Guest-Induced Selective Functionalization of Polyaza[*n*]paracyclophanes

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Received July 21, 1997

A new strategy to the preparation of selectively functionalized polyazamacrocycles is presented. Polyaza[*n*]paracyclophane receptors are able to efficiently direct their own selective functionalization upon interaction with simple guests such as metal cations. This enables the preparation of novel receptors functionalized at one of the benzylic nitrogen atoms with a variety of groups. Selective difunctionalization at both benzylic positions can also be achieved in this way.

Introduction

One of the most interesting features of aza macrocyclic receptors is the possibility of introducing additional groups by functionalization of the nitrogen atoms. As a matter of fact, development of monoaza- and diaza-crown ethers has been associated with their central role as starting materials for the preparation, via N-substitution, of lariat and bibrachial crown ethers, as well as receptors with tridimensional cavities (cryptands).[1]

The introduction of sidearms in a macrocyclic ligand can greatly affect its properties,[2] in particular when the additional functional groups modify the number and nature of the donor atoms or change the lipophilic/lipophobic balance of the receptor.[3] In this sense, N-functionalized polyaza macrocycles represent an important class of synthetic hosts, in particular when development of ligands for biomedical applications is considered. Different N-substituted polyaza macrocycles have been synthesized in order to obtain novel contrast agents in magnetic resonance imaging, or for the preparation of labeled recombinant antibodies and related systems.[4] Introduction of a variety of chromophoric and photoactive subunits in the ligand has been also accomplished is this way.[5] Additionally, selective N-functionalization represents an interesting approach for the preparation of enzyme mimics and catalytic models.[6]

In this context, selective functionalization of polyazamacrocyclic receptors is an important goal in order to obtain more elaborate and selective receptors and to prepare what has been called polyamines with intelligent functions.[7] Accordingly, much effort has been devoted to this end, and different methodologies have been developed recently. For the selective monofunctionalization of symmetrical macrocycles, commonly triaza and tetraaza macrocycles, two different approaches have been used. The first approach involves the use of a large excess of the polyamine over the alkylating agent, the success of the synthesis depending on the possibility of an easy separation of the unreacted macrocycle.[8] The second approach for symmetrical tetraazamacrocyles requires the temporary protection of 3 of the nitrogen atoms. This protection can be accomplished by direct

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S0022-3263(97)01329-7 CCC: $15.00
Published on Web 03/06/1998

reaction with 3 mol of a nitrogen protecting agent, such as the tosyl, mesyl, or boc groups,[9] or by the use of different trivalent compounds such as phosphorus or boron derivatives,[10] metal carbonyls ($Cr(CO)_6$, $Mo(CO)_6$, or $W(CO)_6$, for instance), or some other groups.[5c,11] For triazamacrocycles, besides the use of sulfonyl protecting groups, initial formation of the CH "capped" derivative has been described.[12] For unsymmetrical triaza- and tetraazamacrocycles, however, the synthesis of selectively N-monofunctionalized derivatives usually requires a multistep approach, the desired group being introduced with one of the chains in the cyclization step.[13] Selective N-difunctionalization of azamacrocycles follows similar approaches and usually requires a careful design of the synthetic pathway.[14]

Development of novel synthetic strategies to obtain otherwise difficult targets represents a very active field of research in supramolecular chemistry.[15] Noncovalent interactions which play a key role in supramolecular chemistry, like in the biological world, can provide surprisingly simple ways to prepare apparently complex, even nonnatural, molecules from appropriate substrates.[16a] In this sense, supramolecular interactions have been successfully used to prepare, in a straightforward way, compounds with rotaxane or catenane structures or to develop self-replicating systems and self-assembling aggregates.[16]

Chart 1

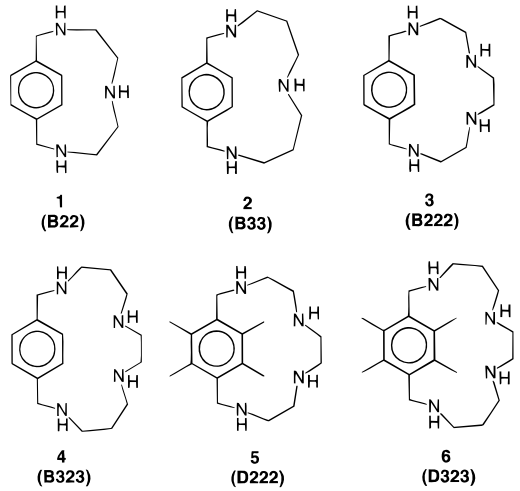
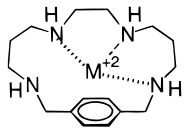


Chart 2



Accordingly, a different approach to the selective N-functionalization in polyazamacrocycles can be considered, as is the design of polyazamacrocyclic receptors programmed to develop very selective reactivity patterns upon interaction with a guest. Polyaza[*n*]paracyclophanes (i.e. **1**−**6**), recently prepared and studied by us as synthetic receptors for cations and anions, represent one of the most simple examples for the development of this strategy.[17−20] One of the central points in the design of those ligands is that the presence of the para-substituted aromatic spacer should preclude the simultaneous involvement of all nitrogen atoms in the coordination to metal centers (see structure **7**). The resulting low symmetry complexes show some interesting properties such as the redox behavior of the metal centers or their participation in catalytic, biomimetic processes.[18] Here we present how this feature can be advantageously used for the selective functionalization of those receptors.

Discussion and Results

Selective Monofunctionalization. Polyaza[*n*]paracyclophanes **1**−**6** could be prepared in good yields ac-

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cording to the general method previously described.[19] As mentioned above, the presence of the *p*-phenylene subunit linking the ends of a polyamine chain precludes the simultaneous coordination of both benzylic nitrogen atoms to a single metal center. Thus, for instance, for 2,6,9,13-tetraaza[14]paracyclophane **4** (**B323**), only three nitrogen atoms are involved in the interaction with transition metals such as Cu^{2+} or Zn^{2+}, yet yielding complexes of appreciable stability (log K = 13 and 6.83 for CuL and ZnL formation).[17a] The consequent low symmetry of the resulting Zn^{2+} complex is clearly denoted by its NMR spectra. When equimolecular amounts of a Zn^{2+} salt and compound **4** were mixed, both the ^{1}H and the ^{13}C NMR spectra displayed broad signals indicating the presence of rapidly exchanging systems. The situation changed, however, when an excess of Zn^{2+} was added. In particular, the ^{13}C NMR spectrum in CD_3CN showed 13 different signals at 24.6, 26.3, 43.9, 46.1, 46.5, 48.9 (two carbon atoms), 52.0, 52.2, 55.1, 131.5 (two carbon atoms), 132.4, 133.3, and 137.6 (two carbon atoms) ppm, while that of the free ligand just displays seven signals at 29.7, 44.7, 47.2, 49.7, 53.1, 129.0 and 140.2 ppm, in accordance with the two-fold symmetry of the ligand. This situation is similar to that found for the Hg^{2+} complex of **6**, where the low symmetry of the complex suggested by the NMR data could be also observed in the crystal structure.[20] The presence of a noncoordinated nitrogen atom in those complexes can also be inferred from their acid−base behavior, the basicity constant of the complex (log $K_{ZnL\rightarrow HZnL}$ = 7.72 for compound **4**) being comparable to the third protonation constant of the free ligand (log $K_{H_2L\rightarrow H_3L}$ = 7.43 for the same ligand).[17a] At the same time, the enthalpy values for the protonation of the complexes ($\Delta H^\circ_{CuL\rightarrow HCuL}$ = −34.4 kJ mol^{-1} for **3**) are also similar or even greater that those obtained for the first protonation of the free ligands ($\Delta H^\circ_{L\rightarrow HL}$ = −35.1 kJ mol^{-1} for **3**), revealing that protonation of one of the nitrogen atoms does not require any cleavage of a N−metal bond.[17c,d]

This behavior suggests the possibility of using the noncoordinated nitrogen atoms as nucleophiles for the selective functionalization of polyaza[*n*]paracyclophanes. Because of the presence of two different kinds of nitrogen atoms in the free ligand, the possibility of obtaining a direct selective alkylation of the polyazamacrocycle was initially analyzed. However, as for other polyaza[*n*]-paracyclophanes, attempted reaction of macrocycle **4** with an alkylating agent such as benzyl or allyl bromide (1:1 molar ratio) in acetonitrile, in the presence of base, afforded a very complex mixture containing different mono-, di-, and polyalkylated compounds in very low yields, along with starting material as the major product. Results were very different when the reaction was carried out in the presence of a stoichiometric amount of a simple Zn^{2+} salt ($ZnCl_2$ or $Zn(OTf)_2$). When the reaction mixture containing a 1:1:1 ratio receptor:metal:alkylating agent was stirred overnight at room temperature, analysis of the crude product, after removal of the metal cation by treatment with an excess of aqueous ammonia, revealed the presence, as the major product, of a monoalkylated macrocycle (see Table 1) accompanied by very minor amounts of starting material and a dialkylated product. Thus, for macrocycle **4**, in the presence of $Zn(OTf)_2$, and using allyl bromide as the electrophile, chromatographic purification of the crude product afforded compound **8f** in 60% yield, while the use of benzyl bromide led to the obtention of **8g** in 56% yield.

