Synthesis and Protonation Behavior of 26-Membered Oxaaza and Polyaza Macrocycles Containing Two Heteroaromatic Units of 3,5-Disubstituted Pyrazole or 1-Benzylpyrazole. A Potentiometric and ^{1}H and ^{13}C NMR Study

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The synthesis and acid−base behavior of two series of 26-membered dioxatetraamine and hexaamine heterocyclophanes containing two nuclei of either pyrazole (**4a** and **6a**) or 1-benzylpyrazole (**4b** and **6b**), respectively, are reported. Dipodal (2 + 2) condensations of 3,5-pyrazoledicarbaldehyde **2a** or its 1-benzyl derivative **2b** with 1,5-diamino-3-oxapentane afford in both cases the stable Schiff bases **3a,b** in 90% yield, which after reduction with $NaBH_4$ gave **4a,b** in 75% and 84% yield, respectively. Condensation of **2a** with diethylenetriamine leads to a complex mixture containing imidazolidine isomers, which was reduced in situ to afford **6a** in 30% yield. Condensation of **2b** with the same amine gave the stable diimidazolidine derivative **5b**, which after crystallization was isolated as a pure compound in 80% yield and fully identified from analytical and ^{1}H and ^{13}C NMR data as a constitutional isomer with both imidazolidine rings located at the side of the pyrazole closer to the benzylic substituents. Reduction of **5b** with $NaBH_4$ afforded the polyamine **6b** in 86% yield. Protonation constants of **4a**,**b** and **6a**,**b** have been determined by potentiometric methods in the pH 2−11 range, and their protonation sequences were established by a ^{1}H and ^{13}C NMR study in D_2O at variable pH. For each compound, the number of protonation constants equals the number of nitrogens in the side chains. In the pH range studied, the pyrazole rings are not involved in protonation or deprotonation processes.

Introduction

Dopamine and norepinephrine are neurotransmitter catecholamines involved in the normal emotional and autonomic control of humans, the physiological levels of which are altered in neurodegenerative and mental illnesses,[1] as well as in toxic syndromes induced by cocaine and psychotropic drugs of hallucinogen effects.[2] Consequently, the development of synthetic receptors able to diminish or increase the level of some of these neurotransmitters by selective complexation and/or transport mechanisms is of great interest.

It is well-known that neutral polyoxa, oxaaza, and polyaza macrocycles containing a trigonal arrangement of binding sites are able to selectively bind the primary ammonium cation of dopamine and norepinephrine.[3] Also, the catechol groups of dopamine and its derivatives,[4] as well as anionic substrates of biological importance such as polycarboxylate anions, carbonate, and phosphates,[5] are selectively recognized by macrocyclic polyamines as polyprotonated species in neutral pH solutions. In such receptors the ammonium groups are separated from each other by hydrocarbon chains and aromatic or heteroaromatic rings.[6] Indeed, these compounds may act as ambivalent receptors; in their fully or partly protonated forms, they may interact with the catechol group or with anionic species, whereas when disposing of free lone pairs they can act as Lewis bases toward metal ions. Hence, their ability to interact with catechol groups, anions, or metal cations can be simply switched by changing the pH of the medium.

Previously, we have reported on a series of heteroaromatic crowns containing two or more units of 3,5- or

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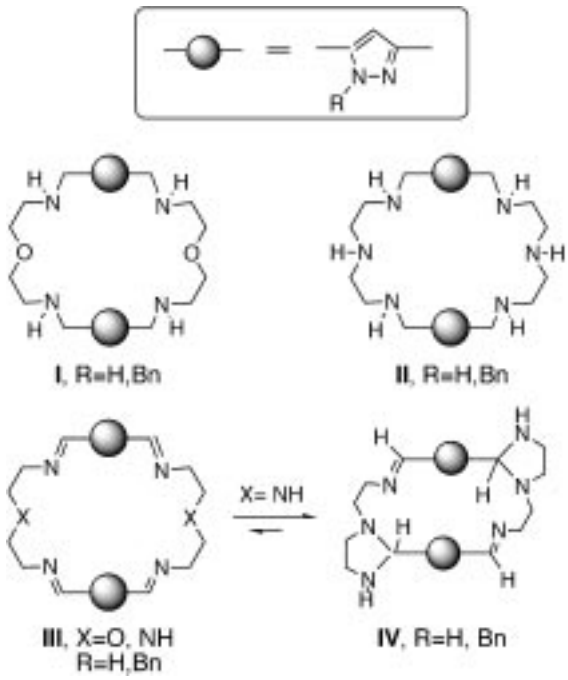
1,3,5-substituted pyrazole linked to the side chains by ester or ether bonds, which are able to either irreversibly complex or transport NH_4^+ ions[7] and/or RNH_3^+ ions of dopamine and norepinephrine.[8] We have also reported a different series of polyaza macrocycles and macrobicycles containing two or three 3,5-disubstituted pyrazole units linked to the polyamine side chains by imine or amine bonds.[9,10] In basic medium, these ligands formed di- or tripyrazolate sodium salts from which di- and/or tetranuclear Zn(II) and Cu(II) complexes were formed.[10,11] Now, we are interested in the study of the basicity of the last mentioned polyamine macrocycles of pyrazole to subsequently evaluate their potential ability as complexing receptors of dopamine and norepinephrine by selective interaction with their catechol groups.

The influence of different aromatic and heteroaromatic rings on the basicity of dinuclear polyamine cyclophanes[12] and heterocyclophanes[13] in relation to [18]aneN_6 (1,4,7,-10,13,16-hexaazacyclooctadecane) has been previously reported. In this paper we have studied the influence of both the 3,5-disubstituted pyrazole and the 1-benzylpyrazole rings on the basicity of two different series of 26-membered dioxatetraamine and hexaamine heterocyclophanes of general structures I and II, respectively (Scheme 1).

Herewith, we present the ^{1}H and ^{13}C NMR spectra in D_2O at different pH values of polyaza macrocycles of 3,5-disubstituted pyrazole of general structure I (R = H) and II (R = H) previously mentioned in a short communication,[9] as well as the synthesis and spectroscopic properties of a new series of 1-benzyl analogue receptors of structures I (R = Bn) and II (R = Bn). All of them were obtained by reduction of tetraimine or diimine derivatives of general structures III (X = O, NH; R = H, Bn) or IV (R = H, Bn), respectively.

Although several groups have detected the formation of imidazolidine derivatives related to IV in equilibrium with Schiff bases similar to III (X = NH), as far as we know there are few examples including X-ray structures[14,15] and a detailed NMR characterization of such compounds has not previously been reported.

Scheme 1



In this paper we also report on the preparation of the pure imidazolidine derivative IV (R = Bn) and its characterization by ^{1}H and ^{13}C NMR spectroscopy.

Results and Discussion

Synthesis. Heteroaromatic polyazamacrocycles containing pyridine, pyrrole, furan, and thiophene rings have been obtained following a two-step synthetic method that includes a first dipodal (2 + 2) condensation of α,ω-diamines with the corresponding dialdehydes, followed by hydrogenation of the Schiff base imine bonds.[14,16,17] However, several authors have pointed out that when such α,ω-diamines have additional NH or OH groups in the middle of the chain, the first condensation step affords a mixture of two isomers. Thus, Fenton and coworkers reported that, in the absence of metal ions, the condensation of 2,5-thiophenedicarbaldehyde with diethylenetriamine affords a solid product whose ^{1}H NMR spectrum corresponds to a mixture of the desired tetraimine Schiff base together with an imidazolidine isomer formed by nucleophilic addition of the two secondary amine groups of the tetraimine macrocycle across the adjacent imine bonds.[14]

Similar processes have also been reported in the synthesis of tetraimine Schiff base macrocycles in which Ba(II)[18] and Pb(II)[19] were used as metal templating agents. In fact, tetraimine dicopper(II) complexes have been prepared from ring-contracted oxazolidine lead complexes by transmetalation with concomitant expansion of the macrocycle.[20] Furthermore, as mentioned above, Martell et al. have characterized by X-ray diffrac-

