New functionalised C,C-bipyrazoles. Synthesis and cation binding properties

Ahmed Attayibat[a], Smaail Radi[a]*, Yahya Lekchiri[b], Abdelkrim Ramdani[a], Brahim Hacht[c], Michel Morcellet[d], Maryse Bacquet[d] and Stéphanie Willai[d]

[a]*Département de Chimie, Faculté des Sciences, Université Med I, 60 000 Oujda, Morocco*

[b]*Département de Biologie, Faculté des Sciences, Université Med I, 60 000 Oujda, Morocco*

[c]*Laboratoire de Spéciation et de Surveillance de la Pollution en Méditerranée, Département de Chimie, Faculté des Sciences, Université Med I, 60 000 Oujda, Morocco*

[d]*Laboratoire de Chimie Macromoléculaire, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France*

The synthesis of two new C,C-bipyrazoles ligands with a side-arm bearing a functionalised donor-group is reported. The complexation properties of these compounds towards bivalent metal ions (Hg^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}) and alkaline metal ions (Li^+, Na^+, K^+) was studied by a liquid–liquid extraction process and the extracted cation percentage was determined by atomic absorption measurements.

Keywords: C,C-Bipyrazoles, liquid–liquid extraction, cations

Pyrazoles have been of particular interest in recent years. In coordination chemistry, polydentate pyrazolic receptors are well known for their ability to complex not only with alkali cations[1-5] but also to form stable complexes with transition metals.[6-9] These complexes are so stable that it is often difficult to obtain the free macrocycles from them.

In our recent work, a series of acyclic pyrazole oligomers containing one, two, three or four pyrazole rings were prepared and demonstrated to extract only transition metal cations[10-13] whereas macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals.[14,15] However, complexation studies of bibyrazole compounds are less well known.

In this context, we developed new functionalised C, C-bipyrazoles (Fig. 1) and studied their complexing properties towards bivalent metal ions (Hg^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}) and alkaline metal ions (Li^+, Na^+, K^+) using a liquid–liquid extraction process. The relative capacities of these receptors in extracting these cations were determined by the measurement of extracted cation percentage by atomic absorption.

Results and discussion

Our strategy was to develop a simple and high yielding procedure, in few steps, to prepare the desired bipyrazolic ligands. The results of our investigation are given below (Scheme 1). The synthesis of compound **1** in its ketoenol form was carried out from ethyl-1,5-dimethyl-1H-pyrazole-3-carboxylate using the method described in the literature.[9] Condensation of **1** with 2-hydroxethylhydrazine in ethanol[16] leads to a mixture of two isomers **4** (9%) and **5** (40%) which were separated by silica column chromatography. The minor product **4** was equally obtained in good yield in another way. Thus, the action of monohydrate hydrazine with **1** in ethanol give bipyrazole **2** in 90% yield. Alkylation of compound **2** with ethylbromoacetate in THF was carried out under solid-liquid phase transfer catalysis to favour the α-isomer.[17] Thus, one isolated major product **3** in 48% yield as the α-isomer was formed. Compound **3** was then converted by $LiAlH_4$ in THF to give a 72% yield of hydroxy-product **4**.

In order to show a possible contribution of a donor oxygen in a side chain on the cation binding, we prepared another similar bipyrazole compound **6**[18] without a donor atom in a side arm. Compound **6** was obtained by alkylation of **2** with methyl iodide under transfer catalysis in 70% yield as the α-isolated major product.

It has been found that a donor atom in a side chain of lariat ethers increases the binding ability of the macrocycle.[19-21] 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 because of greater flexibility, allowing the donor site to have the best binding position.[22]

Liquid–liquid extraction of individual cations

In order to compare the relative capabilities of ligands **4**, **5** and **6** in extracting Hg^{2+}, Cd^{2+}, Pb^{2+}, Cu^{2+}, Zn^{2+}, Li^+, Na^+ and K^+ cations we used liquid-liquid extraction of individual cations. Metal nitrates were extracted into the organic layer by complex formation with bipyrazolic receptors. The percentage limits of extraction were determined by atomic absorption. The results are given in Table 1.

Results in Table 1 show that in analogy to our previous work[10-15] in which acyclic oligo-pyrazoles extract only the transition metal cations when the macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals, we demonstrate also here an affinity of these new acyclic C,C-bipyrazoles only with the transition metal cations, with no complexation being observed toward alkali cations.