Table 1. Results Obtained in the Selective Monofunctionalization of Polyaza[*n*]paracyclophanes 1−6

entry	compound	R−X	metal salt	reagent ratio[a]	compound	yield (%)[b]
1	**B22**	BnBr	$Zn(OTf)_2$	1:1:1	**8a**	<25
2	**B33**	CH_2=$CHCH_2Br$	$Zn(OTf)_2$	1:1:1	**8b**	31
3	**B33**	$BrCH_2CO_2Et$	$Zn(OTf)_2$	1:1:1	**8c**	19
4	**B33**	BnBr	$Zn(OTf)_2$	1:1:1	**8d**	25
5	**B33**	BnBr	$Pd(AcO)_2$	1:1:1	**8d**	−
6	**B222**	BnBr	$Zn(OTf)_2$	1:1:1	**8e**	<30
7	**B323**	CH_2=$CHCH_2Br$	$ZnCl_2$	1:1:1	**8f**	60
8	**B323**	CH_2=$CHCH_2Br$	$Zn(OTf)_2$	1:1:1	**8f**	60
9	**B323**	CH_2=$CHCH_2Br$	$Pd(AcO)_2$	1:1:1	**8f**	68
10	**B323**	BnBr	$Zn(OTf)_2$	1:1:1	**8g**	56
11	**B323**	BnBr	$Pd(AcO)_2$	1:1:1	**8g**	65
12	**B323**	$BrCH_2CO_2Et$	$Zn(OTf)_2$	1:1:1	**8h**	72
13	**B323**	*p*-NO_2-BnBr	$Zn(OTf)_2$	1:1:1	**8i**	61
14	**B323**	*p*-Me-BnBr	$Zn(OTf)_2$	1:1:1	**8j**	64
15	**B323**	*p*-MeO-BnCl	$Zn(OTf)_2$	1:1:1	**8k**	−
16	**B323**	*p*-MeO-BnCl	$Pd(AcO)_2$	1:1:1	**8k**	43
17	**D222**	BnBr	$Zn(OTf)_2$	1:1:1	**8l**	19
18	**D222**	$BrCH_2CO_2Et$	$Zn(OTf)_2$	1:1:1	**8m**	<25
19	**D222**	CH_2=$CHCH_2Br$	$Zn(OTf)_2$	1:1:1	**8n**	35
20	**D323**	BnBr	$Zn(OTf)_2$	1:1:1	**8p**	79
21	**D323**	CH_2=$CHCH_2Br$	$Zn(OTf)_2$	1:1:1	**8q**	89
22	**D323**	$BrCH_2CO_2Et$	$Zn(OTf)_2$	1:1:1	**8r**	73
23	**D323**	BnBr	$Ni(ClO_4)_2$	1:1:1	**8p**	47

[a] Substrate:metal salt:alkylating agent. [b] After chromatographic purification, except for entries 1, 6, and 18 where the pure product could not be isolated.

Spectroscopic characterization of these products revealed that monofunctionalization had occurred at one of the benzylic nitrogen atoms. Thus, for instance, the ^{13}C NMR spectrum of compound **8f** presented eleven signals for the methylenic carbon atoms. The same loss of symmetry was observed in the ^{1}H NMR spectrum, where the singlet characteristic of the central ethylene subunit in **4** disappears and two separate multiplets are observed at ca. 1.5 ppm for the middle methylene groups of the propylenic fragments. Additionally, two different benzylic singlets are observed, one of them having a similar chemical shift to benzylic protons in **4** and the other being shifted 0.4 ppm upfield. Irradiation of the internal vinyl proton produced a clear NOE enhancement of the upfield benzylic signal in agreement with the 2.3 Å distance predicted from molecular mechanics calculations (see Figure 1).

A similar analysis showed that difunctionalized products were the result of the substitution at both benzylic nitrogen atoms. For example, monobenzylation of **4** was accompanied by the formation of **9f** as the main side product. The monofunctionalized product **8g** showed, as described for **8f**, NMR spectra characterized by a complete loss of symmetry, the ^{1}H NMR showing the presence of three benzylic signals. The symmetry was again recovered in the difunctionalized product, only two benzylic singlets being observed in the ^{1}H NMR spectrum (Figure 2).

The results obtained for the selective monofunctionalization of polyaza[*n*]paracyclophanes **1**−**6**, as illustrated in Scheme 2, using different alkylating agents are summarized in Table 1. A 1:1:1 ratio receptor:metal:alkylating agent was always used for those experiments. The monoalkylated products obtained present similar spectral properties to those described for **8f** and **8g**. For the durene derivatives, two different singlets separated by ca. 0.1 ppm are observed for the methyl groups. A

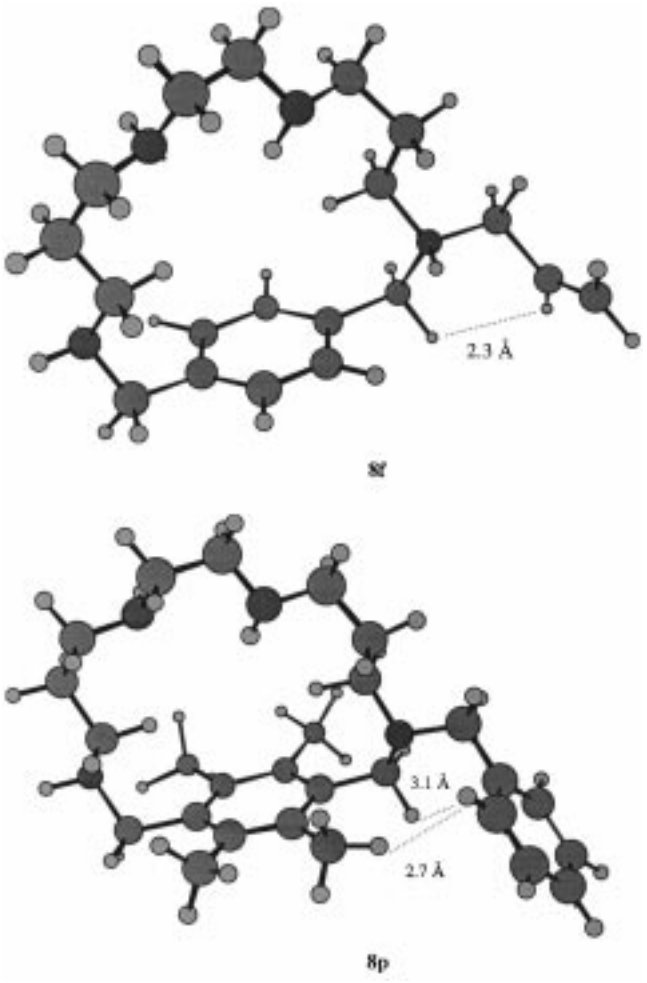


Figure 1. Minimum energy conformers calculated for compounds **8f** and **8p** with molecular mechanics calculations (MACROMODEL 5.0, Monte Carlo conformational search, MM2*).

