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Properties of metal centers in low-symmetry complexes of p-azacyclophanes

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The properties of metal centers in low-symmetry complexes of p-azacyclophanes are reviewed.

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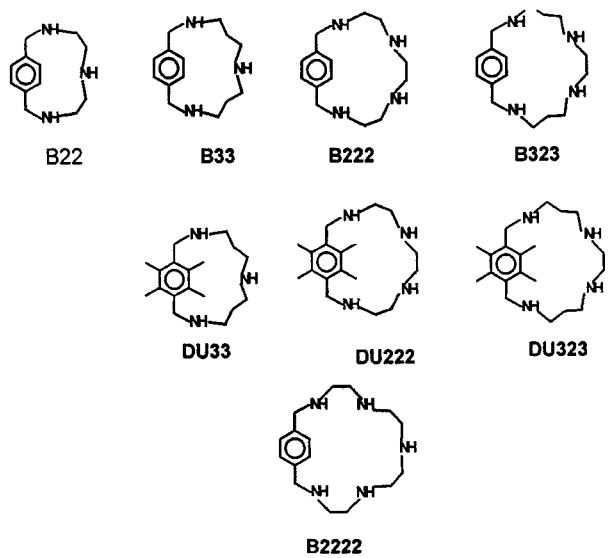
Much effort in molecular recognition has been dedicated to the design of receptors having specific structural features so as to achieve selectivity in the binding of target molecules and specific catalytic effects.[1] In the last three years, we have been interested in the study of a series of macrocyclic compounds characterized by the presence of a single *p*-phenylene subunit interrupting a polyamine chain.[2–6] Despite the synthesis of different cyclophanes containing two or more *p*-phenylene subunits, the number of studies on polyaza[n]cyclophanes with only one 1,4-benzo subunit is small.[7–10] These compounds seemed, at first sight, interesting receptors since, besides the nitrogen donor atoms, they posses a polarizable π-cloud and both could converge, from opposite sides, into the guest species.[11] Additionally, the aromatic moiety may act as a rigid spacer between some of the donor atoms in the chain.

With the present contribution we intend to briefly review the most important characteristics of the chemistry of these new family of receptors regarding their (i) synthesis, (ii) protonation behavior, (iii) coordination to transition metal ions, and (iv) coordination to anionic guests.

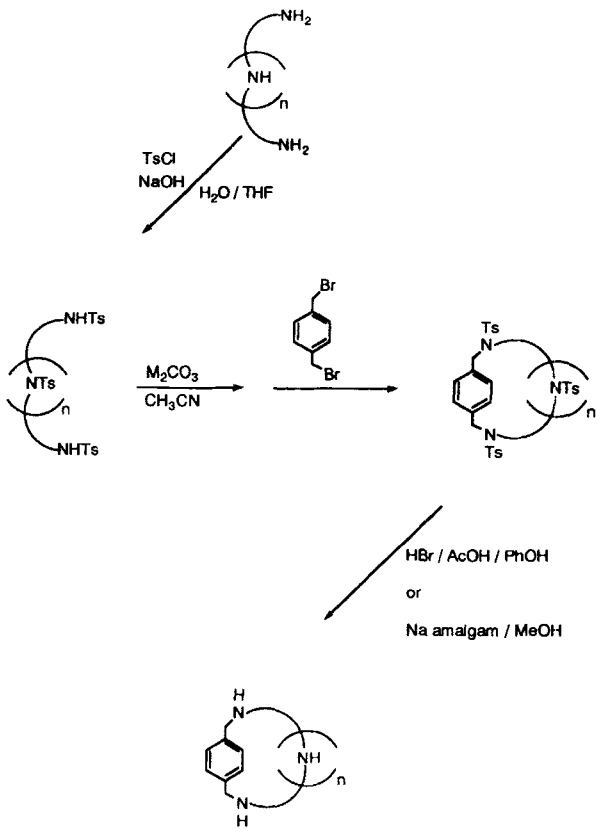
Before describing the chemistry of these ligands, we comment on the nomenclature used hereafter. The names are made of letters **B**, **DU** or **N** followed by a sequence of numerals standing for the aromatic spacer (**B** = benzene, **DU** = durene, **N** = naphthalene) and for the number of carbon atoms of the hydrocarbon chains between them, respectively For instance 2,5,9,12-tetraaza[14]paracyclophane will be abbreviated as **B323** and 2,5,8,11-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane as **DU323** (see Ligand Drawing).



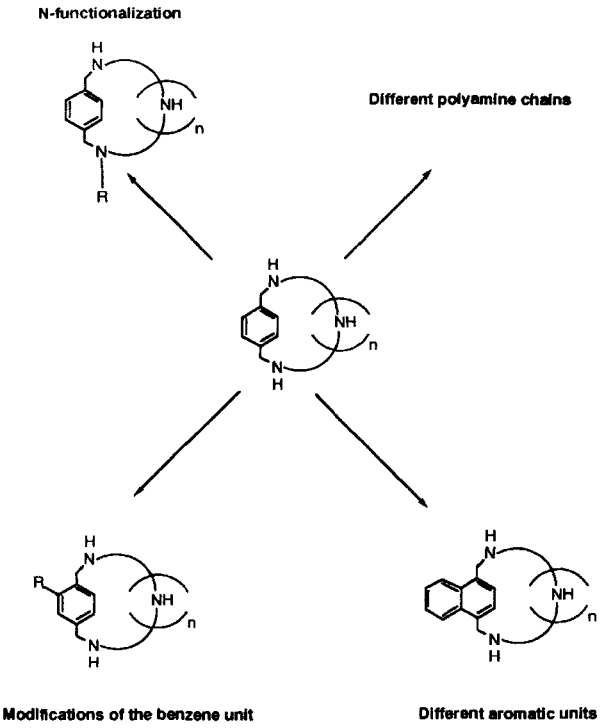
SYNTHESIS

The synthesis of the receptors has been carried out following the general procedure depicted in Scheme 1. Basically, it consists of a one-pot reaction between the tosylated polyamine chain with 1,4-bis(bromomethyl)benzene in refluxing CH_3CN using K_2CO_3 as a base. Interestingly enough, high dilution conditions were not required to achieve very high yields in the cyclization step.[3] The [9]paracyclophane structure (**B22**) seemed to be the smallest ring that could be prepared by this method; when reacting N,N′,-bis(tosylsulfonyl)ethylenediamine with 1,4-bis(bromomethyl)benzene only oligomeric materials and minor amounts of the 2:2 condensation product were obtained. Detosylation of the products was carried out either with HBr/AcOH/PhOH for the benzene derivatives or with sodium amalgam for the durene ones. A

*To whom correspondence should be addressed.



