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New Macrocyclic Polyamines of 3,5-Disubstituted 1H-Pyrazole. A ^{13}C NMR Study of Deprotonation and Formation of Zn^{2+} Dinuclear Complexes.

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Abstract: Dipodal (2+2) condensation of 3,5-(1H-pyrazole)dicarbaldehyde (**3**) with 1,5-diamino-3-oxapentane (**4**) and diethylenetriamine (**5**) followed by hydrogenation of the resulting Schiff bases (**6** and **8**), affords two new 26 membered polyaza macrocycles of 1H-pyrazole (**7** and **9**). The deprotonation of both crowns in basic medium as well as the formation of dinuclear Zn^{2+} complexes (**7b** and **9b**) from the dipyrazolate salts **7a** and **9a** have been studied by ^{13}C NMR.

The interest in the study of polyaza macrocycles with large cavities (24-26 membered) has increased enormously owing to the analogy of their transition metal complexes with the active sites of metalloproteins and metalloenzymes, among which more than 160 zinc enzymes are now known[1,2].

Recently, it has been reported the synthesis of a number of aromatic and heteroaromatic macrocyclic Schiff bases of general structure **1(a-b)** and **1(c-f)** respectively (Figure 1), by a dipodal (2+2) condensation of a series of dialdehydes with diethylenetriamine[3-5]. Hydrogenation of the above mentioned Schiff bases provides the corresponding saturated polyaza macrocyclic ligands of general structure **2(a-f)**.To the best of our knowledge, analogous polyaminic macrocycles containing 1H-pyrazole units have not been reported.

Previously, we have studied the ionophoric properties of some heteroaromatic crowns in which 3,5-disubstituted 1-methyl and 1H-pyrazole units are linked to chains of tetraethylene glycol[6-10], diethylene glycol[11] and 2,6-bis(hydroxymethyl)pyridine[12] by ester or ether bonds. The synthesis of the above mentioned receptors was performed using high dilution conditions, under the influence of the template effect of CsCl. It was found that in general, large di- and trinuclear macrocycles of pyrazole of similar size than valinomycine (36 members), which have different flexibility, symmetry, steric hindrance, as well as different number and type of donor sites, are able to mimic functions of selective complexation and transport of alkali and ammonium ions[7,9,10,12].

Now, following the synthetic procedure previously described by Martell and co-workers[3,4], and using 3,5-(1H-pyrazole)dicarbaldehyde (**3**), 1,5-diamino-3-oxapentane (**4**), and diethylenetriamine (**5**) as starting materials, we have obtained new 26 membered polyaminic macrocycles of structure **6-9**, each of them containing two proton-ionizable units of 3,5-disubstituted 1H-pyrazole (Figure 1).

