NOVEL DOUBLE TRIPODAL PYRAZOLYL MACROCYCLES. SYNTHESIS AND X-RAY STRUCTURE OF HEXA-AZOLE LIGANDS

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Abstract - The synthesis and characterization of two new hexa-azole macrocyclic ligands, MEPY22PZ and ETPY24PZ, are described. The single crystal structure of ETPY24PZ shows two metal-binding sites with a tripodal N_4 geometry. Coordination of 2 Cu(I) or 2 Zn(II) ions by each macrocycle was confirmed by NMR complexation studies.

INTRODUCTION

Copper proteins which contain the type-3 site, such as hemocyanin[1] and tyrosinase,[2] are important in biochemistry because of their central role in dioxygen processing. Hemocyanin is responsible for dioxygen transport in arthropods and molluscs. Tyrosinase is a monooxygenase and catalyses the selective hydroxylation of phenols to *o*-catechols and subsequent oxidation to *o*-benzoquinones.[3] These metalloenzymes contain two copper ions in the active site, each bound by three histidine residues from the protein backbone, leaving a vacant coordination site on each copper ion for dioxygen binding.[4] The spectroscopy and reactivity of metalloproteins are mainly determined by the structure of the active site, and can be mimicked by specially designed coordination complexes.[5]

Model compounds for the type-3 copper site have been obtained with small tripodal ligands (L) containing pyridine,[6] imidazole,[7] or pyrazole[8] donors. These $[Cu(I)L]^+$ fragments need to assemble in solution, to form dicopper(II)peroxo complexes when exposed to dioxygen. In addition, macrocyclic ligands have been used to bind two copper ions in a preorganised fashion, but these macrocycles normally contain hard, *aliphatic* nitrogen donors.[9]

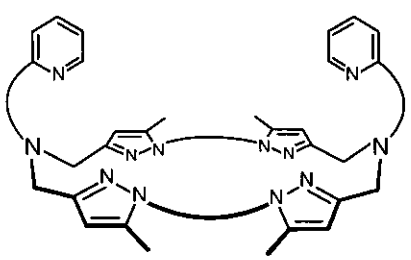


Chart 1. A hexa-azole macrocycle.

Pyrazoles and pyridines have coordination properties similar to those of imidazoles[10] and are often used in synthetic

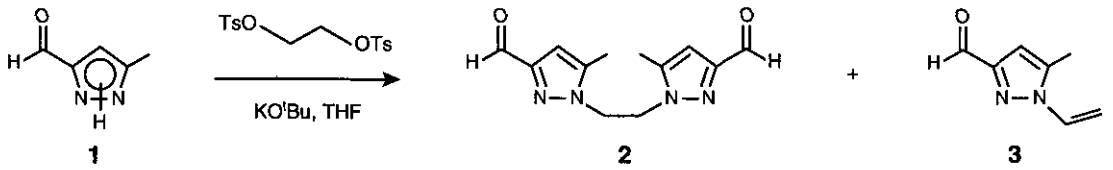
model compounds.[11] A potentially useful model ligand for the type-3 copper site would be obtained by combining six *aromatic* nitrogen donors in one organic molecule, whereby this ligand should provide two specific metal-binding sites with a tripodal geometry. Up till now, only a few macrocycles containing neutral heterocyclic sp^2 N donors, endocyclic bound in a macrocyclic ring, have been reported.[12] These considerations led us to study macrocyclic ligands containing six aromatic nitrogen donors in a preorganised fashion and potentially able to form dinuclear complexes with copper ions (Chart 1).

In this paper we wish to report the synthesis, purification and characterisation of the new macrocycles 10,24-di(2-(pyridin-2-yl)ethyl)-(6,14,20,28-tetramethyl)-1,5,10,15,19,24,29,30,31,32-decaazapentacyclo-[24.2.1.1^{5,8}.1^{12,15}.1^{19,22}]dotriacontane-6,8(30),12(31),13,20,22(32),26(29),27-octaene (**ETPY24PZ**), and 9,22-di(pyridin-2-ylmethyl)-(5,13,18,26-tetramethyl)-1,4,9,14,17,22,27,28,29,30-decaazapentacyclo-[22.2.1.1^{4,7}.1^{11,14}.1^{17,20}]triacontane-5,7(28),11(29),12,18,20(30),24(27),25-octaene (**MEPY22PZ**). Both macrocycles contain four neutral, endocyclic pyrazoles separated by an aliphatic spacer and two pendant 2-alkylpyridyl groups. The X-ray structures of the *bis*-(3)-formylpyrazolyl precursor (**4**) (Figure 1) and macrocycle ETPY24PZ (Figure 2) were determined to establish their spatial conformation.

RESULTS AND DISCUSSION

Preparation of pyrazolyl precursors (1 - 4).

Attempts to synthesise *bis*-(pyrazolyl)aldehyde precursor (**2**) with a C2 spacer using 1,2-dibromoethane, as described by Tarrago *et al.*[13] for the selective alkylation of 3(5)-formyl-5(3)methylpyrazole (**1**) failed and yielded almost exclusively the vinylic 3–formylpyrazolyl derivative (**3**), probably due to elimination of HBr from the monoalkylated intermediate. Therefore, 1,2–*bis*–(*p*-tosyloxy)ethane was used as alkyl spacer, yielding **2** in moderate yield and only traces of **3** (Scheme 1). The selective alkylation of **2** at the N(1) pyrazole position was proven by a NOE-difference ^{1}H–NMR spectrum (300 MHz): irradiation of the Pz-CH_2-α group in **2** showed a strong enhancement of the Pz-CH_3 signal, whereas no intensity changes were observed upon irradiation of the Pz-C*H*O signal.



Scheme 1

The alkylated *bis*-(3)-formylpyrazolyl precursor (**4**) with a C3 spacer was synthesised according to Tarrago *et al.*,[14] and purified by recrystallisation to remove traces of undesired tautomeric side-products. The selective alkylation at the N(1) position[15] was confirmed by NOE-difference ^{1}H-NMR and an X-ray

structure determination of **4**. All N-N, C-N, C-C and C-O distances of the pyrazole ring, alkyl spacer and formyl group are within the normal range for pyrazolyl compounds.[16]