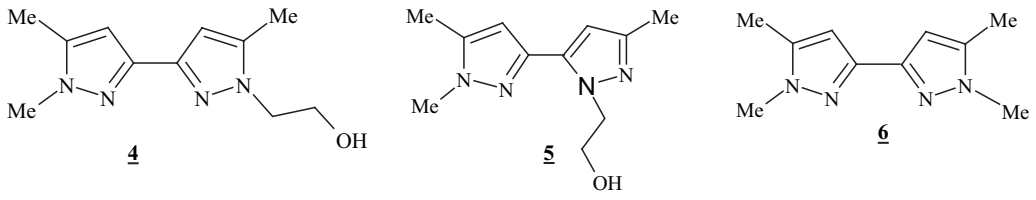
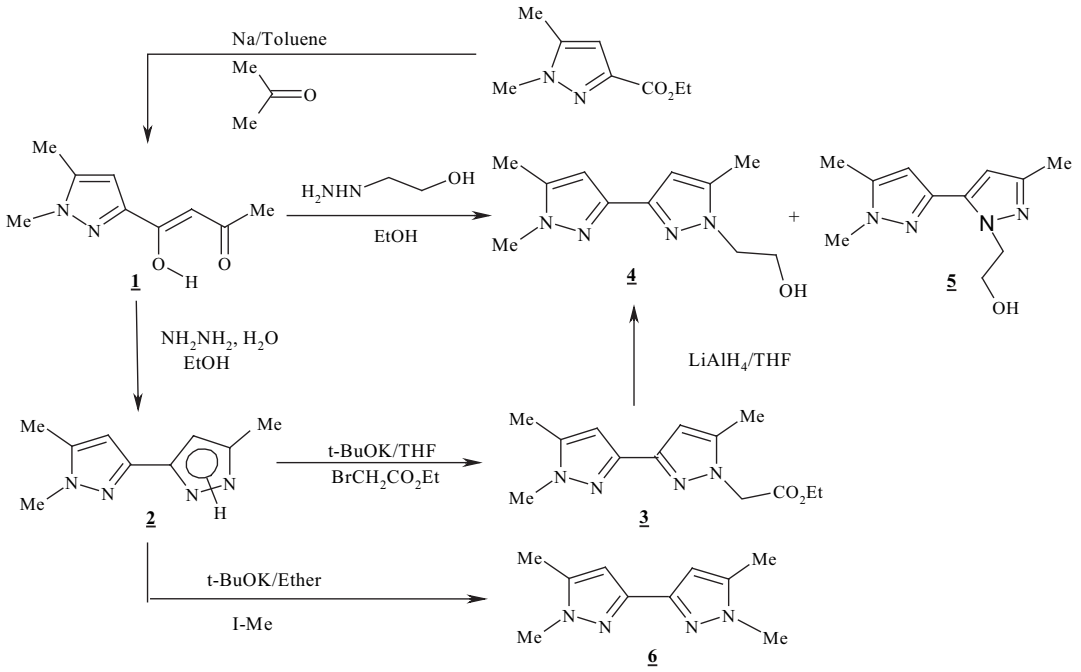


Fig. 1

* Correspondent. E-mail: radi_smaail@yahoo.fr



Scheme 1

Table 1 Yields of extraction of various metals by C,C-bipyrazolic ligands **4**, **5** and **6**

Ligand	Hg^{2+}	Cd^{2+}	Pb^{2+}	Cu^{2+}	Zn^{2+}	Li^{+}	Na^{+}	K^{+}
4	62	7	26	18	7	0	0	0
5	32	3	28	23	0	0	0	0
6	65	9	27	17	6	0	0	0

The affinity of these hosts is especially high for mercury. This is not surprising if the high donor properties of nitrogen towards this metal are considered.

We notice for all transition metals under study that the extraction yield is practically the same for **4** with a side-arm bearing a functionalised donor-group and **6** without a donor-group in a side-arm. Indeed, we can conclude here, contrary to the literature,[19-22] that the complexation was due to the bipyrazole nitrogens without contribution of a side arm.