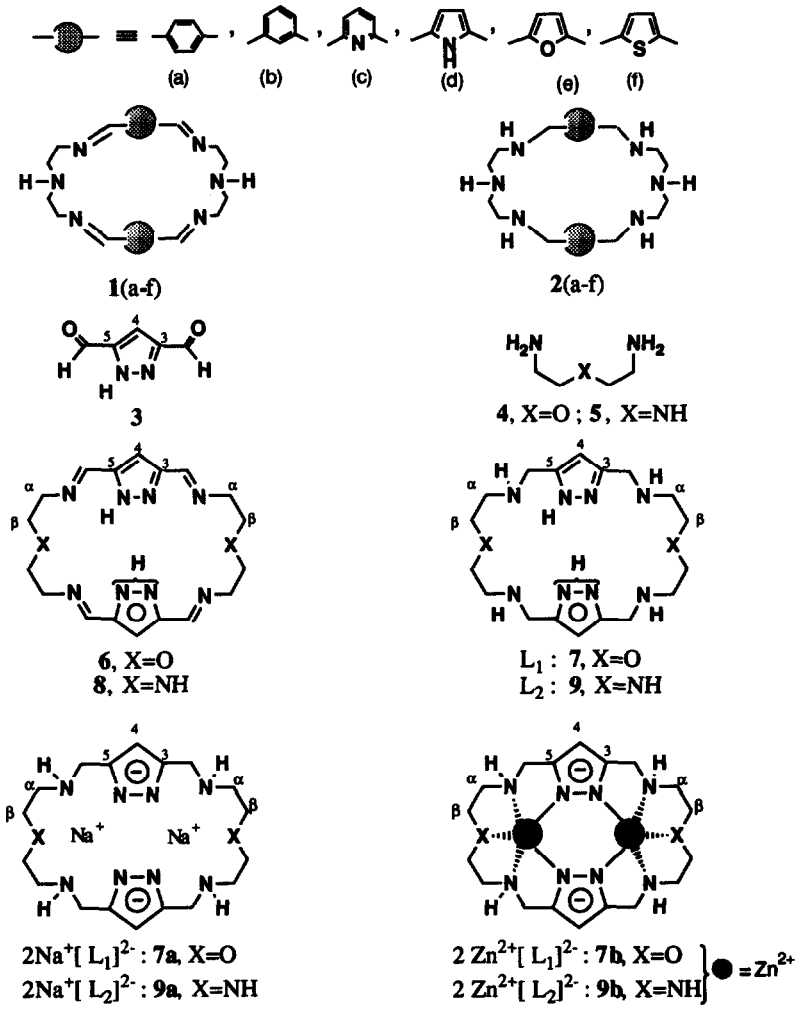

Figure 1

The 3,5-(1H-pyrazole)dicarbaldehyde **3** [193-194°C, M^+ 125] which is reported in this paper for the first time, was prepared from 3,5-bis(hydroxymethyl)-1H-pyrazole[13](3.50 mmol) by oxidation with MnO_2 (35 mmol) in 1,2-dimethoxyethane (50 cm^3) in 70% yield. The Schiff bases **6** and **8** were prepared by dipodal (2+2) condensation of **3** (0.40 mmol dissolved in 10 cm^3 of 1-propanol) with an equimolecular amount of each amine [0.40 mmol of **4** (or **5**) dissolved in 10 cm^3 of 1-propanol]. The Schiff base **6** is a stable compound which precipitated from the reaction mixture as a pure solid [177-178°C (1-propanol), M^+ 384] in 94 % yield. Reduction of **6** (0.28 mmol) with $NaBH_4$ (7.28 mmol) in absolute ethanol (10 cm^3) gave the expected saturated polyazamacrocycle **7** [144-145°C (toluene), M^+ 392, 70 % yield]. The Schiff base **8** is an unstable compound , which was readely hydrogenated *in situ* with $NaBH_4$ (9.40 mmol) to afford the polyaminic macrocycle **9**, which was also isolated as a stable solid [166-167°C (toluene), M^+

390] but in low yield (30%). The structure of all the new compounds reported in this paper agree with their corresponding analytical and spectroscopical data of MS, IR and NMR (Table 1).

Table 1. ^{1}H NMR Data (δ ppm, DMSO-d_6) of the 3,5-(1H-Pyrazole)dicarbaldehyde (3) and the Polyazamacrocycles 6, 7 and 9.

Compound	H_4-Pz	Pz-CH=N	Pz-CH_2-NH	N-$\underline{CH_2}$-CH_2-X	N-CH_2-$\underline{CH_2}$-X
3	7.49 (1H, s)	-	-	-	-
6	6.34 (2H, s)	8.08 (4H, s)	-	3.64 (8H, br s)	3.64 (8H, br s)
7	6.02 (2H, s)	-	3.62 (8H, s)	2.62 (8H, t)	3.42 (8H, t)
9	6.04 (2H, s)	-	3.60 (8H, s)	2.54 (8H, br s)	2.54 (8H, br s)

The macrocyclic cavity of **7** and **9** can assist the formation of dinuclear complexes in two complementary ways. The two proton-ionizable 1H-pyrazole nuclei when deprotonated, they became pyrazolate anions which can coordinate two identical metals through both nitrogen atoms acting as exobidentate ligands[14]. Besides, the flexible macrocyclic moiety of **7** and **9** may cooperate to the complexation via their diethyleneoxadiamine or diethylenetriamine chelating subsunits.