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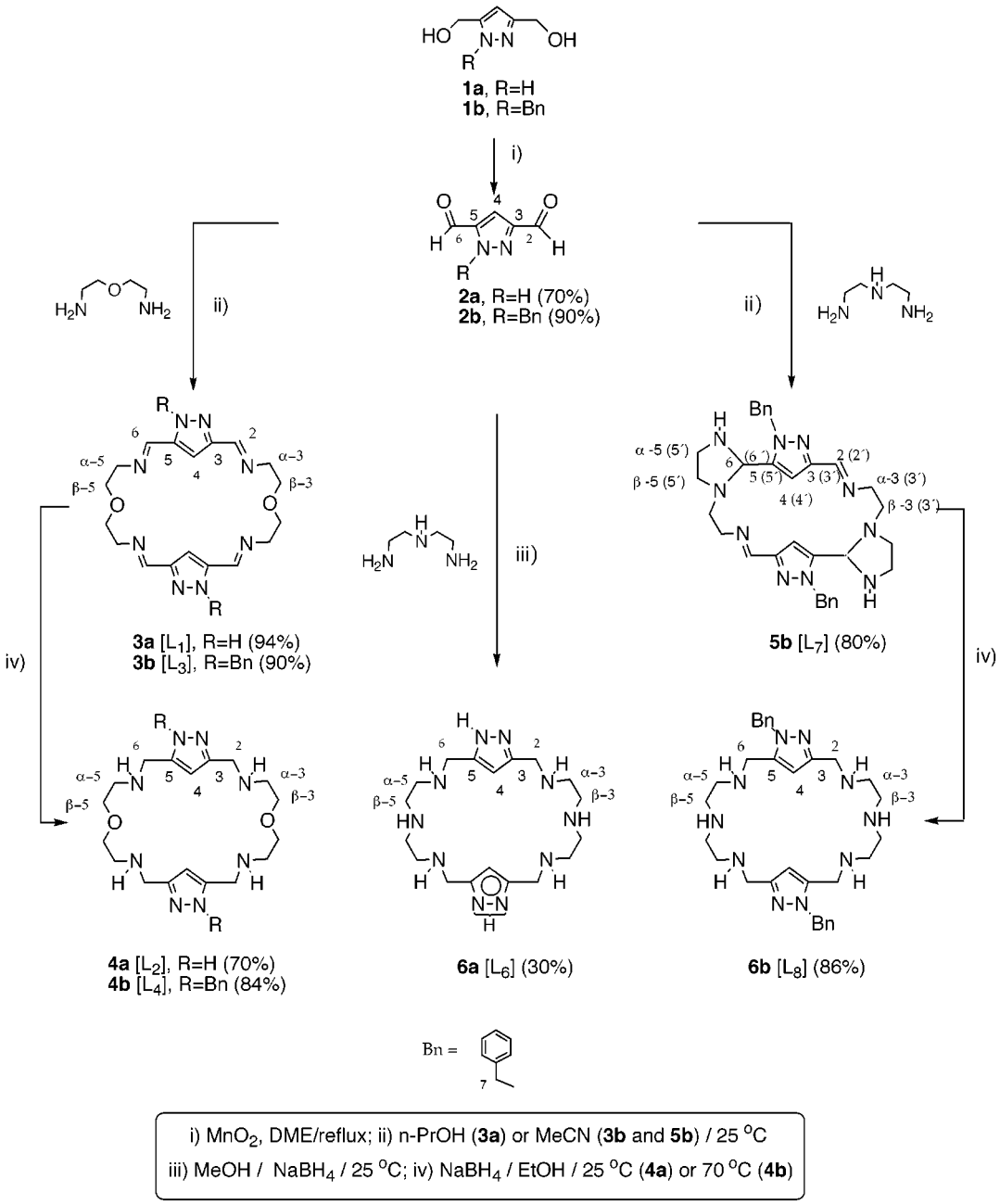
Scheme 2



tion the structure of a crystalline imidazolidine isomer obtained by (2 + 2) Schiff base condensation of diethylenetriamine and *m*-phthalaldehyde.[15]

In a previous communication[9] we have reported briefly the synthesis of 3,5-pyrazoledicarbaldehyde **2a** from 3,5-bis(hydroxymethyl)pyrazole **1a**[21] by oxidation with MnO_2 in 1,2-dimethoxyethane (DME) (Scheme 2). The dioxatetraimine **3a** was obtained as a crystalline solid, which precipitated in almost quantitative yield from the solution by dipodal (2 + 2) condensation of **2a** with 1,5-diamino-3-oxapentane. Further reduction of **3a** with $NaBH_4$ in absolute ethanol gave the expected dioxatetraazamacrocycle **4a**, which after crystallization from toluene was also isolated as a pure compound.

In contrast with the above behavior, in the (2 + 2) dipodal condensation of **2a** with diethylenetriamine in methanol at room temperature there was not precipitation of the expected Schiff base. The ^1H and ^{13}C NMR spectra of the solution indicated the presence of more than one species, which could correspond to a mixture of tetraimine and imidazolidine isomers of structures **III** (X = NH, R = H) and **IV** (R = H) (Scheme 1). Consequently, the mixture was directly reduced in situ with $NaBH_4$ to obtain the hexaamine macrocycle **6a**, which after being carefully purified by chromatography and later crystallized from toluene was obtained as a pure compound in moderate yield (Scheme 2).

Starting from 1-benzyl-3,5-bis(hydroxymethyl)pyrazole **1b**[22] and following similar procedures, we have now obtained the 1-benzyl-3,5-pyrazoledicarbaldehyde **2b** in high yield. With acetonitrile as solvent, the (2 + 2) dipodal condensation of **2b** with 1,5-diamino-3-oxapen-

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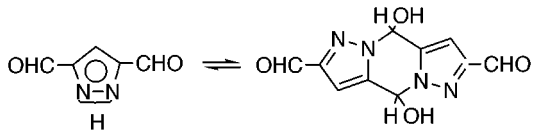
Table 1. ^{13}C NMR (δ, ppm) Spectra of 2a [$(CD_3)_2So$], 2a′ [$(CD_3)_2SO$], and 2b ($CDCl_3$)

	compound		
	2a[a]	**2a′**	2b
$\mathbf{C}_3$	n.o.	151.47	150.50
$\mathbf{C}_5$	n.o.	140.06 (139.78)[c]	135.17
$\mathbf{C}_4$	110.97	104.54 (104.22)[c]	114.55
$O\mathbf{C}_2$	184.85[b]	186.68	185.46
$O\mathbf{C}_6$	184.85[b]		179.50
$N-H\mathbf{C}OH-C_5$		75.48 (74.97)[c]	
$\mathbf{C}_7$			56.14
C*gem*			139.98
C*o*			127.97
C*m*			128.74
C*p*			128.40

[a] Registered from a diluted solution (<0.04 M solution). In such conditions the signals of both $\mathbf{C}_3$ and $\mathbf{C}_5$ carbons could not be observed. [b] Broad signal. [c] These signals correspond to a diastereomeric mixture as **2a′** contains two asymmetric carbons.

Scheme 3



2a **2a′**

tane or diethylenetriamine at room temperature gave in both cases stable solids, which separated from the solution and after crystallization from ethanol were identified as the Schiff base **3b** and the imidazolidine isomer **5b**, respectively (90% and 80% yield) (Scheme 2). Further treatment of **3b** and **5b** with $NaBH_4$ in ethanol afforded in both cases the desired saturated polyamines **4b** and **6b**, which crystallized from toluene and benzene, respectively, and were obtained in yield close to 85%.

Structures Characterization. It is known that the solubility of the 3(5)-pyrazolecarbaldehyde in common solvents is low as a result of its existence in equilibrium with dimers formed by intermolecular addition of the NH protons to the carbonyl groups.[23] For 3,5-pyrazoledicarbaldehyde a similar situation is found. Indeed, we have verified that the 3,5-pyrazoledicarbaldehyde **2a** is not soluble in chloroform and that its ^{1}H NMR spectrum recorded in $(CD_3)_2SO$ shows two sets of signals corresponding to a mixture of the monomer **2a** and the diastereomers of the dimeric **2a′** species (Scheme 3).

We have also observed that in a 0.2 M solution the ratio **2a**:**2a′** increases with the temperature, being 73:27, 93:7, and 98:2 at 30, 60, and 80 °C, respectively. The mentioned ratio also increases with dilution, being 92:8 at 30 °C in a 0.04 M solution. Moreover the signals of **2a′** disappear in highly dilute solutions. A parallel phenomenon has been detected in the ^{13}C NMR spectrum (Table 1). In contrast with the above behavior, the 1-benzyl-3,5-pyrazoledicarbaldehyde **2b** is soluble in chloroform and other common solvents and presents ^{1}H and ^{13}C NMR spectra corresponding to a single species.

The ^{1}H NMR of **3a** shows a very simple spectrum with only three signals at 6.34 ($\mathbf{H}_4$), 8.08 [$N=\mathbf{H}C_{2,6}$] and 3.64 ($\mathbf{H}_2C_{\alpha-3,5}$ and $\mathbf{H}_2C_{\beta-3,5}$) ppm due to the prototropic equilibrium of the pyrazole ring. By the same reason, in the ^{13}C NMR spectrum (Table 2), the C_3 and C_5 carbons appear as a broad signal and in the pairs $\mathbf{C}_2$ and $\mathbf{C}_6$, $\mathbf{C}_{\alpha-3}$ and $\mathbf{C}_{\alpha-5}$, and $\mathbf{C}_{\beta-3}$ and $\mathbf{C}_{\beta-5}$ the carbons are magnetically equivalent.

Table 2. ^{13}C NMR (δ, ppm) Spectra of 3a [$(CD_3)_2SO$], 3b ($CDCl_3$), and 5b ($CDCl_3$)

	compound		
	3a	**3b**	**5b**
$\mathbf{C}_3$	145.32[b]	149.00	150.18 (149.99)
$\mathbf{C}_5$	145.32[b]	139.00	144.70 (145.76)
$\mathbf{C}_4$	104.63	109.00	105.66 (105.22)
$N=\mathbf{C}_2$	153.57	157.00	155.62 (155.37)
$N=\mathbf{C}_6$	153.57	152.00	
$\mathbf{C}_6$<(Im)[a]			74.78 (74.69)
$\mathbf{C}_{\alpha-3}$	59.45	60.53	59.24 (59.52)
$\mathbf{C}_{\beta-3}$	67.94	68.52	54.04 (54.34)
$\mathbf{C}_{\alpha-5}$	59.45	60.67	
$\mathbf{C}_{\beta-5}$	67.94	68.79	
$\mathbf{C}_{\alpha-5}$(Im)[a]			45.18 (45.62)
$\mathbf{C}_{\beta-5}$(Im)[a]			52.35 (52.80)
$\mathbf{C}_7$		54.84	53.44 (53.42)
$\mathbf{C}_{gem}$		137.50	137.10 (136.94)
$\mathbf{C}_m$		127.46; 127.32	126.73; 126.61
$\mathbf{C}_o$		128.43; 128.33	128.68; 128.60
$\mathbf{C}_p$		127.87; 127.56	127.61; 127.49

[a] (Im) = Imidazolidine ring. [b] Broad signal.