Scheme 1



Scheme 2

final purification was performed, in all cases, by silica gel chromatography with MeOH/THF/NH_3 as the eluent.

An interesting point is the facility with which these compounds can be chemically modified in a controlled way to get compounds with different topological features. Several of the possible modifications are (i) changes in the number of nitrogen donors and/or length of the hydrocarbon spacers between them, (ii) changes in the aromatic spacer, (iii) introduction of functional groups in the aromatic moiety, and (iv) functionalization of the nitrogen atoms of the bridge (see Scheme 2). Using approach (ii) we have obtained the related series of naphthalenophane receptors.[4]

PROTONATION

In Table I are presented the successive protonation constants for the ligands **B22**, **B33**, **DU33**, **B222**, **DU222**, **B323** and **DU323** calculated in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K by potentiometry using the program SUPERQUAD.[12] A first analysis of the data allows for the derivation of several general trends. As can be seen in Figure 1, a straight line is obtained when representing the overall basicity *vs.* the number of atoms within the polyamine chain bridging the aromatic spacer. When comparing the couples of ligands with the same polyamine chains and benzene or durene spacers, namely **B33-DU33**, **B222-DU222** and **B323-DU323**, a great similarity between the stepwise protonation constants is observed denoting that the possible electronic and solvation effects originated by methylation of the aromatic spacer do not affect the basicity of the p-azacyclophanes.

The protonation sequences derived from the stepwise basicities of the ligands may be explained, in principle, by considering that the situations of minimum energy are represented by the protonation isomers in which the repulsions between protonated sites are also at a minimum. The stepwise protonation constants of **DU222** and **DU323** can give some insight into this point. The two first protonations of both ligands may take place on any one of the nitrogen atoms as long as they are not adjacent. The third protonation has to occur necessarily adjacent to one already protonated nitrogen. However, while for **DU222** this protonation affects a nitrogen atom separated from the adjacent polyammonium site by an ethylenic chain, for **DU323** it would affect a nitrogen separated from the next polyammonium site by a propylenic chain which would yield different electrostatic situations for both molecules. In fact, while for **DU222** the difference between the second and third stepwise protonation constants is 3.03 logarithmic units, for **DU323** it is 1.79. Moreover, while the difference between the stepwise constants for the first and third protonation steps of **DU323** is 3.10, that between the

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Table I Stepwise protonation constants of the p-azacyclophanes **B323, B222, B2222, B22, B33, DU33, DU222** and **DU323** determined at 298; 1±0.1K in 0.15 mol dm^{-3} $NaClO_4$

Reaction	*B323*	*B222*	*B2222*	*B22*	*B33*	*DU33*	*DU222*	*DU323*
H+L=HL[a]	9.933(4)[b]	9.39(2)[c]	10.68(2)[c]	9.42(1)[d]	10.13(1)	9.96(1)	9.44(3)	10.54(1)
H+HL=H_2L	9.09(1)	8.45(2)	9.29(1)	7.31(1)	8.34(1)	8.59(1)	8.67(3)	9.23(2)
H+H_2L=H_3L	7.43(1)	5.38(2)	8.66(2)	3.26(3)	6.82(2)	7.04(1)	5.64(6)	7.44(2)
H+H_3L=H_4L	3.61(1)	2.51(1)	7.23(2)				2.5(1)	3.59(3)
H+H_4L=H_5L			3.93(2)					

a) Charges have been omitted by means of clarity. b) Figures in parentheses are standard deviations in the last significant figure.

third and fourth one, in which protonation would occur in polyammonium sites separated by just an ethylenic chain, is 3.85 logarithm units. Therefore, the propylenic chains seem to keep the protonated sites far away enough not to severely influence each other from an electrostatic point of view, and other factors, apart from statistical ones, should play an important role in determining the protonation pattern.

Direct microcalorimetric measurements and NMR studies on the variation of the chemical shifts upon protonation are of great interest in order to establish the protonation patterns followed by these polyamines. As an example, in Table II are reported the stepwise enthalpy and entropy contributions to the protonations of all the ligands of the series. It deserves to be noted that the enthalpy terms associated, in many cases, to the first protonation of both ligands are very low when compared to related saturated tetraazacycloalkanes.[13] These data suggest that first protonations of these ligands occur in hydrophobic parts of the *p*-azacyclophanes and, therefore, are accompanied of a large release of water molecules and, consequently, of high translational entropy.

