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# Tetraaza-2,2′-biphenylophanes: larger is not always more flexible. The role of intramolecular H-bonding in polyazamacrocycles

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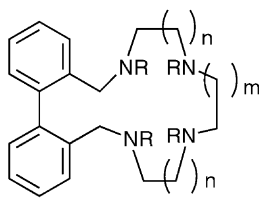
**Abstract**—Intramolecular H-bonding can explain the trends in conformational flexibility for tetraaza-2,2′-biphenylophanes obtained by NMR and molecular dynamics calculations. 

During the last two decades macrocyclic polyamines have been extensively studied by different research groups.[1,2] This type of compounds can interact with anions, cations and with neutral molecules, and the supramolecular species formed are of great interest in a variety of areas. In particular, tetraazamacrocycles have received special attention, being cyclam and related compounds probably the better known example. In our group we have been specially interested in azamacrocycles containing aromatic units derived from benzene, naphthalene, anthracene and biphenyl.[3] The presence of biphenyl subunits in the macrocycles is particularly interesting as a result of the dynamic properties associated with this aromatic moiety as demonstrated, for example, by Rebek in the development of allosteric receptors.[4]

The introduction of 2,2′-biphenylene units can be used advantageously for the study of the dynamic properties of a macrocycle by NMR spectroscopy. The information that can be gained in this way about the preorganization of the receptors is very relevant for a better understanding of the host–guest interactions. Thus, for instance, the presence of conformational constraints such as intramolecular H-bonding, that can be very important in polyazamacrocycles, are amenable to study using this approach. Our aim is to report on the preparation of 2,2′-biphenylenetetraazamacrocycles and the study of their dynamic properties based on NMR experiments and molecular dynamics calculations, putting special emphasis on the information about host preorganization that can be obtained from those studies.

Synthesis of 2,2′-biphenylentetraazamacrocycles **1**–**8** (Chart 1) was carried out according to the general method described by us for the preparation of *N*-tosylated-polyaza[*n*]paracyclophanes.[3a] In this case, dropwise addition of 2,2′-bis(bromomethyl)biphenyl dissolved in $CH_3CN$ over a refluxing suspension of the appropriate pertosylated polyamine and an excess of $K_2CO_3$ in $CH_3CN$ yielded the pertosylated macrocycles **1**–**4**. The corresponding *N*-deprotected derivatives **5**–**8** were obtained after the treatment of **1**–**4** with HBr/AcOH or Na/Hg.




| R = Ts | R = H |
|---|---|
| **1:** n=1, m=1 (36%) | **5:** n=1, m=1 (33%) |
| **2:** n=2, m=1 (72%) | **6:** n=2, m=1 (48%) |
| **3**: n=2, m=2 (53%) | **7**: n=2, m=2 (40%) |
| **4:** n=2, m=3 (63%) | **8:** n=2, m=3 (53%) |

**Chart 1.**

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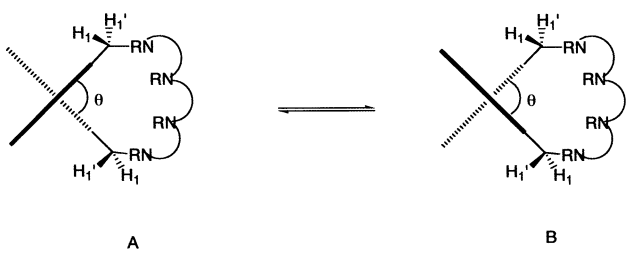
As it was mentioned previously, one of the most interesting features of 2,2′-biphenylene macrocycles is the dynamic properties associated with the rotation through the C–C bond that connects the two phenyl units. As depicted in Scheme 1, variation of the biphenyl dihedral angle ($\theta$) can result eventually in the exchange of enantiomeric conformers **A** and **B**. In favorable cases, such equilibrium can be monitored by variable temperature NMR experiments. For example, the slow (on the NMR time scale) exchange between **A** and **B** conformers results in non equivalent $^1$H NMR signals for benzylic protons labeled as $H_1$ and $H_1'$ in Scheme 1 (AB system), while a fast exchange would yield equivalent resonances for these protons ($A_2$ system).

As could be expected, the dynamic behavior detected for pertosylated macrocycles **1**–**4** by NMR ($CDCl_3$, 300 MHz, 298 K), is explained simply by the size of the macrocycles involved. As shown in Fig. 1, macrocycle **1** displays benzylic $^1$H NMR signals corresponding to an AB system and two doublets are observed ($J=13$ Hz, $\Delta\delta=1.1$ ppm). The $^1$H NMR of **2** and **3** also presents an AB system for the benzylic signals but the lower chemical shift difference detected reflects the faster exchange process that is taking place. Macrocycle **4** shows a singlet for the benzylic protons at 298 K indicating a fast exchange at this temperature.

When macrocycles **5**–**8** were studied by $^1$H NMR in $CDCl_3$ (300 MHz, 298 K), interesting information regarding their conformational flexibility was obtained by analysis of the above mentioned benzylic type protons (see Fig. 1).