We also notice for compound **5** a decrease in complexation ability towards Hg^{2+}, Cd^{2+} and Zn^{2+} probably due to the *chelating* effect. Indeed, in most cases, bipyrazole groups act as *convergent* bidentate donors. The term *convergent* refers to the nitrogen donor atoms coordinating to the same metal centre. The β-isomer (compound **5**) forms a six-membered ring with the complexated metal cation, while the α-isomer (Compounds **4** and **6**) leads to a five-membered ring, which is thus one of several such rings when the whole complex is considered. It is well known[23] that five-membered ring chelates are more stable than six-membered and four-membered ones. However, the observed complexation of **5** towards Pb^{2+} and Cu^{2+} is not surprising since the fragment N-(2-hydroxyethyl)-3,5-dimethylpyrazole may itself act as a didentate N,O ligand in coordination compounds with some transition metal ions.[24]

In conclusion, metal cations and macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals, while the new acyclic bipyrazole ligands reported here only form complexes with transition metal cations. They do not complex alkali metal cations at all.

Experimental

Synthesis of bipyrazole **1**: To a suspension of sodium (0.5 g; 21.7 mmol) in 50 ml of anhydrous toluene, was slowly added ethyl-1,5-dimethyl-1H-pyrazole-3-carboxylate (2.016 g; 12 mmol) in 25 ml of toluene; then acetone (1.2 g; 20.6 mmol) in 10 ml of toluene was added at 0°C. The resulting mixture was stirred at room temperature for two days. The precipitate formed was filtered, washed with toluene, dissolved in water and neutralised with acetic acid to pH = 5. After extraction with CH_2Cl_2, the organic layer was dried over anhydrous sodium sulfate and concentrated in *vacuo*. The obtained residue was chromatographed on silica using CH_2Cl_2 as eluant to give a 30% yield of **1** as a white solid. M.p. = 82–84°C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H, –CH_3); 2.33 (s, 3H, –CH_3); 3.76 (s, 3H, N–CH_3); 6.29 (s, 1H, = HC–OH). 6.54 (s, 1H, Pz–H); *m/z*: 180 $(M)^+$.

Synthesis of bipyrazole 2: To an ethanolic solution (120 ml) of 1-[3,5-dimethyl-1H-pyrazol-3-yl]butan-1,3-dione (1.9 g; 10.5 mmol) was added hydrazine monohydrate (1.05 g; 21.1 mmol) in 40 ml of ethanol. Then, the reaction mixture was stirred at room temperature for 2 h. The solvent was eliminated under reduced pressure and to the residue obtained was added 30 ml of distilled water. A white precipate was observed and was filtered, washed with distilled water and dried to give a 90% yield of **2** as a white solid. M.p. = 154–157°C; ^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3H, –CH_3); 2.30 (s, 3H, –CH_3); 3.80 (s, 3H, N–CH_3); 6.28 (s, 2H, Pz–H); Anal. Calc. for $C_9H_{12}N_4$: C 61.4, H 6.8, N 31.8, Found: C 61.6, H 7.0, N 31.3; *m/z*: 177 (MH^+).

Synthesis of bipyrazole **3**: A mixture of **2** (1 g; 5.68 mmol) and potassium tert-butoxide (0.85 g; 7.59 mmol) in 80 ml of anhydrous THF was refluxed for 1 h. After cooling at 0°C, a solution of ethylbromoacetate (1.3 g; 7.78 mmol) in 20 ml of THF was slowly added. The reaction mixture was stirred for 5 h at room temperature then filtered and the solvent was evaporated to dryness. The obtained residue was purified on alumina using dichloromethane as eluant to give a 48% yield of **3** as a white solid. M.p. = 124–126°C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, 3H, CH_2–$\underline{CH_3}$, J = 7.13 Hz), 2.24 (s, 6H, –CH_3); 3.76 (s, 3H, N–CH_3); 4.18(q, 2H, –$\underline{CH_2}$–CH_3, J = 7.13 Hz); 4.85 (s, 2H, N–CH_2–); 6.27 (s, 1H, Pz–H); 6.33 (s, 1H, Pz–H); ^{13}C NMR ($CDCl_3$) δ: 11.45 (CH_3); 11.57 (CH_3); 14.50 (–CH_2–$\underline{CH_3}$); 36.44 (N–CH_3); 51.14 (N–CH_2–); 62.02 (–$\underline{CH_2}$–CH_3); 103.26 (C–H); 103.9 (C–H); 139.57 (C); 140.55 (C); 144.94 (C); 146.32 (C); 168.25 (C=O); Anal. Calc. for $C_{13}H_{18}N_4O_2$: C 59.5, H 6.9, N 21.4, Found: C 59.6, H 7.0, N 21.1; *m/z*: 263 (MH^+).

