An efficient preparation of ditopic receptors based on polyaza[*n*]paracyclophanes

M. Isabel Burguete,[a] Enrique García-España,*[b] Santiago V. Luis,*[a]† Juan F. Miravet,[a] Lorena Payá,[a] Manuel Querol[a] and Conxa Soriano[b]

[a] *Department of Inorganic and Organic Chemistry, ESTCE, University Jaume I, E-12080 Castellón, Spain*
[b] *Departaments of Inorganic and Organic Chemistry, University of Valencia, c/ Doctor Moliner 50, E-46100, Burjassot, (Valencia), Spain*

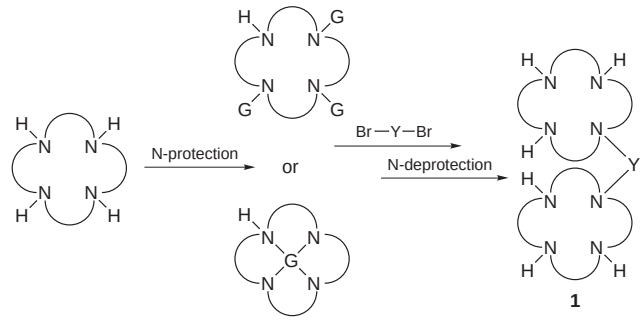
Coordination patterns of tetraaza[*n*]paracyclophanes allow for the selective protection of three out of the four nitrogen atoms *via* the use of simple Zn^{2+} salts; accordingly, a simple method for the preparation of ditopic receptors based on polyaza[*n*]paracyclophanes has been devised.

Ditopic polyaza receptors containing two macrocyclic subunits have become a very important synthetic target, in particular since the discovery of the anti-HIV activity associated to some of those systems.[1] Accordingly, a number of different synthetic strategies have been put forward in recent years to achieve this goal. In this way, several families of receptors having the general structure **1** have been recently prepared.[2]

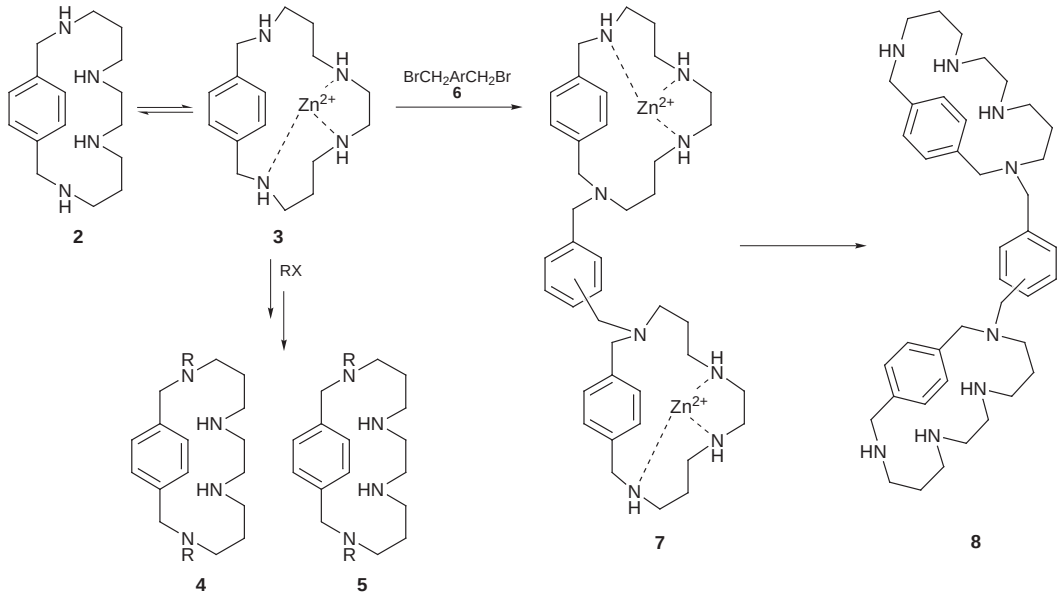
One of the most general synthetic routes for the preparation of this class of compounds is based on the selective protection of the nitrogen atoms in such a way as to leave only one unprotected, reactive nitrogen atom in the macrocycle.[2,3] This intermediate is then reacted with a dihalide to afford, after N-deprotection, the expected ditopic receptor (Scheme 1). As a matter of fact, preparation of ditopic receptors has been one of the central motifs for the development of synthetic strategies for the selective N-functionalization of polyazamacrocycles.

Polyaza[*n*]paracyclophanes **2** represent a very interesting kind of polyaza macrocyclic receptors.[4] One of their most remarkable ligational features is the fact that the presence of the aromatic spacer precludes the simultaneous involvement of all the nitrogen atoms in the coordination to a metal centre (see structure **3**). Thus, for instance, 2,6,9,13-tetraaza[14]paracyclophane **2a** coordinates M^{2+} ions with just three out of its four nitrogen atoms. One of the benzylic nitrogen atoms remains non-coordinated, thus being able to act as a base or as a nucleophile. This property has allowed the development of a simple and novel procedure for selective mono- and di-functionalization of this kind of macrocycle with a variety of reactive alkyl halides, according to the general scheme shown in Scheme 2, to give compounds **4** and **5**.[5] In this way, the otherwise experimentally difficult selective protection of three of the nitrogen atoms can be easily achieved *via* the use of simple metal ions, like Zn^{2+}, without the need of more elaborate reagents or synthetic routes.