However, for the derivative **3b** (Scheme 2), the 1-benzyl substituents break the magnetic equivalence of the pyrazole environment. In the ^{13}C NMR spectrum, different signals can be observed for the quaternary carbon atoms labeled as C_3 and C_5 [the pyrazole $N=\mathbf{C}_3$ appears at lower field than $C_4=\mathbf{C}_5$], as well as for those of the imine carbons [the $\mathbf{C}_2$ more deshielded than $\mathbf{C}_6$] (see Table 2).

To fully characterize compound **5b**, a comparison with the tetraimines **3a** and **3b** is very illustrative, because in these compounds the formation of imidazolidine rings is precluded by the presence of the oxygen atoms. The ^{13}C NMR spectrum of **5b** was rather complex, showing 28 different signals (Table 2). The signals are arranged in two sets of 14 of close relative intensities. All of these spectral features suggest that the species formed could be either a unique one with all its carbon nuclei magnetically nonequivalent or a mixture of at least two different species with 2-fold symmetry in almost the same proportion. To decide which one of these two possibilities was the correct one, it was necessary to analyze the HMQC (Figure 1a) and multiple-bond HMBC (Figure 1b) 2D-NMR heteronuclear correlation spectra.

In addition to the expected one bond correlations shown in Figure 1a, the long-range heteronuclear correlations presented in Figure 1b are very important for a correct assignment. In particular, the correlation of protons H_4 and $H_{4'}$, which present well-separated chemical shifts in the ^{1}H NMR spectrum [7.72 and 7.23 ppm, see Figure 1a] is a key point. In Figure 1b, it can be seen that one of these signals ($H_{4'}$) only presents cross-peaks with the carbon resonance of $C_{5'}$ and $C_{3'}$, whereas the other one (H_4) correlates with C_5 and C_3. Similarly, it can be observed that C_4 correlates with H_2 and H_6, and $C_{4'}$ correlates with $H_{2'}$ and $H_{6'}$. Additionally, H_7 and $H_{7'}$ only present cross-peaks with C_5 and $C_{5'}$ respectively.

All these spectral features indicate that both pyrazole rings present the same arrangement with respect to the imidazolidine rings and confirm that these rings are located at the side of the pyrazole ring closer to the benzyl substituents. Taking into account that in the HMBC NMR spectra there are not cross-peaks between proton

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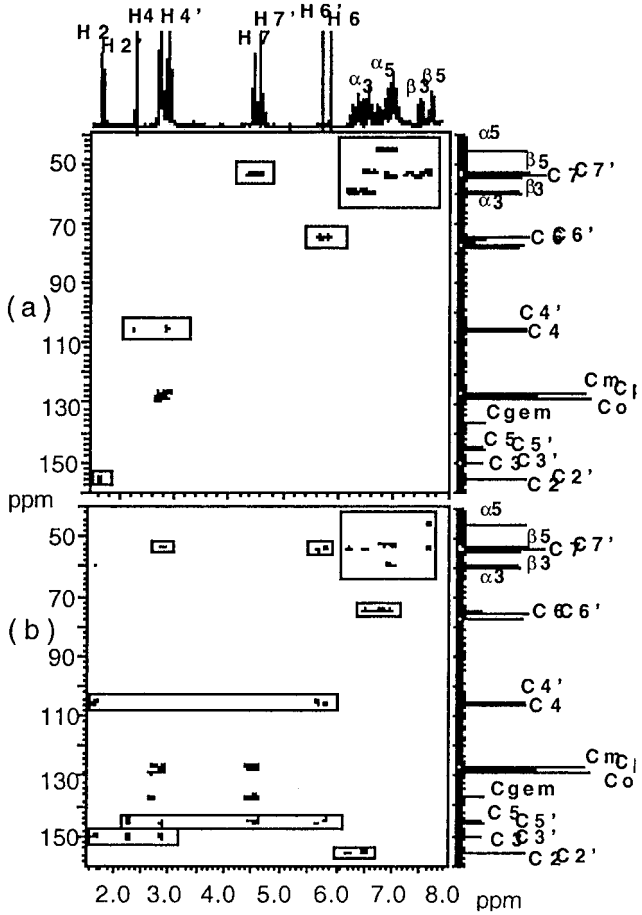


Figure 1. HMQC (a) and HMBC (b) spectra for compound **5b** in $CDCl_3$. Most significant correlations have been marked.

and carbon resonances of the atoms labeled as prime and nonprime, it has to be concluded that the 28 carbon resonances should be attributed to two different diastereoisomers with C_2 symmetry each displaying 14 signals. The only possible structural type fulfilling all these requirements is the one presented as **5b** in Scheme 2.

In the expansions of the aliphatic regions of the $^1H-^1H$ and $^1H-^{13}C$ NMR spectra of **5b** it can be seen that each one of the signals of the methylene carbons correlates with its two different protons as a consequence of the rigidity afforded by the five-membered imidazolidine rings of the molecule (Supporting Information, Figure 1). This rigidity is particularly evident from the nonequivalence of the benzyl protons that, in contrast to **3b**, display an AB spin-system and also from the fact that the ethylene chains of the imidazolidine fragments, α(3)−β(3), α(5)−β(5) in one diastereoisomer and α(3′)−β(3′) and α(5′)−β(5′) in the other one, present ABCD spin-systems.

On the basis of the above results, and taking into account both the structure of the imidazolidine derivative **5b** and the fact that the NMR spectra of the Schiff base **3b** suggest the existence of only one constitutional isomer, it is reasonable to suppose that although the condensation of **2b** with either 1,5-diamino-3-oxapentane or diethylenetriamine could afford a mixture of the two possible constitutional isomers, the most abundant should be the one with the 1-benzylpyrazole substituents in opposing position and displaying C_2 symmetry. This isomer has to be just the one that we have isolated by crystallization in both cases. Consequently, the saturated polyamines **4b** and **6b**, which were obtained by reduction of crystalline compounds **3b** and **5b**, respectively, may also correspond to the isomers with the same disposition depicted in Scheme 2 (with the benzyl groups in opposing positions).

Table 3. ^1H NMR (δ, ppm, D_2O) of 4a (pH 9.0), 4b (pH 12.0), 6a (pH 11.0), and 6b (pH 12)

	compound			
	4a	**4b**	**6a**	**6b**
$\mathbf{H}_4$	6.22 (s)	6.12 (s)	6.13 (s)	6.17 (s)
$\mathbf{H}_2C_2$	3.82 s)	3.54 (s)	3.60 (s)	3.57 (s)
$\mathbf{H}_2C_6$	3.82 s)	3.54 (s)	3.60 (s)	3.57 (s)
$\mathbf{H}_2C_{\alpha-3}$	2.87 (t)	2.56 (t)	2.45 (t)	2.41 (s)
$\mathbf{H}_2C_{\alpha-5}$	2.87 (t)	2.49 (t)	2.45 (t)	2.41 (s)
$\mathbf{H}_2C_{\beta-3}$	3.54 (t)	3.37 (t)	2.45 (t)	2.32 (t)
$\mathbf{H}_2C_{\beta-5}$	3.54 (t)	3.27 (t)	2.45 (t)	2.23 (t)
$\mathbf{H}_2C_7$		5.13 (s)		5.17 (s)
$\mathbf{H}_o$		6.96 (m)		6.97 (m)
$\mathbf{H}_m$, $\mathbf{H}_p$		7.15 (m)		7.15 (m)

Table 4. ^{13}C NMR (δ, ppm, D_2O) of 4a (pH 9.0), 4b (pH 12.0), 6a (pH 11.0), and 6b (pH 12)

	compound			
	4a	**4b**	**6a**	**6b**
$\mathbf{C}_3$	148.33[a]	151.20	148.53[b]	150.75
$\mathbf{C}_5$	148.33[a]	143.69	148.53[b]	143.70
$\mathbf{C}_4$	104.68	105.86	104.72	106.34
$\mathbf{C}_2$	45.43	46.15	45.01	45.90
$\mathbf{C}_6$	45.43	43.73	45.01	43.42
$\mathbf{C}_{\alpha-3}$	48.60	47.80	47.59	47.14
$\mathbf{C}_{\alpha-5}$	48.60	48.22	47.59	47.14
$\mathbf{C}_{\beta-3}$	70.64	70.33	48.58	48.15
$\mathbf{C}_{\beta-5}$	70.64	69.99	48.58	46.73
$\mathbf{C}_7$		53.24		53.20
$\mathbf{C}_{gem}$		137.94		138.03
$\mathbf{C}_m$		127.73		127.64
$\mathbf{C}_o$		130.03		130.02
$\mathbf{C}_p$		129.05		129.05

[a] Low singlet. [b] Singlet.

The ^1H and ^{13}C NMR spectra of pyrazole-derived polyamines **4a,b** and **6a,b** registered in D_2O at basic pH (were the nonprotonated species predominates) are reported by the first time in Tables 3 and 4, respectively. As usually occurs for 3,5-disubstituted 1*H*-pyrazole derivatives, **4a** and **6a** show very simple ^1H and ^{13}C NMR spectra in which signals indicate that, because of the prototropic equilibrium of the pyrazole ring, both compounds present average 4-fold symmetry on the NMR time scale. The quaternary $\mathbf{C}_3$ and $\mathbf{C}_5$ carbons appear together as a more or less broad signal, and the pairs of methylene carbons $\mathbf{C}_2$ and $\mathbf{C}_6$, $\mathbf{C}_{\alpha-3}$ and $\mathbf{C}_{\alpha-5}$, and $\mathbf{C}_{\beta-3}$ and $\mathbf{C}_{\beta-5}$ are magnetically equivalent. However, in **4b** and **6b**, the 1-benzyl substituents break the magnetic equivalence of the pyrazole environment, and as a consequence both compounds show a reduction from 4- to 2-fold symmetry with respect to **4a** and **6a**. The ^{13}C NMR spectra of **4b** and **6b** show that in general, the carbon atoms $\mathbf{C}_5$, $\mathbf{C}_6$, and $\mathbf{C}_{\beta-5}$, which are closer to the pyrazole 1-benzyl substituent, appear at higher field than $\mathbf{C}_3$, $\mathbf{C}_2$, and $\mathbf{C}_{\beta-3}$ which are closer to the pyrazole sp^2 nitrogen (see Table 4).

