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Formation of Mono- and Di- Nuclear Complexes of Zn^{2+} from a 26 Membered Tetraester Crown of 3,5-Disubstituted Pyrazole Able to Act as Neutral and Dianionic Ligand

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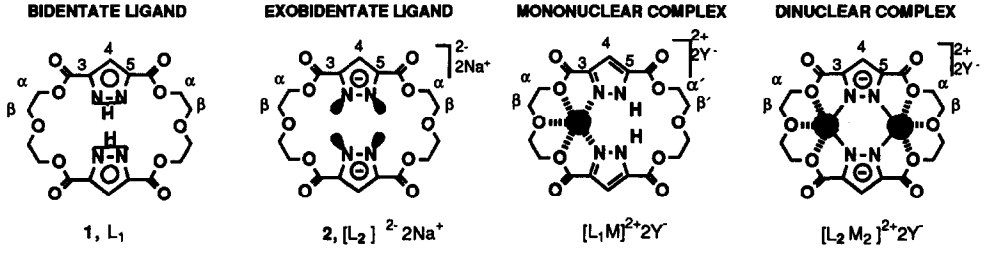
Abstract. A selective synthesis of bis(3,5-diketo-1H-pyrazole)-[26]crown-12 (**1**, L_1) has been performed. Its deprotonation pK_a values, and those of the acyclic analogues (**3-5**) have been measured. The disodium dipyrazolate salt of **1** (**2**, $[L_2]^{2-}$ $2Na^+$) has been isolated, and mono- and di- nuclear complexes of Zn^{2+} obtained from **1** ($[L_1Zn]^{2+}$) and **2** ($[L_2Zn_2]^{2+}$) have been studied by ^{13}C NMR spectroscopy in DMSO-d_6 solution.

INTRODUCTION

The interest in the study of macrocyclic receptors able to form mono- and di- nuclear complexes with transition metals has increased in the last few years owing to their resemblance with the active site of metalloproteins and metalloenzymes.[1]

In previous work, we have reported the synthesis and ionophoric properties towards alkali and ammonium ions of tetraester crowns of 3,5-disubstituted 1-methyl- and 1-H-pyrazole of size similar to Valinomycin (36- membered), which were built by using tetraethylene glycol [2-5] and 2,6-bis (hydroxymethyl)pyridine[6] chains.

The two pyrazole units introduced into the cavity of a 26- membered tetraester-polyether crown **1** (L_1) (Figure 1) can assist complexation of transition metals ions in two different ways. In neutral medium, each heteroaromatic unit of pyrazole can act as a monodentate ligand; however, in alkaline medium it can be deprotonated, affording a powerful pyrazolate anion which behaves as an exobidentate one.



1, L_1 2, $[L_2]^{2-}2Na^+$ $[L_1M]^{2+}2Y^-$ $[L_2M_2]^{2+}2Y^-$

Figure 1

Thus, crown **1** can form mononuclear complexes of structure $[L_1M]^{2+}2Y^-$, while crown **2** ($[L_2]^{2-}2Na^+$) is able to form dinuclear complexes of general structure $[L_2M_2]^{2+}2Y^-$. Such complexes can provide a novel entry into the study of metalloenzyme models.[7]

In general, the synthesis of proton-ionizable tetraester-polyether crowns, derived from 1H-pyrazole by direct cyclization of 1H-substituted pyrazole-3,5-dicarbonyl dichloride and tetraethylene glycol, is very difficult and occurs in much lower yields than that of their 1-alkyl substituted analogues.[2] By this reason, additional efforts were devoted to improve it by using an alternative procedure *via* debenzylation.[8] Following this last method, we have reported previously the synthesis of **1** by Lewis acid-catalyzed debenzylation of its 1-benzyl substituted precursor.[8] It is important to point that the last mentioned synthesis involves the previous cyclization of 1-benzylpyrazole-3,5-dicarbonyldichloride with diethylene glycol (DEG) to give a mixture of tetra-, hexa- and octa- esterpolyether crowns 26-, 39- and 52- membered respectively, together acyclic diols of different molecular weight. Consequently, this is a troublesome procedure from which **1** is obtained in very low yield.

Taking into account the known complexing properties of **1**(L_1) towards catecholamine derivatives[9], and its potential ability to form mono- and di- nuclear complexes with transition metals, in this paper we have achieved an easier and more selective synthesis. We report by the first time the disodium salt of **1** (**2**, $[L_2]^{2-}2Na^+$) (Fig.1) as well as their deprotonation pK_a values which are compared with those belonging to acyclic podands **3-5** (Scheme 1) of related structure. Using ^{13}C NMR spectroscopic techniques we have studied the formation of mono- and di- nuclear Zn^{2+} complexes formed from both (**1**) and (**2**) ligands.

