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A Remarkable Selectivity in the N-Functionalization of Polyaza[n]paracyclophanes. Synthesis of N-(4-Picolyl)-Substituted 2,6,9,13-Tetraaza[14]paracyclophanes

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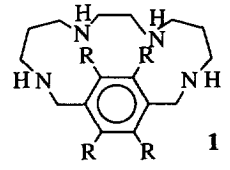
Abstract: Interaction of cationic host species, in particular Zn^{2+} salts, with polyaza[n]paracyclophanes (i.e. 2,6,9,13-Tetraaza[14]paracyclophane, **B323** (**1a**)) directs their selective N-functionalization. In this way compounds mono- or difunctionalized with $ArCH_2$- groups at the benzylic nitrogen atoms can be easily obtained. Direct reaction with the alkylating agent, in the absence of the Zn^{2+} species, produces, in general, very complex mixtures of mono- and polyalkylated compounds except when 4-picolyl chloride is used. In this case, mono-, di-, tri- and tetra N-substituted derivatives of **D323** can be isolated depending on the amount of the alkylating agent used. In this case, the mono- and dialkylated products obtained differ from the ones prepared using the metal assisted synthesis.

N-Functionalization of polyaza macrocycles[1] represents a general step towards the preparation of synthetic receptors with important applications in the development of novel contrast agents for nuclear magnetic resonance imaging (i.e. Gd(DOTA)$^-$ and related systems),[2] complexes for radioinmunoassay and radioinmunotherapy,[3] monoclonal antibodies labelling,[4] etc. In general, complete N-functionalization can be easily accomplished for these macrocyclic systems by the use of the appropiate alkylating agent. Under some circumstances, however, selective mono- or difunctionalization of the synthetic macrocycle is of greater interest in order to prepare more elaborate receptors, in particular from a biomimetic perspective. Different strategies have been evaluated in this respect, and, for symmetrical macrocycles, statical approaches or the use of multifunctional N-protecting groups being able to interac with just two or three nitrogen atoms have been used.[5,6] For unsymmetrical macrocycles, the synthetic scheme generally involves the introduction of the side arm or its precursor in one of the linear components for the macrocyclization reaction.

In recent years our group has been involved in the development and study as synthetic receptors of polyaza[n]paracyclophanes (i.e. **1**).



1

a) R=H **(B323)**

b) R=CH_3 **(D323)**

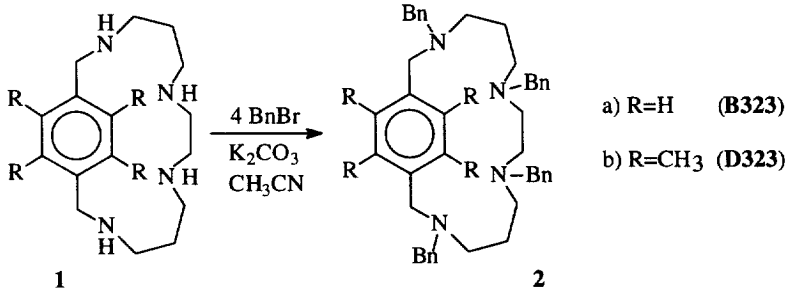
The presence of the aromatic spacer precludes the simultaneous involvement of all the nitrogen atoms in the coordination to a transition metal cation, giving rise to the formation of low symmetry complexes.[7,8] On the other hand, the topology of those ligands favor the convergence on the cavity of the nitrogen donor atoms and the aromatic system.[9] Both factors cooperate to confer some interesting properties to the resulting complexes with metal cations such as Zn^{2+} or Cu^{2+}. In this respect the stabilization of Cu^{+} species or the resulting biomimetic hydrolytic properties of Zn^{2+} complexes can be considered.[10,11,12] Additionally, as one of the benzylic nitrogen atoms is not involved in the coordination to the metal center, a simple methodology for the selective mono- and difunctionalization at the benzylic nitrogen atoms has been developed.[13]

N-Functionalization of polyaza[n]paracyclophanes can be of interest in order to improve some of those properties. Thus, for instance, it is generally accepted that an increase in the lipophilicity of the receptor is reflected in a larger stabilization of the low valences of the metal cations complexed.[10,12] In connection with the above mentioned catalytic properties of some Zn^{2+} complexes, it has been shown that the selective monofunctionalization with lipophilic or lipophobic fragments can have a dramatic effect on the catalytic properties of the resulting Zn^{2+} complexes.