NMR spectroscopy gives further informations about the protonation trends of polyamine ligands in general and of polyaazacyclophanes in particular. It is well known that the carbon and hydrogen nuclei most sensitive to protonations are those placed in the β-position and α-position to the nitrogen atom taking up the proton which is shifted upfield and downfield, respectively.[14] In our compounds, the variations of the quaternary aromatic carbon atom CB1 (see Figure 2) are of great help in order to establish the protonation sequence since they are only affected by the protonation of the benzylic nitrogens (N1). For instance, in Figure 2, such variations are presented for the ligand **DU323** together with its distribution diagrams. The large downfield shifts observed between pH values 11.0-7.0 for **DU323** strongly support that the first protonation is occurring in the benzylic or naphthylic positions. This would explain the large favorable entropy contribution observed for these protonations. The ^1H and ^{13}C NMR data for the ligands with only propylenic chains, **B33** and **DU33**, shows, however, that for these compounds the first proton is more randomly shared by all the nitrogen atoms in the macrocyclic framework.[5]

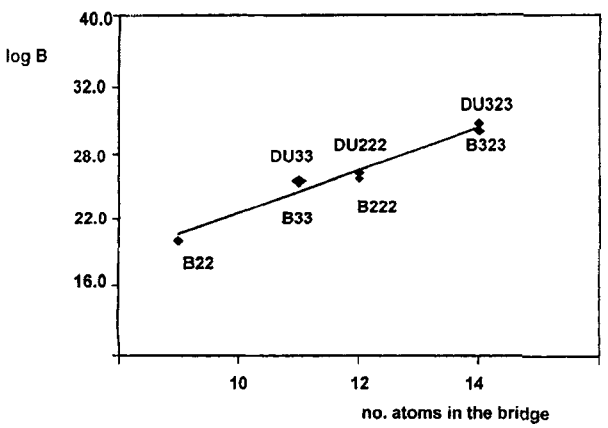

Figure 1 Plot of the logarithms of the overall basicity constants β as a function of the number of atoms in the bridge for the different *p*-azacyclophanes containing benzene or durene as spacers.

As a general conclusion, the azaparacyclophanes here considered can be classified according to their protonation behavior into three different groups. The first group would include those ligands containing only ethylenic chains in the bridge. The second group is represented by those with only propylenic chains and the third one by those with propylenic and ethylenic ones.

The first group of ligands display the lowest basicities in their protonation steps. In their diprotonated forms, H_2L^{2+}, both protons seem to bind preferentially the benzylic nitrogens. Within this group **B222** presents a higher stabilization of the first proton in the benzylic position.

The second group of ligands presents a large enthalpic term for all the protonation terms and the NMR analysis does not show any preferred coordination sites and the protons should be randomly sharing all the nitrogen donors.

The third group of compounds displays, in their three first protonations, analogous basicities to those of the second one. NMR data analysis shows that the entry of the third proton blocks two of the protons in the benzylic positions. As a general point it should be noted that methylation does not alter the basicity of the molecules.

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Table II Stepwise enthalpy and entropy terms (kcal mol^{-1}) for the successive protonations of the ligands **B323**, **B222**, **B33**, **DU33**, **DU222** and **DU323**

			$-\Delta H°$			
Reaction	*B323*	*B222*	*B33*	*DU33*	*DU222*	*DU323*
H+L=HL[a]	9.55(4)[b]	8.22(5)	9.81(7)	9.6(1)	9.34(7)	10.35(3)
H+HL=H_2L	10.91(6)	9.7(1)	10.4(1)	10.2(1)	9.5(1)	11.01(7)
H+H_2L=H_3L	10.70(6)	8.7(1)	10.3(1)	10.5(1)	9.0(1)	11.01(7)
H+H_3L=H_4L	7.01(7)	4.1(1)			3.9(1)	6.7(1)
			$T\Delta S°$			
Reaction	*B323*	*B222*	*B33*	*DU33*	*DU222*	*DU323*
H+L=HL[a]	4.0(1)[b]	4.7(2)	4.0(1)	3.4(1)	3.5(2)	4.0(1)
H+HL=H_2L	1.5(1)	1.7(2)	1.0(1)	1.5(1)	2.4(1)	1.6(1)
H+H_2L=H_3L	-0.6(1)	-1.4(1)	-1.1(1)	-0.7(1)	-1.3(3)	-1.0(1)
H+H_3L=H_4L	-2.1(2)	-0.5(1)			-0.5(2)	-1.8(2)

a) Charges have been omitted by means of clarity. b) Figures in parentheses are standard deviations in the last significant figure.

Apart from their intrinsic interest, protonation studies are useful to decide the type of chemistry these molecules may be involved. As a consequence of the presence of the *p*-substituted phenylene subunits, protonation of the benzylic nitrogens occurs in an almost independent way, namely, both protonation constants are very high and take place, in all the cases, above neutral pH. If the hydrocarbon chains between the nitrogen atoms are appropriately chosen, the molecules may take up additional protons at relatively high pH values which results in molecules displaying large accumulations of positive charge even at neutral pH values. This feature prompts these molecules to interact in an organized way with anionic species giving rise to an interesting behavior as anion coordinating agents.

Therefore, the main characteristics of this family of ligands that may be derived from its own synthesis and protonation behavior are:

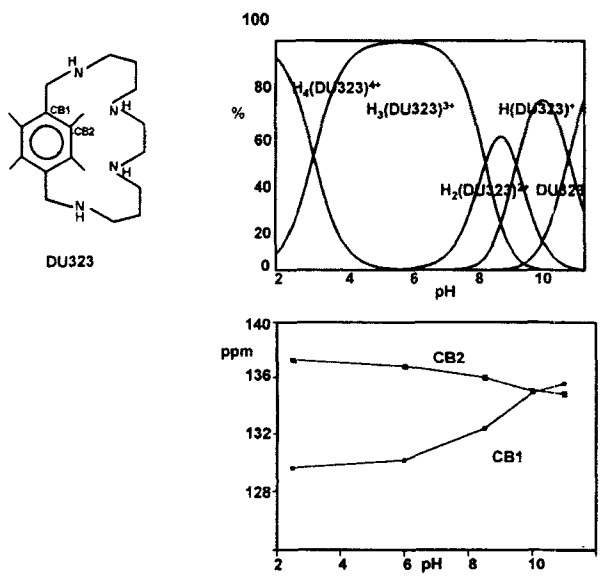

Figure 2 Distribution diagram and plot of the variation of the ^{13}C NMR chemical shifts (ppm) of quaternary aromatic carbon atoms (CB1, CB2) for the system H$^+$-**DU323**.