RESULTS AND DISCUSSION

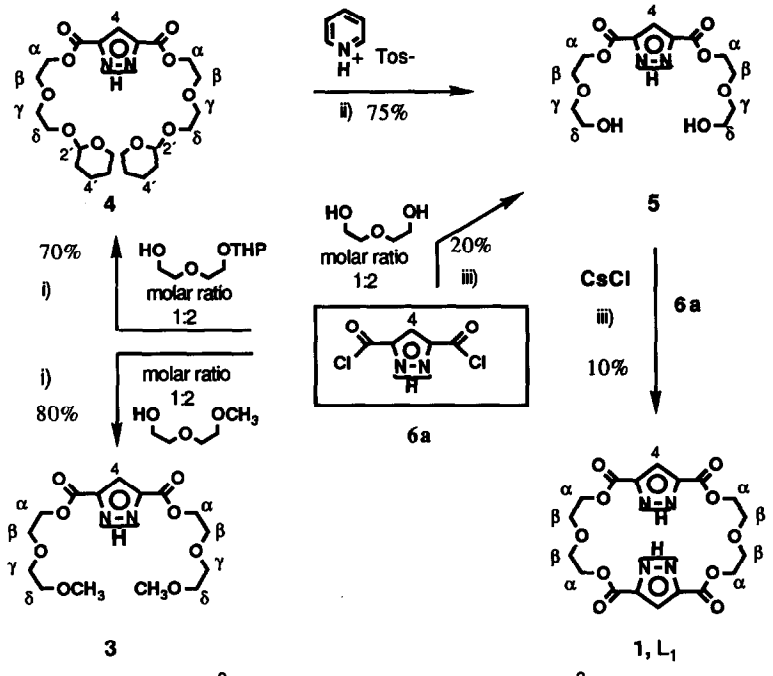
Synthesis and structure of cyclic (1-2) and acyclic (3-5) ligands.

The new synthesis of the 26- membered tetraester-polyether crown (**1**) has been carried out from the acyclic diol 5´-hydroxy-3´-oxapentyl pyrazole 3,5-dicarboxylate **5** as shown in Scheme 1.

The podand **3** and the acyclic precursor of **5** (**4**) were obtained by using pyrazole-3,5-dicarbonyl dichloride **6a** as the starting material.

Previously, we observed that heating pyrazole-3,5-dicarboxylic acid with thionyl chloride, according to traditional procedures, afforded mixtures of **6a** and undesirables amounts of diketopiperazine derivatives, the separation of which was very difficult.[2,4,8] Now, we have verified that the formation of the above mentioned by-products, which are due to dimerization reactions catalyzed by thionyl chloride,[10] can be avoided by raising

the temperature to 140°C and shortening the reaction time (2h). Under these conditions, we have been able to isolate the pyrazole-3,5-dicarbonyl dichloride **6a** as a pure crystalline solid (mp. 72-74 °C) in 92% yield.



i) DME, 60°C, 3h, Et_3N; ii) EtOH-H_2O (10:1 v/v), 60°C, 6h;
iii) High dilution, N_2, C_6H_6-THF, 25°C, Et_3N (1:2 molar ratio).

Scheme 1.

The reaction of **6a** with both diethylene glycol monomethylether and 2-(6′-hydroxy-1,4-dioxahexyl)-tetrahydropyrane using triethylamine as acceptor of hydrochloric acid, afforded the acyclic ligands **3** (MH^+ 361) and **4** (MH^+ 501), which were isolated as pure oils in 80% and 70% yield, respectively.

Following the procedure previously described by Miyashita et al.,[11] partially modified by us (see Experimental Section), elimination of both tetrahydropyranyl protector groups of **4** to afford the diol **5** (MH^+ 333) was successfully performed in high yield (75%). Alternatively, the direct reaction of **6a** with diethylene glycol (1:2 molar ratio) afforded diol **5** in lower yield (22%).

Taking into account the ability of Cs^+ cations to promote ring closures,[12] the cyclization of **5** with pyrazole- 3,5-dicarbonyl dichloride (1:1 ratio) was performed in the presence of CsCl by using high dilution conditions. In this last step, the tetraester crown **1** was obtained as a pure solid (mp. 258-260°C, MH^+ 453) in 10% yield after purification by flash chromatography on silica gel. The disodium dipyrazolate salt **2**, $[L_2]^{2-}2Na^+$ (Fig. 1), was obtained as a pure solid (mp. 338°C dec.) by crystallisation of a acetonitrile-ethanol (6:1 v/v) solution of **1** previously treated with NaOH (2:1 molar ratio). In the mass spectrum of the above salt registered by fast atomic bombardment (FAB) technique, both the MH^+(497) and $[MH-2Na]^+$ (451) peaks are in accordance with the expected molecular weight.

The structure of the new compounds reported in this paper agree with their corresponding analytical and spectroscopical data (MS, IR, ^1H NMR and ^{13}C NMR, see Experimental Section and Tables 1 and 2).