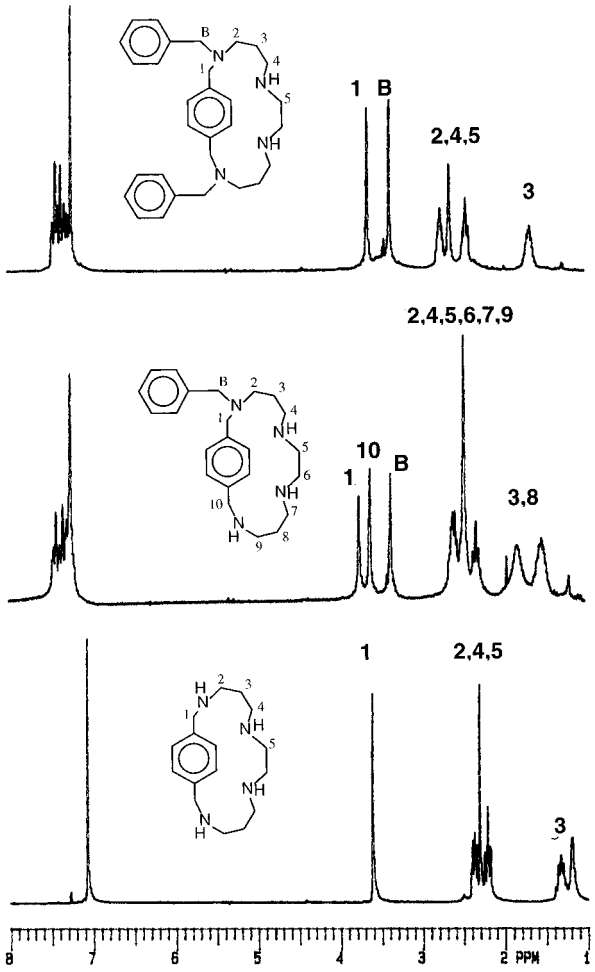
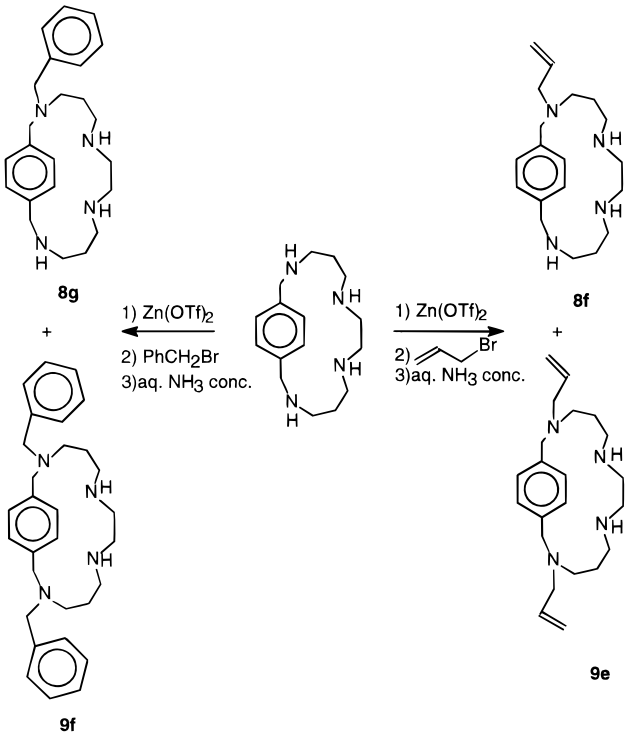


Figure 2. ^{1}H NMR spectra for compounds **4**, **8g**, and **9f**.

significant case was that of the monobenzylated derivative of **D323** (**8p**), for which irradiation of the aromatic protons of the side chain produced a NOE enhancement of one of the benzylic signals of the macrocycle and an even larger enhancement of one of the singlets corresponding to the methyl groups. This agrees with molecular mechanics calculations that show that the distance between the ortho protons and the protons of one of the methyl groups is slightly shorter (2.7 Å) than that with the contiguous benzylic hydrogen atoms of the macrocycle (3.1 Å) (Figure 1).

From data in Table 1, several points can be highlighted. The best results were always obtained for **B323** (**4**) and **D323** (**6**), the receptors being able to form the most stable Zn^{2+} complexes (log K = 6.83 and 6.86, respectively).[18b] For **B222** (**3**) and **D222** (**5**), the lower stability of their Zn^{2+} complexes (log K = 4.55 and 5.07)[17e] was reflected in the lower yields obtained for the respective monofunctionalized products, as can be observed when comparing entries 10 and 20 with entries 6 or 17. Triaza[*n*]paracyclophanes **B22** (**1**) and **B33** (**2**) should form the less stable Zn^{2+} complexes, as only two nitrogen atoms can participate in the coordination to the metal center, and, accordingly, the lower yields were observed for these compounds (see entries 1−4 in Table 1). Moreover, for 2 the respective difunctionalized compounds **9** were obtained in yields comparable to those of

Scheme 1



the expected monofunctionalizated products (see entries 2−4 in Table 2). As can be seen, compounds containing

Scheme 2

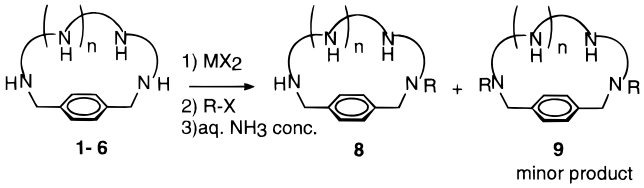


Table 2. Results Obtained in the Selective Difunctionalization of Polyaza[*n*]paracyclophanes 1−6

entry	compound	R−X	metal salt	reagent ratio[a]	compound	yield (%)[b]
1	**B22**	BnBr	$Zn(OTf)_2$	1:2:1	**15a**	−, (33)[c]
2	**B33**	CH_2=$CHCH_2Br$	$Zn(OTf)_2$	1:1:1	**9a**	20
3	**B33**	BnBr	$Zn(OTf)_2$	1:1:1	**9b**	35
4	**B33**	$BrCH_2CO_2Et$	$Zn(OTf)_2$	1:1:1	**9c**	21
5	**B33**	BnBr	$Zn(OTf)_2$	1:2:1	**9b**	55
6	**B222**	BnBr	$Zn(OTf)_2$	1:2:1	**9d**	25
7	**B323**	CH_2=$CHCH_2Br$	$Zn(OTf)_2$	1:1:1	**9e**	20
8	**B323**	BnBr	$Zn(OTf)_2$	1:2:1	**9f**	48
9	**D222**	BnBr	$Zn(OTf)_2$	1:2:1	**15b**	−, (38)[c]
10	**D222**	$BrCH_2CO_2Et$	$Zn(OTf)_2$	1:2:1	**15c**	−, (46)[c]
11	**D323**	BnBr	$Zn(OTf)_2$	1:2:1	**9g**	45

[a] Substrate:metal salt:alkylating agent. [b] Yelds after chromatographic purification. [c] In parentheses the yields for the tri (entry 1) or tetrafunctionalized (entries 9 and 10) compound based on the cyclophane. Yields based on the alkylating agent, which is the limiting reagent, are, respectively, 65, 76, and 92% (entries 1, 9 and 10).

only ethylenic spacers between the nitrogen atoms always give the worst yields. As a matter of fact, only for **D222** some pure monofunctionalized products could be isolated although in low yields (entries 17 and 19). The whole set of data can be understood by considering the processes outlined in Scheme 3.

According to this scheme, difunctionalized products **9** should be produced through the isomerization of the initially formed complexes **10** to complexes **11** and subsequent reaction of this product. An increase in the stability of the corresponding Zn^{2+} complexes would be reflected in a decrease in the amount of uncomplexed macrocycles present and preclude the **10** → **11** isomerization process, both factors giving place to an increase in the amount of the desired monofunctionalized product obtained. On the other hand, molecular mechanics calculations have shown that, as a consequence of the presence of the four methyl groups, durene derivatives (i.e. **D323**, **6**) are much less flexible than the related benzene derivatives (i.e. **B323**, **4**).[21] This feature has to be reflected in a less favorable isomerization of complex **10** for durene derivatives, and it is clearly denoted by the higher yields obtained for **6** (entries 20−22 in Table 1) when compared with those of **4** (entries 8, 10, and 12 in Table 1).