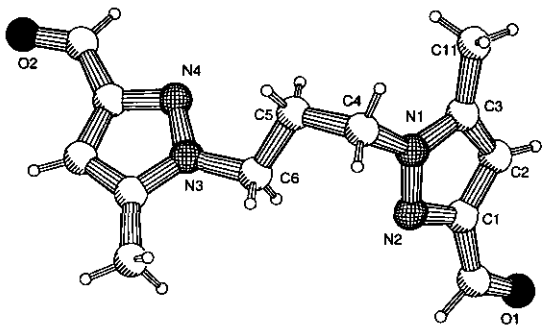
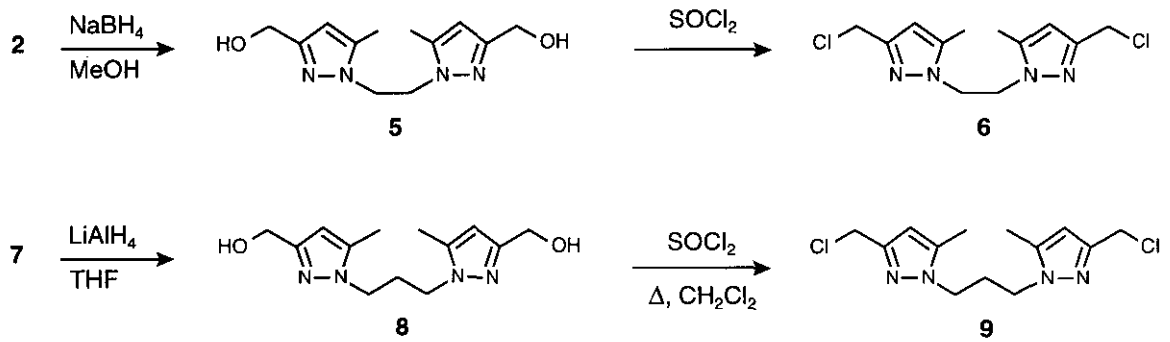


Figure 1. X-Ray structure of *bis*-formylpyrazolyl precursor (**4**).

Selected bond lenghts (Å): N(1)-N(2) 1.346(2), N(2)–C(1) 1.338(2), C(1)-C(2) 1.405(3), C(2)-C(3) 1.365(3), C(3)–N(1) 1.361(2), C(1)-C(10) 1.459(3), C(10)-O(1) 1.203(3), C(3)-C(11) 1.493(3), N(1)-C(4) 1.459(2), C(4)-C(5) 1.520(3). Selected bond angles (°): N(1)-N(2)-C(1) 104.5(1), N(2)–C(1)-C(2) 111.1(2), C(1)-C(2)-C(3) 105.5(2), C(2)–C(3)-N(1) 106.2(2), C(2)-C(3)-C(11) 131.4(2), N(2)-C(1)-C(10) 117.7(2), C(1)-C(10)-O(1) 124.9(2), C(3)-N(1)-C(4) 128.0(2), C(4)-C(5)-C(6) 113.3(2).

Preparation of pyrazolyl precursors (5 - 9).

The *bis*-(3)-hydroxymethylpyrazolyl compound (**5**), containing a C2 spacer, was obtained by sodium borohydride reduction of **2**. Subsequent chlorination with $SOCl_2$ gave the expected *bis*-chloromethyl precursor (**6**). The shorter C2 spacer in **6** required different chlorination conditions compared to **8** (Scheme 2). *Bis*-(3)-hydroxymethylpyrazolyl precursor (**8**), containing a C3 spacer, was synthesised according to a modified literature procedure, by reduction of the diester 1,3-*bis*(3'-carbethoxy-5'-methyl-1'-pyrazolylpropane) (**7**).[17] The corresponding *bis*-(3)-chloromethylpyrazole (**9**) was obtained after chlorination of **8** in diluted $SOCl_2$ at elevated temperature.

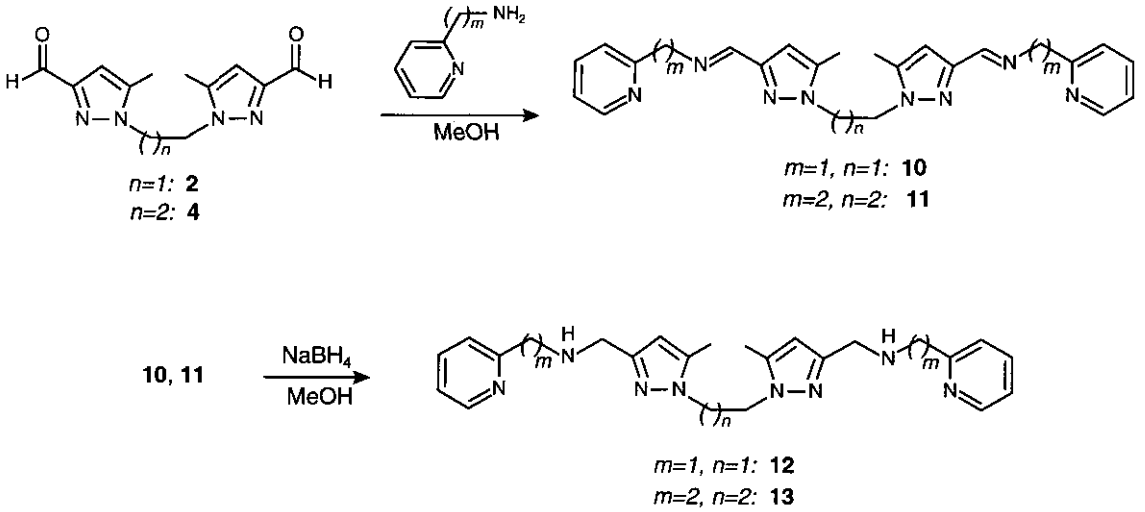


Scheme 2

The *bis*-formyl precursors **2** and **4** reacted smoothly with primary α–pyridinealkylamines, resulting in Schiff bases **10** and **11** in almost quantitative yields. The imine groups were hydrogenated *in situ* to the corresponding secondary amines **12** and **13**, (Scheme 3) in high yields.

Synthesis of the hexa-azole macrocycles MEPY22PZ and ETPY24PZ.

Synthesis of macrocycles ETPY24PZ and MEPY22PZ was realized by a double alkylation of amines **12** and **13** with the appropriate precursor **6** or **9** (Scheme 4).[18] To enhance the nucleophilicity of the amino groups, the corresponding potassium, sodium and lithium amides of **12** and **13** were prepared *in situ* with KO^{t}Bu/THF, NaH/DMF and BuLi/THF, respectively. Subsequent attempts to couple the metallated amines with **6** and **9** were unsuccessful and yielded polymeric side products.[19] Best results were obtained with dry Na_2CO_3/THF under diluted conditions, which gave the macrocyclic products in 16% to 20% yield.



Scheme 3

The macrocyclisation initially seems to proceed faster in DMF or MeCN (no further changes in the ^{1}H–NMR after 48 h), but at the same time, the Pz-CH_2-Cl signal of **9** disappears faster then the Pz-CH_2-N signal of the corresponding secondary amine. This side reaction of **9** lowers the yield of macrocyclic product (≤ 10%). A possible explanation could be the relative fast formation of quaternary ammonium salts, due to successive reaction of **6** or **9** with already formed macrocyclic product. This reaction is kinetically enhanced in polar solvents.[20] In case of ETPY24PZ, this reaction might be followed by a Hoffmann elimination of the pendant (2)-ethylaminopyridine group, resulting in vinylic pyridyl side products.[21]

No specific positive template effect of K^+ or Cs^+ ions was detected.[22] In contrast, dark brown reaction mixtures were observed in the formation of ETPY24PZ when using K_2CO_3 or Cs_2CO_3, with rather low yields (≤ 10%). The pyrazolyl macrocycles were purified by column chromatography and obtained as off-white solids. The ^{1}H- and ^{13}C-NMR spectral data of the hexa-azole macrocycles and the corresponding Cu(I) and Zn(II) complexes are presented in Tables 1 and 2. Recrystallisation of ETPY24PZ from MeOH/Et_2O yielded stable single crystals of adequate quality for an X-ray structure determination.

