# Polyazacyclophanes containing biphenyl fragments

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**Polyaza[*n*]cyclophanes containing the 2,2′-biphenyl subunit are prepared in good yields by reaction of the corresponding pertosylated polyamine and 2,2′-bis(bromomethyl)biphenyl in basic media followed by detosylation with Na/Hg; the dynamic behaviour of those receptors is clearly affected by their interaction with different cationic and anionic guests.**

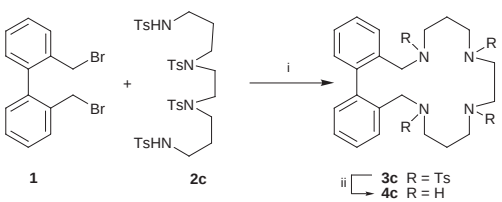
Macrocyclic receptors containing biphenyl subunits represent a very interesting class of hosts because of their dynamic properties provided by the presence of the biphenyl moiety. A clear example of the interest of this kind of compound is the work of Rebek in the development of simple allosteric systems.[1] Most work in this area has been directed towards the preparation of the all-oxygen macrocycles,[2] and only rarely has the synthesis of compounds in which some of the oxygen atoms have been substituted by nitrogen been reported.[3,4] However, our recent work on polyaza[*n*]cyclophanes[5] suggested to us that biphenyl polyaza macrocycles could represent a very interesting target as they combine the coordination trends of polyazacyclophanes with the dynamic properties of biphenyl crown ethers, giving rise to better regulated systems when supramolecular assemblies and catalytic properties are considered. Here we report on the first synthesis of such macrocyclic receptors and on preliminary results on their coordination properties that confirm their very interesting behaviour.

Synthesis of the expected macrocyclic receptors was carried out using a Richman–Atkins procedure optimized by us for the preparation of polyaza[*n*]cyclophanes (Scheme 1).[5a]

Cyclization of pertosylated polyamines **2** with **1** was performed very efficiently in 60–70% yield for **3c** and **3d** using MeCN as the solvent and $K_2CO_3$ as the base, without the need of high dilution conditions. Lower yields were obtained for the smaller macrocycles **3a** and **3b** due to the simultaneous formation of dimeric cyclic species **5** and **6**.[4] Detosylation was best carried out with Na/Hg,[5a] very good yields (*ca.* 70–80%) were obtained for the crude products. Chromatographic purification afforded the pure compounds in *ca.* 40% yield.

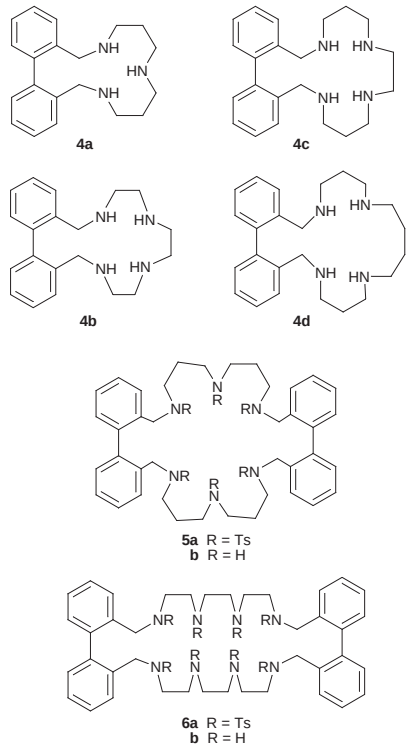
The dynamic properties of these systems are clearly seen in their $^1$H NMR spectra, in particular when benzylic C–H signals are considered. In general, benzylic protons in compounds **4**, at 200 MHz in $CDCl_3$ at room temperature, appear as AB systems, in agreement with the presence of the slow equilibrium shown in Scheme 2.

Coalescence of the AB benzylic peaks occurs at not very high temperatures for the larger macrocycles, and variable temperature experiments allowed, for instance, us to determine for




1 2c

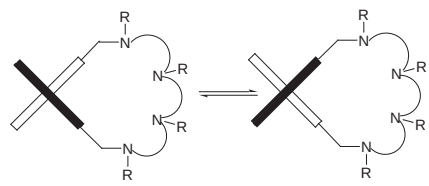
**Scheme 1** *Reagents and conditions*: i, $K_2CO_3$, MeCN; ii, Na/Hg, THF–MeOH.