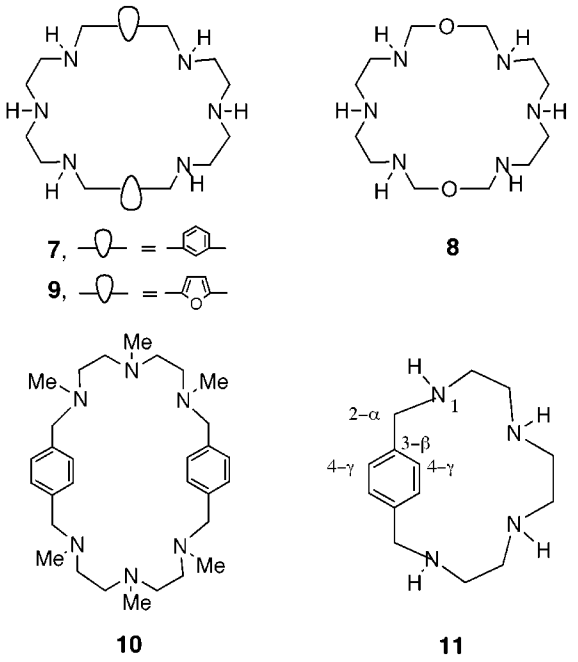
Protonation Constants. In Table 5 are shown the logarithms of the stepwise stability constants of receptors **4a**, **4b**, **6a**, and **6b** determined at 298.1 K in 0.15 mol dm^{-3} NaCl. For comparison, the values reported in the literature[12,13,24,25] for the related azamacrocycles **7**−**10**

Table 5. Logarithms of Stepwise Protonation Constants of Receptors 4a, 4b, 6a, and 6b[a]

reaction	4a	4b	6a	6b	7[d]	8[e]	9[f]	10[g]
$H + L = HL$[b]	8.49(3)[c]	8.74(1)	9.74(2)	8.90(3)	9.51	9.62	9.44	8.93
$H + HL = H_2L$	7.92(2)	7.74(1)	8.86(2)	8.27(2)	8.77	8.89	8.68	8.22
$H + H_2L = H_3L$	6.97(3)	6.40(2)	7.96(2)	6.62(3)	7.97	8.29	7.63	7.35
$H + H_3L = H_4L$	6.31(4)	5.42(3)	6.83(2)	5.85(4)	7.09	7.62	6.46	6.44
$H + H_4L = H_5L$			4.57(3)	3.37(4)	3.79	3.82	3.84	1.5
$H + H_2L = H_6L$			3.19(3)	2.27(6)	3.27	3.30	3.16	
log β[h]	29.69	28.30	41.15	36.28	40.40	41.54	39.21	32.44

[a] Determined in 0.15 mol dm^{-3} NaCl at 298.1 K. Constants of related compounds **7**, **8**, **9**, and **10** taken from the literature are also included. [b] Charges have been omitted for clarity. [c] Figures in parentheses are standard deviations in the last significant figure. [d] Taken from ref 12, I = 0.1 mol dm^{-3} KCl, 298.1 K. [e] Taken from ref 24, I = 0.1 mol dm^{-3} KCl, 298.1 K. [f] Taken from ref 13, I = 0.1 mol dm^{-3} KCl, 298.1 K. [f] Taken from ref 25, I = 0.15 mol dm^{-3} NaCl, 298.1 K. [g] Taken from ref 25, I = 0.15 mol dm^{-3} NaCl, 298.1 K. [h] log β = Σ log K_{H_iL}.

Scheme 4



(Scheme 4) are also included in Table 5. In Figure 2 are presented the distribution diagrams of receptors **4b** and **6b**.

A first analysis of the protonation constants of these compounds allows one to derive several general features. Dioxatetraamines **4a** and **4b** show relatively high constants in all of their four protonation steps, whereas **6a** and **6b** display high basicity in their first four protonation steps and greatly reduced basicity constants for the fifth and sixth protonation steps. For instance, for **6a** log K_{H_3L} − log K_{H_4L} = 1.13, log K_{H_4L} − log K_{H_5L} = 2.26, and for **6b**, log K_{H_3L} − log K_{H_4L} = 0.77, log K_{H_4L} − log K_{H_5L} = 2.48. This grouping of constants has also been observed in related [2.2]-macrocycles containing *m*-xylylene **7**, oxydimethyl **8**, or 2,5-furandimethyl **9** linkages connecting two diethylenetriamine side chains and can be explained considering minimum electrostatic repulsion criteria.[12,13,24] Indeed, these macrocycles may bind four protons at the terminal nitrogens of both diethylenetriamine side chains without introducing severe electrostatic repulsions between ammonium groups. Fifth and sixth protonation steps necessarily involve the nitrogen atoms in the middle of the side chains, which are adjacent to two ammonium groups, yielding then a drop in basicity.

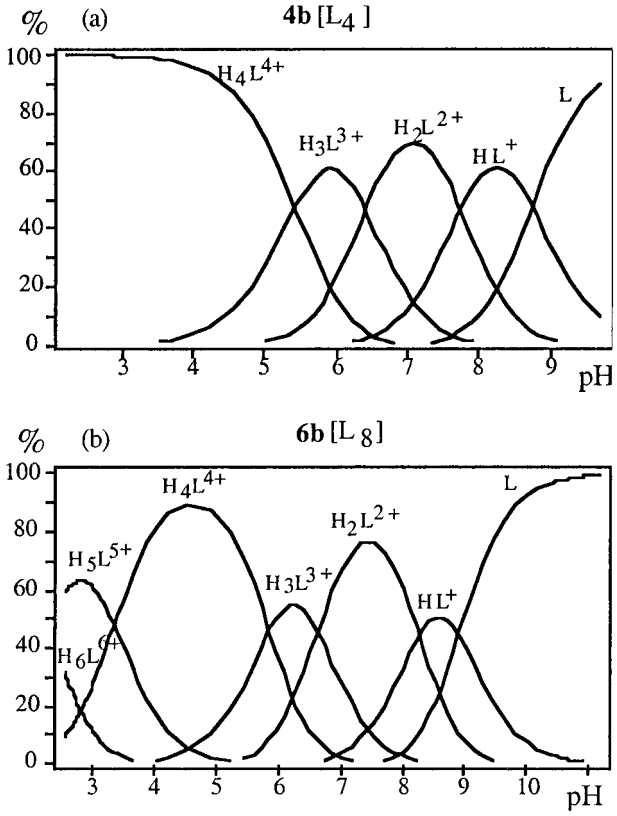


Figure 2. Distribution diagram for the systems (a) **4b**[L_4]−H^+ and (b) **6b**[L_8]−H^+.

Another point to be considered is that the 1-benzylpyrazole derivatives display lower overall basicities than the nonbenzylated ones. As a matter of fact, whereas **6a** has basicity constants similar to those of **7** and **8**, **6b** presents lower values of basicity than these receptors. The two first basicity constants of **6b** compare well with the corresponding ones of **10** with all tertiary nitrogens,[25] and it is well-known that the basicity of such tertiary nitrogens in aqueous solution is lower than that of secondary ones as a result of solvation effects. The remaining constants for these two receptors (**6b** and **10**) differ markedly probably because of the particular hydrogen bond network that has been evidenced for the last receptor.[25] Therefore, benzylation of the pyrazole moiety produces a marked drop in basicity.

A last point that deserves comment is the protonation of the pyrazole fragments in **4a**,**b** and **6a,b**. First of all,

(24) Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1992**, *31*, 5534−5542.

(25) Bazzicaluppi, C.; Bencini, A.; Bianchi, A.; Fusi, V.; Giorgi, C.; Paoletti, P.; Stefani, A.; Valtancoli, B. *J. Chem. Soc., Perkin Trans. 2* **1995**, 275−280.

for all these receptors the number of protonation steps detected in the pH range of study, pH 2−12, equals the number of nitrogen atoms in the side chains. Moreover, the magnitude of the protonation constants for **4a** and **6a** correlates well with those of [2.2]-macrocycles with diethylenetriamine side chains, such as **7**−**9**. These results would suggest that there is not net involvement of the pyrazole moieties in protonation or deprotonation processes in aqueous solution, as can be expected according to the pK_a values found in the literature for pyrazole derivatives.[26] Thus, with regard to protonation of **4a** and **6a**, despite alkyl substituents in position 3 and/or 5 of pyrazole, increase in the basicity of the ring (pyrazole, log K = 2.48; 3(5)-methylpyrazole, log K = 3.27; 3,5-dimethylpyrazole, log K = 4.06), a 3(5)-(2-aminoethyl) moiety (log K = 1.97) has a strong opposite effect. However, considering the protonation of 1-benzylpyrazole derivatives **4b** and **6b**, the available data show that alkylation or arylation of the pyrazole nitrogen yields a significant drop in basicity (1-methylpyrazole, log K = 2.06; 1-ethylpyrazole, log K = 1.94; 1-phenylpyrazole, log K = 0.43). Nevertheless, this aspect will be further discussed in the following NMR section.