Similar results were obtained for $ZnCl_2$ and $Zn(OTf)_2$ salts, as is shown in entries 7 and 8, but the later seems to be slightly more convenient because of its higher solubility in organic solvents and its easier manipulation. Mono N-alkylation was best carried out at temperatures between 0 °C and room temperature. Lower temperatures generally afford the unchanged starting materials, and higher temperatures increase the amount of dialkylated products, probably because of the faster isomerization of the initially formed complex **10**. In general, good yields of monofunctionalizated products could be obtained for reactive alkylating agents such as allylic or benzylic halides. The use of less reactive species (alkyl halides, for instance) did not allow us to obtain the expected compounds (**8**) in good yields. The same was observed when very reactive halides were used (see, for instance, entry 15 in Table 1). The narrow temperature range that can be used can probably explain these results. Indeed, less reactive alkylating agents would require higher reaction temperatures that are not suitable according to the general scheme considered. The use of lower temperatures for very reactive alkylating species is also precluded, as precipitation of some of the complexes takes place. However, it has to be taken into account that these complexes are able to catalyze hydrolytic processes,[18b] and this can be an unfavorable factor for very reactive systems or for the introduction of pendant arms with hydrolyzable groups. Thus, for instance, the attempted Michael addition of **B323** to ethyl acrylate yielded a compound containing a pendant group with the carboxylic acid functionality instead of the expected ester group. No hydrolytic process was, however, observed for ethyl bromoacetate derivatives (see, for instance, entries 12 or 22).

According to this general scheme, several strategies could be used in order to increase the yield and selectivity in this monofunctionalization reaction. A change in the ratio substrate:metal salt to values lower than 1 would decrease the amount of uncomplexed substrate and favor its selective reaction. However, when such experiments were carried out, a decrease in the yields was always observed. The formation of binuclear species in which all nitrogen atoms are involved in the coordination to a metal center, which has been observed under some circumstances (see, for instance, structures **13** and **14**),[17d] has to be considered in order to explain those results.

On the other hand, the use of metal cations which are able to form stronger complexes should afford an increase in the yield of the monofunctionalized products **8**. In this respect, selective functionalization of cyclophanes **1**−**6** using CuX_2 species instead of ZnX_2 salts was attempted, as, in general, Cu^{2+} complexes of polyaza[*n*]paracyclophanes show stability constants which are 5−6 logarithmic units larger than those of the related Zn^{2+} complexes.[17a,18a] Unsatisfactory results were, however, found when copper salts were used. With the use of Cu^{2+} species, hydrolytic and redox processes (as evidenced by the presence of color changes during the reaction) seem to prevail instead of the desired substitution reaction.

Nevertheless, some interesting results were obtained with the use of Pd^{2+} compounds. As shown by their NMR spectra, Pd^{2+} forms strong complexes with polyaza[*n*]-paracyclophanes which do not experience exchange processes on the NMR time scale. Thus, for instance, when cyclophane **4** and $Pd(OAc)_2$ were mixed in a 1:1 ratio in $DCCl_3$, a complete loss of symmetry was observed both in the ^1H and the ^{13}C NMR spectra (Figure 3) in agreement with the existence of a complex with a structure similar to that shown in **7**. Two different multiplets are observed, between 0.8 and 1.4, for the central methylene groups of the propylene subunits. The four aromatic protons appear as four different doublets, two of them showing a very similar chemical shift (ca. 7.2 ppm) and the other two being separated by 0.6 ppm. One of the benzyl groups is separated in two doublets at 3.65 and 4.2 ppm, while for the other, coupling with the

(21) Altava, B.; Bianchi, A.; Bazzicalupi, C.; Burguete, M. I.; García-España, E.; Luis, S. V.; Miravet, J. F. *Supramol. Chem.* **1997**, *8*, 287.

Scheme 3

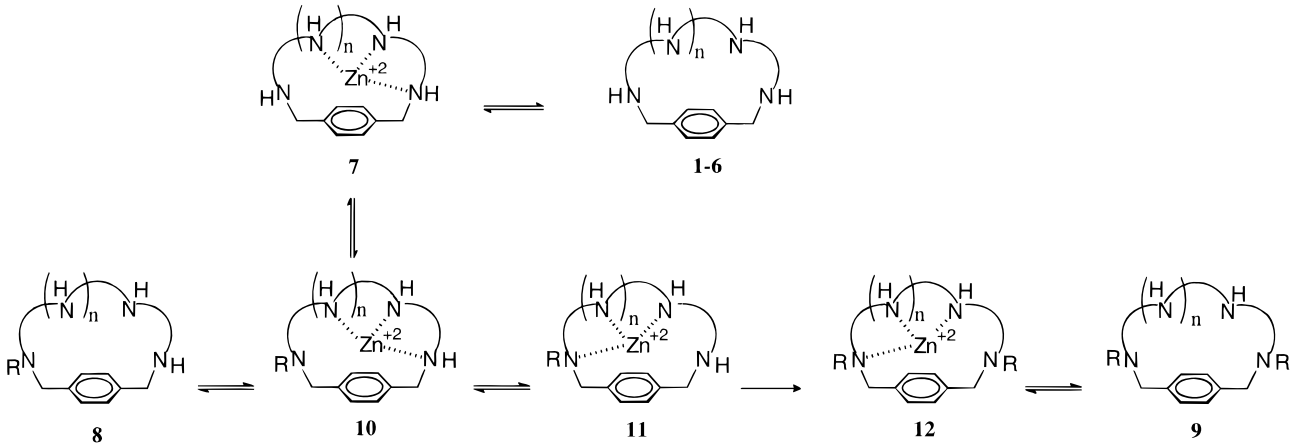
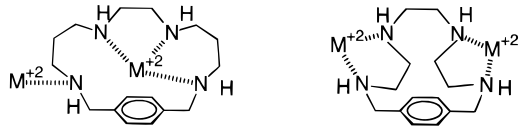


Chart 3



proton of the NH group is observed and two dd at ca. 3.55 and 4.05 ppm. At the same time, four different N−H signals are present at ca. 3.2, 4.8, 7.9, and 8.5 ppm, which indicates that two of the nitrogen atoms are strongly involved in the coordination to the metal center, one is less involved, and the other does not participate at all, its chemical shift being in the normal range for the free receptor. The signal at 7.9 ppm corresponds to a benzylic amino group, being connected in the H−H correlation spectrum with the two signals of one of the benzylic CH_2 groups. For durene derivatives, four different singlets can be observed for the methyl groups. This is the case, for instance, for the complex between **D323** and $Pd(OAc)_2$. The use of K_2PdCl_4 in aquous solutions yielded similar results.

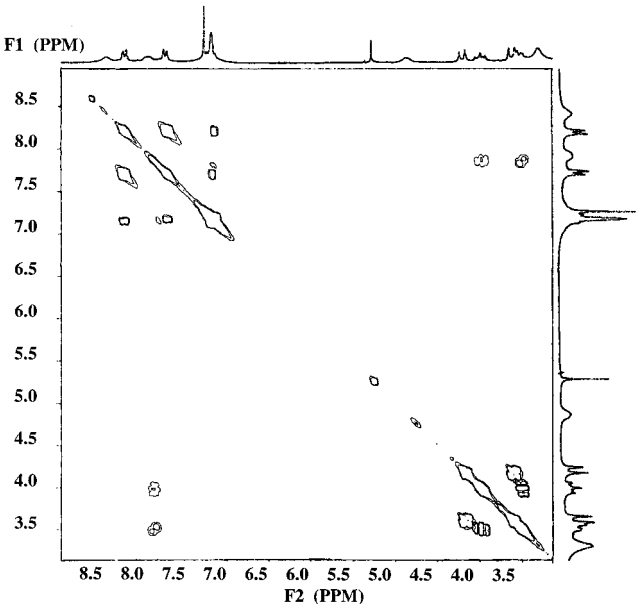


Figure 3. $^1H-^1H$ NMR correlation spectrum for the complex **4**−$Pd(OAc)_2$ in $CDCl_3$.

