# Synthesis and Cations Binding Properties of a New C,N-bipyrazolic Ligand

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The synthesis of a new C,N-bipyrazolic ligand with a functionalized donor-group is reported. The binding properties of the ligand and two other ligand of similar structures towards heavy metal ions ($Hg^{2+}$, $Cd^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $Cu^{2+}$) and alkaline metal ions ($K^+$, $Na^+$, $Li^+$) were studied by a liquid-liquid extraction process and the extracted cation percentage was determined by atomic absorption measurements. The selectivity of the ligand to Hg(II) has been mentioned in the abstract.

**Key Words :** Synthesis, Bipyrazole ligands, Complexing properties, Liquid-liquid extraction, Atomic absorption

## Introduction

There is a continuing interest in the preparation of functionalized pyrazole derivatives. This is evident from the large number of articles, several of them being reviews.[1,2] Moreover, polydentate pyrazolic receptors are well known for their ability to complex not only alkali cations[3-7] but also to form stable complexes with transition metal ions.[8-11] These complexes are so stable that it is often difficult to obtain the free macrocycles from them.

In our recent work,[12-18] a series of acyclic pyrazole compounds containing one to four pyrazole rings were prepared and demonstrated to extract only transition metal cations whereas macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals. However, complexation studies of a kind of bibyrazole ligands are less met in the literature.

In this paper we describe the synthesis of new C,N-bipyrazolic structure **4** (Fig. 1) with a donor heteroatom in a side arm and its binding ability towards alkali and transition metal ions compared to two other similar structures **5** and **6** (Fig. 1) which are equally studied here for there complexation properties for the first time. It has been found that a donor atom in a side chain of lariat ethers increases the binding ability of the macrocycle.[19-21] The presence of a functional chain also provides this structure with the possibility of being immobilized on the surface of a solid material (organic resin or silica gel) by covalent bonding.

## Results and Discussion

The route to prepare the new bipyrazole compound **4** is shown in Scheme 1. Compound **2** was prepared from commercially available 3(5)-amino-5(3)-methylpyrazole **1** by diazotation in HCl followed by reduction with Tin chloride[22] and the intermidiate diamine is not isolated but has immediately undergone a condensation with the $\beta$-diketones[4] to give the ester **2** as a white solid in a 36% yield. The methylation of this product in the presence of *t*-BuOK as base led to one isolated $\alpha$-isomer[23] product **3** in a 29%

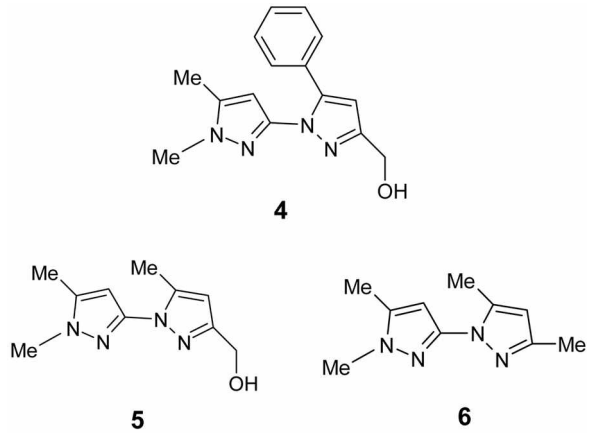
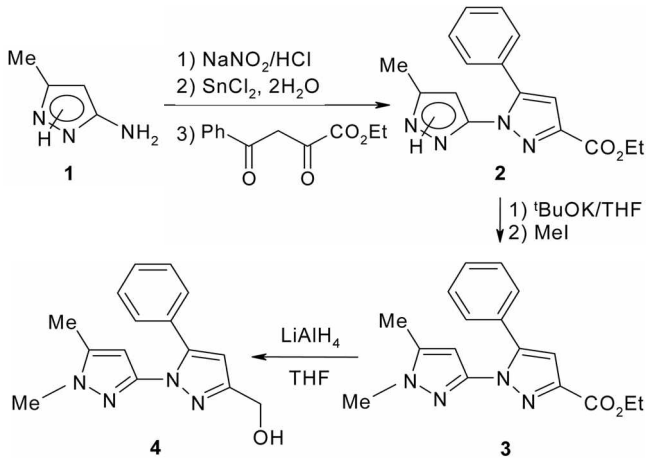



**Figure 1**




**Scheme 1**

**Table 1**. Yields of extraction of individual heavy and alkali metal ions

| | Mercury | Cadmium | Lead | Copper | Zinc | Potassium | Sodium | Lithium |
|---|---|---|---|---|---|---|---|---|
| **4** | 27 | 9 | 11 | 19 | 4 | 0 | 0 | 0 |
| **5** | 46 | 6 | 7 | 18 | 3 | 0 | 0 | 0 |
| **6** | 10 | 7 | 12 | 20 | 0 | 0 | 0 | 0 |

**Table 2**. Yields of competitive extraction of various heavy and alkali metal ions

| | Mercury | Cadmium | Lead | Zinc | Potassium | Sodium | Lithium |
|---|---|---|---|---|---|---|---|
| **4** | 45.11 | 6.20 | 6.22 | 3.77 | 0 | 0 | 0 |
| **5** | 47.77 | 6.65 | 1.30 | 0.46 | 0 | 0 | 0 |

yield. Finally, the compound **3** was convert to the target product **4** using $LiAlH_4$ as agent of reduction.