The ^{13}C NMR spectra of acyclic (**3-5**) and cyclic (**1**) free ligands (Table 2) show a symmetrical structure in which the broad signal belonging to both pyrazolic C_3 and C_5 carbons is indicative of a prototropic equilibrium[13]. As expected, the spectrum of the disodium dipyrazolate salt **2** display sharp equivalent signals for carbons C_3 and C_5 which are strongly deshielded ($\Delta\delta$ 4.8 ppm) with respect to the neutral ligand. Furthermore, C_4 experiments a chemical shift of 0.5 ppm to higher field.

It is interesting to note that, neither the ^1H NMR spectra of podands **3** and **4**, (registered in $CDCl_3$) nor that of **5** (registered in DMSO-d_6, a solvent characterised by its ability to diminish the protonic interchange rate), allow the identification of the signal corresponding to the NH protons. In contrast with the above behaviour, the

Tables 1 and 2. ^1H and ^{13}C NMR Spectral Data [300 MHz, δ(ppm)][a] of ligands **1-5** and **6a**

Comp.	CH-4	NH	CH_2-α	CH_2-β	CH_2-γ	CH_2-δ	CH_3	CH-2′	CH_2-6′	CH_2-3′,4′,5′
1[b]	7.03 (s)	14.50[c]	4.39 (m)	3.76 (m)	-	-	-	-	-	-
2	7.09 (s)	-	4.34 (m)	3.85 (m)	-	-	-	-	-	-
3	7.34 (s)	d	4.50 (m)	3.83 (m)	3.68 (m)	3.57 (m)	3.38 (s)	-	-	-
4	7.35 (s)	d	4.50 (m)	3.80 (m)	3.60 (m)	3.60 (m)	-	4.70 (m)	3.55 (m)	1.60 (m)
5	7.19 (s)	d	4.38 (m)	3.71 (m)	3.48 (m)	3.48 (m)	-	-	-	-
6a	7.78 (s)	3.10[e]	-	-	-	-	-	-	-	-

Comp.	C-3,5	C-4	CO-3,5	C-α	C-β	C-γ	C-δ	CH_3	C-2′ C-6	C-3′ C-4′ C-5′
1[b]	138.4[f]	110.6	159.6	63.3	67.8	-	-	-	-	-
2	143.2[g]	110.1	161.6	62.2	68.0	-	-	-	-	-
3	140.0[f]	111.8	159.9	64.3	68.8	71.8	70.5	58.3	-	-
4	139.4[f]	111.5	159.8	64.1	68.7	70.5	66.9	-	98.8 62.0	30.4 19.3 25.3
5	139.2[f]	111.1	159.8	64.2	68.2	72.4	60.3	-	-	-
6a	143.3[h]	117.1	159.3	-	-	-	-	-	-	-

a) Compounds **1**,**2** and **5** were registered in DMSO-d_6; compounds **3** and **4** in Cl_3CD and compound **6a** in $(CD_3)_2CO$. b) These signals were taken from reference 8. c)Broad singlet which disappear with D_2O. d)This signal could not be identified. e)Very broad signal which disappear with D_2O. f) Broad signal. g) Sharp singlet. h) Broad singlet.

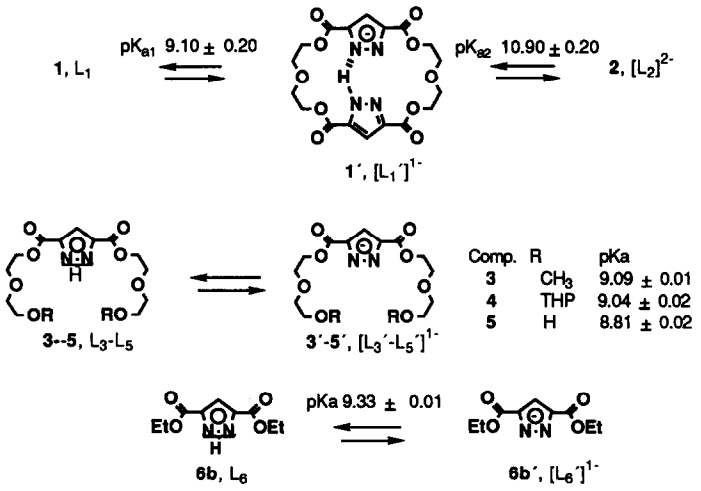
two NH pyrazole protons belonging to crown **1** clearly appear in its ^1H NMR spectrum under a broad signal strongly deshielded at δ 14.50 ppm. This fact could be explained if the macrocylic cavity size of **1** is favouring a conformation in which the four pyrazole nitrogens are simultaneously interacting through two intramolecular NH...N hydrogen bonds.[14] On the basis of above observations, the migration of crown **1** NH protons between nitrogens atoms N(1) and N(2) may occur through an interannular mechanism similar to that previously suggested by Williams for two pyrazole tautomers rapidly interconverting through a cyclic dimer.[15]

In the ^1H NMR spectrum of the disodium dipyrazolate salt **2**, the NH signals cannot be observed. Furthermore, the ^{13}C NMR spectrum of **2** show a sharp singlet corresponding to both C-3 and C-5 confirming that the tautomeric equilibrium of **1** has disappeared after the formation of the disodium salt.

