Complexation Behavior of a Highly Preorganized 7,7-Diphenylnorbornane-Derived Macrocycle: Towards the Design of Molecular Clocks

Antonio García Martínez,*[a] José Osío Barcina,*[a] María del Rosario Colorado Heras,[a] Álvaro de Fresno Cerezo,[a] and María del Rosario Torres Salvador[b]

Abstract: The syntheses of two new cyclophane hosts, **4** and **6**, are described. The main difference between them is the higher degree of preorganization of **4** as a consequence of the inclusion of the 7,7-diphenylnorbornane (DPN) subunit. The inner cavity of **4** adopts a belt-shaped structure, while **6** has a twisted geometry. In the solid state, the molecules of macrocycle **6** are stacked along an axis to form nanotubular structures. Compounds **4** and **6** form two of the strongest complexes between arene cyclophanes and Ag^+ reported up to date. The silver cation is located inside the cavity of the macrocycles. The stability of $\mathbf{4}\cdot Ag^+$ is considerably higher than that of $\mathbf{6}\cdot Ag^+$. The additional stabilization of $\mathbf{4}\cdot Ag^+$ is attributed to higher preorganization of macrocycle **4**. DNMR experiments as well as theoretical calculations carried out with $\mathbf{4}\cdot Ag^+$ show evidence of Ag^+-hopping between two different binding sites inside the macrocycle. This phenomenon could be the basis for the design of molecular clocks.

Keywords: diphenylnorbornane · host–guest systems · molecular clock · pi interactions · silver

Introduction

The design of supramolecular assemblies, in which one of the subunits moves or oscillates in a very regular and precise way in relation to another, could be the basis for the construction of molecular clocks.[1] These molecular machines[2] should be added to a list that already includes chemical [1, 3] and atomic clocks.[4]

On the other hand, one of the main areas of interest in supramolecular chemistry is the study of host–guest interactions, which are the basis of molecular recognition.[5–9] A large number of different structures have been used as synthetic hosts for both ionic (cationic and anionic) and neutral guests, whereby macrocyclic structures are the most widely studied receptors.[5–7]

Two important factors play a fundamental role in determining the stability of host–guest complexes: complementarity between the associating partners and preorganization.[9–11] This last principle is of basic importance, since placement of the donor groups of the host in exactly correct positions normally leads to higher binding constants. If transition metals act as guests, association is favored if the donor groups of the host are directed towards the d and f orbitals of the guest involved in the formation of the complex.[12]

A considerable number of complexes between simple aromatic substrates and metallic cations, such as Ag^+[13] and others,[14] are known. Usually, the stability of this type of complex increases considerably if the structure of the host offers several bindings sites and some degree of preorganization.[14c, 15–17]

In this paper, we describe the differences in complexation behavior of macrocyclic hosts when a highly preorganized subunit of 7,7-diphenylnorbornane instead of diphenylmethane is incorporated into the structure of the receptor.

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Results and Discussion

Diphenylmethane (DPM, **1**) (Scheme 1) derivatives are used very often in the design of cyclophane receptors (diphenylmethanophanes).[18] These building blocks can be found in the architecture of a large series of macrocycles,[19] catenanes,[20] rotaxanes,[21] cage receptors,[22] crown ethers,[23] and other hosts including open-chain receptors[24] and chiral supramolecular catalysts.[25] The benzene rings of DPM provide an