(i) They are simple ligands that can be relatively easily synthesized and purified by general procedures.

(ii) They can be chemically modified in a number of different ways.

(iii) They are polydentate ligands able to incorporate metal ions. The stiffening imposed by the aromatic ring may provide interesting patterns in their coordination to metal ions as well as in their chemical reactivity.

(iv) There is potential capability in their protonated forms to interact with anions giving discrete adducts. In the next paragraphs are some examples to outline the most significant aspects related to points (iii) and (iv).

COORDINATION TO METAL IONS

Interaction with Zn^{2+}. In Table III are presented the logarithms of the stepwise stability constants for the interaction of the ligands **B323** and **B222** with Zn^{2+}. All the constants have been determined in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K. Distribution diagrams, calculated for 1×10^{-3} mol dm^{-3} metal and ligand concentrations are presented in Figure 3. First of all, the low stability constants this macrocycles display in comparison with related tetraazacycloalkanes deserve to be noted.[13] This fact, together with the very close values between the

Table III Logarithms of the stepwise stability constants for the formation of Zn^{2+} complexes of **B323** and **B222** determined at 298.1 K in 0.15 mol dm^{-3} $NaClO_4$

Reaction	*B323*	*B222*
Zn+L = ZnL[a]	6.83(1)	4.55(4)
ZnL+H = ZnHL	7.77(2)	
ZnL+H2O=ZnL(OH)+H	-8.66(2)	-8.20(2)
ZnL(OH)+H_2O = ZnL(OH)$_2$+H		-10.12(4)
H_2L+H = H_3L	7.43	

a) Charges have been omitted by means of clarity. b) Figures in parentheses are standard deviations in the last significant figure.

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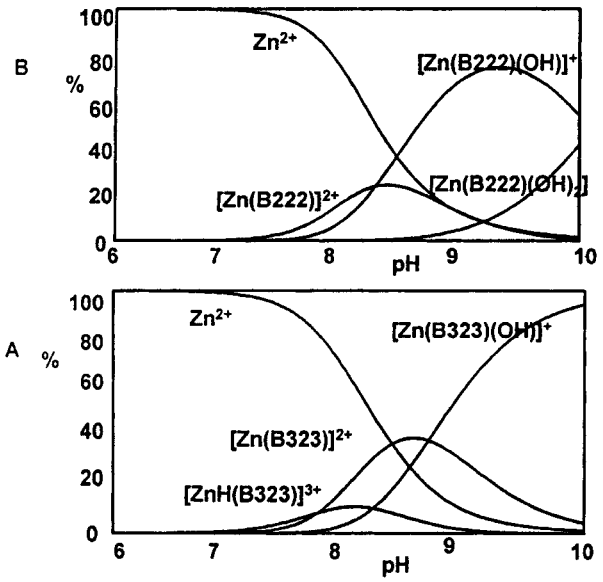

Figure 3 Distribution diagrams for the systems Zn^{2+}-**B323** and Zn^{2+}-B222 calculated for 1×10^{-3} mol dm^{-3} concentration in both reagents.

constants associated to the first protonation of the complex $[Zn(\mathbf{B323})]^{2+}$($[Zn(\mathbf{B323})]^{2+}+H^{+}_{aq}$ = $[ZnH(\mathbf{B323})]^{3+}$, log K = 7.77) and to the third protonation of the free-ligand ($H_2(\mathbf{B323})^{2+}+H^{+}_{aq} = H_3(\mathbf{B323})^{3+}$, log K = 7.43), suggests that not all the nitrogen donors in the macrocycle are involved in the coordination to the metal center. A first hypothesis could be that one nitrogen in **B323** an two in **B222** remain non-coordinated. Further support for this low participation of the nitrogen atoms of the polyamine chain in the coordination to the metal center comes from the presence in both systems of important hydroxo species which, above pH = 9, are predominant in solution. The water molecules completing the presumably tetrahedral coordination sites of the Zn^{2+} ions present remarkable acidic character (see Table III and Figure 3).

Further support to the low-symmetry coordination of the complex $[Zn(\mathbf{B323})]^{2+}$ is also provided by its NMR spectral features. When adding Zn^{2+} to a CH_3CN solution of the complex to reach a molar ratio 1:1 the ligand loses its binary symmetry; all the carbon nuclei become non-equivalent and the spectrum displays as many ^{13}C NMR signals as there are carbon atoms in the molecule. As can be seen in the model presented in Figure 4 for the complex $[Zn(\mathbf{B323})]^{2+}$, the presence of the *para*-substituted aromatic spacer precludes the simultaneous participation of both benzylic nitrogens in the coordination to a single metal center. These coordination features give rise to two interesting consequences: (i) the possibility of working up the non-coordinated nitrogen atoms to selectively functionalize the receptors and (ii) its possible use for the hydrolytic cleavage of substrates.

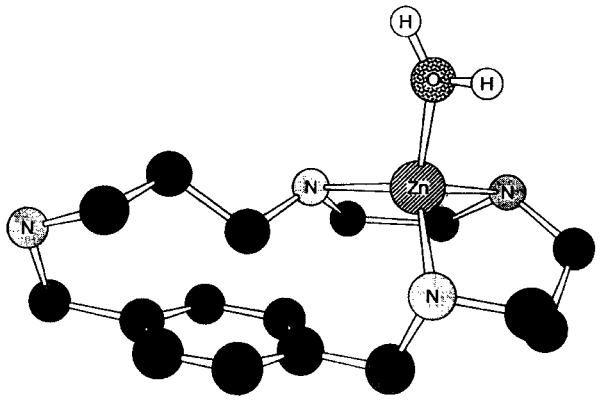

Figure 4 Possible coordination mode for the complex $[Zn(\mathbf{B323})]^{2+}$.