NMR Studies at Different pH Values. To identify the protonation sequences and to verify whether the pyrazole moieties are involved in the protonation steps of the receptors we have recorded the ^{1}H and ^{13}C NMR spectra of **4a**, **4b**, **6a**, and **6b** at different pH values, and the signals have been analyzed on the basis of their HMQC and multiple-bond HMBC 2D-NMR heteronuclear correlation spectra (Supporting Information, Tables 1−4).

In general, the variation with the pH of the NMR resonances of the β-carbon atoms and the α-hydrogens with respect to the nitrogen atoms bearing the protonation processes are of great help in establishing protonation schemes of polyamine molecules.[27]

For compound **4a**, the carbon resonance of the pyrazole quaternary carbon atoms $C_{3,5}$ is of particular interest because are only placed in β-position with respect to the aliphatic nitrogen atoms and might serve as a probe for their protonation. This signal experiences a great upfield variation (7.76 ppm) in the pH 9−6 range where protonation of **4a** occurs. Analogously, the signal of carbon atoms $\mathbf{C}_{\beta-3,5}$, also placed in β-position with respect to aliphatic nitrogens, strongly shifts upfield (3.9 ppm) in this pH range in agreement with the protonation of these nitrogens. The downfield variation of the proton resonance of the methylene groups $\mathbf{H}_2C_{2,6}$ (0.57 ppm) and $\mathbf{H}_2C_{\alpha-3,5}$ (0.62 ppm) in this pH range further confirms this fact.

It is important to point out that the pyrazole carbons $C_{3,5}$ and C_4 are respectively located in β- and γ-position in relation to the closer aliphatic nitrogens. The upfield (7.76 ppm for $C_{3,5}$) and downfield (3.96 ppm for C_4) variations that such carbons experience upon protonation do not reflect any particular implication of the pyrazole subunits in the protonation mechanism, because it is well-known that similar β and γ aromatic carbons belonging to [1:1] and [2:2] polyamine cyclophanes containing benzene units also experience similar chemical shifts upon protonation.[28,29] For instance, in the case of the 2,5,8,11-tetraaza[12]paracyclophane **11** (Scheme 4), the $C_{3-\beta}$ aromatic carbon atoms experience an upfield shift of 7.3 ppm upon full protonation, and the $C_{4-\gamma}$ atoms experience a downfield shift of 2.8 ppm. Also, the lower pK_a value of **4a** is 6.31, and as commented before, the expected pK_a values for protonation of aminoalkyl-substituted pyrazole rings should be much lower.

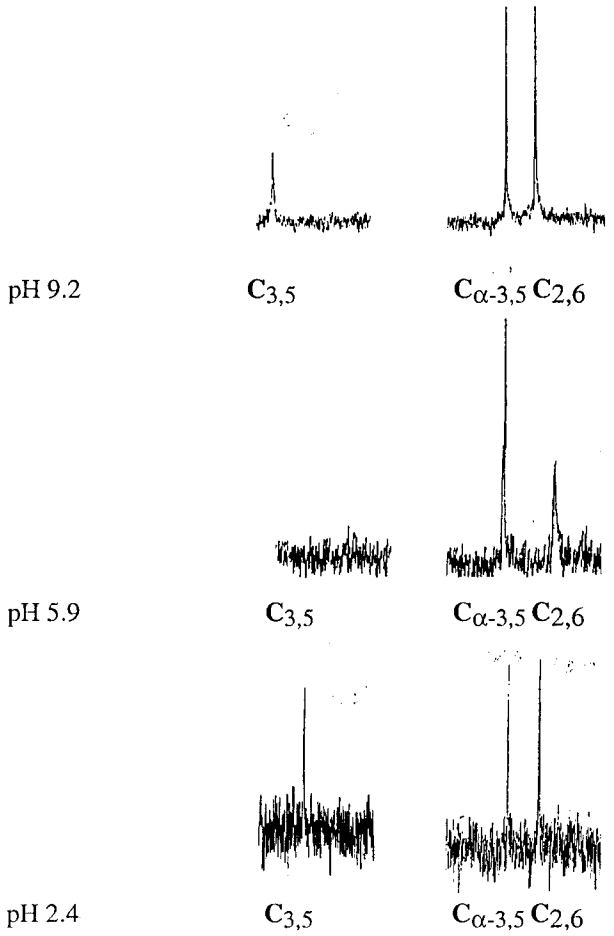


Figure 3. Variation with pH of the line width of signals $\mathbf{C}_{3,5}$ and $\mathbf{C}_{2,6}$ of **4a**.

However, it is interesting to observe that upon protonation the signal corresponding to the pyrazole carbon atoms $C_{3,5}$ of **4a** experience a progressive line-broadening that disappears within the baseline of the spectrum at pH 5.9 where the macrocycle is almost fully protonated (see Figure 3). In a similar way, the neighboring methylene carbon atoms $C_{2,6}$ also experience a significant broadening, whereas both signals become sharp singlets at stronger acid medium.

It is known that such ^{13}C NMR spectroscopic changes are usually produced by alterations in the dynamic exchange rate of the pyrazole prototropic equilibrium.[30]

(26) Catalan, J.; Abboud, J. L. M.; Elguero, J. *Adv. Heterocycl. Chem.* **1987**, *41*, 187−274.

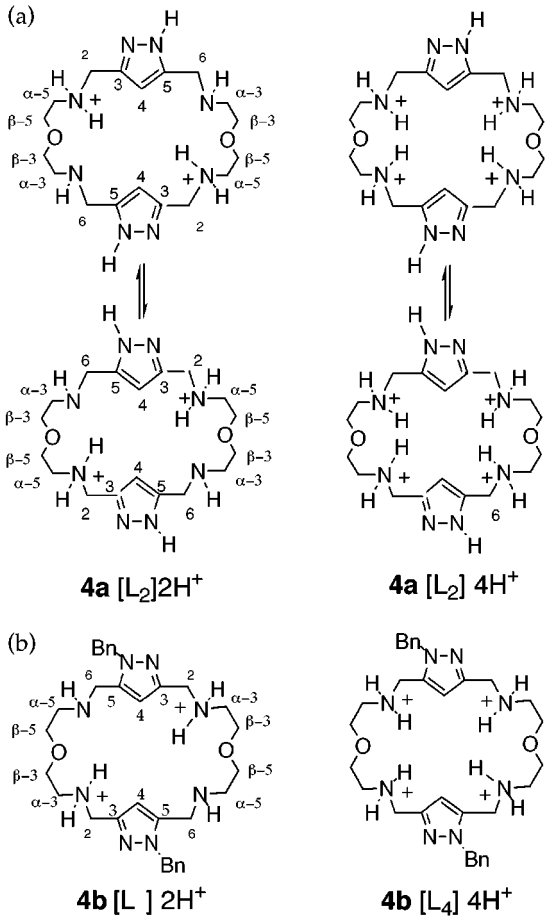
(27) Sarnesky, J. E.; Surprenant, H. L.; Molen, F. K.; Reilley, C. N. *Anal. Chem.* **1975**, *47*, 2116−2124.

(28) (a) Andrés, A.; Burguete, M. I.; García-España, E.; Luis, S. V.; Miravet, J. F.; Soriano, C. *J. Chem. Soc., Perkin Trans. 2* **1993**, 749−755. (b) Bianchi, A.; Escuder, B.; García-España, E.; Luis, S. V.; Marcelino, V.; Miravet, J. F.; Ramírez, J. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1253−1259. (c) Andrés, A.; Bazzicaluppi, C.; Bianchi, A.; García-España, E.; Luis, S. V.; Miravet, J. F.; Ramírez, J. A. *J. Chem. Soc., Dalton Trans.* **1994**, 2995−3004.

(29) Aguilar, J. A.; García-España, E.; Guerrero, J. A.; Llinares, J. M.; Ramírez, J. A.; Soriano, C.; Luis, S. V.; Bianchi, A.; Ferrini, L.; Fusi, V. *J. Chem. Soc., Dalton Trans.* **1996**, 239−246.

(30) Elguero, J.; Marzin, Z.; Katrytzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic Press: New York, 1976.

Scheme 5



Depending on the nature of the pyrazole C-substituents, the N−H proton exchange rate can be slowed to the point where separate signals can be observed for the C_3 and C_5 pyrazole carbons.[31] Taking this into account, MM_2 calculations seem to support that consecutive conformational changes induced by the progressive protonation of **4a** (see Scheme 5a) may lead to N···NH interactions between the sp^2 pyrazole nitrogens and the closer protonated aliphatic nitrogens.

With respect to the protonation of the 1-benzyl substituted dioxatetraamine **4b**, in Figure 4 are presented plots of the variation of the ^{13}C chemical shifts of carbon atoms C_3, C_5, $C_{\beta-3}$, and $C_{\beta-5}$ that allow some interesting conclusions. From this figure it is evident that the signals of carbon atoms C_3 and $C_{\beta-3}$ start moving upfield at pH values higher than those for C_5 and $C_{\beta-5}$, which are closer to the benzyl substituent. The latter signals do not move significantly upfield until pH 8.0, when the third proton starts binding **4b** (see Figure 4a). The variations in the ^1H chemical shifts also support this point. In the pH 12−7.5 range protons on $C_{\alpha-3}$ and C_2 move downfield 0.42 and 0.51 ppm, respectively, while those closer to the benzyl substituents $C_{\alpha-5}$ and C_6 experience downfield shifts of only 0.18 and 0.10 ppm. Therefore, the sp^2 pyrazolic nitrogens somehow address the protonation to this side, which probably may be explained in terms of differences in hydrophobicity between both sites or the formation of intramolecular hydrogen bonds between the sp^2 pyrazole nitrogen and positively charged polyammonium sites. Therefore, for this receptor a protonation model in which the two first protons preferentially bind the amino groups closer to the nonbenzylated position of the pyrazole heterocycle may be assumed (see Scheme 5b).