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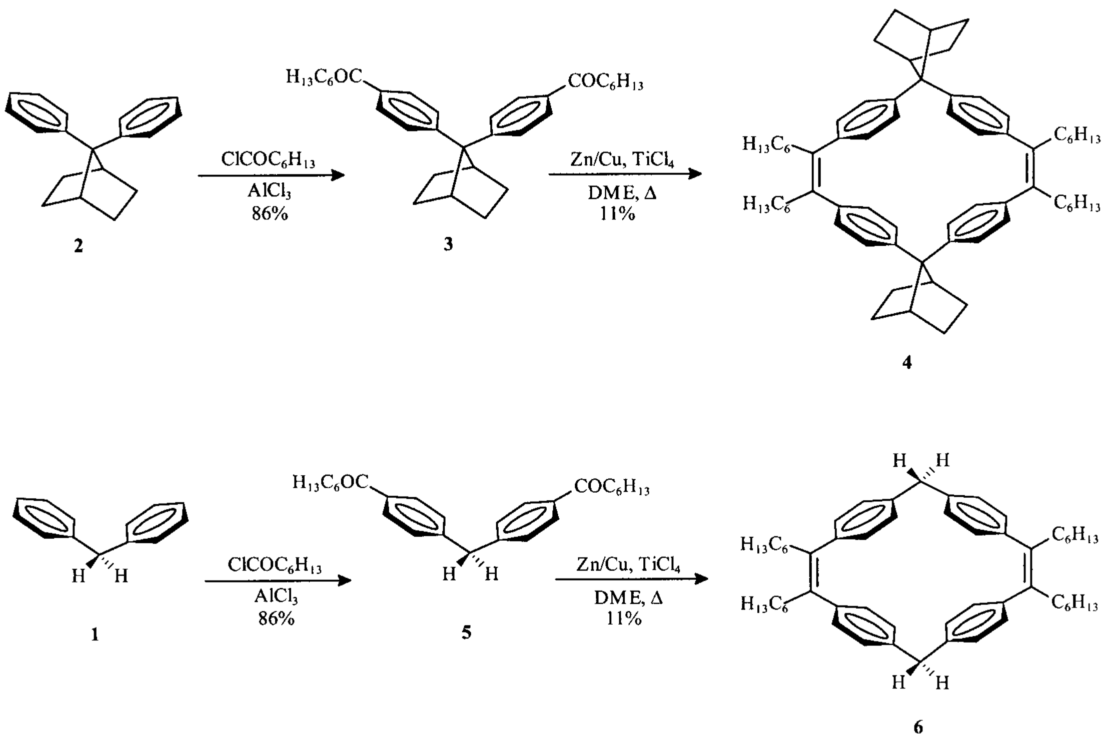

Scheme 1. Synthesis of macrocycles **4** and **6**.

electron-rich inclusion cavity with a depth of ≈650 pm and an angle of ≈110°,[18] which favors the complexation of the guest. Evidently, a face-to-face arrangement of the phenyl rings may facilitate this process. However, the DPM moiety is not rigid, and this factor diminishes the preorganization of the DPM-derived hosts. Considering the well-known principle that "the smaller the changes in organization of host, guest, and solvent required for complexation are, the stronger the binding will be", it can be easily concluded that "flexibility is the enemy" in these systems.[18]

In a recent publication,[26] we have shown that inclusion of 7,7-diphenylnorbornane (DPN, **2**)[27] (Scheme 1) in the structure of open-chain hosts considerably increases the degree of preorganization in comparison to DPM-derived receptors. This difference in preorganization has an important influence on the determination of the edge-to-face aromatic interaction, estimated by chemical double-mutant cycles.[26]

The high preorganization of DPN is based on the fact that the *exo*-hydrogen atoms of the norbornane framework hinder the rotation of the aryl rings and, as a consequence, the face-to-face conformation is the most stable in DPN and its derivatives. This situation is, to our knowledge, unique, since in DPM compounds the most stable conformation is the propeller arrangement and the mobility in DPM is higher than in DPN. The rotational barrier in DPM,[28] according to the B3LYP/6-31G* method,[28b] is 2.7 kJ mol^{-1}. In 1,1-diphenylcyclohexane (DPC), one of the most widely used DPM-derivatives, a rotational barrier of 5.3 kJ mol^{-1} has been calculated according to ab initio RHF/STO-3G method. In DPC, both perpendicular and propeller conformations are more stable than the face-to-face arrangement.[26] However, in DPN, the face-to-face conformation is the most stable, and a barrier to rotation of ≈12.5 kcal mol^{-1} (52 kJ mol^{-1}) has been estimated.[27] For this reason, DPN is a suitable model compound for the study of aromatic interactions,[26, 29] for the synthesis of homoconjugated polymers,[30] and the design of homoconjugated chromophores with nonlinear optic (NLO) properties.[31]

In order to explore the influence that DPN may exert on the preorganization of macrocyclic receptors, we have synthesized macrocycles **4** and **6** (Scheme 1) and compared their relative behavior with respect to complexation of a silver cation.