Here we report on the preparation of polyaza[n]paracyclophanes N-functionalized with benzyl and 4-picolyl groups, as well as on the remarkable selectivity observed in the partial N-functionalization of **B323** (**1a**) and **D323** (**1b**) with 4-picolyl chloride in the absence of metal cations.

RESULTS AND DISCUSSION

The lipophilic character of the receptor is one of the main factors which have been related to the stabilization of "unusual" valences of metal cations.[12] In previous work, we could observe that a change from receptor **B323** (**1a**) to macrocycle **D323** (**1b**), having a more lipophilic character as a consequence of the four methyl groups bound to the aromatic ring, was reflected in a relatively higher stabilization of the corresponding Cu^{+} complex.[10] Accordingly, a simple approach to further increase such a stabilization should be the functionalization of the nitrogen atoms of the chain with lipophylic groups. In this respect, the preparation of N-benzylated polyazacyclophanes seems to be an interesting target.

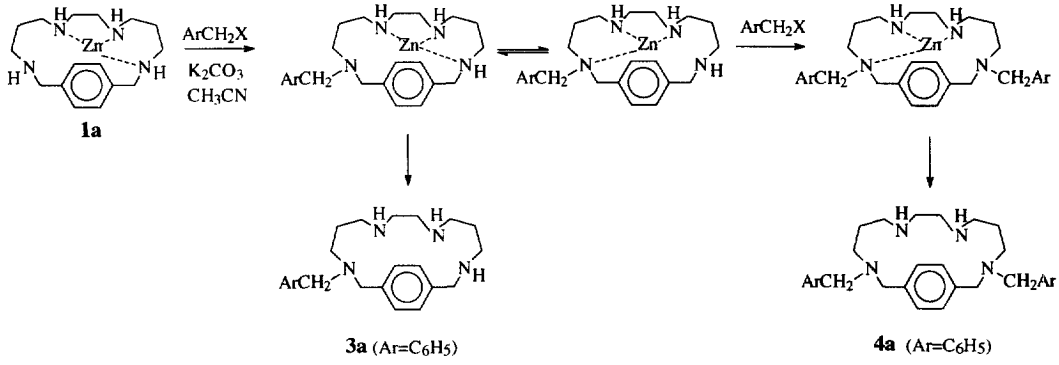


1 2

Scheme 1

Preparation of N-benzylated macrocycles **2** could be carried out in practically quantitative yields (99%), by reaction of four moles of benzyl bromide with **B323** (**1a**) or **D323** (**1b**) in dry CH_3CN containing an excess of anhydrous K_2CO_3 (*Scheme 1*). The resulting compounds showed the expected spectroscopic features, the ^1H and ^{13}C NMR spectra corresponding to the presence of a two-fold symmetry. Thus, for instance, for compound **2a** (R=H) the ^{13}C NMR spectrum showed the presence of seven methylenic carbons, while the ^1H NMR displayed four singlets, three corresponding to the benzylic positions and one to the ethylenic protons, one complex multiplet for the central methylene group of the propylenic subunit and two broad triplets for the other propylenic protons. Similar results were obtained for other cyclophanes such as **B222** and **D222**. It has to be noted that yields for this procedure are very sensitive to the presence of minor impurities in the starting materials.

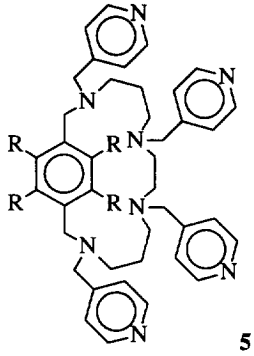
Mono- and dibenzylated polyaza[n]paracyclophanes N-functionalized at the benzylic positions were prepared in good yields making use of the coordination trends of their Zn^{2+} complexes, which provides a non coordinated, nucleophilic nitrogen atom at one of the benzylic positions.[13] The general procedure is illustrated in the *Scheme 2* for receptor **B323** (**1a**).



Scheme 2

An important drawback of compounds **2-4** is their low solubility in water which can cause difficulty in or completely hinder the study of their properties in aqueous solutions. This is important as data obtained from aqueous solutions are more relevant for comparison with other systems. In order to overcome this problem we considered the substitution of the benzyl group by different alternative $ArCH_2$- groups. The aromatic fragment has to contribute to increase the lipophylic character in the surroundings of the cavity while the presence of an appropiately located polar functional group has to be able to solubilize the resulting molecule. The 4-picolyl group seems to be ideally suited for this purpose.