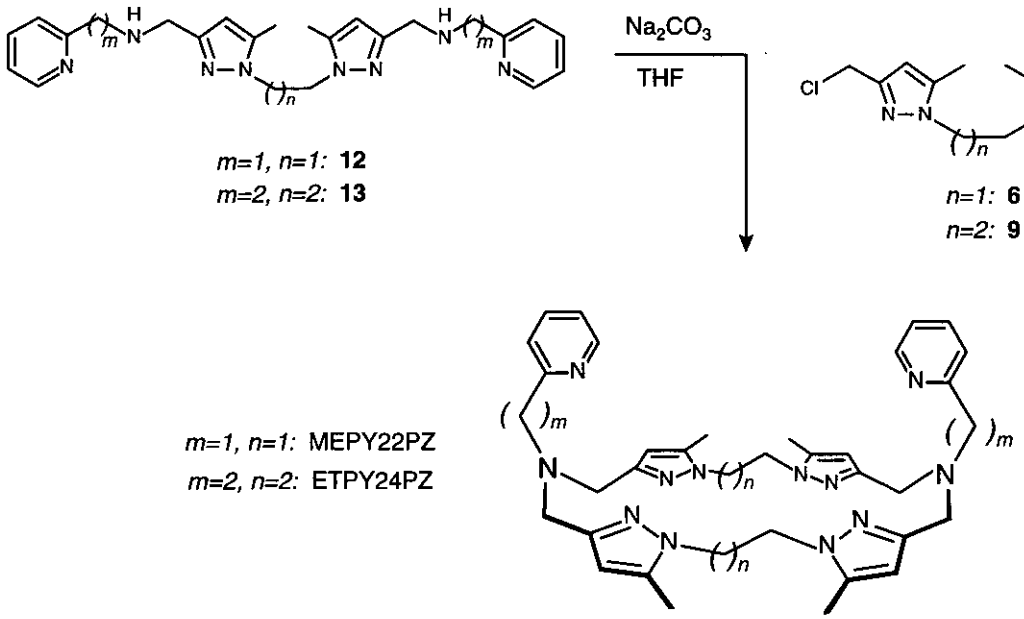
Table 1. ^{1}H-NMR Spectral Data [300 MHz, CD_3CN/CD_3OD (4:1), δ(ppm)][a] of hexa-azole macrocycles and complexes.

Comp.	Py-**H**(6)[b]	Py-$CH_2\alpha$	Py-$CH_2\beta$	Pz-**H**(4)	Pz-CH_3	Pz-CH_2N	Pz-$CH_2\alpha$	Pz-$CH_2\beta$
MEPY22PZ	8.41	3.56	--	5.92	2.15	3.36	4.41	--
	(d, J = 5.6 Hz)	(s)		(s)	(s)	(s)	(s)	
$[Cu_{2(MEPY22PZ)}]^{2+}$	8.51	3.86	--	5.94	2.18	3.63	4.45	--
	(d, J = 4.6 Hz)	(s)		(s)	(s)	(s)	(br s)	
$[Zn_{2(MEPY22PZ)}]^{4+}$	8.94	4.22	--	6.26	2.36	3.99[d]	4.57[c]	--
	(d, J = 5.6 Hz)	(s)	(s)	(s)	(s)	(d, J = 1.5 Hz)	(d, J = 6.1 Hz)	
ETPY24PZ	8.37	2.88[c]	2.78[c]	5.81	2.18	3.53	3.94	2.08
	(d, J = 5.1 Hz)	(m)	(m)	(s)	(s)	(s)	(t, J = 7.2 Hz)	(qui, J = 7.2 Hz)
$[Cu_{2(ETPY24PZ)}]^{2+}$	8.48	3.04	3.04	6.18	2.27	3.67	4.24	2.82
	(d, J = 4.4 Hz)	(br, m)	(br, m)	(s)	(s)	(s)	(br m)	(br m)
$[Zn_{2(ETPY24PZ)}]^{4+}$	8.75	3.18	3.04	6.20	2.20	3.92[c]	4.41[d]	2.15
	(d, J = 5.6 Hz)	(br, m)	(br, m)	(s)	(s)	(d, J = 5.6 Hz)	(double qui)	(ps qui)
							(J = 6.7 Hz)	(J = 6.7 Hz)

Table 2. ^{13}C-NMR Spectral Data [75 MHz, CD_3CN/CD_3OD (4:1), δ(ppm)][e] of hexa-azole macrocycles and complexes.

Comp.	Py**C**(6)[f]	Pz**C**(3)	Pz**C**(5)	Py$CH_2\alpha$	Py$CH_2\beta$	Pz**C**(4)	PzCH_3	PzCH_2N	Pz$CH_2\alpha$	Pz$CH_2\beta$
MEPY22PZ	149.6	149.3	138.5	60.1	--	107.5	10.8	50.7	47.7	--
$[Cu_{2(MEPY22PZ)}]^{2+}$	150.5	150.2	138.8	61.4 (br)	--	106.2	11.3	54.3	48.9	--
$[Zn_{2(MEPY22PZ)}]^{4+}$	152.2	157.0	142.8	58.1	--	106.6	11.8	52.3	47.9	--
ETPY24PZ	149.9	149.3	138.4	54.9	36.6	106.6	11.0	51.7	46.8	31.9
$[Cu_{2(ETPY24PZ)}]^{2+}$	150.4	149.0	138.5	58.2 (br)	36.1	107.0	11.5	53.7 (br)	45.8	31.6
$[Zn_{2(ETPY24PZ)}]^{4+}$	150.0	148.8	142.0	57.2	34.4	106.6	11.5	54.3	48.0	31.0

a) Reference TMS at δ 0.00 ppm. b) Py-**H**(3) 7.3-7.6 (d, J = 7.7 Hz), Py-**H**(4) 7.7-8.2 (dd, J = 1.4/7.7 Hz), Py-**H**(5) 7.2-7.6 (m). c) AA'BB' pattern. d) Geminal coupling. e) Internal reference d^3-MeCN at δ 1.30 ppm. f) Py-**C**(2) 159-162, Py-**C**(3) 123-126, Py-**C**(4) 141-147, Py–**C**(5) 123–126.



Scheme 4

Description of the X-ray structure of ETPY24PZ.

The X-ray structure of ETPY24PZ shows all four pyrazoles endocyclicly bound in the [24]–membered macrocyclic ring, with pyrazole N(12) and N(12a) atoms pointing inwards (Figure 2). Pyrazole N(21) and N(21a) are pointing upwards, possibly to diminish lone pair repulsions between adjacent pyrazole rings. All -CH_2- groups in the alkyl spacers are staggered, indicating a stable, minimal strain conformation of the hexa-azole macrocycle. The unit cell contains two non-identical molecules, conformers (**A**) and (**B**), differing only in the orientation of the pyridine nitrogen atoms with respect to the macrocyclic ring. Both conformers contain a C_2 axis of symmetry. There are no stacking interactions in the crystal: the intermolecular distance between two identical molecules in adjacent unit cells is 9.72 Å for conformer (**A**) and 10.85 Å for conformer (**B**).