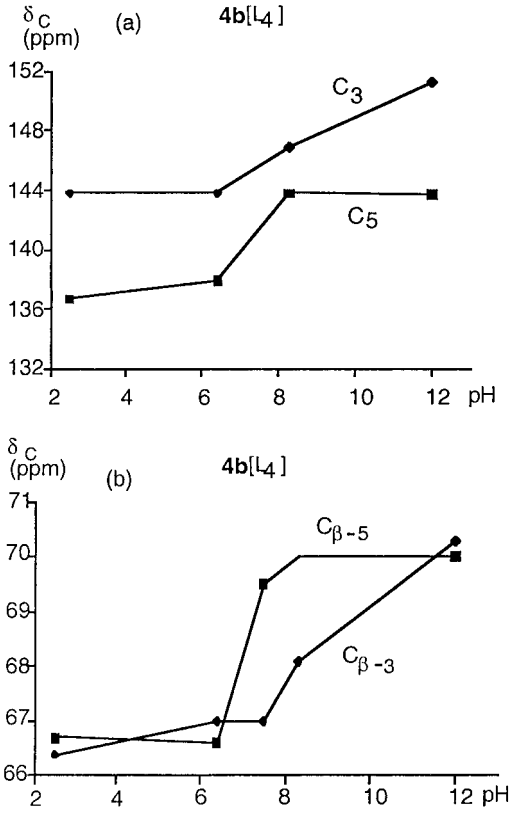


Figure 4. (a) Variation with pH of ^{13}C chemical shifts of carbon atoms C_3 and C_5 of **4b**. (b) Variation with pH of ^{13}C chemical shifts of carbon atoms $C_{\beta-3}$ and $C_{\beta-5}$ of **4b**.

For the hexaamine **6a**, the two first protonations occur in the pH 11−8 range. In this case, the signal shifted most upfield is that of carbon atoms $C_{\alpha-3,5}$, whereas the signal of carbons $C_{\beta-3,5}$ and those of the quaternary carbon atoms $C_{3,5}$ do not experience significant shifts in this pH region (see Figure 5).

This observation implies that **6a** protonates first on the middle nitrogens of the diethylenetriamine side chains. In Figure 5b it can be seen that below pH 7 the signals of carbon atoms $C_{\alpha-3,5}$ start moving downfield, while those of $C_{\beta-3,5}$ move upfield. This can be explained by assuming that third and fourth protonations promote the migration of the protons in the middle nitrogens of the side chains to those at the end to achieve a minimum energy situation (see Scheme 6a).

Fifth and sixth protonations (pH < 5) yield again upfield shifts of the signal of CH_2-α carbons, denoting the reprotonation of nitrogen atoms located in the middle of the chains at these stages. In this receptor, for intermediate pH values, a line broadening of the $C_{3,5}$ signals is also observed, which can probably be attributed to reasons similar to those already discussed for **4a** (Supporting Information, Figure 4).

In relation to **6b**, when the pH is decreased from 12 to 8 the ^{13}C signal of carbon C_3 in β-position in respect to $C_3-H_2C_2-HN$ aliphatic nitrogens shifts upfield considerably more (2.69 ppm) than that of C_5 (1.00 ppm), suggesting that as in **4b** the first two protonations are

(31) Claramunt, R. M.; Elguero, J.; Marzin, C.; Seita, J. *An. Chim.* **1979**, *75*, 701.

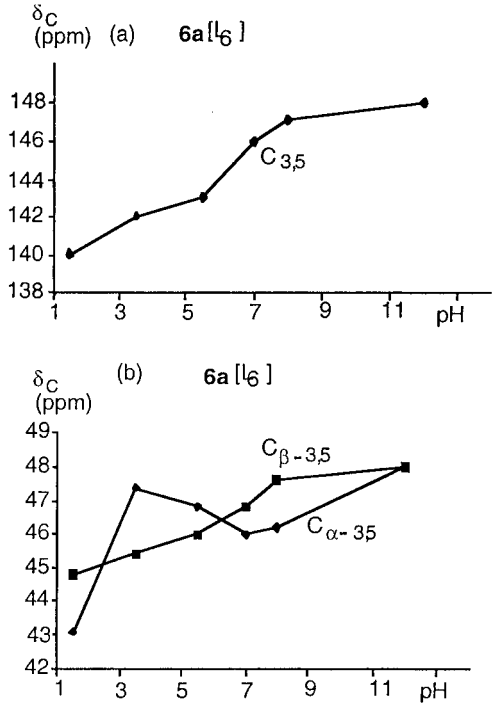


Figure 5. (a) Variation with pH of ^{13}C chemical shifts of carbon atoms $C_{3,5}$ of **6a**. (b) Variation with pH of ^{13}C chemical shifts of carbon atoms $C_{\alpha-3,5}$ and $C_{\beta-3,5}$ of **6a**.

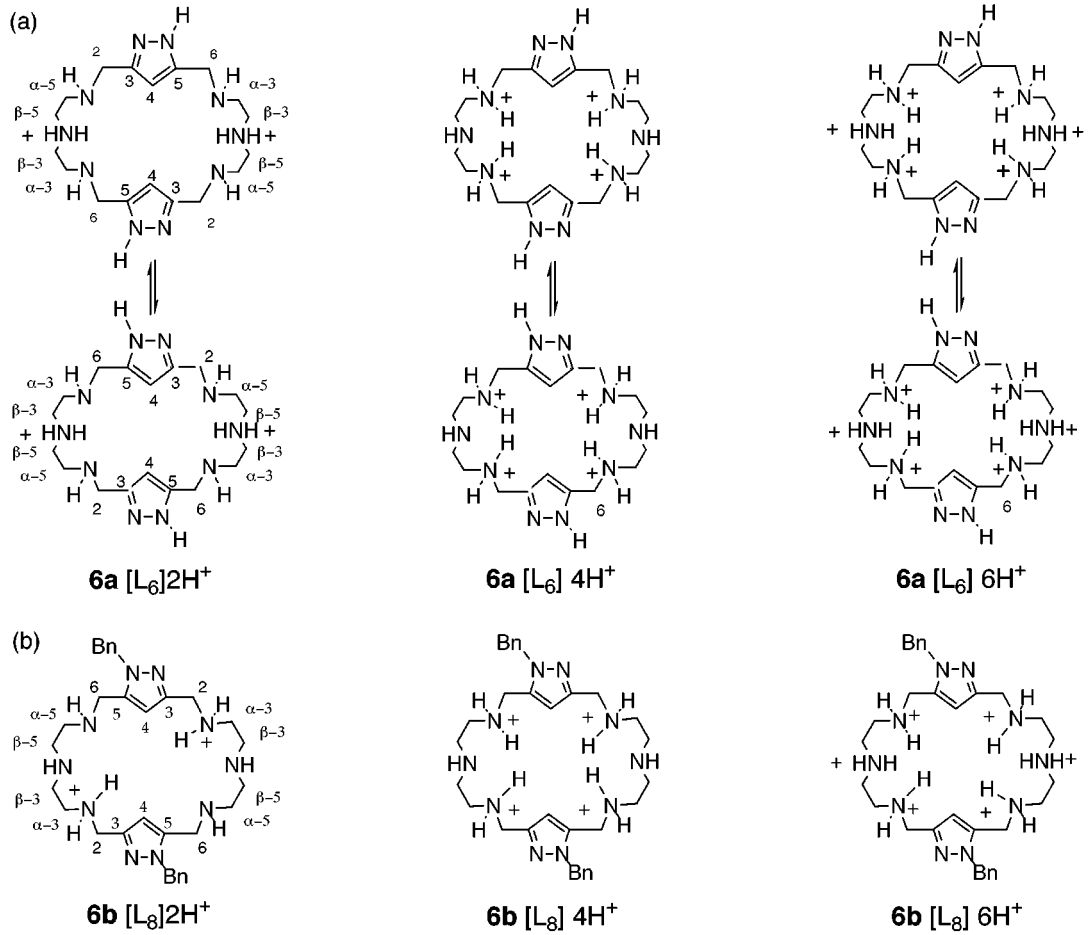
mainly affecting terminal nitrogens closer to the non-benzylated side of pyrazole. At difference with **6a** in this pH range, carbons $C_{\alpha-3}$ and $C_{\alpha-5}$ do not bear significant shielding effects, indicating that central nitrogens are not the preferential targets in these early protonation steps. These last signals, however, bear strong upfield shifts ($C_{\alpha-3}$, 3.51 ppm; $C_{\alpha-5}$, 4.01 ppm) below pH 5 where the last two protonations of the macrocycle occur. Therefore, these data support the preferential protonation order shown in Scheme 6b.

Conclusions

(i) Dipodal (2 + 2) condensation of 3,5-pyrazoledicarbaldehyde **2a** or its 1-benzyl derivative **2b** with 1,5-diamino-3-oxapentane gave the tetraimine Schiff bases **3a** or **3b** (in 90% yield), which after reduction with $NaBH_4$ afforded the corresponding dioxatetraamines **4a** and **4b** (75% and 84% yield, respectively). Similar condensation of **2a** with diethylenetriamine leads to the formation of a mixture of imine and imidazolidine isomers, which after being reduced in situ gave the hexamine **6a** in only 30% yield. In contrast with the above behavior, the condensation of **2b** with the same amine gave a stable diimine−diimidazolidine isomer (**5b**) (80% yield), which when reduced with $NaBH_4$ afforded the dibenzyl-substituted hexaamine **6b** in high yield (86%).