**4c** a coalescence temperature of 22 °C with $\Delta G = 14.5 \pm 0.3$ kcal mol$^{-1}$.

Blocking of the interconversion can be easily achieved by protonation of the nitrogen atoms, as indicated by the observation of the benzylic protons as two well-defined AB doublets. Protonation of compounds **4** could be followed by potentiometry and NMR techniques and showed similar trends to those found for related polyaza[*n*]cyclophanes.[5a] The observed separation of the two benzyl doublets is dependent on the pH. For **4c**, $\Delta\delta$ values at 300 MHz and room temperature vary from 41 Hz at pH 11 to 69 Hz at pH 2. Obviously interconversion of the two rotamers has to proceed through a coplanar disposition of the aromatic rings in which electrostatic repulsions are maximized, in particular when the protonated benzylic nitrogen atoms are considered.

These compounds seem to present a more versatile coordination chemistry than their simple polyaza[*n*]paracyclophane analogues, and this can be ascribed to the dynamic behaviour of



**Scheme 2**

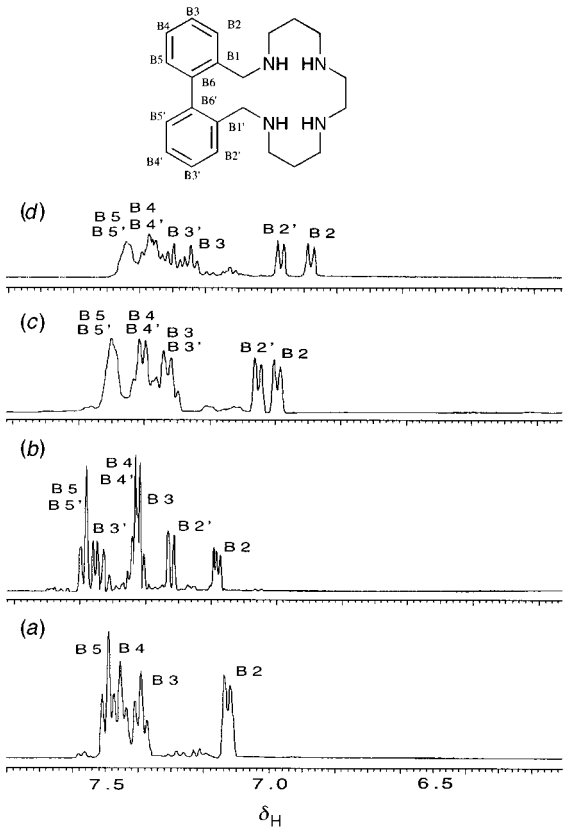



**Fig. 1** $^1$H NMR spectra ($D_2O$) (aromatic region): (*a*) **4c** at acidic pH, (*b*) **4c**·$Pd^{2+}$ at basic pH, (*c*) **4c**·ATP at acidic pH, (*d*) **4c**·ATP at basic pH.

the biphenyl spacer. Thus, for instance, while coordination of **4c** to $Cu^{2+}$ gives rise to a $[CuL]^{2+}$ complex with a stability constant of 18.7 logarithmic units, the related $[ZnL]^{2+}$ complex presents a constant of only 8.7 logarithmic units, strongly suggesting that the strength of the coordinative bonds formed tunes the conformation of the receptor. In the case of $Cu^{2+}$ all the N donors would be participating in the recognition of the metal ion, while for $Zn^{2+}$ just three out of the four N donors would be involved. These results are further supported by the presence in the $Zn^{2+}$·**4c** system of a hydroxylated species as well as by the large constant found for the protonation of the $[ZnL]^{2+}$ complex.† This behaviour is clearly dependent on the nature of the polynitrogenated bridge, which plays a very important role in determining the dynamic properties of the biphenyl moiety.‡