Synthesis and spectroscopic properties of macrocycles 4 and 6: The synthesis of macrocycles **4** and **6** was carried out by means of a McMurry cyclization following the procedure described in the literature for the preparation of analogous macrocyclic[2.1.2.1]paracyclophanes (Scheme 1).[32] Alkyl chains were introduced into the structure of both receptors to increase their solubility.

Significant differences are observed in the ^{1}H NMR spectra of **4** and **6**. The aromatic region of **4** shows a AA′XX′ system at $\delta = 7.00$ and 6.70 ppm, shifted upfield because of the rigid cofacial arrangement of the aromatic rings induced by the norbornane structure. However, the spectrum of **6** shows only one signal, centered at $\delta = 6.78$. Although no appreciable variation of this signal is observed upon cooling to −60 °C, mobility of the aryl rings of **6** is probably the responsible of the differences observed between the ^{1}H NMR spectra.

Crystal structure of 4 and 6: The X-ray crystal structures of **4**[33] and **6**[34] reveal some interesting features about the geometry of these receptors. The structure of **4** is shown in Figure 1. As expected, there is almost no twisting in the aromatic inner core of the macrocycle, resulting in a highly

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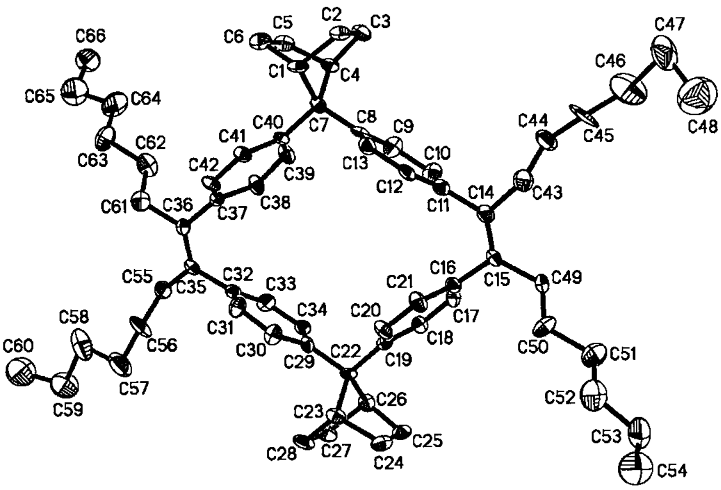


Figure 1. ORTEP diagram of macrocycle **4** (hydrogen atoms are omitted for clarity).

symmetric, belt-shaped face-to-face structure of the four aromatic rings involved. The torsional angle C40-C7-C8-C13 is only 5°, and deviation from coplanarity between the arenes of the stilbene subunit is 8°. The size of the cavity of this irregular hexagon is given by the distances C7–C22 = 7.99 Å and C14–C36 = 9.56 Å.

Figure 2 shows the X-ray structure of **6**. The torsional angles between the aromatic rings of the DPM subunit C7-C6-C24A-C25A is 49.2°, considerably higher than in **4** (5°). However, considering the stilbene subunit, the deviation from planarity between the aryl groups is only 6°, very similar to that observed for **4** (8°). Hence, as a result of the different arrangement around the DPM subunit, the inner core structure of **6** is not belt-shaped but distorted. In this case, the distances C24–C24A and C1–C2A are 7.67 Å and 9.72 Å, respectively. Therefore, the inclusion of the norbornane framework in the structure of macrocycle **4** has a significant influence on the shape of the inner core of the host. Considering that face-to-face arrangement of the aryl rings of diphenylmethanophanes facilitates the complexation of the guest, it is to be expected that the rigid and preorganized structure of **4**, with the donor group sites in their optimal positions, will lead to improved complexation behavior in this case.