Selective monofunctionalization

Much effort has been devoted to get selectively monofunctionalized macrocycles and different synthetic strategies have been developed to this purpose. For symmetrical macrocycles, the most general approaches are the use of a large excess of amine over the alkylating agent or the protection of three nitrogen atoms via phosphorous or boron derivatives, metal carbonyls, or some other groups.[15,16] However, for unsymmetrical macrocycles, the synthesis of selectively N-monofunctionalized derivatives usually requires a multistep approach, the group being introduced with one of the chains in the cyclization step.[17] Regarding this aspect, the paraazacyclophanes here considered constitute good and simple examples of molecules programmed to developed selective reaction patterns upon interaction with an appropriate guest.

Attempted reaction of **B323** with an alkylating agent such as allyl bromide (1:1 molar ratio) in CH_3CN, in the presence of base, afforded a very complex mixture containing all the possible mono-, di- and polyalkylated compounds in very low yields, along with the starting materials as the major component. However, when the reaction was carried out in the presence of a stoichiometric amount of Zn^{2+} (as its chloride or triflate salt), the analysis of the crude reaction product revealed the presence, as the predominant product, of the macrocycle **B323** functionalized at one of the benzylic nitrogens together with very small amounts of the dialkylated product at both benzylic positions. Chromatographic purification of the crude product afforded the N-benzylmonoalkylated derivative in 60% yield.[18] NMR spectroscopic characterization of the product clearly revealed that monoalkylation had occurred at the benzylic position. The only experimental care to be taken for this reaction to proceed satisfactorily is that the temperature has to be kept between room temperature and 0 °C. Lower temperatures generally afforded the starting materials unchanged and higher ones increased the amount

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of dialkylated products probably because isomerization reactions are favored. However, this could be an important point since the obtention of mono- or dialkylated products may be switched by the temperature. In Table IV are shown the results obtained for different alkylating agents. All yields refer to the isolated product after chromatographic purification. This synthetic approach could be, in principle, used for selective functionalization of other polynitrogenated receptors in which their structural features provide non-coordinated nucleophilic nitrogen atoms when interacting with guest species.

Participation in hydrolytic catalysis

Zn^{2+} is the metal ion primarily chosen by nature to participate in hydrolytic catalysis. This is usually attributed to its Lewis acid behavior, the stability of the 2+ oxidation state and thus, lack of participation in redox processes, the comparable stability of its four-, five- and six-coordinated complexes and the lability of its complexes.[19] Therefore, Zn^{2+} is present in many hydrolytic enzymes and, most often, its role is to bind the substrate and activate it. Three of the most well known Zn^{2+} containing enzymes are carbonic anhydrase (CA), liver alcohol dehydrogenase (LADH), and carboxypeptidase A.

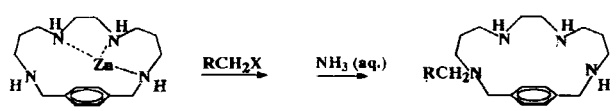
A great deal of attention has been recently focused on the design of metal complexes able to mimic the active center of these proteins. In the case of CA, the Zn^{2+} complex of the saturated triazamacrocycle [12]aneN$_3$[20] is good model because it reproduces the distorted tetrahedral geometry of CA (three nitrogen donors and a water molecule) and particularly, presents a pK_a value of the coordinated water molecule (pK_a = 7.4) close to the value assigned for the deprotonation of the water molecule in CA. On the other hand, the catalysis of this molecule is also inhibited by the presence of appropriate anions.

The above-mentioned coordination features proposed for [Zn(**B323**)]$^{2+}$ has made this complex a potential carbonic anhydrase mimic. Although this compound does not present a low enough value for the deprotonation of the coordinated water molecule (pK_a = 8.67), the presence of a non-coordinated nitrogen atom could be an interesting feature in order to assist the catalytic process. We have studied the catalytic efficiency of this compound using *p*-nitrophenyl acetate as a substrate. The results obtained, which are graphically presented in Figure 5, show for [Zn(**B323**)]$^{2+}$ a similar catalytic efficiency to [12]aneN$_3$, but the curve K_2 *vs.* pH is displaced to higher pH values.[20] The mean point of this *s*-shaped curve is coincident with the pK_a value of the coordinated water molecule. Thus, these data clearly reveal that the hydroxo species should be the active one and there is no participation of the non-coordinated nitrogen in the catalytic pathway. However, [Zn(**B323**)]$^{2+}$ does not represent an end point in these studies, but rather a starting one, since the chemical modifications that can be carried out on this molecules by using the procedure mentioned in the latter paragraph may serve to introduce functional groups able to cooperate in the catalytic processes. We are currently exploring this area and some promising results are envisaged.

Copper coordination

In Table V are presented the stability constants obtained for the interaction of copper(II) with different members of this series of ligands. As it happened with Zn^{2+}, the first remarkable aspect to be noticed is the low stability displayed by the Cu^{2+} complexes. Again, first protonation constants of the Cu^{2+} complexes are very close to the values of the third stepwise protonations of the free ligand suggesting the presence of non-coordinated nitrogens within the macrocyclic framework. However, the most unambiguous evidence for this low coordination of

Table IV Isolated yields of monofunctionalized polyaza[n]paracyclophanes



Substrate	*R-*	*Yield* [%][a),b)]
B323	CH_2=CH-	60
B323	Ph-	56
B323	EtO_2C-	72
B323	p-$NO_2C_6H_4$-	61
B323	p-MeC_6H_4-	64

a) Yields after chromatographic purification. b) All new compounds gave the expected analytical results.