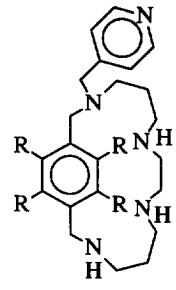
The presence of the basic nitrogen atoms at the outer part of the compound should impart a reasonable water solubility to the molecule. At the same time this nitrogen atom seems to be located so as not to interfere with the coordination to a metal cation in the cavity.



a) R=H (**B323**)

b) R=CH_3 (**D323**)

5



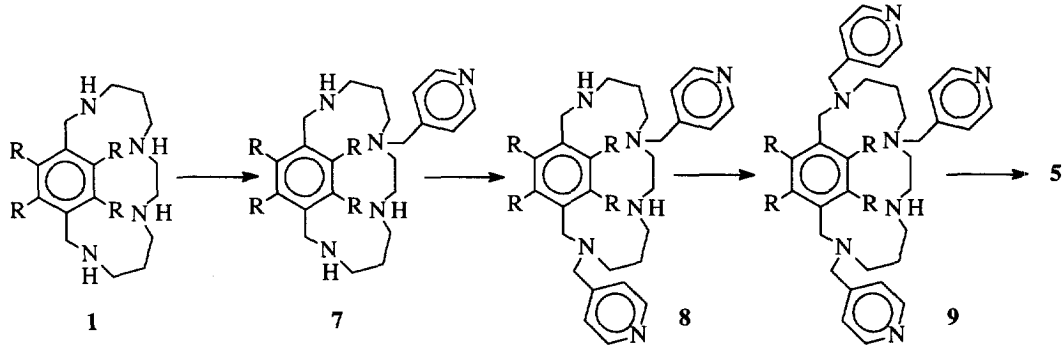
6

Initially, the use of 4-picolyl chloride for the N-functionalization of polyaza[n]paracyclophanes gave slightly less satisfactory results than other alkylating agents. This compound was less reactive than other benzylic chlorides, and, in general, better results were obtained when the reagent was introduced in the reaction mixture as the free base and not as its hydrochloride. For **B323** and **D323**, yields of 34 and 28% were obtained, respectively, for the selective monofunctionalization at one of the benzylic nitrogen atoms (compounds **6a** and **6b**) when a 1:1:1 substrate:metal:reagent was used according to the general procedure previously described for the introduction of the benzyl group.

More interesting results were obtained, however, when complete N-functionalization was performed with 4-picolyl chloride. Thus, for instance, when the reaction was carried out for **D323** using a 1:4 macrocycle:reagent ratio, a mixture of the expected tetrafunctionalized product (**5b**)(35 %) and a trifunctionalized compound (**9b**)(25 %) was obtained. An increase in the amount of alkylating agent used did not cause improvement to those results. The trifunctionalized compound was not obtained in this case, but the tetraalkylated compound was contaminated with other impurities, most likely quaternary ammonium salts. Additionally, when the polyaza[n]paracyclophane was introduced as its tetrahydrobromide, a monofunctionalized (**7b**)(21 %) and a difunctionalized compound (**8b**)(27 %) were obtained as the main products. Very similar results were obtained for the receptor **B323**.

Structural assignment of the different products obtained was carried out using NMR techniques. The most simple case was that of the monofunctionalized compound **7b**, as this compound had spectroscopic features clearly different from that of compound **6b** prepared in the Zn^{2+} directed process. This compound showed in its ^1H NMR three different benzylic singlets. One of them, corresponding to the picolyl fragment, at 3.40 ppm, and the other two, corresponding to the benzylic positions of the macrocyclic ring, at 4.04 and 4.08 ppm. These later chemical shifts roughly correspond to those found for similar protons in non-substituted

systems (4.03 for **1b** and 3.95 for the Ar-CH_2-N close to the secondary benzylic nitrogen atom in **6b**). The ^1H and ^{13}C NMR spectra showed the absence of a two-fold symmetry in the difunctionalized product obtained. Accordingly, the structure where both benzylic nitrogen atoms have been substituted has to be discarded, as well as the one for which disubstitution takes place at both ethylenic positions. The structure shown (**8b**) was selected instead of the one with the substituents on consecutive nitrogen atoms by taking into account the ^{13}C NMR data, which showed, for instance, the presence of two very similar -CH_2- groups corresponding to the central methylene of the propylenic subunit. In the trisubstituted product, the ^1H NMR displayed five benzylic singlets, all of them in the 3.4-3.6 range, revealing the absence of secondary benzylic nitrogen atoms, in good agreement with the structure **9b**. Additional NMR experiments, in particular NOE techniques, confirmed the structural assignments.[13]



a) R=H (**B323**)

b) R=CH_3 (**D323**)