In addition, another striking difference between the crystal structures of **4** and **6** can be outlined by comparing their crystal packing. As can be seen in Figure 3, the molecules of **6** in the crystal are stacked along one axis to form tubular structures that resemble the discotic mesophases of liquid crystals.[35] The resulting three-dimensional structure is formed by nanotubes separated by the intercalated hexyl chains. These types of crystalline aggregates are very interesting, since the design of artificial supramolecular channels composed of organic compounds is actually an important field on account of their potential use as one-dimensional materials with size-selective transporting properties.[36] In contrast, the crystal packing of **4** shows a different pattern, and the molecules are not in a tubular arrangement, probably as a result of the steric hindrance of the norbornane framework.

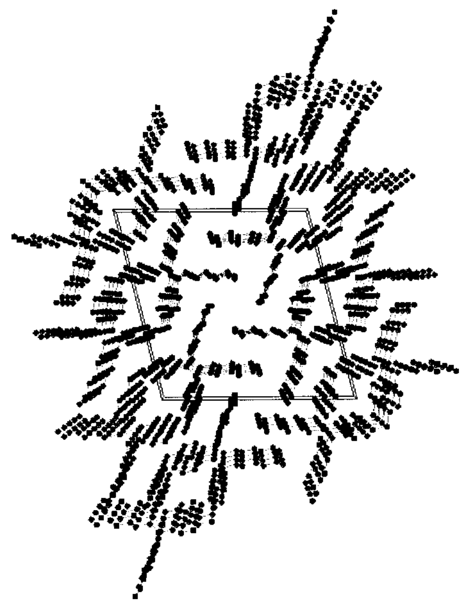


Figure 3. Crystal packing of macrocycle **6**.

Complexation behavior: The structures of macrocycles **4** and **6** can be considered to be the sum of two different subunits: DPN (or DPM) and (*Z*)-stilbene. It is known that cofacial (*Z*)-stilbene is able to form a stable 1:1 silver complex ($7\cdot Ag^{+}$, Figure 4), in which the metal ion is located between the cleft formed by the aromatic rings.[15e] On the other hand, the complexation of diphenyl-

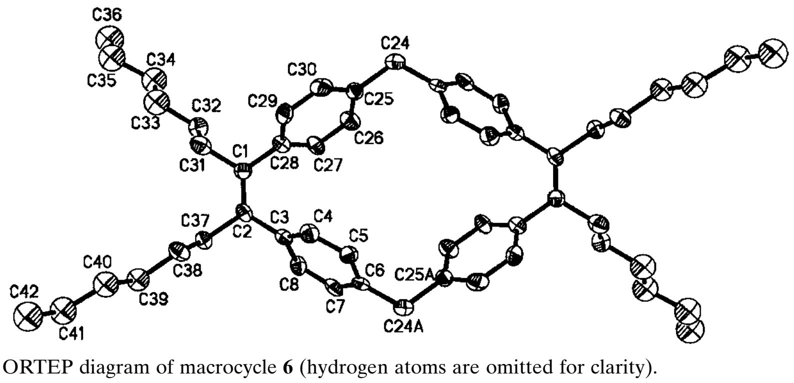


Figure 2. ORTEP diagram of macrocycle **6** (hydrogen atoms are omitted for clarity).