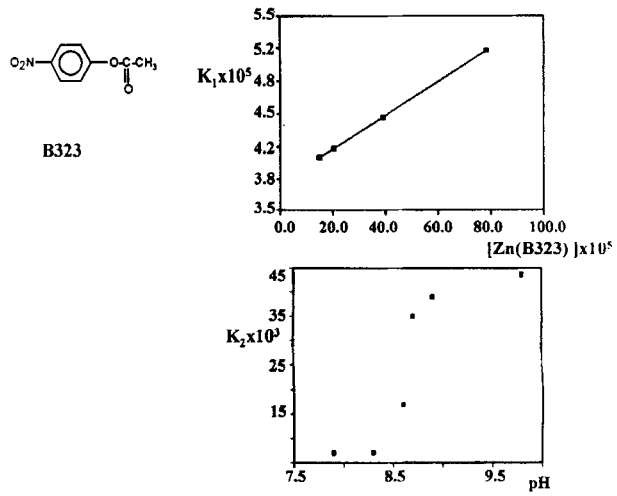


Figure 5 Plots of the pseudo-first order rate constant K_1 vs. the concentration of [Zn(**B323**)]$^{2+}$ complex and of the variation of the second order rate constant as a function of pH for the hydrolysis of 4-nitrophenylacetate.

Table V Stability constants for the formation of Cu^{2+} complexes by the p-azacyclophanes **B323**, **B222** and **B222** determined at 298.1±0.1 K in 0.15 mol dm^{-3} $NaClO_4$

Reaction	*B323*	*B222*	*B2222*
Cu+L=CuL[a]	13.02(1)	10.41(2)	17.73(5)
CuL+H=CuHL	7.80(1)	6.51(3)	9.13(7)
$CuHL+H=CuH_2L$			6.42(4)
$CuH_2L+H=CuH_3L$			4.37(3)
$CuL+H_2O=CuL(OH)+H$	-9.10(2)	-8.14(8)	-11.1(1)
$2Cu+L=Cu_2L$			24.29(4)
$Cu_2L+H_2O=Cu_2L(OH)+H$			-7.34(8)
$Cu_2L(OH)+H_2O=Cu_2L(OH)_2+H$			-9.5(1)

a) Charges have been omitted by means of clarity. b) Values in parentheses are standard deviations in the last significant figure.

the ligands comes from direct microcalorimetric measurements. In Table VI are presented the enthalpy and entropy terms for the Cu^{2+} complexes of the ligands **B323** and **B222**. It can be seen that the enthalpy values for the protonation of the complexes (**B323**; ΔH° = -47.3 kJ mol^{-1}; **B222**, ΔH° = -34.4 kJ mol^{-1}) are close to or even greater than those associated to the first protonation of the respective ligands (**B323**; ΔH° = -39.9 kJ mol^{-1}; **B222**, ΔH° = -35.1 kJ mol^{-1}), indicating that in the protonation process there is no energy waste due to the cleavage of Cu^{2+}-N bonds. Moreover, the low stability constant and enthalpy term obtained for **B222** could even suggest that, in this case, just two out of the four nitrogen donors are effectively coordinating the Cu^{2+} ion.

Bimetallic copper(II) complexes have found a wealth of implications in the biomimetic chemistry of copper(II) proteins and substrate activation by metal centers.[21,22] In order to obtain such compounds several general strategies have been followed: (i) synthesis of large macrocycles or macrocrobicycles with a high number of donor atoms and thus ability to incorporate more than one metal ion,[23] (ii) synthesis of bis(macrocycles),[24] and (iii) use of chelating agents bridging two macrocyclic ligands.[25] The topological features induced in the ligands herein studied by the *p*-phenylene subunit may represent a new strategy to obtain binuclear complexes.

In fact, potentiometric studies show for **B222**, **N222** and **B2222** the formation of stable binuclear complexes

Table VI Enthalpy and entropy terms (kcal mol^{-1}) for the formation of Cu(II) complexes of **B323** and **B222**

	B323	
Reaction	$-\Delta H^\circ$	$T\Delta S^\circ$
Cu+L = CuL[a]	11.9(1)[b]	5.9(2)
CuL+H = CuHL	11.3(3)	-2.3(3)
H+L = HL	9.55(4)	4.0(1)
	B222	
Reaction	$-\Delta H^\circ$	$T\Delta S^\circ$
Cu+L = CuL[a]	9.1(2)[b]	5.0(2)
CuL+H = CuHL	8.4(3)	0.1(3)
H+L = HL	8.22(5)	4.7(2)

a) Charges have been omitted by means of clarity. b) Values in parentheses are standard deviations in the last significant figure.

in aqueous solution (see Figure 6 and Table V). This is the first time that formation of such species has been reported in tetraaza- or pentaazamacrocycles containing a continuous set of nitrogen donors linked together by ethylenic chains.

Crystals of $[Cu_2(\mathbf{B222})]Cl_4 \cdot 1.5H_2O$ suitable for X-ray analysis were obtained by slow evaporation at room temperature of basic aqueous solutions of copper(II) and **B222** in the presence of an excess of chloride anions.[6] The coordination spheres around both Cu^{2+} ions are very similar and show a fairly distorted square pyramidal coordination geometry. Two contiguous nitrogens of the macrocycle and two chloride atoms form the basal plane of the coordination sphere, the apical position being occupied for another chloride atom at a much larger distance. The Cu^{2+} ions lie at opposite sides of the macrocyclic plane at a distance of 6.077(3) Å.

This crystal structure (Figure 7) clearly shows that the combined effects of the *para*-substituted spacer and the length of the polyamine bridge are key points in determining the bis(chelating) properties of the ligand. As a matter of fact, **B323** which differs from **B222** in the presence of two additional carbon atoms in the bridge does not form such species. The greater flexibility of the polyamine bridge in **B323** should allow for tighter coordination of the metal center in the mononuclear complex precluding therefore the coordination of additional Cu^{2+} ions.