A 75 MHz ^{13}C NMR study of deprotonation of compounds **7** and **9** and formation of Zn^{2+} dinuclear complexes in DMSO-d_6-D_2O (9:1 v/v) solution is shown in Table 2. In neutral medium, compound **9** as free ligand (L_1) shows a symmetrical structure, in which the broad signal belonging to both pyrazolic carbons C_3 and C_5 (147.53 ppm) indicate a prototropic equilibrium in which the migration of protons can occur through an interanular mechanism, similar to that previously proposed for two pyrazole tautomers rapidly interconverting through a cyclic dimer[15]. In contrast with the above behavior, the pyrazole rings of **7** as free ligand (L_2) show unsymmetrical structure ($\Delta\delta$ C_3-C_5= 7.50 ppm), probably due to the formation of intramolecular NH···O hydrogen bonds.

Table 2. ^{13}C NMR [δ, ppm, DMSO-d_6/D_2O (9:1 v/v)] Data of the Polyazamacrocycles **7** and **9** Compared with those of their Sodium Dipyrazolates (**7a** and **9a**) and their Corresponding Zn^{2+} Dinuclear Complexes (**7b** and **9b**).

	Pyrazole ring			Side Chain			
Comp.	C_3	C_4	C_5	C_3-$\underline{C}H_2$	C_5-$\underline{C}H_2$	C_α	C_β
7	151.00[a]	103.60[c]	143.50[a]	45.29[b]	45.29[b]	48.45[c]	70.08[c]
7a	148.60[c]	101.54[c]	148.60[c]	46.85[c]	46.85[c]	48.45[c]	70.26[c]
Δδ(7a-7)	**-2.40**	**-2.06**	**+5.10**	**+1.56**	**+1.56**	**0.00**	**+0.18**
7b	150.21[c]	97.66[d]	150.21[c]	47.13[c]	47.13[c]	48.32[c]	66.03[c]
Δδ(7b-7a)	**+1.61**	**-3.88**	**+1.61**	**+0.28**	**+0.28**	**-0.13**	**-4.23**
9	147.53[a]	103.13[c]	147.53[a]	45.27[c]	45.27[c]	48.03[c]	48.61[c]
9a	148.06[c]	100.41[c]	148.06[c]	47.10[c]	47.10[c]	48.56[c]	48.98[c]
Δδ(9a-9)	**+0.53**	**-2.72**	**+0.53**	**+1.83**	**+1.83**	**+0.53**	**+0.37**
9b	149.15[c]	96.26[c]	149.15[c]	43.96[c]	43.96[c]	46.81[c]	46.81[c]
Δδ(9b-9a)	**+1.09**	**-4.15**	**+1.09**	**-3.14**	**-3.14**	**-1.75**	**-2.17**

[a] Very broad signal; [b] broad signal; [c] sharp singlet; [d] broad singlet.

In basic medium, the dipyrazolate salts (**7a** and **9a**) formed by addition of NaOH (molar ratio 2:1) to DMSO-d_6/D_2O (9:1 v/v) solutions of **7** and **9**, afford ^{13}C NMR spectra which display sharp equivalent signals for carbons C_3 and C_5 deshielded in relation to the neutral ligands. Besides, the signal corresponding to carbon C_4 show in both cases upfield shift (-2.40 ppm for **7a** and -2.72 ppm for **9a**) characteristic of pyrazolate anions[16] (Table 2).

Finally, the addition of $ZnCl_2$ to **7a** and **9a** (molar ratio 2:1) show identical ^{13}C downfield shifts for both carbon atoms C_3 and C_5 and a large highfield shift for carbon C_4 in the pyrazole moiety, which confirm the participation of each of the two pyrazolic nitrogens in the formation of dinuclear Zn^{2+} complexes of symmetrical structure schematically represented by **7b** and **9b**. Furthermore, all the methylene carbons experiment upfield shifts which show the different cooperation in the complexations of the heteroatoms contained in the flexible moiety (O and/or NH), as it has been previously demonstrated in ligands of related structure[17].

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