Synthesis of bipyrazole **4**: To a solution of $LiAlH_4$ (200 mg; 5.26 mmol) in 10 ml of anhydrous THF, cooled at 0°C, was slowly added bipyrazole **3** (0.63 g; 2.40 mmol) in 20 ml of THF. The mixture was stirred under reflux for 2 h. After cooling, water (0.2 ml), 15% aqueous sodium hydroxide (0.2 ml) and then water (0.6 ml) were added successively to the mixture at 0°C. The solid material was filtered and the residue was washed with hot THF. The filtrate and THF washings were concentrated under reduced pressure to give a 72% yield of **4** as a white solid. M.p. = 178–180°C (THF); ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3H, –CH_3); 2.29 (s, 3H, –CH_3); 3.79 (s, 3H, N–CH_3); 4.03 (t, 2H, N–CH_2–, *J* = 4.67 Hz); 4.13 (t, 2H, –$\underline{CH_2}$–OH, *J* = 4.77 Hz); 6.32 (s, 1H, Pz–H); 6.34 (s, 1H, Pz–H); ^{13}C NMR ($CDCl_3$) δ: 11.39 (CH_3); 11.46 (CH_3); 36.34 (N–CH_3); 50.55 (N–CH_2–); 62.07 (–$\underline{CH_2}$–OH); 103.17 (C–H); 103.29 (C–H); 139.61 (C); 140.06 (C); 145.22 (C); 146.06 (C); Anal. Calc. for $C_{11}H_{16}N_4O$: C 60.0, H 7.3, N 25.45. Found: C 59.9, H 7.3, N 24.8; *m/z*: 221 (MH^+).

Synthesis of bipyrazole **5**: To a solution of 1-[3,5-dimethyl-1H-pyrazol-3-yl]butan-1,3-dione (1.80 g; 10 mmol) in 50 ml of absolute ethanol, cooled at 0°C, was slowly added 2-hydroxyethylhydrazine (0.76 g; 10 mmol) in 17 ml of absolute ethanol. After addition, the mixture was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the residue obtained was separated on silica using the mixture (5% ethanol/95% diethylether) as eluant to give a 9% yield of **4** and 40% yield of **5** as a white solid. M.p. = 137–138°C; ^{1}H NMR ($CDCl_3$) δ: 2.21 (s, 3H, –CH_3); 2.23 (s, 3H, –CH_3); 3.73 (s, 3H, N–CH_3); 3.96 (t, 2H, N–CH_2–, *J* = 4.89 Hz); 4.47 (t, 2H, –$\underline{CH_2}$–OH, *J* = 4.89 Hz); 6.11 (s, 2H, Pz–H); ^{13}C NMR ($CDCl_3$) δ: 11.07 (CH_3); 13.46 (CH_3); 36.32 (N–CH_3); 52.00 (N–CH_2–); 62.95 (–$\underline{CH_2}$–OH); 104.90 (C–H); 105.24 (C–H); 137.29 (C); 139.69 (C); 141.05 (C); 147.98 (C). Anal. Calc. for $C_{11}H_{16}N_4O$: C 60.0, H 7.3, N 25.45. Found: C 59.8, H 7.5, N 25.6; *m/z*: 221 (MH^+).

Synthesis of bipyrazole **6**: A mixture of **2** (1.76 g; 10 mmol) and potassium tert-butoxide (1.20 g; 10.71 mmol) in 50 ml of anhydrous diethylether was stirred under reflux for 30 mn. After cooling at 0°C, methyl iodide (2.4 g; 15 mmol) was slowly added. The reaction mixture was refluxed for 4 h then filtered and the solvent was evaporated. The obtained residue was purified on silica using CH_2Cl_2 as eluant to give a 70% yield of **6** (white solid). M.p. = 220–222°C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 6H, –CH_3); 3.65 (s, 6H, N–CH_3); 6.21 (s, 2H, Pz–H). *m/z*: 190 $(M)^+$.