Selected bond lengths for conformer (**A**) (Å): N(11)-N(12) 1.370(1), N(12)–C(13) 1.336(9), C(13)-C(14) 1.396(1), C(15)–C(16) 1.489(1), C(15)–N(11) 1.365(1), C(13)-C(40) 1.512(1), N(11)-C(17) 1.474(9), C(17)–C(18) 1.517(1), C(18)-C(19) 1.530(1), C(19)-N(20) 1.469(9), N(20)-N(21) 1.355(1), N(21)–C(22) 1.335(9), C(22)-C(23) 1.380(1), C(23)–C(24) 1.367(1), C(22)–C(26) 1.513(1), C(26)-N(27) 1.469(9), N(27)-C(28) 1.467(1), C(28)-C(29) 1.527(1), C(29)–C(30) 1.506(1), C(30)-C(31) 1.379(1), C(31)-C(32) 1.372(1), N(35)–C(30) 1.341(1). The corresponding bond lengths for conformer (**B**) differ 0.02 Å or less from conformer (**A**).

Selected bond angles for conformer (**A**) (°): N(11)-N(12)-C(13) 103.3(6), N(12)–C(13)-C(14) 111.6(7), C(13)-C(14)-C(15) 106.7(7), C(14)–C(15)-N(11) 105.0(7), N(12)-N(11)-C(15) 113.2(6), N(11)-C(15)-C(16) 122.0(7), N(12)-

C(13)-C(40) 118.9(6), N(12)-N(11)-C(17) 117.9(6), N(11)-C(17)-C(18) 110.4(6), C(17)-C(18)-C(19) 113.3(6) C(18)-C(19)-N(20) 111.7(6), N(21)-C(22)-C(26) 119.4(7), C(22)-C(26)-N(27) 116.4(5), C(26)-N(27)-C(28) 114.2(6), N(27)-C(28)-C(29) 111.8(6), C(29)-C(30)-C(31) 120.2(7), C(29)-C(30)-N(35) 116.4(5), C(30)-C(31)-C(32) 118.7(8), C(34)-N(35)-C(30) 118.6(8). The corresponding bond angles for conformer (**B**) differ 3° or less from (**A**).

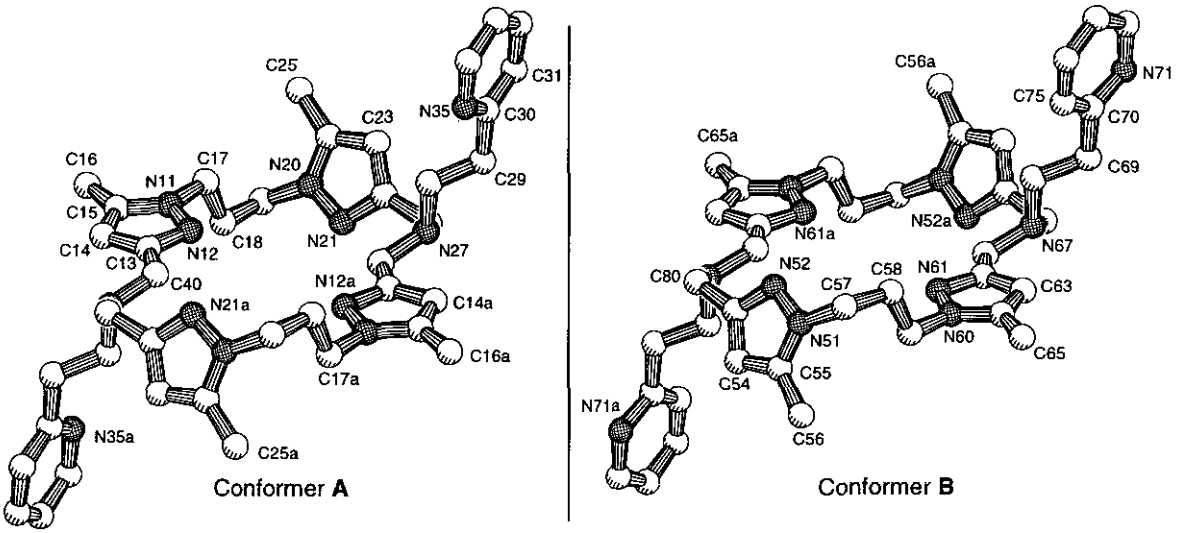


Figure 2. X-Ray structure of the [24]-membered hexa-azole macrocycle ETPY24PZ.

In both conformers, the pendant pyridine groups are arranged in an *anti* conformation, *i.e.:* one pyridine is pointing 'up' and one is pointing 'down' with respect to the plane comprising the pyrazoles. The main difference between conformers (**A**) and (**B**) is the orientation of the pyridine ring. The pyridine N(35) and N(35a) atoms in conformer (**A**) (Figure 2) is pointing towards the inside of the macrocyclic ring, whereas the corresponding nitrogen atoms in the pyridine rings of conformer (**B**) are pointing outwards. Apparently, only weak effects determine the conformation of the pyridine rings when no metal is bound. The free N atoms of the pyrazole groups in both conformers form a diamond shaped box of 4.9 Å (N(12)···N(21)) by 5.4 Å (N(12)···N(21a)). The pyridine N atoms of conformer (**A**) are positioned approximately 5.9 Å above and under the plane defined by the four pyrazole N atoms. The average N···N distance in ETPY24PZ of 5.1 Å is comparable to the average N···N distance between two adjacent imidazole groups in the equatorial plane comprising both copper ions in the active site of deoxy-hemocyanin, which range from 5.2 Å to 5.8 Å.[23] From the X-ray structure depicted in Figure 2, it is expected that ETPY24PZ (and MEPY22PZ) will bind two metal ions in a double tripodal, tetradentate N_4 coordination geometry.[24] NMR complexation studies with Cu(I) and Zn(II) perchlorate salts were carried out to confirm this.

Complexation studies of ETPY24PZ and MEPY22PZ with Cu(I) and Zn(II) ions.

^{1}H-NMR titrations of ETPY24PZ and MEPY22PZ with copper(I) and zinc(II) perchlorate showed that each ligand binds two Cu(I) or Zn(II) ions in MeCN/MeOH solution. The observed M:L ratio of 2:1 makes the possibility of *inter*molecular metal binding by pyridine groups from two different macrocyclic ligands unlikely. The overall pattern in the NMR spectra for Cu(I) and Zn(II) coordination is similar, with most pronounced changes in chemical shift for Zn(II), due to the higher charge on the zinc ion (Tables 1 and 2). In all four cases, the H(6) pyridine proton and pyridine-CH_2-α group shift to lower field, due to the electron withdrawing effect of the metal ion upon coordination to the pyridine ring. Also, the pyridine H(3) proton, which is observed downfield from H(5) in the free macrocycles, appears upfield from the pyridine H(5) proton when a metal is coordinated. The downfield shift of both the pyridine and pyrazole CH_2-N groups (Δδ ranging from 0.2 to 0.6 ppm in the ^{1}H-NMR spectra), indicates that the tertiairy amino nitrogen participates in coordinating the metal ion as well.

