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Selective Monofunctionalization of Polyaza[n]paracyclophanes

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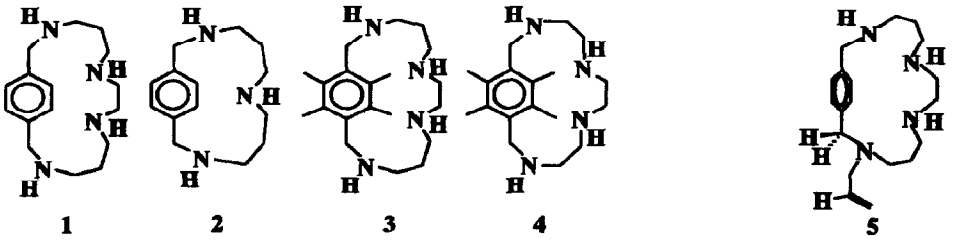
Abstract: A new strategy to the preparation of selectively functionalized polyazamacrocycles is presented. Polyaza[n]paracyclophanes receptors are able to efficiently direct their own selective monofunctionalization upon interaction with simple guests such as metal cations. This enables the preparation of novel receptors functionalized at one of the benzylic nitrogen atoms with a variety of groups.

Development of novel synthetic strategies to obtain otherwise difficult targets represents a very active field of research in supramolecular chemistry.[1] In this sense, supramolecular interactions have been successfully used to prepare compounds with rotaxane or catenane structures or to develop self-replicating systems.[2-6] Selective monofunctionalization 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 recently developed. 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.[8,9] 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.[10]

Here we report on a different approach as is the design of polyazamacrocyclic receptors programmed to develop very selective reactivity patterns upon interaction with an appropriate guest. Polyaza[n]paracyclophanes (i.e. **1-4**), 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.[11] One interesting characteristic of these ligands is that the presence of the *para*-substituted aromatic spacer precludes the simultaneous involvement of all nitrogen atoms in the coordination to metal centers (see structures **6-8**).[12] Here we present how this feature can be advantageously used for the selective monofunctionalization of those receptors.



1 2 3 4 5

Attempted reaction of macrocycle **1** with an alkylating agent such as allyl bromide (1:1 molar ratio) in acetonitrile, 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 starting material as the major product. However, when the reaction was carried out in the presence of a stoichiometric amount of Zn^{2+} (as its chloride or triflate salt), results changed dramatically. 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 the monoalkylated macrocycle **5** accompanied by very minor amounts of starting material and a dialkylated product with the general structure depicted in **10**. Chromatographic purification of the crude product afforded compound **5** in 60% yield.

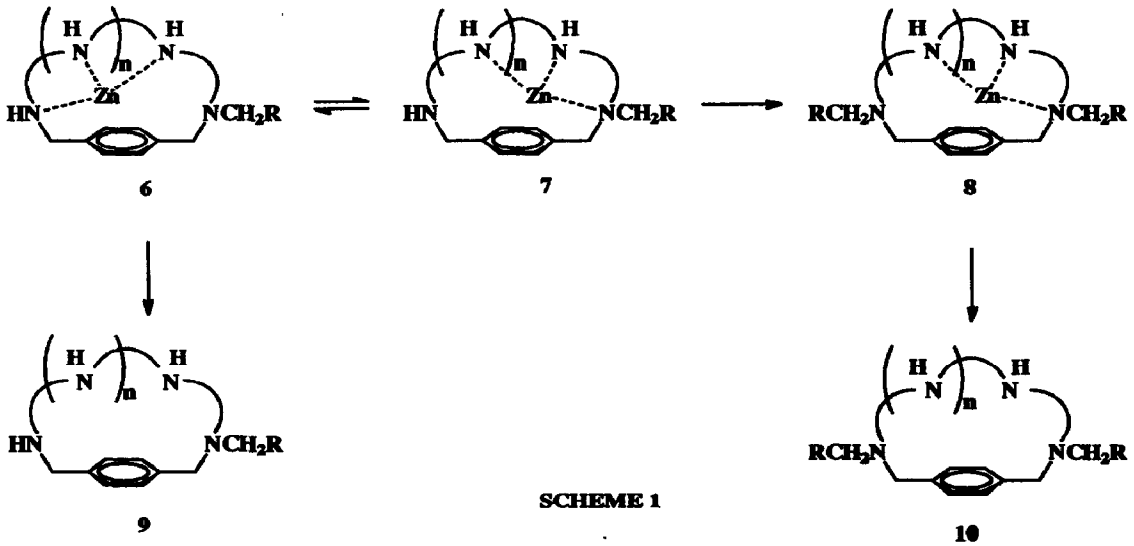
Spectroscopic characterization of this product revealed that monofunctionalization had occurred at the benzylic nitrogen. ^{13}C NMR spectrum showed the presence of eleven methylenic carbon atoms and the same loss of symmetry was observed in the ^{1}H NMR spectrum, where the singlet characteristic of the central ethylene subunit in **1** disappears and two separate multiplets are observed at ca. 1.5 ppm for the middle methylene of the propylenic fragments. Additionally, two different benzylic singlets are observed, one of them having a similar chemical shift than benzylic protons in **1** 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 2.8 Å distance predicted from molecular mechanics.

The results obtained for different alkylating agents and receptors are summarized in **Table 1**. All yields refer to the isolated product after chromatographic purification. All monoalkylated products present similar spectral properties to those of **5**. 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 product. This behavior can be explained in terms of the isomerization of the initially formed complex **6** to complex **7** and subsequent reaction of this product (Scheme 1). This is in agreement with the observed lower yields obtained for the monofunctionalization of **2**, for the lower stability of its Zn^{2+} complexes would favor isomerization and, therefore, increase the formation of dialkylated compounds **10**. On the contrary, the less flexible receptor **3**, for which isomerization is not so favorable, always afford the higher yields of monofunctionalizated product.

Table 1. Isolated Yields of MonofunctionalizedPolyaza[n]paracyclophanes.

Substrate	*R-*	*Yield (%)[a),b)]*	*Substrate*	*R-*	*Yield (%)[a),b)]*
1	CH_2=CH-	60	2	CH_2=CH-	31 (20)[c)]
1	Ph-	56	2	EtO_2C-	21 (21)[c)]
1	EtO_2C-	72	2	Ph-	25 (35)[c)]
1	*p*-$NO_2C_6H_4$-	61	3	CH_2=CH-	89
1	*p*-MeC_6H_4-	64	3	EtO_2C-	73
4	CH_2=CH-	52	3	Ph-	79

a) Yields after chromatographic purification. b) All new compounds gave the expected analytical results. c) Yields in parentheses correspond to the difunctionalized product, according to the general structure depicted in **10**.



SCHEME 1

Accordingly, polyaza[n]paracyclophanes represent a simple example of receptors which selectively direct their own functionalization upon interaction with a substrate. This synthetic approach could be, in principle, used for selective functionalization of other polynitrogenated receptors in which structural features provide uncoordinated nucleophilic nitrogen atoms when interacting with guests species.

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12. For instance, ^{13}C NMR spectrum in CD_3CN of the complex between ligand **2** and Zn^{2+} consists of 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, 132.4, 133.3, 137.6 ppm.

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