Extraction experiments: A solution of 7×10^{-5} M of bipyrazolic group in CH_2Cl_2 (50 ml) was stirred for 2 h with an aqueous solution (50 ml) of metal nitrates (7×10^{-5} M); the complexation was followed by measuring the concentration of cations in an aqueous solution by atomic absorption. The temperature remained constant during all the experiments at 25°C and at pH 7.

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References

1 B. Lupo and G. Tarrago, *Bull. Soc. Chim. Fr*., 1984, **2**, 473.
2 A. Ramdani and G. Tarrago, *Tetrahedron,* 1981, **37**, 987.
3 M. Gal, G. Tarrago, P. Steel and C. Marzin, *New J. Chem*., 1985, **9***,* 617.
4 S. Boudouche, C. Coquelet, L. Jacquet, C. Marzin, R. Sandeaux and G. Tarrago, *J. Inclusion Phenom*., 1993, **16**, 69.
5 F. Malek, M. Persin, A. Ramdani, J. Sarrazin and I. Zidane, *New J. Chem*., 2002, **26**, 876.
6 J. Elguero, M. Espada, A. Ramdani and G. Tarrago, *J. Heterocyc. Chem*. 1980, **17**, 137.
7 C. Marzin, G. Tarrago, G. Gal, I. Zidane, T. Hours, D. Lerner, C. Andrieux, H. Camp and J.M. Saveant, *Inorg. Chem*., 1986, **25**, 1775.
8 J.E. Bol, B. Mars, G. Gonesh, W.L. Driessen, K. Goubitz and J. Reedijk, *Heterocycles*, 1997, **45**, 1477.
9 F. Mary, C. Marzin, S. Salhi and G. Tarrago, *Supramol. Chem*., 1993*,* **3**, 57.
10 S. Radi, A. Ramdani, Y. Lekchiri, M. Morcellet, G. Crini, J. Morcellet and L. Janus, *Eur. Polym. J.* 2000, **36**, 1885.
11 S. Radi, A. Ramdani, Y. Lekchiri, M. Morcellet, G. Crini, L. Janus and M. Bacquet, *New J. Chem.* 2003, **27**, 1224.
12 F. Malek, A. Ramdani and S. Radi, *J. Chem. Res*. 2004, **9**, 640.
13 F. Malek, A. Ramdani, I. Zidane, A. Yahyi and S. Radi, *Tetrahedron*, 2005, **61**, 2995.
14 S. Radi, A. Ramdani, Y. Lekchiri, M. Morcellet, G. Crini, J. Morcellet and L. Janus, *J. Chem. Res*. 2003, **11**, 712.
15 S. Radi, A. Ramdani, Y. Lekchiri, M. Morcellet, G. Crini and L. Janus, *Tetrahedron,* 2004, **60**, 939.
16 W.G. Haanstra, W.L. Driessen, J. Reedijk, U. Turpeinen and R. Hämäläinenn, *J. Chem. Soc., Dalton Trans.*, 1989, 2309.
17 J. Fifani, A. Ramdani and G. Tarrago, *New J. Chem*., 1977, **1**, 521.
18 E. Tjiou, A. Fruchier, V. Pellegrin and G. Tarrago, *J. Het. Chem.,* 1989, **26**, 893.
19 R.A. Schultz, D.M. Dishong and G.W. Gokel, *Tetrahedron Lett.,*1981, **22**, 2623.
20 R.B. Davidson, R.M. Izatt, J.J. Christensen, R.A. Schultz, D.M. Dishong and G.W. Gokel, *J. Org. Chem.,* 1984, **49**, 5080.
21 A. Kaifer, D.A. Gustowski, L.A. Echegoyen, V.J. Gatto, R.A. Schultz, T.P. Cleary, C.R. Morgan, D.M. Goli, A.M. Rios and G.W. Gokel, *J. Am. Chem. Soc*., 1985, **107**, 1958.
22 F.R. Fronczek, V.J. Gatto, R.A. Schultz, S.J. Jungk, W.J. Colucci, R.D. Gandour and G.W. Gokel, *J. Am. Chem. Soc*., 1983, **105**, 6717.
23 J.M. Lehn and J.P. Sauvage, *J. Am. Chem. Soc*. 1975, **97**, 6700.
24 W.L. Driessen, S. Gorter, W.G. Haanstra, L.J.J. Laarhoven, J. Reedijk, K. Goubitz and F.R. Seljée, *Reel. Trav. Chim. Pays-Bas*, 1993, **112**, 309.