In all four dinuclear Cu(I) and Zn(II) complexes, the shifts in the ^{1}H-NMR spectra of the pyrazole groups are less pronounced compared to the pyridine resonances upon coordination. All Pz-*H*(4) and Pz–CH_3 signals in the ^{1}H-NMR shift to lower field, although the effect of metal coordination is more variable compared to the pyridine shifts. Upon binding of Cu(I), a typical AA' pattern of the Pz-CH_2-α groups in the alkyl spacers is observed, indicating less conformational freedom for the ligand and therefore points to *intra*molecular Cu(I) binding. Similarly, when 2 equivalents Zn(II) coordinate to MEPY22PZ or ETPY24PZ, a rather complicated ^{1}H–NMR spectrum is observed (even at 600 MHz), with an AA'BB' pattern for the Pz–CH_2-α groups and geminal coupling of the Pz-C*HH'*-N groups. This also indicates a rigid structure of the $[Zn_2(L)]^{4+}$ cation, with less conformational flexibility compared to the free macrocycle. The Pz-*H*(4) and Pz–CH_3 signals remain singlets in all cases, however, indicating preservation of high symmetry when two metals are bound.

Participation of the pyrazole moieties is shown furthermore in the ^{13}C-NMR by a downfield shift (average $\Delta\delta \approx 3.5$ ppm) of the C(5) carbon atoms in the pyrazole rings. The changes in chemical shift of the pyrazole C(3) carbon atoms are more variable and often less pronounced (Δδ ranging from 0.5 ppm up to 7.7 ppm in the ^{13}C-NMR). Remarkably, the chemical shift of the pyrazole C(4) carbon atom in the ^{13}C-NMR is hardly affected by coordination to a metal ion (both Cu and Zn), in contrast to the observation of Navarro *et al.*[25] Still, the overall NMR pattern clearly indicates participation of all pyrazole groups in coordination to the metal ions.

Further complexations and reactivity studies with Cu(I) and Cu(II) ions are in progress, to establish if the *anti* conformation of the pendant pyridine groups in the hexa-azole ligands ETPY24PZ and MEPY22PZ is preserved when two metal ions are coordinated.[26] In any case, the overall conformation of the azole donors in the X-ray structure of ETPY24PZ depicted in Figure 2 resembles the arrangement of the six histidine residues in (de)oxy-hemocyanin.[5]

CONCLUSIONS

The novel [22]- and [24]-membered hexa-azole macrocycles MEPY22PZ and ETPY24PZ have been successfully synthesized in yields of 15% to 20%, by a general synthetic route involving a double cyclisation between secondary amines **12** and **13**, combined with chlorinated pyrazolyl precursors **6** and **9**. The macrocyclic receptor molecules are obtained in this way by a 10-step synthesis, including a column purification.

The *anti* conformation of the two pendant pyridine groups with respect to the four pyrazole groups around the macrocyclic cavity in the X-ray structure of ETPY24PZ, mimicks the arrangement of the six histidine donors in the type-3 active site of the dinuclear copper protein (de)oxy-hemocyanin. NMR titrations show that both macrocyclic ligands are capable of complexating two Cu(I) ions or two Zn(II) ions, whereby all azole donors are involved in coordination. The described synthetic pathway allows extension to similar hexa-azole macrocycles of different size and flexibility by varying the pendant donors or alkyl spacers. Other metal ions (*i.e.* Fe, Mn, Co) are expected to coordinate at the tripodal binding sites in a similar way, and therefore the presented macrocycles might also be useful as synthetic model ligands for the active site of other dinuclear metalloproteins.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR (^{1}H decoupled) spectra were recorded on a Jeol JNM-FX 200 spectrometer or a Bruker WM-300 MHz spectrometer. FT-IR spectra were recorded on a Bruker 330v infrared spectrophotometer as KBr disks (4000-400 cm^{-1}, resolution 2 cm^{-1}). Mass spectra (MS) were registered by fast atomic bombardment (FAB) technique in a Finnigan MAT 900 double focussing mass spectrophotometer or by plasma desorption (PDMS) in a ABI Bio-Ion 20 apparatus. Elemental analysis were carried out by the Micro-analytical Department of Groningen University. Data collections for X-ray structure determinations were performed on an Enraf-Nonius CAD-4 diffractometer with CuK_α radiation and ω-2θ scan. Analytical TLC was performed on glass plates coated with sillica gel 60 (Merck). Compounds were detected in a iodine chamber. Column chromatography was performed using the flash chromatography technique on silica gel 60 (230-400 mesh ASTM, Merck). All reagents were of commercial quality (Aldrich or Janssen) and used as received. Thionyl chloride (Merck) was freshly distilled before use. THF and MeOH were dried on sodium and distilled under N_2 prior to use. CH_2Cl_2 (Janssen) was vacuum transferred before using as eluent.

1,2-Di(3'-formyl-5'-methyl-1'-pyrazolyl)ethane (**2**): 15.0 g (136.0 mmol) of **1** was dissolved in 1.5 L of dry THF under reflux until the solution became bright light yellow (*ca.* 2 h). After cooling to -40 °C, 25.21 g (68.1 mmol) of 1,2–di(*p*-toluenesulfonyloxy)ethane and 15.28 g (136.2 mmol) of KO^{t}Bu were added and the suspension was refluxed for 22 h. THF was evaporated and the resulting light brown solid

was suspended in 200 mL ammonia (sat) and extracted 3 times with 300 mL of CH_2Cl_2. After drying on Na_2SO_4 and reducing the solvent volume, the crude product was filtered twice over a short Alumina-*N* (10% H_2O) column. After removal of the solvent, the orange solid was recrystallised from THF/Et_2O/hexane (2:1:4 vv). Off-white, hygroscopic crystals were obtained after 24 h at -20 °C. Yield 4.21 g (28%). ^{1}H–NMR ($CDCl_3$): 9.90 (s, 2H, PzC*H*O), 6.44 (s, 2H, Pz*H*(4)), 4.61 (s, 4H, PzC$H_2\alpha$), 1.83 (s, 6H, PzCH_3). ^{13}C-NMR ($CDCl_3$): 186.3 (Pz–*C*HO), 151.1 (Pz-*C*(3)), 142.0 (Pz-*C*(5)), 105.3 (Pz-*C*(4)), 49.3 (Pz–*C*H_2), 10.2 (Pz-*C*H_3). Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: 57.75; 5.71; 22.10.

Side product 1-(3'-formyl-5'-methyl-1'-pyrazolyl)ethene (3): ^{1}H-NMR ($CDCl_3$): 9.96 (s, 1H, PzC*H*O), 6.58 (s, 1H, Pz–*H*(4)), 7.04 (dd, *J* = 0.8/2.0 Hz, 1H, -C*H*=), 5.91 (d, *J* = 15.2 Hz, 1H, *cis* =C*H*), 5.11 (d, *J* = 9.0 Hz, 1H, *trans* =C*H*), 2.38 (s, 3H, PzCH_3), in agreement with the assignment of other 1–ethenylazoles.[27]

1,3-Di(3'-formyl-5'-methyl-1'-pyrazolyl)propane (4): The compound was synthesised according to published procedures[14] (yield 63%) and purified on an Alumina-*N* (5% H_2O) column using CH_2Cl_2 as eluent. Colourless single crystals were obtained by vapour diffusion of Et_2O in the CH_2Cl_2 mother liquor. ^{13}C-NMR ($CDCl_3$): 186.3 (Pz-*C*HO), 150.6 (Pz-*C*(3)), 140.6 (Pz-*C*(5)), 105.4 (Pz-*C*(4)), 46.2 (Pz-*C*$H_2\alpha$), 28.9 (Pz-*C*$H_2\beta$), 11.0 (Pz-*C*H_3). IR (KBr, cm^{-1}): 1692 ν(C=O), 1549 ν(Pz C-N). Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: 59.64; 6.31; 21.17.