This synthetic approach can be further extended to the preparation of ditopic bis-macrocyclic receptors **8** based on



Scheme 1



Scheme 2

Table 1 Results obtained in the preparation of ditopic receptors **8** derived from tetraaza[*n*]paracyclophanes

Starting macrocycle[a]	Alkylating agent[b]	Polyamine:base ratio	*t*/days	Yield[c] (%)
2a	**6a**	1:1	1	30
2a	**6a**	1:1	3	37
2a·4HBr	**6a**	1:5	3	40
2a·4HBr	**6a**	1:7	3	87
2b	**6a**	1:7	3	24
2b·4HBr	**6a**	1:7	3	75
2a·4HBr	**6b**	1:7	3	78
2a·4HBr	**6b**	1:7	5	78
2b·4HBr	**6b**	1:7	3	59
2b·4HBr	**6b**	1:7	5	60
2a·4HBr	**6c**	1:7	3–5	< 10[d]
2b·4HBr	**6c**	1:7	3–5	< 10[d]

[a] Compound **2a** (B323): 2,6,9,13-tetraaza[14]paracyclophane; Compound **2b** (D323): 2,6,9,13,tetraaza-16,17,19,20-tetramethyl[14]paracyclophane. [b] Compound **6a**: 1,4-bis(bromomethyl)benzene; Compound **6b**: 1,3-bis(bromomethyl)benzene; Compound **6c**: 1,2-bis(bromomethyl)benzene. [c] Product obtained after chromatographic purification. [d] Estimated from the crude product after the reaction.

polyaza[*n*]paracyclophanes when a bis(halomethyl)benzene is used as the alkylating agent (Scheme 2).

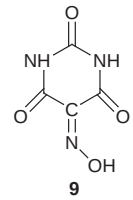
The low coordination of the metal centre in the complexes formed by polyaza[*n*]paracyclophanes **2** has been shown to provide mechanisms for the participation of the coordinated cation in biomimetic catalytic proceses.[4] In this sense, the preparation of ditopic receptors **8** represents an interesting synthetic target.

Results obtained for different macrocycles and aromatic spacers are summarised in Table 1. Careful control of the reaction conditions is required. We used the cyclic polyamines as free bases or as their hydrobromides, and different ratios of macrocycle/base were tested in the range of *ca.* 1 to 10. Best results were obtained when an excess (*ca.* 7:1) of base (anhydrous K_2CO_3) is used and the polyamine is introduced as its hydrobromide. The use of 1,4-bis(halomethyl)arenes gives better yields than the 1,3-substituted analogues. The expected products could not be obtained for 1,2-bis(halomethyl)arenes.‡

The nature of the aliphatic chains between the nitrogen atoms is also very important. Good results were only obtained when propylenic sub-units are present and the expected ditopic receptors could not be prepared starting from cyclophanes containing only ethylenic spacers. This can be related with the different coordination patterns of the macrocycles used.[5b] In this context it is worth mentioning that tetraazacyclophanes containing only ethylenic sub-units have been shown to be able to form dinuclear Cu^{2+} complexes in which all four nitrogen atoms are coordinated.[4b]

Preliminary analyses of the acid-base and coordination tendencies of these compounds have shown some interesting trends. Protonation constants obtained from pH titrations show that in the pH range 2–11 all ligands can take up to seven protons, the eighth protonation not being generally detected under our experimental conditions. At neutral pH values the main species for all ligands are the tetraprotonated ones.§ The high positive charge achieved by these ligands at neutral pH allows us to consider them as potential receptors for anionic species. Thus, for instance, compound **8b** (obtained from **2b** and **6a**) strongly interacts with the barbituric acid derivative 1*H*,3*H*-pyrimidine-2,4,5,6-tetrone 5-oxime (violuric acid) **9** with complexation percentages around 90–100% in a wide pH range (pH < 8).[6]¶

On the other hand, when the interaction with metal cations is considered, compounds **8** revealed the possibility of forming



9

mono- as well as di-nuclear complexes. Thus, for instance, **8d** (obtained from **2b** and **6b**) in the presence of Cu^{2+} salts is able to form both CuL and Cu_2L species with stability constants of $\log K_{CuL}$ = 13.46(3) and $\log K_{Cu2L}$ = 8.8(1). These results also open the possibility for the study of those complexes as potential biomimetic catalysts in aqueous media. Such studies are being presently carried out.