A particular situation is found when $PdCl_4^{2-}$ is used as the guest. The $^1$H and $^{13}$C NMR spectra at basic pH show that $Pd^{2+}$ is coordinated to only three of the nitrogen atoms, introducing a high degree of rigidity in the macrocyclic framework. Thus, the $^{13}$C NMR spectrum shows twelve signals for the aromatic carbons and ten for the aliphatic ones, denoting a complete loss of symmetry. On the other hand, while one of the benzylic signals appears with a chemical shift similar to that of the non-protonated free ligand, the other one is shifted downfield more than 6 ppm. Similar trends are observed in the $^1$H NMR spectrum, all the hydrogen atoms being magnetically non-equivalent [see Fig. 1(*b*) for the aromatic region].

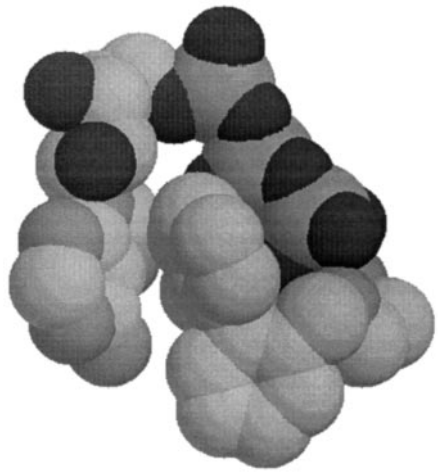


**Fig. 2** CPK model of the calculated structure for the interaction of protonated **4c** and ATP (AMBER*, MACROMODEL® 5.0 package). GB/SA solvation model for water has been considered.

These receptors also strongly interact with anionic guests such as ATP.§ In this case a complete loss of symmetry is only observed for the aromatic region in the $^1$H NMR spectrum [see Fig. 1(*c*) and 1(*d*)]. For **4c** four triplets and four doublets are observed in that region. These spectral features suggest a structure of the adduct in which the adenosine fragment of the ATP is located above the biphenyl moiety, freezing the rotation of and making non-equivalent both aromatic rings. These kinds of structures are also suggested by molecular mechanics calculations (see Fig. 2).

Additional work is being carried out in order to fully understand these interactions and to develop novel supramolecular systems based on these structures.

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## Notes and References

† Protonation constants of **4c** determined in 0.15 mol $dm^{-3}$ $NaClO_4$ at 298.1 K are as follows: $\log K_{HL}$ = 9.91(2), $\log K_{H_2L}$ = 8.85(3), $\log K_{H_3L}$ = 6.55(3), $\log K_{H_4L}$ = 4.05(5). Stability constants for the formation of $Cu^{2+}$ complexes with **4c**; $\log K_{CuI/Cu.L}$ = 18.66(3), $\log K_{CuHL/CuL.H}$ = 4.10(3). Stability constants for the formation of $Zn^{2+}$ complexes with **4c**; $\log K_{ZnI/Zn.L}$ = 8.70(2) $\log K_{ZnHL/ZnL.H}$ = 6.91(3), $\log K_{ZnL(OH)/ZnL.H_2O}$ = −9.33(3). The degrees of protonation of receptor and substrate have been estimated taking into account their basicity constants.

‡ Stability constants for the formation of $Cu^{2+}$ complexes with **4b** and **4d** are: $\log K_{CuI/Cu.L}$ = 23.19(7) and $\log K_{CuL/u.L}$ = 10.18(4).

§ Interaction of **4c** with ATP in 0.15 mol $dm^{-3}$ $NaClO_4$ at 298.1 K gives rise to adduct species with $AH_jL$ ($j$ = 2 to 6) (A = $ATP^{4-}$, L = **4c**) with stability constants: $LH_4 + H_2A = H_6LA$, $\log K$ = 6.01(4). $LH_4 + HA = H_5LA$, $\log K$ = 6.30(4), $LH_3 + HA = H_4LA$, $\log K$ = 5.41(4), $LH_2 + HA = H_3LA$, $\log K$ = 5.55(4) and $LH_2 + A = H_2LA$, $\log K$ = 4.17(3).

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