Crystal data of 4: $C_{13}H_{16}N_4O_2$, monoclinic, space group $P2_1/c$ with *a*=14.964(1), *b*=4.3251(5), *c*=20.838(2) Å, β=101.182(7)°, *V*=1323.0(2) Å^3, *Z*=4, D_c=1.31 g cm^{-3}, *F*(000)=552. A single crystal of **4** (0.35 x 0.35 x 0.80 mm), suitable for X-ray diffraction studies, was mounted in a glass capillary. Intensities were measured at rt with graphite-monochromated radiation λ(CuK_α)=1.5418 Å, (μ(CuK_α)=7.12 cm^{-1}). A total of 2727 unique reflections were measured within the range $0 \le h \le 18$, $-5 \le k \le 5$, $-26 \le l \le 25$ with a maximum value of (sinΘ/λ)=0.63 Å^{-1}. 2292 unique reflections with $I > 2\sigma(I)$ were used in the refinement. Unit-cell parameters were refined by a least-squares fitting procedure using 23 reflections with $80° \le 2\Theta \le 85°$. Corrections for Lorentz and polarization effects were applied. The structure was solved by direct methods using the XTAL package.[28] The hydrogen atoms were placed at idealized positions (C-H 0.97 Å, ∠CCH 109° or 120°). Full-matrix least squares refinement on *F*, anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms, converged at *R*=0.048, R_w=0.061, $(\Delta/\sigma)_{max}$=0.33. Empirical absorption correction DIFABS[29] was applied. The final difference Fourier map revealed a residual electron density (max ± 0.2e Å^{-3}) in the vicinity of heavy atoms. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

1,2-Di(3'-hydroxymethyl-5'-methyl-1'-pyrazolyl)ethane (**5**): 5.00 g (20.30 mmol) of **2** was dissolved under reflux in 250 mL dry MeOH (*ca.* 1 h), after which 2.30 g (60.8 mmol, 1.5 eq/CH=N) of $NaBH_4$ was added. When the evolution of H_2 gas had stopped, the bright yellow solution was refluxed for an additional 3 h, after which the solvent and residual water was removed *in vacuo*. The resulting solid salt-residue was extracted with 2 times 150 mL of DMF upon warming (*ca.* 80 °C, no water should be used during the extraction). After evaporation of the solvent and drying *in vacuo*, a white-yellow solid was obtained, which was sufficiently pure (NMR) for further synthesis. Yield: 5.70 g (93%). ^{1}H-NMR (CD_3OD): 5.95 (s, 2H, Pz–*H*(4)), 4.49 (s, 4H, PzCH_2OH), 4.35 (s, 4H, Pz$CH_2\alpha$), 1.69 (s, 6H, PzCH_3). ^{13}C-NMR (CD_3OD): 153.6 (Pz-*C*(3)), 142.5 (Pz-*C*(5)), 105.1 (Pz-*C*(4)), 58.8 (Pz-CH_2OH), 10.0 (Pz–CH_3). Pz$CH_2\alpha$ signal masked by solvent (47.7-50.3 ppm).

1,2-Di(3'-chloromethyl-5'-methyl-1'-pyrazolyl)ethane (**6**): 5.00 g (16.10 mmol) of **5** was added to 55 mL (0.75 mol) of pure $SOCl_2$ at 0°C. After overnight stirring at rt, the excess $SOCl_2$ was removed by rotary evaporation. The resulting brown oil was washed with Et_2O, dissolved in 125 mL of CH_2Cl_2 and neutralised with 70 mL of a saturated $NaHCO_3$ solution. After drying on Na_2SO_4 and evaporation of the solvent, a viscous brown oil remained, which solidified upon standing at -20 °C. The product was stored under N_2. Yield 5.25 g (93%). ^{1}H-NMR ($CDCl_3$): 5.93 (s, 2H, Pz-*H*(4)), 4.52 (s, 4H, CH_2-Cl), 4.38 (s, 4H, $CH_2\alpha$), 1.69 (s, 6H, Pz–CH_3). ^{13}C-NMR ($CDCl_3$): 148.6 (Pz-*C*(3)), 141.4 (Pz-*C*(5)), 104.9 (Pz-*C*(4)), 48.9 (Pz–$CH_2\alpha$), 38.9 (Pz-CH_2-Cl), 9.9 (Pz-CH_3).

1,3-Di(3'-chloromethyl-5'-methyl-1'-pyrazolyl)propane (**9**): To a solution of 1,3-di(3'-hydroxymethyl-5'-methyl-1'-pyrazolyl)propane **8**[17] (1.00 g, 3.78 mmol) in 50 mL of CH_2Cl_2, 0.61 mL (8.32 mmol) of $SOCl_2$ was added dropwise at room temperature. After 2 h stirring, the white suspension was refluxed additionally for 6 h. The mixture was neutralized with an saturated aqueous $NaHCO_3$ solution. After filtration, the organic layer was separated and dried on Na_2SO_4 (2 h). Evaporation of the solvent gave a light grey, moisture sensitive, solid which was stored under N_2. Yield 0.91 g (80%). ^{1}H-NMR ($CDCl_3$): 6.06 (s, 2H, Pz-*H*(4)), 4.54 (s, 4H, CH_2-Cl), 4.00 (t, J = 6.9 Hz, 4H, $CH_2\alpha$), 2.38 (ps qui, J = 6.8 Hz, 4H, CH_2-β), 2.17 (s, 6H, Pz–CH_3). ^{13}C-NMR ($CDCl_3$): 147.8 (Pz-C(3)), 139.8 (Pz-C(5)), 104.9 (Pz-C(4)), 45.5 (Pz-$CH_2\alpha$), 39.1 (Pz–CH_2-Cl), 29.6 (Pz-$CH_2\beta$), 10.9 (Pz–CH_3).

