (pyrazine).

- *Synthesis of 5 (R=CH_3)*

In the first step the 3-(methylamino)methyl 3'(5'),5-dimethyl 1,5'(3')-pyrazolylpyrazole was obtained by bubbling a great excess of methylamine into an ethereal solution of the 3-bromomethylpyrazolylpyazole 4. The methylamine hydrobromide precipitate was removed by filtration. After evaporation to dryness, the residue was used directly in the next reaction. ^{1}H NMR ($CDCl_3$) δ 2.25 [3'(5')-CH_3] , 2.42 (5-CH_3), 2.50 (N-CH_3), 3.84 (N-CH_2), 6.15 and 6.19 (4- and 4'-H), 7.82 (NH).

In the second step an equimolar amount of compound 4 was added to a solution of the 3-(methylamino)methyl 3'(5'),5-dimethyl 1,5'(3')-pyrazolylpyrazole, in the presence of triethylamine. The mixture was stirred at room temperature for 8 hours. The triethylamine hydrobromide formed was removed by filtration; the filtrate was dried and the residue purified by chromatography on alumina (eluant: CH_2Cl_2/C_2H_5OH 90/10) (75% yield) m.p. 157-158°C; ^{1}H NMR ($CDCl_3$) δ 2.17 [3'(5')-CH_3] , 2.39 (5-CH_3), 2.30 (N-CH_3), 3.60 (N-CH_2), 6.11 (4- and 4'-H).

- *Synthesis of 5 (R= CH_2CH_2Py or CH_2CH_2OPy or CH_2CH_2OPz)*

These tetrapyrazoles were obtained in one step by stirring a THF solution (100 ml) of the bipyrazole 4 ($8x10^{-3}$ mole), the appropriate amine ($4x10^{-3}$ mole) and triethylamine ($8x10^{-3}$ mole) at room temperature for 2 days. The triethylamine hydrobromide was removed by filtration and the filtrate dried . The residue was used directly in the cyclisation reaction.

5 (R=CH_2CH_2Py): ^{1}H NMR ($CDCl_3$) δ 2.10 [3'(5')-CH_3], 2.33 (5-CH_3), 6.00 and 6.06 (4- and 4'-H, 3.77 (N-CH_2), 2.98 (side arm CH_2).

5 (R=CH_2CH_2OPy): ^{1}H NMR ($CDCl_3$) δ 2.21 and 2.23 [3'(5')-CH_3 and 5-CH_3], 5.85 and 5.93 (4- and 4'-H), 3.63 (N-CH_2), 2.89 (side arm N-CH_2), 4.28 (side arm O-CH_2), 7.92 (pyridine H-α), 6.53 (pyridine H-β), 7.35 (pyridine H-γ), 6.53 (pyridine H-δ).

5 (R=CH_2CH_2OPz): ^{1}H NMR ($CDCl_3$) δ 2.17 (5-CH_3), 2.27 [3'(5')-CH_3], 6.00 and 6.07 (4- and 4'-H), 3.70 (N-CH_2), 2.98 (side arm N-CH_2), 4.43 (side arm O-CH_2), 7.95 (pyrazine).

- *Synthesis of macrocycle 1*

Cyclisation of 5(R=CH_2CH_2Py) was carried out using phase transfer catalysis conditions: a toluene solution of dibromomethane ($5x10^{-3}$ mole) was added to a dilute toluene solution of 5 ($5x10^{-3}$ mole in 500 ml of toluene) in the presence of a concentrated NaOH solution (2g in 2 ml of water) and a catalytic amount of tetrabutylammonium bromide. The mixture was refluxed for 8 hours, then filtered and the filtrate evaporated. The residue was chromatographed on alumina using a mixture of CH_2Cl_2/C_2H_5OH 92/8 as eluant (20% yield), m.p. 110-112°C.

- *Synthesis of macrocycles 2*

The same procedure as for macrocycle 1 was used, except for reflux times and chromatography conditions which are reported below. This cyclisation using 1,2-dibromoethane leads to the formation of macrocycles 2 but also to divinylic compounds 8 (see theoretical section).

- *Macrocycle 2a*

Reflux time: 12 hours; eluant used in chromatography: $CH_2Cl_2/CH_3CO_2Et/C_2H_5OH$, 56/40/4. 2a (26% yield), m.p. 180-182°C; 8(R=CH_3) (40% yied), oil, ^{1}H NMR δ 2.25 (5- and 5'-CH_3), 6.17 (4-H), 6.33 (4'-H), 2.50 (N-CH_3), 3.52 (N-CH_2), 6.87 (vinylic =CH) J_{cis}= 8.2 Hz and J_{trans}= 15.0 Hz, 4.73 and 5.60 (vinylic =CH_2).

- *Macrocycle 2b*

Reflux time: 10 hours; eluant used in chromatography: CH_2Cl_2/C_2H_5OH 96/4. 2b (42% yield), m.p. 140-142°C; 8(R=CH_2CH_2Py) (30% yield), oil, ^{1}H NMR ($CDCl_3$) δ 2.20 (5-CH_3), 2.47 (5'-CH_3), 6.03 (4-H), 6.30 (4'-H), 3.73 (N-CH_2), 2.93 (side arm CH_2), 6.85 (vinylic =CH) J_{cis}= 8.4 Hz and J_{trans}= 15.2 Hz, 4.72 (vinylic =CH_2).

- *Macrocycle 2c*

Reflux time: 8 hours; eluant used in chromatography: CH_2Cl_2/C_2H_5OH 96/4. 2c (40% yield), m.p. 90-92°C; 8(R=CH_2CH_2OPy) (28% yield), oil, ^{1}H NMR ($CDCl_3$) δ 2.30 (5-CH_3), 2.48 (5'-CH_3), 6.08 (4-H), 6.31 (4'-H), 3.75 (N-CH_2), 2.96 (side arm N-CH_2), 4.44 (side arm O-CH_2). 6,87 (vinylic =CH) J_{cis}= 8.4 Hz and J_{trans}= 15.5 Hz, 4.75 and 5.60 (vinylic =CH_2).

- *Macrocycle 2d*

Reflux time: 8 hours; eluant used in chromatography: CH_2Cl_2/C_2H_5OH 96/4.
2d (40% yield), m.p. 88-90°C; 8(R=CH_2CH_2OPz) (32% yield), oil, ^1H NMR ($CDCl_3$) δ 2.36 (5-CH_3), 2.46 (5'-CH_3), 6.13 (4-H), 6.33 (4'-H), 3.77 (N-CH_2), 2.95 (side arm N-CH_2), 4.42 (side arm O-CH_2), 6.92 (vinylic =CH) J_{cis}= 8.2 Hz and J_{trans}= 15.6 Hz, 4.78 and 5.62 (vinylic =CH_2).

- *Synthesis of macrocycles 3*

Cyclisation of 5 with 1,2-dibromopropane was carried out following the same procedure as described previously for 1 and 2. The exact conditions are reported below.

- *Macrocycle 3a*

Reflux time: 6 hours; eluant for chromatography: $CH_2Cl_2/CH_3CO_2Et/C_2H_5OH$ 56/40/4.
3a (40% yield), m.p. 178-180°C.

- *Macrocycle 3b*

Reflux time: 3 hours; eluant for chromatography: CH_2Cl_2/C_2H_5OH 96/4.
3b (70% yield), m.p. 180-182°C.

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