In theory, ^{15}N NMR spectroscopy should be ideally suited for the structural analysis of these complexes, but the presence of rapidly exchanging N-bound protons severely limits the use of indirect detection techniques. Nevertheless, the use of long distance $^1H-^{15}N$ correlation spectroscopy (HMBC pulse sequence) did allow the obtention of some interesting data. Thus, for **D323** (**6**) two different signals at ca. 300 ppm can be observed for the two types of nitrogen atoms present in the structure (Figure 4a), while for the abovementioned 1:1 complex

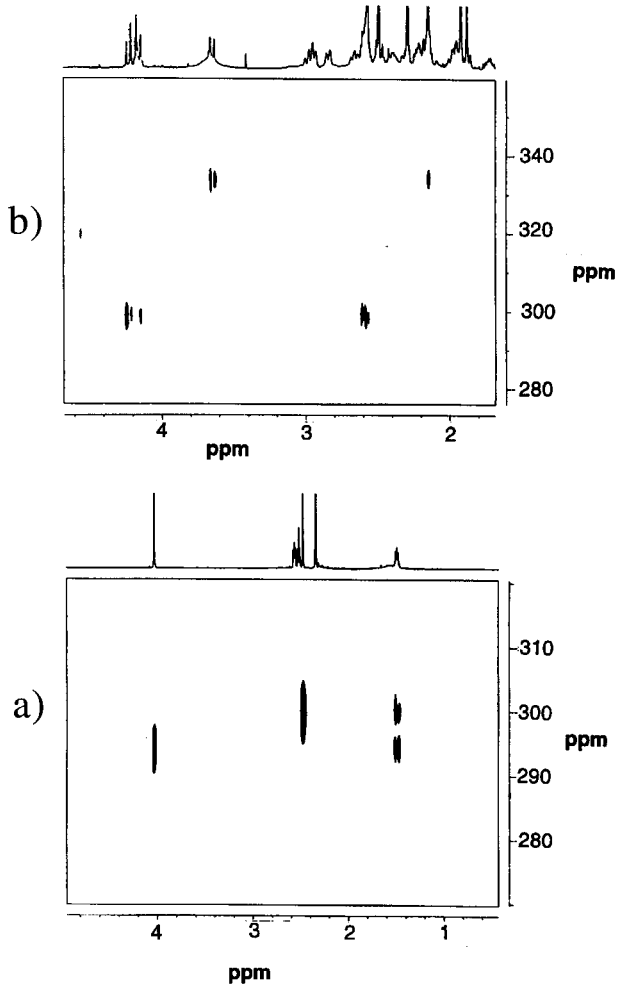
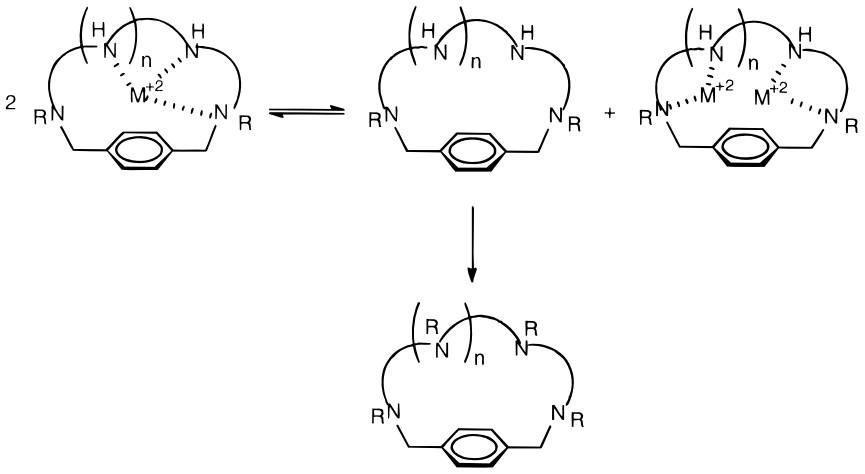


Figure 4. Long range $^1H-^{15}N$ correlation spectra for **6** (a) and the complex **6**−$Pd(OAc)_2$ (b) in $CDCl_3$.

Scheme 4



with $Pd(AcO)_2$ in chloroform, two resonances corresponding to two different benzylic nitrogen atoms can be observed. One of the signals appears at ca. 300 ppm, a similar position to that observed for the free ligand, while the other is shifted more than 30 ppm downfield (Figure 4b). These data support again the general structure considered for metal complexes of polyaza[*n*]paracyclophanes in which only one of the benzylic nitrogen atoms is involved in the binding to the metal center.

In good agreement with these observations, selective monofunctionalization using $Pd(OAc)_2$ afforded better yields than those obtained with ZnX_2 species in most instances, but the increases in yields were, generally, moderate (compare entries 9 and 11 with entries 8 and 10 in Table 1). The best results were obtained for very reactive alkylating agents for which ZnX_2 salts were ineffective, as can be observed when comparing entries 15 and 16 in Table 1. Some redox processes involving Pd^{2+} seem to be responsible of the most important side reactions in this case. Thus, for example, benzaldehyde could be isolated when benzyl bromide was used as the alkylating reagent in accordance with the reactivity described for paladium(II) acetate.[22] The use of other metal cations, such as Ni^{2+}, that do not have such a tendency to participate in redox processes did not give the expected results (see entry 23 in Table 1).

Selective Difunctionalization. A simple consequence of the processes involved in Scheme 3 is that an increase in the alkylating agent:substrate ratio should allow for the obtention of the products of selective N,N′-difunctionalization at both benzylic positions as the main products. In this case ZnX_2 salts which favor the existence of the **10** → **11** isomerization seem the most appropriate choice. Some results are gathered in Table 2. As can be seen in the table, good results for the selectively difunctionalized products can be obtained in some cases, in particular for receptors **B33** (**2**), **B323** (**4**), and **D323** (**6**). However, two factors seem to limit the usefulness of this approach for the selective N,N′-difunctionalization of other receptors such as **B22** (**1**), **B222** (**3**), or **D222** (**5**) having ethylenic chains linking the nitrogen atoms. For **B22** and **D222** the completely tri- or tetrafunctionalized compounds were obtained as the major product (see entries 1, 9, and 10) in high yields. It has been shown that the presence of an additional alkyl group on one of the nitrogen atoms in this kind of receptor is reflected in a lower basicity and a lower coordination tendency of the tertiary nitrogen atom.[18b] Accordingly, the formation of the functionalized compounds would produce new receptors with a much reduced affinity for the metal cation. This would favor the formation of binuclear complexes by the unfunctionalized receptors, thus providing a way for the complete functionalization of the nitrogen atoms in the uncomplexed species (Scheme 4).

On the other hand, it has to be mentioned that the triaza[*n*]paracyclophane **1** shows a high tendency to form N-polyalkylated derivatives as the major products for any substrate:alkylating agent ratio. Thus, for instance, when compound **B22** (**1**) was treated with 2 mol of benzyl bromide in the absence of any metal salt, results obtained were very similar to those reported in entry 1 of Table 2.

Conclusions

Polyaza[*n*]paracyclophanes represent a simple and straightforward example of the design and preparation of synthetic receptors which selectively direct their own functionalization upon interaction with a substrate. Compounds **1**−**6** can be easily converted, in good yields, to the respective N-monoalkylated derivatives **8**, where functionalization has taken place at one of the benzylic nitrogen atoms, with the use of 1 mol of the appropriate alkylating agent and 1 mol of a metal salt MX_2. The best results are obtained with the use of $Zn(OTf)_2$ or $Pd(OAc)_2$. Yields are only slightly higher with the use of $Pd(OAc)_2$ species, and thus, the use of $Zn(OTf)_2$ seems to be the most convenient choice for this purpose. Receptors containing propylenic subunits as separators between the nitrogen atoms give in general better results than those with ethylenic ones. A similar approach, with the use of 2 mol of the alkylating agent allows, in most instances, the preparation, in fair yields, of the corresponding difunctionalized derivatives **9**, where functionalization has taken place at both benzylic nitrogen atoms. Some of those derivatives of polyaza[*n*]paracyclophanes have been very useful in the development of synthetic enzymatic models. This synthetic approach could be, in principle, used for selective functionalization of other nonnatural receptors in which structural features provide uncoordinated nucleophilic atoms in specific positions when interacting with simple guests species.

(22) Pitre, S. V.; Vankar, P. S.; Vankar, Y. D. *Tetrahedron Lett.* **1996**, 12291.