1,2-Di(3'-(2-pyridin-2-ylmethylimino)-5'-methyl-1'-pyrazolyl)ethane (**10**): A solution of 4.83 mL (37.10 mmol) of 2-(2-aminoethyl)pyridine (Aldrich) in 75 mL of MeOH was added dropwise at rt to a solution of 5.57 g (18.60 mmol) of **2** in 400 mL of MeOH. The clear, pale yellow solution was stirred for 2 h at 50 °C. A sample taken for NMR measurement, gave a clear yellow oil after evaporation of the solvent. ^{1}H-NMR ($CDCl_3$): 8.65 (d, J = 5.6 Hz, 2H, Py*H*(6)), 8.42 (s, 2H, C*H*=N), 7.66 (t, J = 7.5 Hz,

2H, Py*H*(4)), 7.38 (d, *J* = 7.5 Hz, 2H, Py*H*(3)), 7.17 (m, 2H, Py*H*(5)), 6.41 (s, 2H, Pz*H*(4)), 4.93 (s, 4H, PzCH_2α), 4.49 (s, 4H, PyCH_2α), 1.74 (s, 6H, PzCH_3). ^{13}C-NMR ($CDCl_3$): 159.0 (Py-*C*(2)), 157.0 (*C*H=N), 149.7 (Pz-*C*(3)), 149.1 (Py-*C*(6)), 141.2 (Pz-*C*(5)), 136.6 (Py-*C*(4)), 122.2 (Py-*C*(3)), 121.9 (Py–*C*(5)), 104.2 (Pz-*C*(4)), 66.8 (Py-*C*H_2), 49.1 (Pz–*C*H_2α), 10.0 (Pz-*C*H_3).

1,3-Di(3'-(2-pyridin-2-ylethylimino)-5'-methyl-1'-pyrazolyl)propane (**11**): The compound was synthesised according to a procedure similar to that described for the preparation of **10**, by using 3.25 g (12.49 mmol) of *bis*-(3)-formylpyrazolyl precursor **4** in 150 mL of MeOH and 3.0 mL of 2-(2-amino-ethyl)pyridine (Aldrich). **11** was obtained as a clear yellow oil after evaporation of the solvent. ^{1}H-NMR ($CDCl_3$): 8.54 (d, *J* = 5.1 Hz, 2H, Py*H*(6)), 8.19 (s, 2H, C*H*=N), 7.56 (t, *J* = 7.7 Hz, 2H, Py*H*(4)), 7.17 (d, *J* = 7.7 Hz, 2H, Py*H*(3)), 7.12 (m, 2H, Py*H*(5)), 6.44 (s, 2H, Pz*H*(4)), 4.03 (t, *J* = 7.2 Hz, 4H, PzCH_2α), 3.98 (t, *J* = 7.9 Hz, 4H, PyCH_2α), 3.18 (t, *J* = 7.9 Hz, 4H, PyCH_2β), 2.42 (ps qui, *J* = 7.1 Hz, PzCH_2β), 2.17 (s, 6H, PzCH_3). ^{13}C-NMR ($CDCl_3$): 159.8 (Py-*C*(2)), 155.8 (*C*H=N), 149.3 (Py-*C*(6)), 149.2 (Pz–*C*(3)), 139.8 (Pz-*C*(5)), 136.1 (Py-*C*(4)), 123.6 (Py-*C*(3)), 121.2 (Py-*C*(5)), 104.0 (Pz-*C*(4)), 61.3 (Py–*C*H_2β), 45.7 (Pz-*C*H_2α), 39.6 (Py-*C*H_2α), 29.5 (Pz-*C*H_2β), 11.0 (Pz–*C*H_3).

1,2-Di(3'-(2-pyridin-2-ylmethylamino)-5'-methyl-1'-pyrazolyl)ethane (**12**): 2.30 g (111.0 mmol, 3 eq/CH=N) of $NaBH_4$ was added *in situ* at rt to the MeOH solution (475 mL) containing 7.93 g (18.60 mmol) of **10**. The clear, colourless solution was refluxed for 3 h. After stirring overnight at rt, the solvent was evaporated, 200 mL of demineralised H_2O was added and acidified with 40 mL of aqueous HCl (2 M). The acidic layer was washed with CH_2Cl_2, and made basic again with concentrated ammonia until pH≥9. The white suspension was extracted with 3 times 100 mL of CH_2Cl_2 and dried 20 min on Na_2SO_4. A hygroscopic, viscous residue was obtained after evaporation of the solvent. The clear yellow oil was stored under nitrogen. Yield 7.31 g (93%). ^{1}H-NMR ($CDCl_3$): 8.54 (d, *J* = 3.6 Hz, 2H, Py*H*(6)), 7.81 (dd, *J* = 1.2/7.7 Hz, 2H, Py*H*(4)), 7.33 (d, *J* = 7.7 Hz, 2H, Py*H*(3)), 7.45 (m, 2H, Py*H*(5)), 5.87 (s, 2H, Pz*H*(4)), 4.35 (s, 4H, PzCH_2α), 3.95 (s, 4H, PyCH_2), 3.79 (s, 4H, PzCH_2N), 1.66 (s, 6H, PzCH_3). ^{13}C-NMR ($CDCl_3$): 161.3 (Py-*C*(2)), 149.2 (Py-*C*(6)), 150.8 (Pz-*C*(3)), 140.4 (Pz-*C*(5)), 142.3 (Py-*C*(4)), 124.2 (Py-*C*(3)), 124.7 (Py-*C*(5)), 104.3 (Pz-*C*(4)), 54.5 (Py-*C*H_2), 48.8 (Pz-*C*H_2α), 46.6 (Pz–*C*H_2N), 9.9 (Pz–*C*H_3). *Sec*-amine N*H* observed as broad singlet around δ 1.8 ppm.

1,3-Di(3'-(2-pyridin-2-ylethylamino)-5'-methyl-1'-pyrazolyl)propane (**13**): 1.59 g (42 mmol) of $NaBH_4$ was added *in situ* at rt to the MeOH solution (150 mL) containing 3.25 g (6.94 mmol) of **11**. The clear, colourless solution was refluxed for 4 h. After stirring overnight at rt, the solvent was evaporated, 200 mL of demineralised H_2O was added and acidified with 40 mL of aquous HCl (2 M). The acidic layer was washed with CH_2Cl_2, and made basic again with concentrated ammonia until pH ≥ 9. The white

suspension was extracted with 3 times 100 mL of CH_2Cl_2 and dried 20 min on Na_2SO_4. A hygroscopic, viscous residue was obtained after evaporation of the solvent. The clear yellow oil was stored under nitrogen. Yield 3.12 g (95%). ^{1}H-NMR ($CDCl_3$): 8.51 (d, J = 4.0 Hz, 2H, Py*H*(6)), 7.96 (t, J = 7.7 Hz, 2H, Py*H*(4)), 7.48 (d, J = 7.7 Hz, 2H, Py*H*(3)), 7.53 (m, 2H, Py*H*(5)), 5.90 (s, 2H, Pz*H*(4)), 3.94 (t, J = 7.1 Hz, 4H, PzC$H_2\alpha$), 3.76 (s, 4H, PzCH_2N), 3.02 (m, 4H, PyC$H_2\alpha$), 3.02 (m, 4H, PyC$H_2\beta$), 2.31 (qui, J = 7.1 Hz, 2H, PzC$H_2\beta$), 2.11 (s, 6H, PzCH_3). ^{13}C-NMR ($CDCl_3$): 161.3 (Py-*C*(2)), 149.2 (Py-*C*(6)), 150.4 (Pz-*C*(3)), 138.8 (Pz-*C*(5)), 145.8 (Py-*C*(4)), 125.2 (Py-*C*(3)), 124.9 (Py-*C*(5)), 104.1 (Pz-*C*(4)), 48.9 (Py-*C*$H_2\alpha$), 47.1 (Pz-*C*H_2N), 45.4 (Pz-*C*$H_2\alpha$), 38.6 (Py-*C*$H_2\beta$), 30.0 (Pz-*C*$H_2\beta$), 10.9 (Pz–*C*H_3). *Sec*-amine N*H* observed as broad singlet around δ 2.6 ppm.