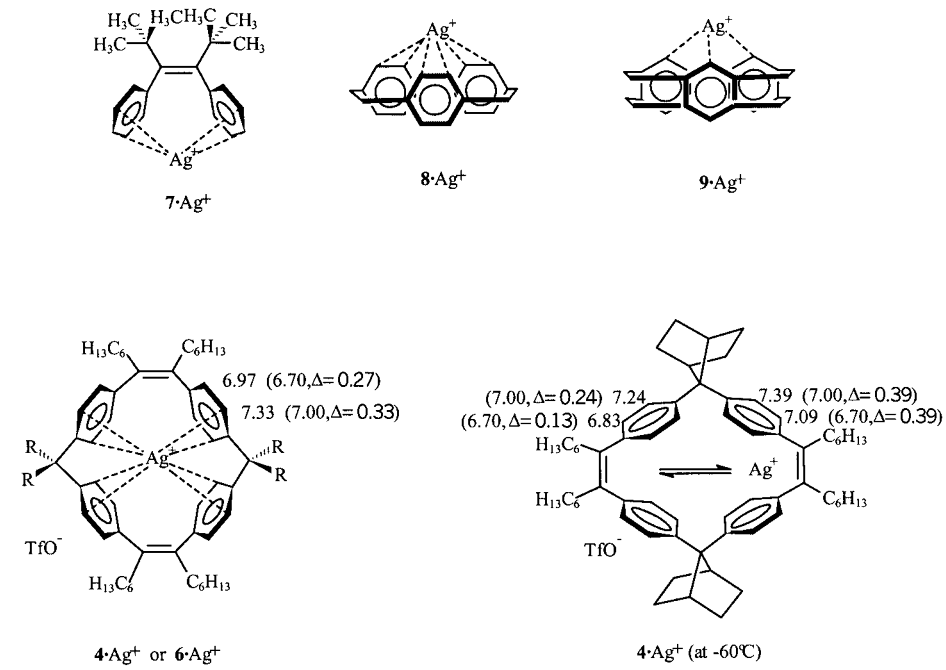


Figure 4. Silver complexes $\mathbf{4}\cdot Ag^+$, $\mathbf{6}\cdot Ag^+$, $\mathbf{7}\cdot Ag^+$, $\mathbf{8}\cdot Ag^+$, $\mathbf{9}\cdot Ag^+$, and $\mathbf{4}\cdot Ag^+$ at -60°C, including the ^{1}H NMR signals (δ, $\Delta\delta$ [ppm]) of **4** (in brackets) and $\mathbf{4}\cdot Ag^+$.

methane with a silver cation has also been studied.[13g] In this case, DPM forms a complex with silver tetrafluoroborate in the molar ratio $AgBF_4$:DPM = 1:2. This result seems to indicate that the complex is formed between the silver ion and the phenyl rings of two different DPM molecules, because the cavity between the aromatic groups in DPM is too small to allow the complexation with the metal ion. This idea is confirmed by the fact that we were not able to obtain complexes of DPN and AgTfO. In DPN, the cavity size is evidently too small, and the other face of the phenyl rings is sterically blocked by the norbornane skeleton. Therefore, **4** and **6** could form silver complexes with the metal ion bonded to the (*Z*)-stilbene subunits, as in complex $\mathbf{7}\cdot Ag^+$.

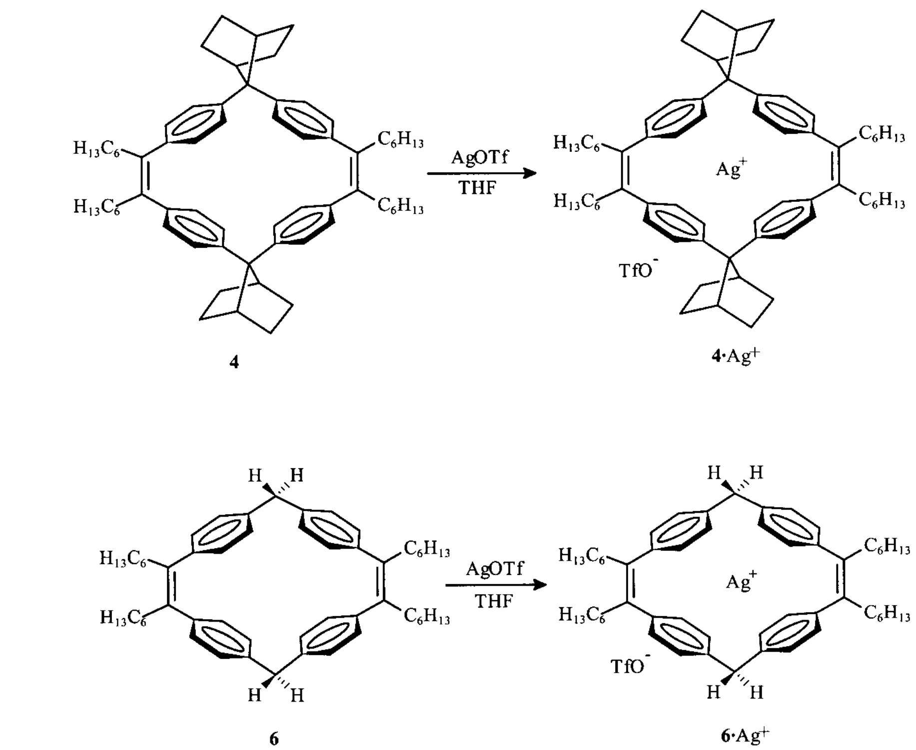
The stochiometric mixture of **4** and **6** with AgTfO in THF leads to the formation of the corresponding silver complexes [Eqs. (1) and (2), Scheme 2], as is clearly revealed by ^{1}H and ^{13}C NMR spectroscopy (Tables 1 and 2).