Initial results show that N-substitution affects to acid−base and coordination patterns of polyaza[*n*]paracyclophanes. In this respect, for N-monosubstituted tetraazacyclophanes, the tertiary nitrogen atom displays a lower basicity and coordination tendency, so that interaction with transition metal cations takes place, preferentially, through the three secondary nitrogen atoms. On the other hand, N-monofunctionalized macrocycles of this class have been revealed to be very useful for the development of efficient enzyme mimics.[18b]

Experimental Section

General. ^{1}H and ^{13}C NMR spectra (ppm, δ) were recorded at 200 and 50.3 MHz respectively in $CDCl_3$. ^{15}N − ^{1}H correlation spectra were obtained with a Bruker Avance DRX 500 spectrometer. For analytical purposes the free amines were converted into their perchlorate, hydrochloride or hydrobromide salts.

General Procedure for the Synthesis of Monoalkylated Polyazaparacyclophanes 8 (a−r) Using Zn(II) as the Cationic Guest. Synthesis of 2-Allyl-2,6,9,13-tetraaza[14]paracyclophane (8f). Paracyclophane **4** (100 mg, 0.36 mmol) was dissolved in CH_3CN (15 mL), and $Zn(OTf)_2$ (130 mg, 0.36 mmol) and anhyd K_2CO_3 (100 mg, 0.72 mmol) were added under an Ar atmosphere. After stirring for 5 min at 25 °C, allyl bromide (32 μL, 0.36 mmol) was injected into the reaction flask. The mixture was stirred overnight, and then the solvent was evaporated under reduced pressure. The solid residue was taken into 25% NH_3 (10 mL) and CH_2Cl_2 (10 mL). The aqueous phase was washed with additional CH_2Cl_2 (3 × 20 mL). The collected organic phases were dried with anhyd Na_2SO_4, and the solvent was removed under reduced pressure to give a colorless oil. Chromatographic purification (SiO_2; MeOH/NH_3 as the eluent) afforded compound **8f** (68 mg, 0.22 mmol, 60%). ^{1}H NMR 1.4−1.6 (m, 4H); 2.39 (t, 2H, 6.8 Hz); 2.4−2.6 (m, 8H); 2.62 (t, 2H, 5.3 Hz); 3.17 (d, 2H, 6.1 Hz); 3.49 (s, 2H); 3.78 (s, 2H); 5.1−5.3 (m, 2H); 5.8−6.1 (m, 1H); 7.2−7.4 (m, 4H); ^{13}C NMR 26.2, 28.5, 44.1, 46.5, 46.6, 49.2 (two carbon atoms), 49.3, 53.1, 57.9, 58.9, 117.1, 128.4, 129.2, 136.3, 138.9, 139.2. Anal. Calcd for $C_{19}H_{36}N_4O_{16}Cl_4$: C, 31.8; H, 5.1; N, 7.8. Found: C, 31.4; H, 5.1; N, 7.6.

General Procedure for the Synthesis of Monoalkylated Polyazacyclophanes 8 Using Pd(II) as Cationic Guest. Synthesis of 2-Allyl-2,6,9,13-tetraaza[14]paracyclophane (8f). Polyazacyclophane **4** (100 mg, 0.36 mmol) was dissolved in $CHCl_3$ (15 mL), and $Pd(OAc)_2$ (81 mg, 0.36 mmol) was added slowly to form a yellow complex. After stirring for 5 min at 25 °C, anhyd K_2CO_3 (100 mg, 0.72 mmol) and allyl bromide (32 μL, 0.36 mmol) were charged into the reaction flask under an Ar atmosphere. The mixture was stirred overnight, and then the solvent was evaporated under reduced pressure. The solid residue was taken into an aqueous solution of NaCN (0.5 M, 10 mL) and CH_2Cl_2 (10 mL). The aqueous phase was washed with additional CH_2Cl_2 (3 × 20 mL). The collected organic phases were then dried with anhyd Na_2SO_4, and the solvent was removed under reduced pressure to give a colorless oil. Chromatographic purification (SiO_2; MeOH/NH_3 as the eluent) afforded compound **8f** (83 mg, 0.22 mmol, 65%).

2-Allyl-2,6,10-triaza[11]paracyclophane (8b): 31% yield; ^{1}H NMR 1.38 (m, 4H); 2.1−2.3 (m, 6H); 2.46 (m, 2H); 3.16 (d, 2H, 6.6 Hz); 3.42 (s, 2H); 3.72 (s, 2H); 5.1−5.3 (m, 2H); 5.9−6.1 (m, 1H); 7.2−7.3 (m, 4H); ^{13}C NMR 28.2, 29.9, 41.6, 45.5, 46.1, 47.7, 52.9, 58.5, 59.0, 117.3, 128.9, 130.1, 136.5, 139.7, 140.1. Anal. Calcd for $C_{17}H_{30}N_3Br_3$: C, 39.6; H, 5.9; N, 8.1. Found: C, 39.2; H, 6.1; N, 8.0.

2-[(Ethoxycarbonyl)methyl]-2,6,10-triaza[11]paracyclophane (8c): 19% yield; ^{1}H NMR 1.33 (m, 7H); 2.25 (m, 4H); 2.38 (m, 2H); 2.49 (m, 2H); 3.47 (s, 2H); 3.68 (s, 2H); 3.73 (s, 2H); 4.22 (q, 2H, 7.3 Hz); 7.31 (d, 2H, 7.7 Hz); 7.40 (d, 2H, 7.7 Hz); ^{13}C NMR 14.3, 27.5, 29.6, 41.8, 45.5, 45.7, 46.6, 53.0, 56.4, 59.6, 60.4, 129.1, 130.1, 139.3, 140.5, 171.2. Anal. Calcd for $C_{18}H_{32}N_3O_2Br_3\cdot H_2O$: C, 37.3; H, 5.9; N, 7.2. Found: C, 37.4; H, 5.7; N, 6.9.

2-Benzyl-2,6,10-triaza[11]paracyclophane (8d): 25% yield; ^{1}H NMR 1.44 (m, 4H); 2.2−2.5 (m, 8H); 3.34 (s, 2H); 3.64 (s, 2H); 3.70 (s, 2H); 7.2−7.5 (m, 9H); ^{13}C NMR 28.0, 29.7, 41.5, 45.5, 46.1, 47.8, 52.8, 58.2, 60.1, 127.0, 128.2, 128.9 (two carbon atoms), 130.0, 139.4, 140.1, 140.2 Anal. Calcd for $C_{21}H_{32}N_3Br_3$: C, 44.6; H, 5.7; N, 7.5. Found: C, 44.2; H, 5.9; N, 7.1.

2-Benzyl-2,6,9,13-tetraaza[14]paracyclophane (8g): 56% yield; ^{1}H NMR 1.60 (m, 4H); 2.37 (t, 2H); 2.5−2.7 (m, 10H); 3.39 (s, 2H); 3.65 (s, 2H); 3.78 (s, 2H); 7.2−7.5 (m, 9H); ^{13}C NMR 26.3, 28.0, 44.6, 46.4, 47.0, 49.1, 49.3, 49.5, 53.0, 59.0, 59.3, 127.0, 128.3, 128.5, 128.8, 129.3 138.9, 139.2, 140.0. Anal. Calcd for $C_{23}H_{38}N_4Br_4$: C, 35.0; H, 5.6; N, 8.1. Found: C, 35.1; H, 5.6; N, 8.0.

2-[(Ethoxycarbonyl)methyl]-2,6,9,13-tetraaza[14]paracyclophane (8h): 72% yield; ^{1}H NMR 1.29 (t, 3H, 7.2 Hz); 1.44 (m, 2H); 1.57 (m, 2H); 2.4−2.6 (m, 10H); 2.43 (m, 2H); 3.45 (s, 2H); 3.71 (s, 2H); 3.79 (s, 2H); 4.19 (q, 2H, 7.2 Hz); 7.26 (d, 2H, 8.1 Hz); 7.35 (d, 2H, 8.1 Hz); ^{13}C NMR 14.3, 26.4, 28.3, 44.5, 46.3, 46.8, 48.4, 49.1 (two carbon atoms), 53.1, 56.0, 59.8, 60.4, 128.5, 129.2, 138.4, 139.3, 171.4. Anal. Calcd for $C_{20}H_{38}N_4O_2Br_4\cdot 2H_2O$: C, 33.3; H, 5.9; N, 7.8. Found: C, 33.1; H, 5.9; N, 7.5.