1,5,10,15,19,24,29,30,31,32-Decaaza-(10,24-di(pyridin-2-ylethyl)-6,14,20,28-tetramethyl)pentacyclo-[24.2.1.1^{5,8}.1^{12,15}.1^{19,22}]triacontane-6,8(30),12(31),13,20,22(32),26(29),27-octaene (ETPY24PZ). Under a N_2 atmosphere, 1.84 g (13.3. mmol) of Na_2CO_3 (heated for 5 min *in vacuo*) and 3.14 g (6.70 mmol) of *bis*-amine **13** were suspended in 300 mL of THF. A solution of 2.01 g (6.67 mmol) *bis*-chloride **9** in 150 mL of THF was added dropwise at rt under vigorous stirring. The suspension was refluxed for 6 days and slowly turned from colourless to yellow. 600 mL of a saturated NaCl solution was added, the mixture was acidified with 50 mL of HCl (2 M) until pH ≤ 1 and washed with Et_2O. The H_2O layer was made alkaline with concentrated ammonia and extracted with 3 times 100 mL of CH_2Cl_2. After drying of the organic layer for 20 min on Na_2SO_4 and evaporation of the solvent, a viscous orange brown oil (~ 4.5 g) remained. Column chromatography on sillicagel (15 cm x ∅ 3.5 cm) using MeCl/MeOH (90/10) as the eluent, gave a pale yellow solid ($R_f \approx 0.6$) after evaporation of the solvent, which was recrystallised from MeOH/Et_2O. Yield 1.32 g (19%). MS (PD, positive ion); 700.90 (M^+ and pp, expected 700.93), 722.0 ($M + Na^+$), 609.2 (M^+-PyCH_2), 595.3 (M^+-PyCH_2CH_2). IR (KBr, cm^{-1}): 1588 (s), 1568 (s): Py $\nu_{C=N}$; 1545 (vs): Pz $\nu_{C=N}$; 1474 (s), 1437 (s), 1398 (s), 1320 (s), 792 (s), 763(s). Anal. Calcd for $C_{40}H_{52}N_{12}$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.28; H, 7.55; N, 23.63. Colourless, single crystals of ETPY24PZ were obtained by vapour diffusion of Et_2O in a MeOH solution of ETPY24PZ.

*Crystal data for **ETPY24PZ**:* $C_{40}H_{52}N_{12}$, triclinic, space group *P-1* (no. 2) with a=9.716(2), b=10.850(3), c=21.288(7) Å, α=90.48(3)°, β=103.17(3)°, γ=116.58(2)°, V=1938(1) Å^3, Z=2, D_c=1.2008(6) g cm^{-3}, F(000)=752.0. A single crystal of ETPY24PZ, suitable for X-ray diffraction studies, was mounted on a glass capillary. Intensities were measured at room temperature with graphite-monochromated radiation λ(MoK$_\alpha$)=0.7107 Å (μ(Mo-Kα)=0.7 cm^{-1}), using an ω-scan (2.1°≤ 2Θ ≤ 27.4°). 3061 unique reflections with I>2σ(I) were used in the refinement. Absorption correction was not applied. The structure was solved by direct methods using the XTAL package.[27] Following refinement of the non-hydrogen atoms using anisotropic thermal parameters, the hydrogen atoms were placed at idealised positions (C-H 0.96 Å, ∠CCH 109° or 120°). Refinement converged at R=0.071, R_w=0.079, S=3.19. Atomic coordinates, bond

lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

(9,21-Di(2-pyridin-2-ylmethyl)-1,4,9,14,17,22,27,28,29,30,-decaaza-5,13,18,26-tetramethyl)pentacyclo-[21.2.1.1^{4,7}.1^{11,14}.1^{17,20}]octaicosane-5,7(28),11(29),12,18,20(30),24(27),25-octaene (MEPY22PZ): The compound was synthesised by a comparable procedure described for the preparation of ETPY24PZ. 5.52 g (12.8 mmol) of **12** and 1 equivalent dichloride of **6** (3.68 g, 12.81 mmol) was dissolved in 1.7 L of dry THF and 300 mL of dry MeCN, to obtain a clear solution. The reaction mixture gradually turned into a light brown suspension and was refluxed for 10 days. After work up, short drying on Na_2SO_4 and evaporation of the solvent, a dark red-brown solid (~ 5.5 g) remained. Column purification of 4.5 g of the crude product on sillicagel (15 cm x ∅ 9.5 cm) using CH_2Cl_2/MeOH (85/15) as the eluent, gave a pale yellow solid ($R_f \approx 0.6$) after evaporation of the solvent, which was recrystallised from MeOH/Et_2O. Yield 1.28 g (16%). MS (ESI, positive ion); 645 [M^++H and pp, expected 644.82], 667 [M + Na^+], 683 [M + K^+], 323 [M + 2H]$^{2+}$. IR (KBr, cm^{-1}): 1588 (s), 1568 (s): Py $\nu_{C=N}$; 1545 (vs): Pz $\nu_{C=N}$; 1474 (s), 1437 (s), 1398 (s), 1320 (s), 792 (s), 763(s). The product was found to contain a half equivalent of H_2O, also visible in ^{1}H-NMR ($CDCl_3$) at δ 1.70 ppm. Anal. Calcd for $C_{36}H_{44}N_{12}$ $(H_2O)_{0.5}$ C, 66.13; H, 6.94; N, 25.71. Found: C, 66.09; H, 6.84; N, 25.57.

ACKNOWLEDGEMENTS

We are grateful to Prof. Dr. A. van der Gen (Leiden University) for fruitful discussions, F. Hulsbergen and R. Bode for comments and improvements on several synthetic procedures and R.A.M. van der Hoeven (Leiden University) for measurement of the ESI mass spectra. The research described in this paper has been performed under the auspices of the Holland Research School of Molecular Chemistry (HRSMC), a research alliance of the universities in Amsterdam and Leiden.

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18. The [24]-membered macrocycle MEPY24PZ with two propyl spacers and (2)-methylaminopyridine pendant substituents was synthesized, but only in low yield (≤ 5%). Apparently, the combination of two unfavourable factors, (i) lower nucleophilic character of the *sec* NH groups, caused by the electron-withdrawing methyl-pyridine substituent and (ii) the greater flexibility caused by the propyl spacers, gives rise to extensive polymerisation. These polymeric products hampered the isolation of MEPY24PZ. Coordination of the crude reaction mixture with $Cu(NO_3)_2$ yielded a small crop of green powder, from which the ligand was recuperated by work-up with NH_3 and extraction with $CHCl_3$. Satisfactory ^1H and ^{13}C-NMR. The macrocyclic nature of MEPY24PZ was established with ESI-MS: 673.4 [M + H and pp, expected 673.8], 695.4 [M + Na], 711.5 [M + K].

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Received, 17th February, 1997