Structures of all compounds were determined on the basis of the corresponding analytical and spectroscopic data.

**Liquid-liquid extraction of individual cations.** We used this method in order to study the complexation properties of this new bipyrazolic ligand **4** compared to two other similar bipyrazole compounds **5**[24] and **6**[4] which are equally studied here for their complexation properties for the first time. The study of individual extraction of cations was carried out toward $Hg^{2+}$, $Cd^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $Cu^{2+}$, $K^+$, $Na^+$ and $Li^+$ cations. Metal nitrates were extracted into the organic phase by complex formation with ligands. The percentage limits of extraction determined by atomic absorption measurements are given in Table 1.

Results in Table 1 show that in analogy to our previous work[12–18] in which acyclic 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 acyclic structures **4-6** only with the transition metal cations, with no complexation being observed toward alkali cations.

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

Bipyrazole groups act as convergent chelating bidentate donors. The term convergent refers to the nitrogen donor atoms coordinating to the same metal centre leading thus to a five membered ring which is part of several such rings when the whole ligand is considered. It is well known[25] that five membered ring chelates are more stable than six-membered and four-membered ones.

In analogy to the literature in which a donor atom in a side chain of a lariat ethers increases the binding ability of the macrocycle,[19-21] the comparison between **5** with a donor atom in a side chain and **6** without a donor atom shows that there is practically a change in the percentage of complexation especially in case of $Hg^{2+}$.

It seemed that Hg(II)-4 should be stayed more in the organic layer than the aqueous layer probably due to solubility. However, We notice a decrease of complexation towards $Hg^{2+}$ for the compound **4** compared to **5**.

The affinity to other metal ions are practically weak and identical. We can thus suggest an important selectivity for these ligands **4** and **5** toward mercury.

**Table 3**. Selectivity ratios in competitive conditions

| | Mercury / Lead | Mercury / Cadmium | Mercury / Zinc |
|---|---|---|---|
| **4** | 7.25 | 7.27 | 11.96 |
| **5** | 35.20 | 7.18 | 103.84 |

**Competitive liquid-liquid extraction measurements.** We have chosen ligands **4** and **5** which seem to have good selective properties towards $Hg^{2+}$. By competitive extraction from aqueous solutions of $Hg^{2+}$, $Cd^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $K^+$, $Na^+$ and $Li^+$ nitrates with a $CH_2Cl_2$ solution of ligand **4** or **5**, we have obtained the results given in Table 2.

These obtained values are in perfect agreement with those measured by separate cation extraction. Indeed, in this competitive extraction, we notice a high affinity only for mercury with zero extraction of alkali cations and a weak extraction of other transition metals. We can thus conclude that these ligands are selective with the extraction of Hg(II). Moreover, the $Hg^{2+}$/cation selectivity ratio obtained (Table 3) in these competitive conditions, shows the good mercury selectivity of **4** and **5**.

## Conclusion

In conclusion, metal cations and macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals, while the acyclic bipyrazole ligands reported here only form complexes with transition metal cations. They do not complex alkali metal cations at all. The bipyrazolic ligands with a donor atom in a side chain show a high affinity and a good selectivity for mercury.

## Experimental Section

All solvents and other chemicals, obtained from usual commercial sources, were of analytical grade and used without further purification. The $^1H$ NMR and $^{13}C$ NMR spectra were obtained with a Bruker AC 300 spectrometer (operating at 300.13 MHz for $^1H$ NMR and 75 MHz for $^{13}C$ NMR). Elemental analysis were performed by Microanalysis Central Service (CNRS). Molecular weights were determined on a JEOL JMS DX-300 Mass Spectrometer.

Atomic absorption measurements were performed by Spectra Varian A.A. 400 Spectrophotometer. The IR spectra were taken with potassium bromide discs on Perkin Elmer 1310 spectrometer.