2-(*p*-Nitrobenzyl)-2,6,9,13-tetraaza[14]paracyclophane (8i): 61% yield; ^{1}H NMR 1.57 (m, 4H); 2.3−2.7 (m, 12H); 3.38 (s, 2H); 3.72 (s, 2H); 3.78 (s, 2H); 7.28 (m, 4H); 7.63 (d, 2H, 8.1 Hz); 8.21 (d, 2H, 8.1 Hz); ^{13}C NMR 26.5, 28.3, 44.5, 46.4, 46.8, 49.2, 49.3, 49.7, 53.1, 58.8, 59.3, 123.7, 128.7, 129.1, 129.3, 138.2, 139.5, 147.2, 148.2. Anal. Calcd for $C_{23}H_{37}N_5O_2Br_4$: C, 37.6; H, 5.1; N, 9.5. Found: C, 37.7; H, 5.5; N, 9.1.

2-(*p*-Methylbenzyl)-2,6,9,13-tetraaza[14]paracyclophane (8j): 64% yield; ^{1}H NMR 1.57 (m, 4H); 2.34 (m, 5H); 2.49 (m, 6H); 2.63 (m, 4H); 3.38 (s, 2H); 3.61 (s, 2H); 3.77 (s, 2H); 7.1−7.4 (m, 8H); ^{13}C NMR 21.1, 26.1, 28.3, 43.9, 46.3, 46.5, 49.3 (three carbon atoms), 53.0, 58.7 (two carbon atoms), 128.4, 128.7, 128.9, 129.1, 136.4, 136.9, 139.1, 139.2. Anal. Calcd for $C_{24}H_{40}N_4Br_4$: C, 40.9; H, 5.6; N, 8.2. Found: C, 40.4; H, 5.8; N, 8.3.

2-(*p*-Methoxybenzyl)-2,6,9,13-tetraaza[14]paracyclophane (8k): 43% yield; ^{1}H NMR 1.56 (m, 4H); 2.41 (m, 4H); 2.49 (s broad, 4H); 2.61 (m, 4H); 3.37 (s, 2H); 3.58 (s, 2H); 3.76 (s, 2H); 3.80 (s, 3H); 6.88 (d, 2H, 8.4 Hz); 7.25 (m, 4H); 7.34 (d, 2H, 8.4 Hz); ^{13}C NMR 26.2, 28.3, 44.1, 46.3, 46.6, 49.2, 49.3, 53.0, 55.2, 58.5, 58.7, 113.6, 128.4, 129.1, 129.8, 131.9, 139.1, 158.5. Anal. Calcd for $C_{24}H_{40}N_4O_1Cl_4$: C, 53.1; H, 7.4; N, 10.3. Found: C, 52.8; H, 7.6; N, 10.2.

2-Benzyl-14,15,17,18-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane (8l): 19% yield; ^{1}H NMR 1.89 (m, 2H); 1.98 (m, 2H); 2.14 (s, 6H); 2.30 (m, 2H); 2.46 (m, 4H); 2.62 (m, 4H); 3.64 (d, 2H); 3.68 (s, 2H); 3.96 (s, 2H); 7.2−7.4 (m, 9H); ^{13}C NMR (D_2O) 16.8, 17.0, 44.9, 46.1, 47.4, 47.8, 48.1, 48.4, 49.6, 52.8, 61.4, 63.5, 127.2, 128.1, 129.9, 132.8, 134.3, 134.5, 136.8, 138.7. Anal. Calcd for $C_{25}H_{42}N_4Br_4$: C, 41.8; H, 5.9; N, 7.8. Found: C, 41.7; H, 5.8; N, 7.8.

2-Allyl-14,15,17,18-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane (8n): 35% yield; ^{1}H NMR (D_2O) 2.17 (m, 2H); 2.24 (s, 6H); 2.29 (s, 6H); 2.31 (m, 2H); 2.55 (m, 4H); 2.76 (m, 4H); 3.30 (d, 2H); 3.67 (s, 2H); 4.32 (s, 2H); 5.37 (m, 2H); 6.08 (m, 1H); ^{13}C NMR (D_2O) 20.3 (four carbon atoms), 46.7, 47.3, 47.7, 47.9, 48.3, 48.9, 49.5, 55.6, 62.1, 123.6, 137.9, 138.2, 138.7, 139.3, 139.7. Anal. Calcd for $C_{21}H_{40}N_4Br_4$: C, 37.8; H, 6.0; N, 8.4. Found: C, 37.5; H, 6.1; N, 8.0.

2-Benzyl-16,17,19,20-tetramethyl-2,6,9,13-tetraaza[14]paracyclophane (8p): 79% yield; ^{1}H NMR 1.39 (m, 2H); 1.62 (m, 2H); 2.18 (s, 6H); 2.29 (m, 8H); 2.42 (m, 4H); 2.53 (t, 2H, 6 Hz); 2.66 (m, 4H); 3.57 (s, 2H); 3.63 (s, 2H); 3.95 (s, 2H); 7.2−7.4 (m, 5H); ^{13}C NMR 16.6, 16.7, 26.7, 28.3, 45.6, 46.0, 47.2, 47.4, 47.6, 49.0, 49.3, 53.5, 60.4, 126.9, 127.9, 129.6, 132.8, 134.4 (two carbon atoms), 135.5, 139.1. Anal. Calcd for $C_{27}H_{46}N_4Br_4$: C, 43.5; H, 6.2; N, 7.5. Found: C, 43.6; H, 6.2; N, 7.4.

2-Allyl-16,17,19,20-tetramethyl-2,6,9,13-tetraaza[14]paracyclophane (8q): 89% yield; ^{1}H NMR 1.28 (m, 2H); 1.73

(m, 2H); 2.2−2.6 (m, 18H); 2.80 (m, 6H); 3.17 (d, 2H, 6 Hz); 3.64 (s, 2H); 4.00 (s, 2H); 5.22 (m, 2H); 6.02 (m, 1H); ^{13}C NMR 16.8, 17.0, 26.3, 26.9, 45.8, 47.1, 47.2, 47.3, 47.7, 48.1, 48.7, 52.9, 58.8, 117.7, 132.8, 134.6 (two carbon atoms), 135.4, 135.8. Anal. Calcd for $C_{23}H_{44}N_4Br_4$: C, 39.7; H, 6.4; N, 8.1. Found: C, 39.3; H, 6.1; N, 7.8.

2-[(Ethoxycarbonyl)methyl]-16,17,19,20-tetramethyl-2,6,9,13-tetraaza[14]paracyclophane (8r): 73% yield; ^{1}H NMR 1.2−1.3 (m, 2H); 1.28 (t, 3H, 7.3 Hz); 1.77 (m, 2H); 2.2−2.5 (m, 18H); 2.61 (m, 2H); 2.78 (m, 4H); 3.43 (s, 2H); 3.91 (s, 2H); 4.01 (s, 2H); 4.17 (q, 2H, 7.3 Hz); ^{13}C NMR 14.4, 16.7, 16.9, 26.5, 28.2, 45.4, 45.7, 47.1, 47.3, 47.5, 48.7, 49.3, 53.5, 55.5, 60.3, 133.0, 134.4, 134.6, 135.7, 171.7. Anal. Calcd for $C_{24}H_{46}N_4O_2Br_4$: C, 38.8; H, 6.3; N, 7.6. Found: C, 38.5; H, 6.1; N, 7.7.