Notes and References

† E-mail: luiss@qio.uji.es

‡ All compounds show the expected spectroscopic data. The most distinctive spectroscopic feature of receptors **2** is the presence in their ^{1}H NMR spectra of three well-defined benzylic singlets at δ 3.4–3.5, 3.6 and 3.7–3.9. *Selected data* for **8a**: $\delta_H(CDCl_3)$ 1.47 (m, 4 H), 1.65 (m, 4 H), 2.34 (t, 4 H), 2.52 (s, 8 H), 2.54–2.66 (m, 8 H), 2.73 (t, 4 H), 3.39 (s, 4 H), 3.62 (s, 4 H), 3.77 (s, 4 H), 7.26 (s, 8 H), 7.39 (s, 8 H); δ_C 26.2, 27.1, 45.3, 46.3, 47.2, 48.4, 48.7, 49.7, 52.7, 59.0, 59.3, 128.7, 129.3, 137.9, 138.5, 139.5.

§ For instance, stepwise protonation constants for receptor **8b**, determined by pH fitrations at 298.1 K in 0. 15 mol dm^{-3}, are: $\log K_{HL}$ = 9.9(2), $\log K_{H2L}$ = 9.53(3), $\log K_{H3L}$ = 8.41(4), $\log K_{H4L}$ = 7.77(4), $\log K_{H5L}$ = 5.95(4), $\log K_{H6L}$ = 4.67(4), $\log K_{H7L}$ = 3.64(4) and $\log K_{H8L}$ < 2. Charges are omitted for clarity.

¶ In the pH range 7–5, the predominant species are H_7LA and H_8LA, obtained by the interaction of the monoanion of violuric acid and the pentaprotonated [log*K* = 4.93(4)] or hexaprotonated receptor [log*K* = 6.18(4)], respectively.

1 G. J. Bridger, R. T. Skerlj, D. Thornton, S. Padmanabban, S. A. Martellucci, G. W. Henson, M. J. Abrams, N. Yamamoto, K. De Vreese, R. Pauwels and E. De Clercq, *J. Med. Chem.*, 1995, **38**, 366; G. J. Bridger, R. T. Skerlj, S. Padmanabban, S. A. Martellucci, G. W. Henson, M. J. Abrams, H. C. Joao, M. Witvrouw, K. De Vreese, R. Pauwels and E. De Clercq, *J. Med. Chem.*, 1996, **39**, 109.

2 K. Wieghardt, I. Tolksdorf and W. Herrmann, *Inorg. Chem.*, 1985, **24**, 1230; M. Ciampolini, L. Fabbrizzi, A. Perotti, A. Poggi, B. Seghi and F. Zanobini, *Inorg. Chem.*, 1987, **26**, 3527; J. L. Sessler and J. W. Sibert, *Tetrahedron*, 1993, **49**, 8727; S. Mallik, R. D. Johnson and F. H. Arnold, *J. Am. Chem. Soc.*, 1994, **116**, 8902; D. Xu, P. G. Mattner, K. Prasad, O. Repic and T. J. Blacklock, *Tetrahedron Lett.*, 1996, **37**, 5301; E. Kimura, S. Aoki, T. Koike and M. Shiro, *J. Am. Chem. Soc.*, 1997, **119**, 3068.

3 A. Filali, J.-J. Yaouanc and H. Handel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 560; P. L. Anelli, M. Murru, F. Uggeri and M. Virtuani, *J. Chem. Soc., Chem. Commun.*, 1991, 1317; V. Patinec, J. J. Yaouanc, J. C. Clément, H. Handel and H. des Abbayes, *Tetrahedron Lett.*, 1995, **36**, 79; B. Boitrel, B. Andrioletti, M. Lachkar and R. Guillard, *Tetrahedron Lett.*, 1995, **36**, 4995; D. Parker and J. A. G. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1581; D. Parker, K. Senanayake and J. A. G. Williams, *Chem. Commun.*, 1997, 1777.

4 (*a*) A. Bencini, M.I. Burguete, E. García-España, S.V. Luis, J.F. Miravet and C. Soriano, *J. Org. Chem.*, 1993, **58**, 4749; (*b*) A. Andrés, C. Bazzicaluppi, A. Bianchi, E. García-España, S.V. Luis, J. F. Miravet and J. A. Ramirez, *J. Chem. Soc., Dalton Trans.*, 1994, 2995; (*c*) E. García-España, J. Latorre, S. V. Luis, J. F. Miravet, P. E. Pozuelo, J. A. Ramírez and C. Soriano, *Inorg. Chem.*, 1996, **35**, 4591; (*d*) B. Altava, M. I. Burguete, S. V. Luis, J. F. Miravet, E. García-España, V. Marcelino and C. Soriano, *Tetrahedron*, 1997, **53**, 4751.

5 (*a*) M. I. Burguete, B. Escuder, S. V. Luis, J. F. Miravet and E. García-España, *Tetrahedron Lett.*, 1994, **35**, 9075; (*b*) M. I. Burguete, B. Escuder, J. C. Frías, E. García-España, S. V. Luis and J. F. Miravet, *J. Org. Chem.*, 1998, **63**, 1810.

6 For the interaction of bis-macrocycles with barbituric derivatives, see: T. Koike, M. Takashige, E. Kimura, H. Fujioka and M. Shiro, *Chem. Eur. J.*, 1996, **2**, 617.

Received in Cambridge, UK, 20th May 1998; 8/03790F