Deprotonation pK_a values of cyclic (1) and acyclic compounds (3-5).

With the aim of evaluate the influence of the macrocyclic cavity in the acidic behaviour of the two 3,5-disubstituted pyrazole units of **1**, their mono- and di- deprotonation pK_a values have been measured in 10% MeOH-H_2O solution. In addition, taking as reference the diethyl pyrazole-3,5-dicarboxylate (**6b**), the resulting data for **1** are compared with those obtained from three acyclic podands (**3-5**) of related structure.

The pK_a values of compounds **3-5** and **6b** were measured by potentiometric methods on an Orion 940-960 using a mixed glass-AgCl electrode. Solutions (5.10^{-3}M) prepared from the above mentioned ligands were adjusted to ionic force I=0.1 with tetraethylammonium chloride and titrated with 0.1M KOH under nitrogen at 25.0 ± 0.5ºC. The resulting data were corrected in order to obtain the thermodynamic pK_a values displayed in Scheme 2.



Scheme 2. pK_a values in H_2O-MeOH (10:1 v/v) at 25 °C.

The measurements of the pK_a values corresponding to mono- and di- deprotonation of the tetraester crown **1** have been carried out by spectrophotometric methods by using a Hewlett-Packard 8451A diode array spectrophotometer[25 solutions (10^{-5}M) covering a 7.0-12.0 pH range were prepared by using the appropriate buffers[16] of constant ionic strength (I=0.01)]. The thermodynamic pK_{a1} and pK_{a2} values obtained in each case were calculated using a Specpk program.[17]

Comparison of compounds **3** (pK_a 9.09), **4** (pK_a 9.04) and **5** (pK_a 8.81) with diethyl pyrazole 3,5-dicarboxylate **6b** (pK_a 9.33) demonstrate the influence of both diethylene glycol chains on the enhanced acidity of all the pyrazole rings belonging to the three podands. However, according with the behaviour previously described by Reinhoudt and co-workers for pyridinium crown ethers,[18] the macrocyclic effect causes a diminished acidity of both pyrazole rings in crown **1**. Its first deprotonation pK_{a1} value (9.10), which affords

the monopyrazolate anion **1'**, is slightly higher than those corresponding to the O-methyl and O-tetrahydropyranyl substituted acyclic ligands **3** and **4**. However, the second deprotonation of **1'** to give **2** (pK_{a2} 10.90) is much more hindered. The last mentioned effect suggests that a strong NH....N^- intramolecular hydrogen bond is formed between the pyrazole and the pyrazolate units of **1'**.

Formation of mono- and di- nuclear complexes of 1 and 2.

A 75 MHz ^{13}C NMR complexation study of neutral ligand **1**, (L_1) and **2**, $[L_2]^{2-}2Na^+$ with $ZnCl_2$ has been performed in DMSO-d_6 solution (See Table 3).

Comparison of the NMR spectra of both ligands with those corresponding to the later addition of $ZnCl_2$ to **1** and **2** (1:1 and 2:1 molar ratios respectively), demonstrates the formation of mono- $[L_1Zn]^{2+}$ and dinuclear $[L_2Zn_2]^{2+}$ complexes (See Table 3).

Table 3. ^{13}C NMR (δ, ppm) spectra of compounds **1** and **2** and of their mono- and di- nuclear complexes of Zn^{2+} ($[L_1Zn]^{2+}$ and $[L_2Zn_2]^{2+}$ respectively) in DMSO-d_6 solution.

1, L_1 $\xleftarrow[\text{DMSO-}d_6]{ZnCl_2\ (1:1)}$ $[L_1Zn]^{2+}2Cl^-$ **2**, $[L_2]^{2-}2Na^+$ $\xrightarrow[\text{DMSO-}d_6]{ZnCl_2\ (1:2)}$ $[L_2Zn_2]^{2+}2Cl^-$