The electrochemistry of copper complexes has attracted a great deal of interest because of the biological significance of the Cu^{2+}/Cu^{+} couple. The ready accessi-

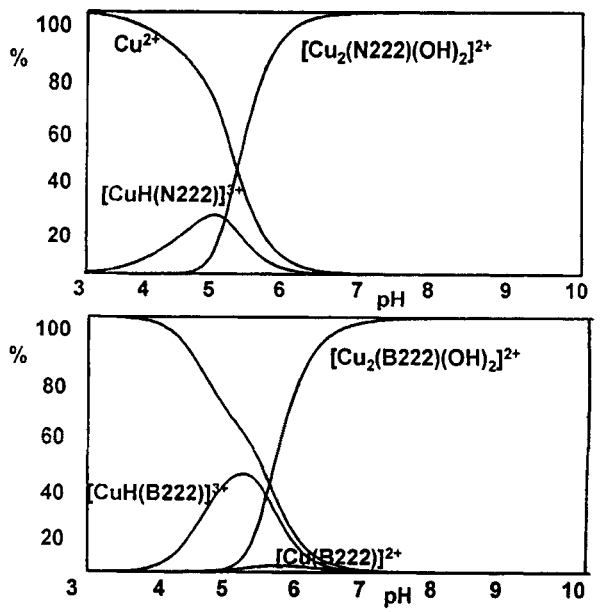


Figure 6 Distribution diagrams for the systems Cu^{2+}-**B222** and Cu^{2+}-**N222** calculated for $[Cu^{2+}]=2\times10^{-3}$ mol dm^{-3} and **[B222]=[N222]**=1×10^{-3} mol dm^{-3}.

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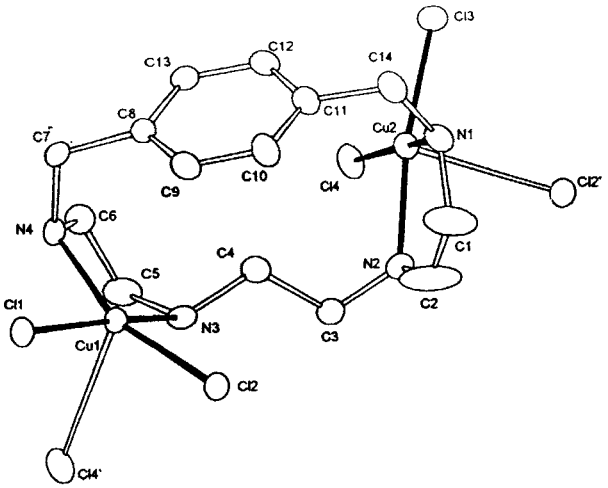

Figure 7 ORTEP drawing showing a single $[Cu_2(\mathbf{B222})Cl_4]$ molecule. Thermal ellipsoids are drawn at the 50% probability level.

bility of the Cu^+ oxidation state is at the origin of the function of the copper electron transfer proteins as well as of the mechanisms of the copper enzymes.[26] All the considerations on the speciation and the structural characteristics of the copper complexes of these paraazacyclophanes made them potentially valuable candidates to test their chemical behavior towards either Cu^+ stabilization or towards avoiding Cu^+ disproportionation into Cu^{2+} and Cu°.

Electrochemical studies have been carried out on the ligands **B323**, **B222**, and **B2222**, which stabilize Cu^+ towards disproportionation into Cu^+ and Cu°. The stability constants reported in Table VII shows that this behavior is reached through a lowering in the stability of the Cu^{2+} complexes rather than from an increase in the stability of the Cu^+ ones with respect to analogous copper complexes of related saturated polyazacycloalkanes. For instance, in Table VI it can be seen that the Cu^+ complex of cyclam[27] displays an order of stability close to the *p*-azacyclophane complexes reported here, while its Cu^{2+} complex is much more stable. A somewhat similar behavior has been reported for a series of mixed saturated thiaazamacrocycles for which it was shown that an increasing number of sulfur donors yielded a decrease in their interaction with Cu^{2+}, rather than an increase in their interaction with the reduced form.[27] Introduction of sulfurs seems to be relevant in order to mimic the behavior of electron transfer copper proteins like plastocyanine, whose active site is based on a tight N_2S coordination with another sulfur atom of a methionine residue lying at a much larger distance forming a very distorted tetrahedral geometry.[28] This coordination site constitutes an entatic state[29] and the reduction of Cu^{2+} into Cu^+ does not produce significant changes in the coordination site and geometry of the metal center. Although the polyazacyclophanes reported here do not, obviously, offer sulfur atoms to the metal center, due the low symmetry of their coordination sites, they may present a similar minimum rearrangement of the coordination site upon reduction to Cu^+. ESR spectra for the Cu^{2+} complexes of all three ligands show preferential square planar geometries and, therefore, reduction to Cu^+ would probably imply a change from square planar to tetrahedral geometry, but no changes in the coordination indexes and type of donor atoms. Moreover, the hydrophobicity afforded by the benzene ring should also be of importance in this respect.[30] These facts may explain why, without having any sulfur atoms, we are getting close to the thermodynamic and electrochemical parameters reported for $[14]aneN_2S_2$ (Table VII). On the other hand, the selective functionalization of these ligands should allow, for instance, the introduction of additional pendant thiol groups to improve the electrochemical approach to the above-mentioned proteins.