General Procedure for the Synthesis of Dialkylated Polyazaparacyclophanes 9(a−h) Using Zn(II) as Cationic Guest. Synthesis of 2,13-Dibenzyl-2,6,9,13-tetraaza[14]paracyclophane (9f). Paracyclophane **4** (100 mg, 0.36 mmol) was dissolved in CH_3CN (15 mL), and $Zn(OTf)_2$ (130 mg, 0.36 mmol) and anhyd K_2CO_3 (200 mg, 1.44 mmol) were added under an Ar atmosphere. After stirring for 5 min at 25 °C, benzyl bromide (85 μL, 0.72 mmol) was injected into the reaction flask. The mixture was stirred overnight, and then the solvent was evaporated under reduced pressure. The solid residue was taken into 25% NH_3 (10 mL) of 25% and CH_2Cl_2 (10 mL). The aqueous phase was washed with additional CH_2Cl_2 (3 × 20 mL). The collected organic phases were dried with anhyd Na_2SO_4, and the solvent was removed under reduced pressure to give a colorless oil. Chromatographic purification (SiO_2; MeOH/NH_3 as the eluent) afforded compound **9f** (79 mg, 0.17 mmol, 48%). ^{1}H NMR δ 1.66 (m, 4H); 2.35 (t, 4H); 2.63 (s, 4H); 2.75 (t, 4H); 3.37 (s, 4H); 3.63 (s, 4H); 5.20 (m, 4H); 7.23 (s, 4H); 7.3−7.5 (m, 10H); ^{13}C NMR δ 25.0, 45.8, 47.8, 49.5, 58.8, 59.1, 127.0, 128.3, 128.8, 128.9, 138.8, 139.7. Anal. Calcd for $C_{30}H_{44}N_4O_{16}Cl_4$: C, 42.0; H, 5.2; N, 6.5. Found: C, 41.6; H, 5.3; N, 6.3.

2,10-Diallyl-2,6,10-triaza[11]paracyclophane (9a): 20% yield; ^{1}H NMR 1.37 (m, 4H); 2.19 (t, 4H); 2.37 (t, 4H); 3.14 (s, 4H); 3.42 (s, 4H); 5.20 (m, 4H); 5.9 (m, 2H); 7.25 (s, 4H); ^{13}C NMR 28.0, 41.5, 46.2, 58.5, 59.0, 117.4, 129.0, 136.7, 139.7. Anal. Calcd for $C_{20}H_{34}N_3Br_3\cdot 2H_2O$: C, 40.6; H, 6.5; N, 7.1. Found: C, 40.1; H, 6.6; N, 6.9.

2,10-Dibenzyl-2,6,10-triaza[11]paracyclophane (9b): 35% yield; ^{1}H NMR δ 1.42 (m, 4H); 2.21 (t, 4H); 2.41 (t, 4H); 3.31 (s, 4H); 3.62 (s, 4H); 7.18 (s, 4H); 7.2−7.5 (m, 10H); ^{13}C NMR 28.1, 41.8, 45.3, 52.6, 60.3, 127.2, 128.7, 128.8, 129.0, 138.7, 139.8. Anal. Calcd for $C_{28}H_{38}N_3Br_3$: C, 51.2; H, 5.8; N, 6.4. Found: C, 51.5; H, 5.7; N, 6.1.

2,10-Bis[(ethoxycarbonyl)methyl]-2,6,10-triaza[11]-paracyclophane (9c): 21% yield; ^{1}H NMR 1.28 (m, 4H); 1.32 (t, 6H); 2.25 (t, 4H); 2.31 (t, 4H); 3.46 (s, 4H); 3.67 (s, 4H); 4.21 (c, 4H); 7.37 (s, 4H); ^{13}C NMR 14.5, 27.6, 41.3, 45.6, 56.4, 60.1, 60.4, 128.3, 138.8. Anal. Calcd for $C_{22}H_{38}N_3O_4Br_3\cdot H_2O$: C, 39.7; H, 6.1; N, 6.3. Found: C, 39.4; H, 6.0; N, 6.4.

2,11-Dibenzyl-2,5,8,11-tetraaza[12]paracyclophane (9d): 25% yield; ^{1}H NMR 2.03 (s, 4H); 2.55 (m, 4H); 2.63 (m, 4H); 3.35 (s, 4H); 3.70 (s, 4H); 7.09 (s, 4H); 7.2−7.5 (m, 10H); ^{13}C NMR 47.3, 48.7, 51.4, 58.1, 60.9, 127.1, 128.3, 129.1, 129.7, 139.5, 139.8. Anal. Calcd for $C_{28}H_{40}N_4Br_4$: C, 44.7; H, 5.4; N, 7.5. Found: C, 44.8; H, 5.5; N, 7.2.

2,13-Diallyl-2,6,9,13-tetraaza[14]paracyclophane (9e): 20% yield; ^{1}H NMR 2.52 (m, 4H); 2.35 (t, 4H); 2.52 (s, 4H); 2.62 (t, 4H); 3.16 (d, 4H); 3.48 (s, 4H); 4.00 (s, 2H); 5.20 (m, 4H); 5.90 (m, 2H); 7.29 (s, 4H); ^{13}C NMR 25.1, 46.2, 48.6, 48.9, 57.6, 58.8, 117.4, 129.0, 136.1, 138.9. Anal. Calcd for $C_{22}H_{40}N_4Br_4\cdot H_2O$: C, 37.9; H, 6.1; N, 8.0. Found: C, 37.4; H, 6.3; N, 7.6.

2,13-Dibenzyl-16,17,19,20-tetramethyl-2,6,9,13-tetraaza-[14]paracyclophane (9g): 45% yield; ^{1}H NMR 1.62 (m, 4H); 2.11 (s, 12H); 2.42 (t+s, 8H); 2.70 (t, 4H); 3.47 (s, 4H); 3.62 (s, 4H); ^{13}C NMR 16.7, 25.5, 45.3, 46.4, 49.1, 53.2, 59.5, 127.0, 127.9, 129.8, 134.0, 134.5, 138.8. Anal. Calcd for $C_{34}H_{52}N_4Br_4$: C, 48.8; H, 6.3; N, 6.7. Found: C, 48.9; H, 6.0; N, 6.5.

2,5,8-Tribenzyl-2,5,8-triaza[9]paracyclophane (15a): 33% yield; ^{1}H NMR 1.55 (t, 4H, 7.8 Hz); 2.20 (t, 4H, 7.8 Hz); 3.10 (s, 2H); 3.57 (s, 4H); 3.65 (s, 4H); 7.0−7.4 (m, 19H); ^{13}C NMR 49.7, 53.3, 58.4, 60.3, 62.6, 126.4, 126.8, 127.9, 128.1, 128.4, 128.9, 131.5, 139.2, 139.6, 139.9. Anal. Calcd for $C_{33}H_{40}N_3Br_3$: C, 55.2; H, 5.6; N, 5.9. Found: C, 54.9; H, 5.9; N, 5.8.

2,5,8,11-Tetrabenzyl-14,15,17,18-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane (15b): 38% yield; ^{1}H NMR 1.98 (s, 4H); 2.02−2.15 (m, 8H); 2.23 (s, 12H); 3.28 (s, 4H); 3.55 (s, 4H); 6.74−7.59 (m, 20H); ^{13}C NMR 17.1, 48.9, 50.4, 53.6, 53.9, 59.3, 61.7, 126.5, 126.9, 127.9, 128.6, 129.5, 134.1, 134.5, 139.3. Anal. Calcd for $C_{46}H_{60}N_4Br_4$: C, 55.9; H, 6.1; N, 5.7. Found: C, 55.8; H, 6.1; N, 5.4.

2,5,8,11-Tetrakis[(ethoxycarbonyl)methyl]-14,15,17,18-tetramethyl-2,5,8,11-tetraaza[12]paracyclophane (15c): 46% yield; ^{1}H NMR 1.25 (m, 12H); 2.08 (s, 4H); 2.2−2.5 (m, 20H); 3.47 (s, 4H); 3.65 (s, 4H); 3.93 (s, 4H); 4.12 (q, 4H, 7.2 Hz); 4.20 (q, 4H, 7.2 Hz); ^{13}C NMR 14.2, 14.3, 16.9, 47.4, 51.6, 52.9, 53.4, 56.4, 56.6, 134.4, 134.5, 171.7. Anal. Calcd for $C_{34}H_{60}N_4O_8Br_4$: C, 42.0; H, 6.2; N, 5.8. Found: C, 41.7; H, 6.0; N, 5.7.

Molecular Mechanics. Conformational analysis of the polyaza[*n*]paracyclophanes **8f** and **8p** was carried out with the MACROMODEL 5.0 package. Conformational search was performed with torsional Monte Carlo method as exploited by the BATCHMIN program, MM2* force field and simulation of chloroform as solvent were used (GB/SA). Each starting structure was minimized 1000 times. Convergence was observed when searches from different starting conformations were performed.

Acknowledgment. We thank DGICYT (PB93-0700) and BANCAJA (P1B94-001) for financial support. We are indebted to Bruker AG for obtaining the H−N correlation spectra.

JO971329E

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