Comp.	C_3	C_4	C_5	Pz_3-CO	Pz_5-CO	C_α $C_{\alpha'}$	C_β $C_{\beta'}$
1, L_1	138.4[a]	110.6	138.4[a]	159.6	159.6	63.3	67.8
$[L_1Zn]^{2+}$	143.3[b]	110.6	134.3[b]	161.0	158.2	63.8[a], 62.7[a]	67.7, 67.9
Δδ	**+4.9**	**0.00**	**-4.1**	**+1.4**	**-1.4**	**+0.5, -0.6**	**-0.1, +0.1**
2 $[L_2]^{2-}$ $2Na^+$	143.2[b]	110.1	143.2[b]	161.6	161.6	62.1	68.0
$[L_2Zn_2]^{2+}$	143.0[c]	110.7	143.0[c]	160.7	160.7	62.6[b]	67.4[a]
Δδ	**-0.2**	**+0.6**	**-0.2**	**-0.9**	**-0.9**	**+0.5**	**-0.6**

a) Broad signal; b) Sharp singlet. c) Broad singlet

The ^1H NMR spectrum of **1** (L_1) after addition of 1 equiv. of $ZnCl_2$ shows that the two pyrazole NH protons (which in **1** were shown as a broad signal at δ 14.50 ppm due to the prototropic equilibrium) appear together under a singlet which, in relation to the free ligand, experiments an appreciable shift to higher field (0.19 ppm). Furthermore, the ^{13}C NMR spectrum of the mononuclear complex $[L_1Zn]^{2+}$ exhibits an asymmetrical structure in which the left and right sides of the molecule are clearly different [$\Delta\delta$ (C_3-C_5)= 9.0 ppm); $\Delta\delta$ (OC-Pz_3-OC-Pz_5) = 2.8 ppm]. However, the addition of 2 equiv. of $ZnCl_2$ to the dipyrazolate salt 2 $[L_2]^{2-}2Na^+$ leads to the formation of a symmetrical dinuclear complex of structure $[L_2Zn_2]^{2+}$ in which the left and the right sides are equivalents and display significant shifts to higher ($C_{3,5}$, CO-$Pz_{3,5}$ and $C_{\beta,\beta'}$) or to lower ($C_{\alpha,\alpha'}$) field (See Table 3).

CONCLUSIONS

-The 1H-pyrazole-3,5-dicarbonyl dichloride (**6a**) has been isolated as a pure solid (mp. 72-74°C) in 92% yield. The reaction of **6a** with O-methyl and O-tetrahydropyranyl monosubstituted di(ethylene glycol) gave the new proton-ionizable podands **3** and **4** in 80% and 70% yield respectively.

-Elimination of the tetrahydropyranyl protector groups of **4** with pyridinium tosilate at 60°C gave the corresponding diol **5**. Alternatively, the direct reaction of **6a** with di(ethylene glycol) (molar ratio 1:2) afforded (**5**) in lower yield (20%)..

-An easier and more selective synthesis of the 26-membered tetraester-polyether crown **1** has been carried out in 10% yield by direct cyclization of **6a** with **5** under the template effect of CsCl.

-In the ^1H NMR spectrum of **1** the strong deshielding experimented by the two NH pyrazole protons (δ 14.50 ppm) indicates that, in this coronand, the size of the macrocyclic cavity is favouring a conformation in which the four pyrazole nitrogens are simultaneously interacting through two intramolecular NH···N hydrogen bonds. Moreover in the ^{13}C NMR spectrum of **1**, the C_3 and C_5 pyrazole carbons appear as a broad signal which confirms that a prototropic equilibrium may occur through an interannular mechanism.

- Using an acetonitrile-ethanole mixture as solvent, treatment of **1** with NaOH (2:1 molar ratio) afforded the new disodium dipyrazolate salt **2** $[L_2]^{2-}$ $2Na^+$ (MH^+ 497). The above salt was isolated as a crystalline solid (mp. 338°C dec.) in 93% yield.

-In the ^{13}C NMR spectrum of **2**, the signal of the C_3 and C_5 carbons appear as a sharp singlet, confirming that the pyrazole NH protons have disappeared. Moreover, the formation of pyrazolate anions induces characteristic chemical shifts on the carbons belonging to the pyrazole ring, to higher (C_4: Δδ -0.5 ppm) and to lower ($C_{3,5}$: Δδ 4.8 ppm) field.

-The deprotonation pK_a values of the pyrazole rings belonging to **1**, **3** -**5** and **6a**, have been measured in 10% MeOH-H_2O solution.The resulting data demonstrate the following: a) Taking as reference **6a** (pK_a 9.33), the O-methyl and O-tetrahydropyranyl substituted di(ethylene)glycole chains of acyclic ligands **3** (pK_a 9.09) and **4** (pK_a 9.04), increase the acidic character of the pyrazole ring, probably due to intramolecular NH····O interactions b) The above effect is stronger in the acyclic intermediate **5** (pK_a 8.81), since the terminal hydroxy groups may favour the formation of NH··O··HO hydrogen bonds, either by direct interactions with side chains oxygens atoms or through interaction with water molecules.