$$\mathbf{4} + Ag^+TfO^- \rightleftharpoons \mathbf{4}\cdot Ag^+ \quad (1)$$

$$\mathbf{6} + Ag^+TfO^- \rightleftharpoons \mathbf{6}\cdot Ag^+ \quad (2)$$

The spectra ($CDCl_3$) of the neutral hosts and the complexes are similar; however, significant changes are observed in the peaks of protons and carbon atoms involved in the complexation (Tables 1 and 2). The data of cofacial stilbene **7** and its silver complex $\mathbf{7}\cdot Ag^+$ (Figure 4) are also included in Tables 1 and 2 for comparison. No changes in the spectra were detected if higher amounts of AgOTf were added during the synthesis of the complexes. On the other hand, the excess silver salt remained insoluble, showing that these receptors are able to bind one silver ion only. The signals of the corresponding uncomplexed macrocycles are not observed, which indicates that the equilibrium between each host and the silver ion is completely shifted toward the complex.

We were not able to obtain single crystals of $\mathbf{4}\cdot Ag^+$ and $\mathbf{6}\cdot Ag^+$ for X-ray crystal structure analysis, but some conclusions about the geometry of these complexes can be reached from the NMR data. ^{1}H NMR of $\mathbf{4}\cdot Ag^+$ shows that the aromatic protons are shifted downfield relative to those of **4**. The shift is slightly higher for H5 than for H6 ($\Delta\delta = 0.33$ vs 0.27 ppm). The same effect is observed in the case of $\mathbf{6}\cdot Ag^+$; however, in this case, the variation in the displacement of the signals is not so pronounced compared to the variations observed for $\mathbf{4}\cdot$



Scheme 2. Synthesis of silver complexes $\mathbf{4}\cdot Ag^+$ and $\mathbf{6}\cdot Ag^+$.

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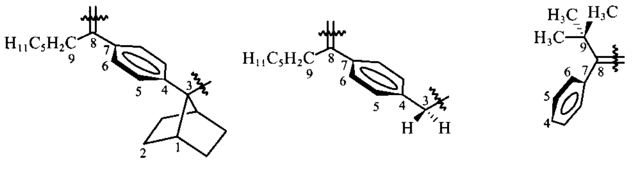
Table 1. ^{1}H NMR ($CDCl_3$) shifts of macrocycles **4**, **6**, and **7** and silver complexes **4** · Ag^+, **6** · Ag^+, and **7** · Ag^+.



4 or **4**·Ag^+ **6** or **6**·Ag^+ **7** or **7**·Ag^+

	H1	H3	H4	H5	H6	H9
4	2.79	–	–	7.00	6.70	2.33
4 · Ag^+	2.98	–	–	7.33	6.97	2.29
$\Delta\delta$	0.19	–	–	0.33	0.27	– 0.04
6	–	3.71	–	6.78	6.78	2.56
6 · Ag^+	–	3.76	–	7.04	6.94	2.51
$\Delta\delta$	–	0.05	–	0.26	0.16	– 0.05
7	–	–	6.77	6.87	6.67	
7 · Ag^+	–	–	7.13	7.20	6.84	
$\Delta\delta$	–	–	0.33	0.39	0.27	

Table 2. ^{13}C NMR ($CDCl_3$) shifts of macrocycles **4**, **6**, and **7** and silver complexes **4** · Ag^+, **6** · Ag^+, and **7** · Ag^+.