(ii) The analytical and spectroscopical ^1H and ^{13}C NMR data of **3b** and **5b** indicate the following conclusions: (a) Although condensation of **2b** with either 1,5-diamino-3-oxapentane or diethylenetriamine could afford a mixture of two possible constitutional isomers, the most abundant

Scheme 6



should be the one with the 1-benzylpyrazole substituents in positions opposite each other and displaying C_2 symmetry. (b) The structure of **5b** corresponds to a diastereomeric mixture of a unique constitutional isomer with both imidazolidine rings located at the side of the pyrazole closer to the 1-benzyl substituted nitrogens.

(iii) The analysis of the protonation constants of dioxatetraamine and hexaamine receptors **4a,b** and **6a,b** allows one to derive the following conclusions: (a) In the studied pH range (2−11) the number of protonation steps detected equals the number of nitrogen atoms in the side chains. Consequently, in such pH range there is not net involvement of the pyrazole moieties in protonation or deprotonation processes. (b) In general, the benzyl-substituted derivatives **4b** and **6b** display lower overall basicities than the nonbenzylated **4a** and **6a**. (c) The dioxatetraamines **4a,b** show relatively high constants in all of their protonation steps. (d) The hexaamines **6a,b** display high basicity in their first four protonation steps and basicity constants much more reduced for the fifth and sixth ones, which involve the nitrogen atoms located in the middle of the side chains.

(iv) For either dioxatetraamines (**4a,b**) or hexaamines (**6a,b**), the variation with the pH of the NMR resonances of the β-carbon atoms and the α-hydrogen atoms with respect to the nitrogen atoms bearing the protonation procesess have allowed for the conclusions on the protonation sequences graphically indicated in Schemes 5 and 6, respectively.

(v) In **4a**,**b** and **6a**,**b** the upfield and downfield shifts experienced upon protonation by the carbon atoms $C_{3,5}$ and C_4 of the pyrazole rings, respectively, are parallel to those found for aromatic rings of [1:1] and [2:2] cyclophanes and do not reflect a direct implication of the pyrazole subunits in the protonation mechanism.

(vi) The most significant change for the pyrazole rings in the different protonation steps comes from the remarkable line-broadening observed for carbon atoms $C_{3,5}$ of **4a** and **6a**, which could be attributed to an alteration in the dynamic exchange rate of the pyrazole prototropic equilibria due to consecutive conformational changes induced by the gradual protonation process.

Now, work is in progress to evaluate the complexing ability of polyamine receptors **4a**,**b** and **6a**,**b** toward dopamine in aqueous solution at variable pH using potentiometric and NMR methods.

Experimental Section

General. All starting materials were purchased from commercial sources and used without further purification. The solvents were dried using standard techniques. All reactions were monitored by thin-layer chromatography (TLC) on precoated aluminum sheets of silica gel; compounds were detected with UV light (254 nm) and/or iodine chamber. Flash column chromatography was performed in the indicated solvent system on silica gel (particle size 0.040−0.063 mm). Melting points were determined in a hot-stage microscope and are uncorrected. The ^{1}H NMR spectra were recorded at 300 or 400 MHz, and the ^{13}C NMR spectra were recorded at 75 or 100 MHz at room temperature, employing D_2O, $(CD_3)_2SO$, or $CDCl_3$ as solvent. The chemical shifts are reported in ppm from TMS (δ scale) but were measured against the solvent signals; dioxane (δ 67.4 ppm) was used as reference for ^{13}C NMR spectra in D_2O. All assignments have been performed by means of different standard ^{1}H−^{1}H homonuclear correlation experiments (COSY, GCOSY) and ^{1}H−^{13}C heteronuclear multiple quantum coherence experiments (HMQC, HMBC, GHMQC, and GHMBC). Confirmation of the assignments has been performed by combined 2D NMR GHSQC-TOCSY experiments. Bibliographic studies for similar compounds have also been taken into account for the assignment and interpretation of the NMR data. In the NMR study of the protonation sequences of ligands, the pH was calculated from the measured pD values using the correlation pH = pD − 0.4.[32] The mass spectra (MS) were registered by electronic impact (EI) at 70 eV ionizing potential or by fast atomic bombardment (FAB) technique using a *m*-nitrobenzyl alcohol matrix.

Electromotive Force (emf) Measurements. The potentiometric titrations were carried out in 0.15 M NaCl at 298.1 ± 0.1 K by using the experimental procedure (buret, potentiometer, cell, stirrer, microcomputer, etc.) that has been fully described elsewhere.[33] The acquisition of the emf data was performed with the computer program PASAT.[34] The reference electrode was a Ag/AgCl electrode in saturated KCl solution. The glass electrode was calibrated as a hydrogen ion concentration probe by titration of well-known amounts of HCl with CO_2-free NaOH solutions[35] and determination of the equivalent point by Gran's method,[36] which gives the standard potential, $E°'$, and the ionic product of water (pK_w = 13.73(1)). The computer program HYPERQUAD[37] was used to calculate the protonation and stability constants, and the DISPO[38] program was used to obtain the distribution diagrams. The titration curves for each system (ca. 200 experimental points corresponding to at least three measurements, pH 2−11, concentration of ligands 1×10^{-3} to 5×10^{-3} M) were treated either as a single set or as separated curves without significant variations in the values of the stability constants. Finally, the sets of data were merged together and treated simultaneously to give the final stability constants.

Preparation of Pyrazole Precursors. Diethyl 3,5-Pyrazoledicarboxylate. This compound was prepared following a procedure similar to that previously reported by Bosnich and co-workers[21] for the dimethyl ester. To a stirred solution of 3,5-dimethylpyrazole (7.20 g, 75 mmol) in 300 mL of H_2O heated at 60 °C was added solid $KMnO_4$ (65 g, 0.41 mol) portionwise. When the addition was complete, the temperature was carefully raised to 80 °C until the foam stopped and then refluxed for 5 h. The reaction mixture was cooled to room temperature and filtered on a Celite pad. The solvent was then removed under reduced pressure, the resulting solid was dissolved in 150 mL of EtOH, and the solution was saturated with HCl(g) and stirred for 24 h at room temperature. Removal of the solvent afforded a white solid, which was treated with H_2O (100 mL) and extracted with $CHCl_3$ (3 × 40 mL). This extract was dried ($MgSO_4$) and evaporated to give an oily residue, which after being purified by flash column chromatography (hexane/Et_2O, 2:3) afforded the title compound as a white solid (8.51 g, 53%); mp 52−54 °C, lit.[22] mp 53−54 °C.

3,5-Bis(hydroxymethyl)pyrazole (1a). To a solution of diethyl 3,5-pyrazoledicarboxylate (10.60 g, 50 mmol) in 100 mL of dry toluene cooled at −78 °C was slowly added 170 mL of a 1.5 M solution of DIBALH in toluene under argon. After addition, the reaction was allowed to reach room temperature overnight, cooled to 0 °C, and treated with 150 mL of MeOH. The precipitated solid was collected by filtration, air-dried, and extracted in a Soxhlet apparatus with MeOH for 4 d. Evaporation of MeOH afforded an oil, which after trituration with

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EtOAc gave compound **1a** as a white solid, which was crystallized from EtOAc (5.38 g, 84%); mp 95−96 °C, lit.[39] mp 91−92 °C.

1-Benzyl-3,5-bis(hydroxymethyl)pyrazole (**1b**). A solution of diethyl 1-benzyl-3,5-pyrazoledicarboxylate[22] (4.83 g, 16 mmol) in 100 mL of dry THF was slowly added under argon to an ice-cooled solution of 3.04 g (80 mmol) of $LiAlH_4$ in 100 mL of the same solvent. After addition, the reaction was allowed to reach room temperature overnight, cooled to 0 °C, and hydrolyzed by slow and consecutive addition of 15 mL of MeOH and 100 mL of saturated aqueous NH_4Cl. After separation of the solid in suspension by filtration and evaporation of organic solvents, the aqueous phase was extracted with 5 × 50 mL of $CHCl_3$. This solution was dried ($MgSO_4$) and evaporated to afford the title compound as a white solid, which was crystallized from EtOAc (2.48 g, 71%); mp 92−94 °C, lit.[22] mp 92−93 °C.

Preparation of Pyrazoledicarbaldehydes 2a and 2b. These compounds were prepared by oxidation of 3,5-bis(hydroxymethyl)pyrazoles **1a** and **1b** as follows. To a refluxing solution of 10 mmol of the corresponding dialcohol in DME (250 mL for **1a** and 100 mL for **1b**) was added solid MnO_2 (10 g, 115 mmol) portionwise. The reflux was then continued, and after 2 h the reaction was usually complete. Insoluble material was then removed by filtration through a Celite pad and washed with 3 × 100 mL of hot MeOH. The solution was decolorized with some charcoal and, after filtration, evaporated to dryness to give the corresponding dicarbaldehydes (**2a** and **2b**) as chromatographically homogeneous materials. Each of them was crystallized in solvent as indicated below.

3,5-Pyrazoledicarbaldehyde (**2a**). White microcrystals (0.93 g, 75%); mp 193−194 °C (PrOH or H_2O); IR (KBr) 3125 and 1710 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 9.94 (s, 2H), 7.49 (s, 1H) (monomer **2a**), 9.99 (s, 1H), 9.98 (s, 1H), 7.01 (s, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 6.90 (s, 1H) (dimer **2a′**) (**2a**/**2a′** ratio at 30 °C in 0.2 M solution, 73/27); MS (EI) *m*/*z* 124 (M^+, 100). Anal. Calcd for $C_5H_4N_2O_2$: C, 48.39; H, 3.25; N, 22.57. Found: C, 48.20; H, 3.52; N, 22.60.