-In crown **1**, the deprotonation pK_a value of the first pyrazole ring (pK_{a1} 9.10) is of similar order to that of its acyclic analogue **3** (pK_a 9.09). However, the deprotonation of the second pyrazole ring (pK_{a2} 10.90) is much more hindered. The last mentioned effect suggests that a strong NH···N- intramolecular hydrogen bond is formed due to the macrocyclic cavity size of this ligand.

-A ^{13}C NMR complexation study of both cyclic ligands (**1** and **2**) with $ZnCl_2$ has been performed in DMSO-d_6 solution. The addition of 1 equiv. of $ZnCl_2$ to the neutral ligand **1** (L_1) leads to the formation of a mononuclear complex $(L_1Zn)^{2+}$, in which the carbons belonging to the right (C_3, CO-Pz_3, Cα and Cβ) and to the left (C_5, CO-Pz_5, Cα´ and Cβ´) sides of the molecule are not equivalent.

-The addition of 2 equiv. of $ZnCl_2$ to the dipyrazolate ligand **2**$[L_2]^{2+}$ leads to the formation of a dinuclear complex of symmetrical structure $[L_2Zn_2]^{2+}$, which carbons display significant shifts to lower (C_4 and Cα,α´) or to higher ($C_{3,5}$, CO-$Pz_{3,5}$ and Cββ´) field.

EXPERIMENTAL SECTION

Melting points were determined with a Köfler apparatus and are uncorrected. Elemental analyses were carried out by the Organic Chemistry Department of the Centro Nacional de Química Orgánica (CSIC), Madrid, Spain. The IR spectra were recorded with a Perkin-Elmer 257 spectrometer and the ^1H NMR and ^{13}C NMR

ones with a Varian XL-300 using Me_4Si as an internal standard. The mass spectra (MS) were registered by electronic impact (EI) at 70 eV in a VG-12-250 spectrometer, or by fast atomic bombardment (FAB) technique in a FAB-HF apparatus. Analytical TLC was performed on aluminium sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck). Chromatographic separations were performed on columns, using the flash chromatography technique on silica gel (Merck), 200-400 mesh. Compounds were detected with UV light (254 nm) and/or iodine chamber. All reagents were of commercial quality from freshly opened containers. Thionyl chloride (Scharlau), diethylene glycol (Aldrich) and triethylamine (Scharlau) were freshly destilled prior its use. Caesium Chloride (Fluka), pyrazole 3,5-dicarboxylic acid (Aldrich) and reagent quality solvents were used without further purification. Diethyl pyrazole-3,5-dicarboxylate **6b** (mp 54-55°C) was obtained following a procedure previously described by us.[19]

*Pyrazole-3,5-dicarbonyl dichloride (**6a**).* A suspension of pyrazole 3,5-dicarboxylic acid (2g) in thionyl chloride (350 mL) was heated at 140°C over 2 hours. The hot reaction mixture was filtered and the resulting solution evaporated to dryness to give 2 g.(92%) of pyrazole-3,5-dicarbonyldichloride as a white solid. Mp. 72-74°C. IR (KBr, cm^{-1}): 3150 (NH); 1760 (CO). MS (EI): 157 (M^+-Cl, 100); 121 (157-HCl, 46); 93 (121-CO, 10); 65 (93-CO, 76). Anal. Calc. for $C_5H_2Cl_2N_2O_2$: C, 31.12; H, 1.04; N, 14.51. Found, C, 31.21; H, 1.30; N, 14.88.

Synthesis of acyclic ligands

2-(6′-hydroxy-1′,4′-dioxahexyl)-tetrahydropyrane. To a solution of diethylene glycol (10 g, 94 mmol) in anhydrous chloroform (300 mL), solid pyridinium tosilate (2.36 g, 9.4 mmol) was added. Then, a solution of 3,4-dihydro-2H-pyrane (7.9 g, 94 mmol) in chloroform (100 mL) was slowly added. When the addition was complete, the reaction was allowed to stand for 24 h at room temperature. The residual solution was evaporated to dryness to give an oil which was dried *in vacuo* and purified by flash chromatography on a silica gel column, using a mixture of acetone and chloroform (1:4 v/v). After evaporation of the fractions containing the product of Rf 0.55 the 2-(6′-hydroxy-1,4-dioxahexyl)-tetrahydropyrane was isolated as a colourless pure oil (10.8 g, 60% yield). IR (neat, cm^{-1}): 3450 (broad OH); 1120, 1070, 1030 (C-O). Anal. Calc. for $C_9H_{18}O_4$: C, 56.82; H, 9.53. Found, C, 56.81; H, 9.44.

*Compounds **3** and **4** (General Method).* To a solution of pyrazole-3,5-dicarbonyl dichloride (6 mmol) in anhydrous dimethoxyethane vigourously stirred and heated at 60°C, a mixture of the corresponding alcohol (12 mmol) and triethylamine (12 mmol) dissolved in dimethoxyethane (50 mL) was slowly added. When the addition was complete, the reaction was allowed to proceed for 3 h and then cooled to room temperature. The residual solid was filtered off and the filtrate evaporated to dryness to give a syrup which was dried *in vacuo*.