**Synthesis of 3-ethylcarboxylate-1-(4-methylpyrazol)yl-5-phenyl pyrazole 2.** To a cooled (−5 °C) solution of HCl 6 N (75 mL) and aminopyrazole (0.123 mole, 12 g) was successively added $NaNO_2$ 1 M (125 mL) and a very cooled solution of HCl 6 N (50 mL) containing $SnCl_2$, $2H_2O$ (0.25 mole, 56.5 g). The mixture was let under agitation at 0 °C for 4 h and then evaporated to dryness. The obtained residue was taken by absolute ethanol (150 mL), filtered and the filtrate was evaporated. The residue was treated with ethyl acetyl pyruvate ($9.49 \times 10^{-2}$ mole, 15 g) in absolute ethanol (200 mL). The mixture was thereafter refluxed for 2 h and then placed in the fridge for 3 h. The formed precipitate was dissolved in water, neutralized with sodium carbonate and extracted with $CH_2Cl_2$ (3 × 20 mL). The organic solution was dried with $Na_2SO_4$ and evaporated to dryness. The residue was recrystallized in diethyl ether to give (13.1 g, 36%) of compound **2** as a white solid. R*f* = 0.52 ($CH_2Cl_2$/ethyl acetate, 6/4); mp=149-151 °C (from diethyl ether); $^1$H NMR (300 MHz; $CDCl_3$; $Me_4Si$) $\delta_H$: 1.39 (3H, t, Et, *J* = 7.2 Hz), 2.23 (3H, s, Me), 4.41 (2H, q, Et, *J* = 7.2 Hz); 6.00 (1H, s, H-5-Pyr), 6.98 (1H, s, H-pyr), 7.32 (5H, br s, ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 11.16; 14.37; 61.12; 100.61; 109.38; 128.39; 128.62; 128.80; 140.72; 144.57; 145.60; 162.36. Anal. Calc. for $C_{16}H_{16}N_4O_2$, $1H_2O$: C 61.08; H 5.73; N 17.82%; Found: C 61.02; H 5.79; N 17.78. IR: $\nu_{max}$/cm$^{-1}$ 1700 (C=O); *m/z*: 297 ($MH^+$).

**Synthesis of 3.** A mixture of compound **2** (3 g, 10.13 mmol) and potassium *tert*-butoxide (1.14 g, 10.17 mmol) in anhydrous THF (80 mL) was stirred under reflux for 30mn and cooled to 0 °C. Then, a solution of methyl iodide (7.2 g, 50.7 mmol) in anhydrous THF (10 mL) was slowly added and the mixture was refluxed for 4 h, filtered and evaporated to dryness. The residue obtained was purified on silica (ethyl acetate / hexane : 4 / 6) to give (0.93 g, 29%) of **3** as a white solid; mp 91-92 °C (from $CH_2Cl_2$); R*f* = 0.85 (ethyl acetate / $CH_2Cl_2$: 4 / 6); $^1$H NMR (300 MHz; $CDCl_3$; $Me_4Si$) $\delta_H$: 1.39 (3H, t, Et, *J* = 7.2 Hz), 2.22 (3H, s, Me), 3.73 (3H, s, N-Me), 4.41 (2H, q, Et, *J* = 7.2 Hz), 5.87 (1H, s, H-5-Pyr), 6.98 (1H, s, H-5-Pyr), 7.32 (5H, br s, ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 11.30; 14.40; 36.34; 60.98; 101.47; 109.23; 128.29; 128.71; 129.40; 139.74; 144.47; 145.39; 146.07; 162.44 17.82; Anal. Calc. For $C_{17}H_{18}N_4O_2$: C 65.80; H 5.80; N 18.06%; Found: C 66.13; H 5.94; N 17.82; IR: $\nu_{max}$/cm$^{-1}$ 1700 (C=O); *m/z*: 311 ($MH^+$).

**Synthesis of 4.** To a solution of $LiAlH_4$ (400 mg, 10.52 mmol) in anhydrous THF (20 mL) cooled at 0 °C, was slowly added bipyrazole **3** (1.5 g; 4.84 mmol) in 30 mL of THF. The mixture was stirred under reflux for 2 h and cooled to 0 °C. To a resulting mixture was successively added water (0.4 mL), 15% aqueous sodium hydroxide (0.4 mL) and water (1.2 mL). The solid material was filtered and the residue was washed with hot THF. The filtrate and THF washings were concentrated under reduced pressure and purified on silica to give (1.12 g, 86%) of **4** as a white solid. mp 111-113 °C (from THF); Rf = 0.22 (ethyl acetate / $CH_2Cl_2$: 4 / 6); $^1$H NMR (300 MHz; $CDCl_3$; $Me_4Si$) $\delta_H$: 2.19 (3H, s, Me), 3.75 (3H, s, N-Me), 4.76 (2H, s, $CH_2$), 5.64 (1H, s, H-5-pyr), 6.45 (1H, s, H-5-pyr), 7.32 (5H, br s, ph); $^{13}$C NMR ($CDCl_3$) $\delta$: 11.28; 36.25; 59.10; 100.58; 105.63; 128.22; 128.37; 128.72; 130.19; 139.59; 144.86; 146.55; 153.17. Anal. Calc. For $C_{15}H_{16}N_4O$: C 67.16; H 5.97; N 20.89%. Found: C 67.57; H 6.20; N 20.46; IR: $\nu_{max}$/cm$^{-1}$ 3410 (HO); m/z: 269 ($MH^+$).

**Extraction experiments:** A solution of $7 \times 10^{-5}$ M of the ligand in $CH_2Cl_2$ (50 mL) was stirred for 2 h with an aqueous solution (50 mL) of metal nitrates ($7 \times 10^{-5}$ 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 measured by a pH-meter. This was explained by the absence of nitrogen protons in ligands.

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