Scheme 3

The former data seem to suggest the stepwise mechanism shown in the *Scheme 3* for the alkylation of these cyclophanes. According to this general scheme, treatment of **1b** with one mole of 4-picolyl chloride gave **7b** as the main monofunctionalized compound. In the same way, the reaction of **7b** with a second mole of the benzylic chloride gave **8b**, while the treatment of **8b** with a third mole of alkylating agent allowed us to obtain the trifunctionalized product **9b**.

CONCLUSIONS

N-Functionalization of polyaza[n]paracyclophanes represents a simple and useful procedure for the modification of these macrocyclic compounds in order to prepare more elaborate receptors. 2,6,9,13-Tetraaza[14]paracyclophanes, are able to undergo very selective partial N-functionalization reactions in the presence of suitable alkylating agents. With the use of 4-picolyl chloride as the alkylating agent, this remarkable

selectivity can be obtained both in the presence and in the absence of divalent metal cations (i.e. Zn^{2+}). In the presence of a metal salt the benzylic nitrogen atoms are the preferred substitution positions. On the contrary, in the absence of the metal cation, this selectivity is reversed and the initial alkylation reaction takes place on a non-benzylic nitrogen atom, subsequent alkylation steps being also very selective. This confirms that the selectivity trends observed in the presence of divalent metal cations are a direct consequence of the coordination patterns described for these receptors in which one of the benzylic nitrogen atoms remains uncoordinated to the metal cation.

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EXPERIMENTAL SECTION

General. Unsubstituted polyaza[n]paracyclophanes were prepared according to the general method that has been previously described.[8] ^1H and ^{13}C NMR spectra were obtained at 200 and 50.3 MHz in $CDCl_3$ (unless otherwise stated) using TMS or the solvent signal (7.27 ppm) as an internal standard.

General procedure for the preparation of N-perbenzylated polyaza[n]paracyclophanes. Synthesis of 2,6,9,13-tetraaza-2,6,9,13-tetrabenzyl[14]paracyclophane (2a). The cyclophane **B323·4HClO$_4$** (0.1 g, 0.15 mmol) was dissolved in dry CH_3CN (30 mL) containing anhydrous K_2CO_3 (0.41 g, 2.96 mmol). Benzyl bromide (70 μL, 0.6 mmol) was then added at 0°C and the mixture was stirred at rt for 24 h. After this period, the solution was filtered and the solvent was vacuum evaporated to give the crude product that was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH as the eluent) to afford pure **2a** as an oil (90 mg, 99% yield). ^1H NMR: 1.43 (m, 4H), 2.17-2.32 (m, 8H), 2.33-2.47 (m, 4H), 3.41 (s, 4H), 3.44 (s, 4H), 3.65 (s, 4H), 7.06-7.61 (m, 24H); ^{13}C NMR: 25.4, 51.3, 52.4, 52.6, 58.9, 59.2, 60.5, 126.6, 126.7, 128.0, 128.1, 128.7, 128.8, 138.9, 140.1. Anal. Calcd. for $C_{44}H_{56}N_4Br_4·H_2O$: C, 54.0; H, 6.0; N, 5.7. Found: C, 54.1; H, 6.1; N, 6.0.

2,6,9,13-tetraaza-2,6,9,13-tetrabenzyl-16,17,19,20-tetramethyl[14]paracyclophane (2b). 99% yield. ^1H NMR: 1.37 (m, 4H), 2.24 (s, 12H), 2.28 (s, 4H), 2.34-2.47 (m, 8H), 3.47 (s, 4H), 3.59 (s, 4H), 3.65 (s, 4H), 7.11-7.55 (m, 20H); ^{13}C NMR: 16.8, 25.9, 50.8, 52.2, 54.1, 59.2, 61.2, 126.5, 126.8, 127.9, 128.0, 128.6, 129.6, 134.0, 134.4, 139.5, 140.1. Anal. Calcd. for $C_{48}H_{64}N_4Br_4·H_2O$: C, 55.8; H, 6.2; N, 5.4. Found: C, 55.9; H, 6.0; N, 5.5.