*3′,6′-Dioxahepthyl pyrazole 3,5-dicarboxylate (**3**).* Following the general method from pyrazole-3,5-dicarbonyl dichloride (5.18 mmol) and the appropriate amounts of diethylene glycol monomethylether (10.36 mmol) and triethylamine (10.36 mmol), a syrup was obtained, which was purified by flash chromatography on a silica gel column, using a mixture of acetone and chloroform (1:1 v/v). After evaporation of the fractions containing the product of Rf 0.6, compound **3** was isolated as a colourless pure oil.(1.5 g, 80% yield). IR (neat,

cm^{-1}): 3150 (NH); 1720(CO). MS(FAB$^+$): 361(MH^+, 100). Anal. Calc. for $C_{15}H_{24}N_2O_8.H_2O$: C, 47.61; H, 6.87; N, 7.40. Found, C, 47.80; H, 6.55; N, 7.52.

*6′-(2′′-Tetrahydropyranyl)-3′,6′-dioxahexyl pyrazole-3,5-dicarboxylate (4).*Following the general method from pyrazole-3,5-dicarbonyl dichloride (5.74 mmol) and the appropriate amounts of 2-(6′-hydroxy-1′,4′-dioxahexyl)tetrahydropyrane (11.48 mmol) and triethylamine (11.48 mmol) a syrup was obtained, which was purified by flash chromatography on a silica gel column, using a mixture of (4:1 v/v) acetone and chloroform . The fractions containing the product of Rf 0.8 were evaporated to dryness *in vacuo* affording compound **4** as a colourless pure oil (2.0g, 70% yield). IR (neat, cm^{-1}): 3400 (NH); 1740(CO). MS(FAB$^+$): 501(MH^+, 2); 333 (MH^+-2THP, 100). Anal. Calc. for $C_{23}H_{36}N_2O_{10}$: C, 55.19; H, 7.25; N, 5.59. Found, C, 55.30; H, 7.08; N, 5.73.

5′-Hydroxy-3′-oxapentyl pyrazole 3,5-dicarboxylate (5). a) Synthesis from **6a**: Following the general method, from pyrazole-3,5-dicarbonyl dichloride (30.3 mmol) and diethylene glycol (61.04 mmol) a syrup was obtained, which was purified by flash chromatography on silica gel column, using a mixture of acetone and chloroform (v/v 4:1) . The fractions containing the product of Rf 0.2 were evaporated to dryness *in vacuo* affording compound **5** as a colourless pure oil (2.3 g, 23% yield). b) Synthesis from **4**: To a solution of **4** (1.52 g, 3 mmol) in anhydrous ethanol vigourously stirred and heated at 60°C, solid pyridinium tosilate (0.8 g, 3.2 mmol) was slowly added. When the addition was complete, the reaction was allowed to proceed for 6 h and then cooled to room temperature. The residual solution was evaporated to dryness to give a syrup which was purified by flash chromatography on a silica gel column, using a mixture of acetone and chloroform (4:1 v/v). Evaporation of the fractions containing the product of Rf 0.2 as before afforded compound **5** in 75% yield (0.7 g). IR (KBr, cm^{-1}): 3400 (broad NH); 1730 (CO). MS(FAB$^+$): 333 (MH^+, 100). Anal. Calc. for $C_{13}H_{20}N_2O_8.C_3H_6O.\ 2H_2O$: C, 45.06; H, 7.09; N, 6.56. Found, C, 45.24; H, 7.40; N, 6.21.

Synthesis of cyclic compounds

25(26),27(28)-H,H-3,6,9,15,18,21-hexaoxa-25,26,27,28-tetraazatricycle[21.2.1.2^{11,13}] octacosa-1(26),13(28),11,23-tetraen-2,10,14,22-tetraone (1). Following the high dilution technique, a solution of **5** (1.18 g, 3.56 mmol) in tetrahydrofurane (60 mL) was added to a suspension of caesium chloride (0.6 g, 3.56 mmol) in a mixture of anhydrous benzene (200 mL) and anhydrous tetrahydrofurane (80 mL) stirred under nitrogen and heated at 55°C. Then the stirring was increased and two solutions of anhydrous tetrahydrofurane (30 ml) containing: a) pyrazole-3,5-dicarbonyl dichloride (0.69 g, 3.56 mmol) and b) triethylamine (0.72 g, 7.12 mmol) were simultaneously and slowly added. After the addition was complete the reaction was allowed to proceed for 24h and then cooled to room temperature. The residual solid was filtered off and the filtrate evaporated to dryness to give a sirup which was purified by flash chromatography on silica gel column, using a mixture of acetone and chloroform (v/v 4:1). When the fractions containing the product of Rf 0.5 were evaporated to dryness *in vacuo*, compound **1** was isolated as a white solid. Mp. 258-260°C. (0.16 g, 10% yield). IR (KBr, cm^{-1}): 3250 (NH); 1720 (CO). MS(FAB$^+$): 453 (MH^+, 100). Anal. Calc. for $C_{18}H_{20}N_4O_{10}$: C, 47.78; H, 4.42; N, 12.38. Found, C, 47.76; H, 4.53; N, 12.38.