For the smallest macrocycle **5**, which contains three ethylenic spacers, the spectrum shows two doublets ($J=13$ Hz, $\Delta\delta=0.26$ ppm) as a result of coupling between the non equivalent geminal protons in a situation analogous to that found for **1**. The appearance of these signals did not change upon heating to 333 K (just below the boiling point of chloroform). Reasonably, the equilibrium depicted in Scheme 1 is faster for larger macrocycles such as **6** and **7** as demonstrated by their NMR spectra. The benzylic signals of **6** (which presents an additional methylene group in the chain when compared to **5**) at 298 K are almost a singlet (coalescence temperature 304 K), while **7** (which contains three propylenic spacers) shows a singlet at that temperature (coalescence occurs at 263 K). However, the largest macrocycle **8**, containing one butylenic and




**Scheme 1.**

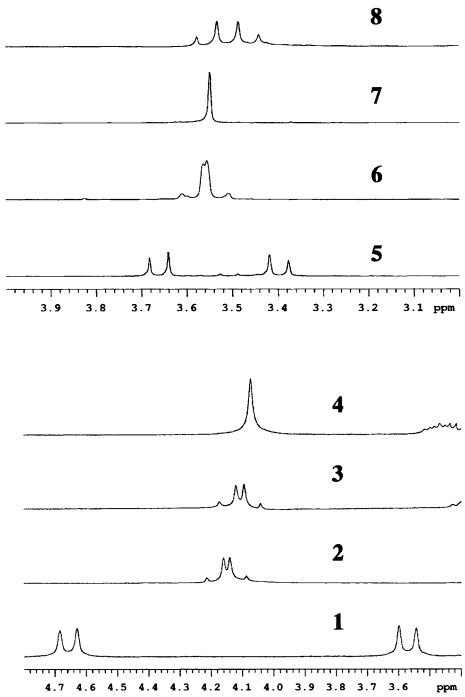



**Figure 1.** $^1$H NMR spectra (300 MHz, 298 K) of the benzylic protons of *N*-pertosylated compounds **1**–**4** and the corresponding *N*-deprotected derivative **5**–**8** in $CDCl_3$.

two propylenic spacers, did not show a singlet for the benzylic protons as expected but two doublets ($J=13$ Hz, $\Delta\delta=0.1$ ppm) which did not change upon heating to 333 K, a situation similar to that observed for macrocycle **5**.

This behavior is, at first sight, rather surprising but can be understood in terms on the role that intramolecular hydrogen bonding plays in the conformational flexibility of the studied macrocycles. As a matter of fact, when molecular dynamics calculations were carried out departing from the minimum energy structure found by extensive conformational search (MACROMODEL 7.0,[5] OPLS/AA, GB/SA simulation of chloroform as the solvent) it was found that macrocycle **8** presents a strong tendency to form an intramolecular H-bond between its central amino groups.

As illustrated in Table 1, 30% of the sampled structures during a 2000 ps simulation present a H-bond between the amino groups separated by a butylenic spacer. The study of macrocycle **7**, presenting only one methylene unit less than **8**, results in fewer H-bonded structures (19%) that also correspond to the interaction between central amino groups. For the smaller macrocycles **5** and **6** intramolecular H-bonding is found to be much less important.

The described calculations are in agreement with the $^1$H NMR spectra mentioned previously and indicate that, for a size of the polyamine chain large enough, the presence of a butylenic separator between two amino groups is a most favorable situation for intramolecular

**Table 1.** Percentages of intramolecularly H-bonded structures found in the Molecular Dynamics simulations for compounds **5**–**8**[a]

| Compound | % of H-bonded structures |
|---|---|
| **5** | 3[b] |
| **6** | 0 |
| **7** | 19[c] |
| **8** | 30[c] |

[a] OPLS/AA force-field, GB/SA simulation of solvent, simulation time = 2000 ps, 100 structures were sampled, H-bond presence was determined according to the standard cutoffs.
[b] H-bond between benzylic amino groups.
[c] H-bond between central amino groups.

H-bonding in these macrocycles. In order to illustrate graphically the notable effect that this constraint imposes to the conformational space of the macrocycles, a superimposition of the structures sampled during the molecular dynamics simulation for macrocycles **7** and **8** is shown in Fig. 2. It seems clear that this restricted mobility correlates with the spectroscopic data mentioned above.

More information can be obtained by a detailed analysis of the lowest energy structures obtained after extensive Monte Carlo conformational search. As it can be seen in Fig. 3, for both compounds **7** and **8** the most stable structure presents an intramolecular H-bond bridging the central amino groups. The H-bond in **8** is specially stable due to the formation of a seven-membered ring that permits an almost linear disposition of the three atoms involved, which, in addition, results in shorter bond distances that in the case of **7**. For the latter molecule, the corresponding six-membered cyclic disposition implies a H-bond disposition distorted from the ideal 180° angle.

Finally, when fully protonated receptors **5**–**8** were studied in $D_2O$, all the systems presented a $^1H$ NMR spectrum with an AB pattern for the benzylic signals.


**Figure 2.** Superimposition of 100 structures sampled during the Molecular Dynamics simulation carried out for compounds **7** and **8**.

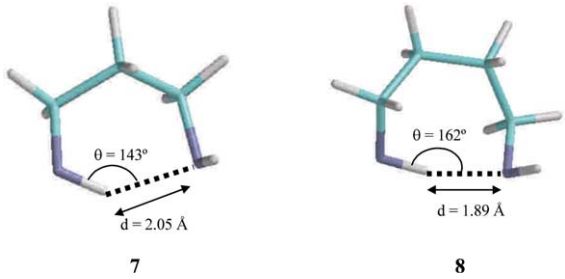



**Figure 3.** Conformations of the central propylenediamine unit of **7** and butylenediamine unit of **8** as found in the lowest energy structures obtained by molecular mechanics (OPLS/AA).

This can be explained due to the strong electrostatic repulsion in the would exist at the transition state for the exchange process depicted in Scheme 1 and the stiffening that protonation causes resulting in highly preorganized hosts.

## Acknowledgements

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