ANION COORDINATION

Anion coordination chemistry is a rapidly growing area within the field of supramolecular chemistry.[31] Polyammonium entities containing a large number of nitrogens have been revealed to be good co-ordinating agents for anions. Some of the main characteristics of their chemistry making these species suitable for developing anion co-ordination are (i) high water solubility, (ii) ability to form highly charged species even at neutral pH, and (iii)

Table VII Formal potentials and stability constants for the formation of CuL^{2+} and CuL^+ complexes of some selected ligands

Ligand	*E°'(V vs. SCE)*	*log* $\beta^{II\,a}$	*log* $\beta^{I\,b,d}$	*log* $K'_d{}^{\,d}$
B323	-0.15	13.0	11.9(2)[c]	-4.5(5)
B222	-0.18	10.4[c]	8.8(2)	-1.0(4)
B2222	-0.17	17.7[c]	16.2(2)	-8.4(5)
$[14]aneN_4$	-0.90[c]	27.2	13.8	
$[14]aneN_2S_2$	-0.20[c]	15.2	13.9	
$[14]aneS_4$	0.34[c]	4.3	12.0	

a) Values determined from the potentiometric titrations. β^{II} refers to the reaction $Cu^{II} + L = Cu^{II}L$.
b) Values estimated from the electrochemical data by using the equation: $\log \beta^{I} = \log\beta^{II} + [E°'\text{-}E°'(Cu2+/Cu+)]/59$(mV at 298.1 K). β^{I} refers to the equilibrium $Cu^{I} + L = Cu^{I}L$.
c) Values in parentheses are standard deviations in the last significant figure.
d) Values calculated by means of the equation: $\log K'_d = \log\beta^{II} - 2\log\beta^{I} + \log K_d$. K_d, dismutation constant of the free-aqueous ion.

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possibility to form multisite hydrogen-bond networks with the guest species. When the guest species is itself a complex, the word "super-complex" has been coined[32] to define the molecular assembly resulting from its interaction with an appropriate receptor. The protonation pattern of the p-azacyclophanes formerly described pointed out their possible capabilities to coordinate anions. In this last section one example highlighting this chemistry is presented.

Macrocycles **B222**, **DU222**, **B323** and **DU323** have been tested as coordinating agents for $[Co(CN)_6]^{3-}$. In Table VIII are reported the constants determined both by direct potentiometric measurements and by quenching of the steady state fluorescence emission for the adduct formation between $[Co(CN)_6]^{3-}$ and the fully protonated forms of the receptors in 0.15 mol dm^{-3} $NaClO_4$ at 298.1 K. Two points of interest are the agreement between the values obtained by both techniques and the significantly larger constants displayed by the non-methylated receptors. For the couples of ligands with the same spacer, namely durene or benzene, changes in the length of the hydrocarbon chains in between the nitrogens do not seem to affect greatly the strength of the interaction. These results clearly show that methylation of the aromatic ring, although it does not affect the basicities of the receptors (vide supra), somehow hinders the approach between host and guest species. In fact CPK models and structural data show that the polyamine ring is arching above the aromatic moiety and consequently the methyl groups are directed towards both sides of the macrocyclic cavity. Thus, the matching between host and guest species should be more difficult in the durene-containing paraazacyclophanes.

Photochemical studies on the aquation reaction of $[Co(CN)_6]^{3-}$ in the presence of the receptors[33] denotes a reduction of the quantum yield of the reaction by $\frac{1}{2}$ with respect to that of the aqueous free ion. This result can be interpreted as an effect of hydrogen bonding between the protonated nitrogens of the receptor and the nitrogens of the cyanide groups which prevents three out of the six cyanide groups from escaping out of the first coordination sphere of the complex. CPK models show that, due to the remarkable rigidity of the receptors, for geometric reasons only three facial cyanide groups can interact with three contiguous polyammonium sites of the macrocyclic framework (see Figure 8). One of the benzylic nitrogens would not participate in the hydrogen bonding network.

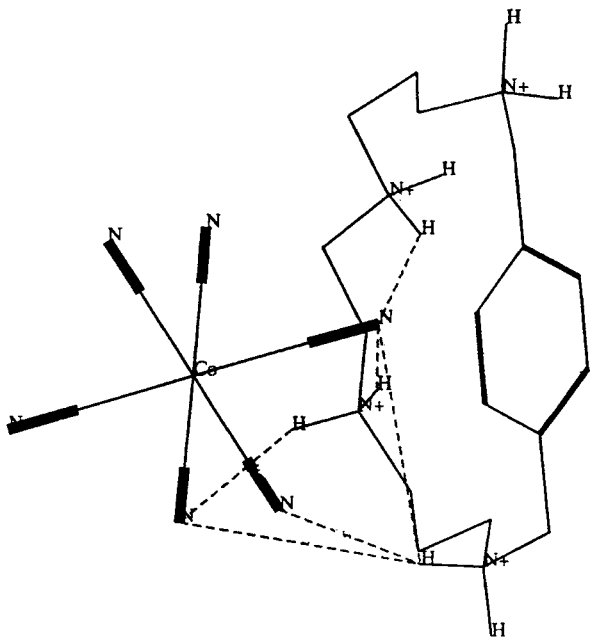

Figure 8 Possible model showing the formation of hydrogen bonds for the interaction of $[Co(CN)_6]^{3-}$ and H_4(**B323**)$^{4+}$.

CONCLUSION

The *p*-azacyclophanes here in described constitute a new series of ligands with a very versatile coordination chemistry, both towards metal ions and anionic species. Of special interest is their use in promoting catalytic processes. On the other hand, they allow for easy chemical modifications that can be modulated as a function of the reactivity to be achieved by their complexes.

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Table VIII Logarithms of the association constants for the formation of adducts with polyazacyclophane receptors **B323, DU323, B222** and **DU22** with hexacyanocobaltate(III) at 298.1 K in 0.15 mol dm^{-3} $NaClO_4$

	B323		*DU323*		*B222*		*DU222*	
Reaction	*Pot.*[a]	*Em.*[b]	*Pot.*	*Em.*[b]	*Pot.*	*Em.*	*Pot.*	*Em.*
$[Co(CN)_6]^{3-}+H_4L^{4+}$	3.48(5)	3.5	3.59(6)	3.5	3.12(4)	2.95	3.12(6)	2.9

a) Values determined by potentiometry. b) Values estimated by the quenching of the steady state fluorescence emission.

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