Sodium dipyrazolate salt (2). A vigourously stirred suspension of 0.1 g. (0.22 mmol) of **1** in anhydrous acetonitrile (60 mL) was heated at 75°C until a clear solution was obtained. The resulting mixture was slowly cooled to room temperature and a solution of 0.018 g (0.45 mmol) of sodium hydroxide dissolved in anhydrous ethanol (10 mL) was slowly added. After the addition was complete a fine solid was formed, which was dried *in vacuo* to give compound **2** as a white crystalline solid. Mp. 338°C (dec.) (0.108 g, 99% yield). IR (KBr, cm^{-1}): 1710 (CO). MS(FAB$^+$); 497 (MH^+, 2); 475 [MH^+-(Na^++1),4]; 453 [MH^+-(2Na^++2),17]; 451(MH^+-2Na^+, 2). Anal. Calc. for $C_{18}H_{18}N_4O_{10}Na_2$: C, 43,55; H, 3.62; N, 11.29. Found, C, 43.61; H, 3.80; N, 11.28.

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REFERENCES

1. Tsuru, D. in *Bioactive Moleculess*: Otsuka, S. ; Yamanaka, T. Eds.; Elsevier, **1988**, vol. 8. p. 343.
2. Elguero, J.; Navarro, P.; Rodriguez-Franco, M.I. *Chem. Lett.*,**1984**, 425.
3. Navarro, P.; Rodriguez-Franco, M.I.;Samat, A. *Synth. Commun.* **1985**, 1976.
4. Elguero, J.; Navarro, P.; Rodríguez Franco, M.I.; Cano, F.M.; Foces-Foces, C.; Samat, A. *J. Chem. Research (S)* **1985**, 312-313; *J. Chem. Research (M)* **1985**, 3401-3418.
5. Navarro, P.; Rodríguez-Franco, M.I. *J. Chem. Soc. Chem. Commun.* **1988**, 1365-67.
6. Navarro, P.; Pueyo, E.; Rodríguez-Franco, M.I.; Samat, A., *Tetrahedron* **1990**, *46*, 2917-2926.
7. Sorrel, T.N. *Tetrahedron* **1989**, *45*, 3.
8. Bueno, J.M.; Navarro, P.; Rodriguez-Franco, M.I.; Samat, A. *J. Chem. Research (S)* **1991**, 126-127; *J. Chem Research (M)* **1991**, 1101-1116.
9. Campayo, L.; Bueno, J.M.; Ochoa, C.; Navarro, P.; Samat, A., *Tetrahedron Lett.*, **1993**, in press.
10. Baraldi, P.G.; Guarneri, M.; Moroder, F.; Simoni, D.; Beneti, S. *Synthesis* **1981**, 727.
11. Miyashita, N.; Yoshikoshi, A.; Grieco, P.A., *J. Org. Chem.* **1977**, *42*, 3772-3774.
12. Kruizinga, W.H.; Kellog, R.M., *J. Am. Chem. Soc.* **1981**, *103*, 5183-5189.
13 Elguero, J. in *Comprenhensive Heterocyclic Chemistry* Eds. Katritzky, A.F. and Rees, C.W. Pergamon Press, Oxford, **1984**, vol. 5, p. 190.
14. Hibbert, F. in *Advances in Physical Organic Chemistry* Eds Gold, V. and Bethell, D. Academic Press, London, **1986**, vol. 22, p. 138.
15. Williams P. *J. Org. Chem.* **1964**, *29*, 1377.
16. Perrin, D.D.; Dempsey, B. *"Buffers of pH and Metal Control"* Chapman and Hall, **1987**.
17. Albert, A.; Serjeant, E.P. *"The Determination of Ionization Constants"*. Chapman and Hall, **1984**.
18. Grootenhuis, P.D.J.; Staveren, C.J.; Hertoj, H.J.; Reinhoudt, D.N. Bos, M. Uiterwijk, J.V.H.M. Kruise, L; Harkema, S. *J. Chem. Soc., Chem. Commun* . **1984**, 1412-1413.
19. Iturrino, L.; Navarro, P.; Rodriguez-Franco, M.I.; Contreras, M.; Escario, J.A.; Martinez, A.; Pardo, M.R. *Eur. J. Med. Chem.* **1987**, *22*, 445-451.

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