Reaction of 2,6,9,13-tetraaza-16,17,19,20-tetramethyl[14]paracyclophane with 4-picolyl chloride. Procedure A, synthesis of 5b and 9b. The cyclophane **D323** (55.4 mg, 0.17 mmol) was dissolved in dry CH_3CN (30 mL) containing anhydrous K_2CO_3 (0.17 g, 1.23 mmol). 4-Picolyl chloride (0.11 g, 0.68 mmol), obtained from its hydrochloride by extraction in basic media, was then added and the mixture was refluxed for 4 days. After this period, the solution was filtered and the solvent was vacuum evaporated to give the crude product that was purified by column chromatography (SiO_2, MeOH/aq. NH_3 10/0.5 as the eluent) to afford pure **9b** (41.4 mg, 35%) and **5b** (25.7 mg, 25% yield) as oily products.

2,6,9,13-tetraaza-16,17,19,20-tetramethyl-2,6,13-tris(4-picolyl)-[14]paracyclophane (9b). ^1H NMR: 1.35 (m, 2H), 1.47 (m, 2H), 2.1-2.45 (m, 22H), 2.52 (t, 2H), 3.39 (s, 2H), 3.56 (s, 2H), 3.57 (s, 2H), 3.61 (s, 2H), 3.64 (s, 2H), 7.10 (d, J=5.6 Hz, 2H), 7.28 (d, J=5.2 Hz, 2H), 7.34 (d, J=4.8 Hz, 2H), 8.53 (m, 4H), 8.57 (d,

J=4.8 Hz, 2H); ^{13}C NMR: 16.9, 16.9, 26.3, 26.8, 45.9, 46.5, 48.1, 50.7, 52.5, 53.1, 54.0, 55.1, 58.1, 59.4, 60.2, 123.5, 124.3, 124.5, 133.8, 134.1, 134.2, 134.3, 148.1, 148.6, 149.0, 149.5, 149.6.

2,6,9,13-tetraaza-16,17,19,20-tetramethyl-2,6,9,13-tetra(4-picolyl)-[14]paracyclophane (5b). ^{1}H NMR: 1.25 (m, 4H), 2.13 (m, 4H), 2.19 (s, 4H), 2.23 (s, 12H), 2.36 (t, 4H), 3.39 (s, 4H), 3.58 (s, 4H), 3.61 (s, 4H), 7.11 (d, J=5.3 Hz, 4H), 7.27 (d, J=5.3 Hz, 4H), 8.53 (m, 8H); ^{13}C NMR: 17.0, 26.2, 50.8, 52.5, 54.8, 58.3, 60.5, 123.4, 124.4, 134.1, 134.2, 149.6. Anal. Calcd. for $C_{44}H_{64}N_8Cl_8 \cdot 6H_2O$: C,48.2; H, 7.0; N, 10.2. Found: C, 48.2; H, 6.8; N, 10.1.

2,6,9,13-tetraaza-2,6,13-tris(4-picolyl)-[14]paracyclophane (9a). 30% yield. ^{1}H NMR: 1.44 (m, 2H), 1.52 (m, 2H), 2.00-2.45 (m, 10H), 2.60 (t, 2H), 3.38 (s, 2H), 3.39 (s, 2H), 3.43 (s, 2H), 3.62 (s, 2H), 3.67 (s, 2H), 7.05 (d, J=5.6 Hz, 2H), 7.31 (d, J=5.6 Hz, 2H), 7.34 (m, 4H), 7.41 (d, J=5.6 Hz, 2H), 8.57 (m, 6H); ^{13}C NMR: 25.8, 29.6, 45.9, 46.4, 49.7, 52.0, 52.9, 58.1, 58.4, 59.0, 59.2, 59.8, 63.6, 123.4, 123.5, 123.6, 128.7, 129.1, 138.3, 149.1, 149.3, 149.6, 149.7, 149.8.

2,6,9,13-tetraaza-2,6,9,13-tetra(4-picolyl)-[14]paracyclophane (5a). 35% yield. ^{1}H NMR: 1.35 (m, 4H), 2.12-2.27 (m, 8H), 2.39 (t, 4H), 3.38 (s, 4H), 3.39 (s, 4H), 3.62 (s, 4H), 7.09 (d, J=5.9 Hz, 4H), 7.27 (s, 4H), 7.34 (d, J=5.9 Hz, 4H), 8.48 (d, J=5.9 Hz, 4H), 8.54 (d, J=5.9 Hz, 4H); ^{13}C NMR: 25.8, 51.7, 52.5, 52.7, 58.1, 59.6, 59.7, 63.6, 123.4, 123.7, 128.9, 138.7, 149.4, 149.6, 149.8. Anal. Calcd. for $C_{40}H_{56}N_8Cl_8 \cdot 3H_2O$: C, 48.7; H, 6.3; N, 11.4. Found: C, 48.4; H, 6.4; N, 11.2.