1-Benzyl-3,5-pyrazoledicarbaldehyde (2b). White crystals (1.93 g, 90%); mp 96−97 °C (hexane); IR (KBr) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.01 (s, 1H), 9.85 (s, 1H), 7.40 (s, 1H), 7.30 (s, 5H), 5.78 (s, 2H); MS (EI) *m*/*z* 214 (M^+, 24). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.00; H, 4.50; N, 12.79.

Preparation of Macrocyclic Ligands. 6,19-Dioxa-3,9,12,13,16,22,25,26-octaazatricyclo-[22.2.1.1^{11,14}]-octacosa-1(27),2,9,11,14(28),15,22,24-octaene (3a). 3,5-Pyrazoledicarbaldehyde **2a** (248 mg, 2.0 mmol) was dissolved in 20 mL of warm PrOH. This solution was then cooled to room temperature and added dropwise to a stirred solution of 1,5-diamino-3-oxapentane (208 mg, 2.0 mmol) in 10 mL of PrOH. After the mixture stirred overnight, the title Schiff base separated as white crystals, which were isolated by filtration, washed with PrOH and Et_2O, dried under vacuum, and crystallized from EtOH (346 mg, 90%); mp 177−178 °C. MS (FAB) *m*/*z* 385 (MH^+, 64). Anal. Calcd for $C_{18}H_{24}N_8O_2$: C, 56.24; H, 6.29; N, 29.15. Found: C, 56.50; H, 6.44; N, 28.95.

13,26-Dibenzyl-6,19-dioxa-3,9,12,13,16,22,25,26-octaazatricyclo-[22.2.1.1^{11,14}]-octacosa-1(27),2,9,11,14(28),15,22,24-octaene (3b). A solution of 1-benzyl-3,5-pyrazoledicarbaldehyde (**2b**) (428 mg, 2.0 mmol) in 20 mL of MeCN was added dropwise to a stirring solution of 1,5-diamino-3-oxapentane (208 mg, 2.0 mmol) in 20 mL of the same solvent. After the mixture stirred overnight, the desired Schiff base separated as white crystals, which were isolated by filtration, washed with MeCN and Et_2O, dried under vacuum, and crystallized from EtOH (508 mg, 90%); mp 173−175 °C. IR (KBr) 1650 cm^{-1}; MS (EI) *m*/*z* 564 (M^+, 18). Anal. Calcd for $C_{32}H_{36}N_8O_2$: C, 68.06; H, 6.43; N, 19.84. Found: C, 67.96; H, 6.51; N, 19.63.

13,26-Dibenzyl-3,6,9,12,13,16,19,22,25,26-decaazapentacyclo-[22.2.1.1^{11,14}.0^{2,6}.0^{15,19}]-octacosa-1(27),9,11,14(28),22,24-hexaene (5b). This compound was prepared as described for **3b**, using diethylenetriamine (206 mg, 2.0 mmol) instead of 1,5-diamino-3-oxapentane. The desired compound separated as a thick oil, which solidified after scratching to give a white solid that was crystallized from EtOH (450 mg, 80%); mp 160−162 °C. ^1H NMR ($CDCl_3$) δ 8.35 (s, H_2), 8.31 (s, $H_{2'}$), 7.72 (s, H_4), 7.23 (s, $H_{4'}$), 5.55 (d, H_{7A}), 5.41 (d, H_{7B}), 5.47 (d, $H_{7'A}$), 5.40 (d, $H_{7'B}$), 4.17 (s, H_6), 4.32 (s, $H_{6'}$), 3.78 (m, $H_{\alpha-3A}$), 3.54 (m, $H_{\alpha-3B}$), 3.67 (m, $H_{\alpha-3'A}$), 3.49 (m, $H_{\alpha-3'B}$), 3.05 (m, $H_{\beta-3A}$), 2.51 (m, $H_{\beta-3B}$), 3.01, (m, $H_{\beta-3'A}$), 2.57 (m, $H_{\beta-3'B}$), 3.22 (m, $H_{\alpha-5A}$), 3.17 (m, $H_{\alpha-5B}$), 3.18 (m, $H_{\alpha-5'A}$), 3.12 (m, $H_{\alpha-5'B}$), 3.47 (m, $H_{\beta-5A}$), 2.34 (m, $H_{\beta-5B}$), 3.33 (m, $H_{\beta-5'A}$), 2.37 (m, $H_{\beta-5'B}$); MS (FAB) *m*/*z* 563 (MH^+, 54). Anal. Calcd for $C_{32}H_{38}N_{10}$: C, 68.30; H, 6.81; N, 24.89. Found: C, 68.60; H, 7.05; N, 24.68.

6,19-Dioxa-3,9,12,13,16,22,25,26-octaazatricyclo-[22.2.1.1^{11,14}]-octacosa-1(27),11,14(28),24-tetraene (4a). To a stirred suspension of Schiff base **3a** (154 mg, 0.4 mmol) in 10 mL of EtOH was added solid $NaBH_4$ (151 mg, 4.0 mmol) portionwise. After 2 h at room temperature the solvent was evaporated, and after addition of 10 mL of H_2O the pH was adjusted to 9 by addition of 5% aqueous HCl. Water was then evaporated, and the dry residue was extracted with toluene in a Soxhlet apparatus. Evaporation of toluene gave a solid, which was crystallized from benzene, affording pure compound **4a** as white crystals (118 mg, 75%); mp 144−146 °C. MS (FAB) *m*/*z* 393 (MH^+, 100). Anal. Calcd for $C_{18}H_{32}N_8O_2$: C, 55.08; H, 8.22; N, 28.55. Found: C, 55.30; H, 8.17; N, 28.30.

13,26-Dibenzyl-6,19-dioxa-3,9,12,13,16,22,25,26-octaazatricyclo-[22.2.1.1^{11,14}]-octacosa-1(27),11,14(28),24-tetraene (4b). This compound was prepared as described for **4a** from Schiff base **3b** (226 mg, 0.4 mmol) and $NaBH_4$ (151 mg, 4.0 mmol), but in this case the reduction was carried out at 70 °C for 2 h. The solvent was then evaporated, and after addition of 10 mL of water the pH was adjusted to 9 as before. The solution was extracted with 3 × 25 mL of $CHCl_3$, and the organic layer was dried (Na_2SO_4) and evaporated to yield **4b** as a white solid, which was crystallized from benzene (192 mg, 84%); mp 131−133 °C. MS (FAB) *m*/*z* 573 (MH^+, 100). Anal. Calcd for $C_{32}H_{44}N_8O_2$: C, 67.11; H, 7.74; N, 19.56. Found: C, 66.92; H, 8.04; N, 19.34.

3,6,9,12,13,16,19,22,25,26-Decaazatricyclo-[22.2.1.1^{11,14}]-octacosa-1(27),11,14(28),24-tetraene (6a). 3,5-Pyrazoledicarbaldehyde **2a** (400 mg, 3.2 mmol) was dissolved in 250 mL of hot MeOH. This solution was then cooled to room temperature and added dropwise under an argon atmosphere to a stirred solution of diethylenetriamine (328 mg, 3.2 mmol) in 60 mL of MeOH. The reaction was monitored by TLC ($CHCl_3$/MeOH, 10:1), and when it was complete (ca. 3.5 h) $NaBH_4$ (268 mg, 4.1 mmol) was added portionwise. After 2 h the solvent was evaporated to dryness under reduced pressure; the residual syrup was purified by flash column chromatography (MeOH/30% aqueous NH_4OH, 49:1 to 43:7 mixtures). The fractions containing the product of R_f 0.40 (TLC, MeOH/30% aqueous NH_4OH, 5:2) were evaporated to dryness. The residue was then extracted with boiling toluene and on concentration and cooling gave **6a** as a white solid, which was crystallized from toluene (188 mg, 30%); mp 167−169 °C. MS (FAB) *m*/*z* 391(MH^+, 39). Anal. Calcd for $C_{18}H_{34}N_{10}$: C, 55.36; H, 8.78; N, 35.87. Found: C, 55.35; H, 8.77; N, 35.57.

13,26-Dibenzyl-3,6,9,12,13,16,19,22,25,26-decaazatricyclo-[22.2.1.1^{11,14}]-octacosa-1(27),11,14(28),24-tetraene (6b). This compound was prepared from Schiff base imidazolidine **5b** (225 mg, 0.4 mmol) and $NaBH_4$ (151 mg, 4.0 mmol) as described for oxapolyamine **4b**, but the reduction was carried out at room temperature. The title compound was thus isolated as a white solid, which was crystallized from toluene (196 mg, 86%); mp 136−138 °C. MS (FAB) *m*/*z* 571 (MH^+, 69). Anal. Calcd for $C_{32}H_{46}N_{10}$: C, 67.34; H, 8.12; N, 24.54. Found: C, 67.12; H, 8.36; N, 24.63.

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Supporting Information Available: ^{1}H and ^{13}C NMR data registered in D_2O at different pH values and chemical shift differences between protonation steps of **4a**[L_2], **4b**[L_4], **6a**[L_6], and **6b**[L_8]. $^{1}H-^{1}H$ correlation for the aliphatic region of the spectrum of **5b**[L_7] in $CDCl_3$ and expansion of the aliphatic region of the HMBC spectrum of **5b**[L_7]. Variation with the pH of ^{13}C chemical shifts of carbon atoms $C_{3,5}$ and $C_{\beta-3,5}$ of **4a**[L_2]. Variation of the line width of signals $C_{3,5}$ of **6a**[L_6] with pH. Variation with the pH of ^{13}C chemical shifts of carbon atoms C_3, C_5 and $C_{\alpha-3}$, $C_{\alpha-5}$, $C_{\beta-3}$, and $C_{\beta-5}$ of **6b**[L_8]. This material is available free of charge via the Internet at http://pubs.acs.org.

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