Procedure B, obtention of 7b and 8b. As in procedure A but starting from **D323·4HBr** (0.1 g, 0.15 mmol), to give **7b** (14 mg, 21.3%) and **8b** (21.1 mg, 26.7%) as oily products.

2,9-Bis(4-picolyl)- 2,6,9,13-tetraaza-16,17,19,20-tetramethyl-[14]paracyclophane (8b). ^{1}H NMR: 1.22 (m, 2H), 1.53 (m, 2H), 1.90-2.70 (m, 24H), 3.42 (s, 2H), 3.67 (s, 4H), 4.00 (s, 2H), 7.14 (d, J=5.7 Hz, 2H), 7.34 (d, J=5.9 Hz, 2H), 8.56 (m, 4H); ^{13}C NMR: 16.8, 17.2, 28.0, 28.2, 46.7, 47.2, 47.4, 53.4, 53.9, 54.5, 58.4, 60.3, 123.6, 124.4, 132.8, 134.2, 149.7.

6-(4-picolyl)-2,6,9,13-tetraaza-16,17,19,20-tetrametil-[14]paracyclophane (7b). ^{1}H NMR: 1.40 (m, 4H), 2.10-2.70 (m, 24H), 3.40 (s, 2H), 4.04 (s, 2H), 4.08 (s, 2H), 7.12 (d, J=5.8 Hz, 2H), 8.53 (d, J=5.8 Hz, 2H); ^{13}C NMR: 16.8, 16.9, 28.5, 46.3, 47.0, 47.2, 47.4, 47.6, 53.8, 54.1, 123.4, 133.0, 149.7.

General procedure for the preparation of N-substituted polyaza[n]paracyclophanes in the presence of Zn2+. Synthesis of 2-(4-picolyl)-2,6,9,13-tetraaza-16,17,19,20-tetramethyl[14]paracyclophane (6b). The cyclophane **D323** (50 mg, 0.15 mmol) and $Zn(OTf)_2$ (55.4 mg, 0.15 mmol) were dissolved in dry CH_3CN (25 mL). After stirring for some minutes, anhydrous K_2CO_3 (62.1 mg, 0.45 mmol) was added and then 4-picolyl chloride (24.6 mg, 1.5 mmol) at 0°C. The mixture was stirred at rt overnight and then was filtered. The solvent was vacuum evaporated and the residue was treated with conc. aq. NH_3 (5 mL) and extracted with CH_2Cl_2. The organic phase was dried and the solvent was eliminated to give the crude product that was purified by column chromatography (SiO_2, MeOH/NH_3 mixtures as the eluent) to afford pure **6b** as an oil (21.7 mg, 34.2% yield). ^{1}H NMR: 1.33 (m, 2H), 1.62 (m, 2H), 2.22 (s, 6H), 2.25-2.33 (m, 8), 2.36-2.52 (m, 6), 2.63-2.74 (m, 4), 3.60 (s, 2H), 3.64 (s, 2H), 3.94 (s, 2H), 7.34 (d, 2H), 8.57 (d, 2H); ^{13}C NMR: 16.7, 16.9, 28.7, 29.0, 45.9, 46.4, 47.1, 48.3, 48.8, 50.5, 54.5, 58.9, 128.4, 134.7, 136.4, 149.9.

2-(4-picolyl)-2,6,9,13-tetraaza-[14]paracyclophane (6a). 28% yield. ^{1}H NMR: 1.56 (m, 4H), 2.32-2.72 (m, 12H), 3.40 (s, 2H), 3.66 (s, 2H), 3.78 (s, 2H), 7.26 (s, 4H), 7.41 (d, 2H, J=5.9 Hz), 8.58 (d, 2H, J=5.9 Hz); ^{13}C NMR: 26.4, 28.5, 44.1, 46.3, 46.6, 49.3, 49.5, 53.2, 58.2, 59.3, 123.7, 128.6, 129.0, 138.1, 139.6, 149.5, 149.8.

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