	C1	C2	C3	C4	C5	C6	C7	C8	C9
4	41.4	28.1	63.5	142.7	128.8	126.2	138.3	140.5	34.6
4 · Ag^+	42.1	27.9	64.2	144.4	127.7	126.7	138.1	141.9	34.5
$\Delta\delta$	0.7	– 0.2	0.7	1.7	– 1.1	0.5	– 0.2	1.4	– 0.1
6	–	–	41.2	141.0	127.8	129.7	137.8	138.8	34.0
6 · Ag^+	–	–	40.8	142.3	125.5	130.8	138.2	141.9	33.8
$\Delta\delta$	–	–	– 0.4	1.3	– 2.3	1.1	0.4	3.1	– 0.2
7	–	–	–	123.9	126.2	130.0	146.9	147.4	–
7 · Ag^+	–	–	–	119.1	124.0	131.2	147.9	148.2	–
$\Delta\delta$	–	–	–	– 4.7	– 2.2	1.2	1.0	0.8	–

Ag^+ ($\Delta\delta = 0.26$ vs 0.33 ppm for H5; 0.16 vs 0.27 ppm for H6). It is noteworthy that the downfield shift of the ^{1}H NMR signals of the aromatic protons H5 and H6 observed in **4** · Ag^+ upon complexation with the silver ion, are nearly the same than those described for **7** · Ag^+ ($\Delta\delta = 0.33$ vs 0.39 ppm for H5; 0.27 ppm for H6 in both cases, Figure 4). This fact clearly points to similar geometries of the corresponding silver complexes or, in other words, the silver cation in **4** · Ag^+ is placed in an equivalent position to the one adopted by this ion in **7** · Ag^+. Therefore, the silver cation in both **4** · Ag^+ and **6** · Ag^+ is located inside the cavities of the macrocycles, resulting in a highly symmetrical structure in the case of **4** · Ag^+, as revealed by the simplicity of the ^{1}H NMR spectrum.

Taking into account the results of the X-ray analysis of **4** and **6** as well as the remarkable differences between the ^{1}H NMR spectra of the neutral hosts, and considering that the spectra of complexes **4** · Ag^+ and **6** · Ag^+ are more similar than those of the corresponding neutral macrocycles **4** and **6**, it can be concluded that during complexation, the aryl rings of **6** adopt a conformation similar to that adopted by **4**, more favorable for the coordination of the silver ion, but with the final arrangement of the aromatic rings in **6** · Ag^+ not completely in the face-to-face arrangement, as in **4** · Ag^+.

^{13}C NMR spectra provide information about the binding sites of silver ion in the complexes. It has been reported[15e] that in **7** · Ag^+ (Figure 4), the metal is bound mainly to the *para* (C4) positions of the phenyl rings. The *meta* (C5) positions also have an important participation in the complexation (Table 2). However, this situation differs from that found for **4** · Ag^+ and **6** · Ag^+, in which the highest upfield shift is found for C5, while C4 shows a downfield shift. The C6 atom, not participating in the complexation, shows significant downfield shifts in **4** · Ag^+, **6** · Ag^+, and **7** · Ag^+. This indicates that complexation takes place through C5 of the phenyl rings in both macrocycles, but not through C4 (Figure 4).

All this information and the simplicity of the NMR spectra points to a very symmetrical geometry in which the silver ion is placed in the center of the internal cavity of the macrocycles, bound mainly to the C5 carbon atoms of the aryl rings (Figure 4). The main differences between **4** · Ag^+ and **6** · Ag^+ is the conformation adopted by the aryl rings, coplanar in the case of the preorganized, belt-shaped complex **4** · Ag^+, and somewhat twisted in the case of **6** · Ag^+.

Additional important information about the structure of **4** · Ag^+ arises from the low-temperature NMR spectra of **4** · Ag^+. On going from room temperature to $-60\,^{\circ}$C, the signals at $\delta = 7.33$ and 6.97 ppm gradually broaden and finally separate into four new peaks of equal intensity: two signals at $\delta = 7.39$ and 7.24 ppm, which result from the separation of the peak at $\delta = 7.33$ ppm, and two signals at $\delta = 7.09$ and 6.83 ppm from the peak at $\delta = 6.97$ ppm. Coalescence occurs at $-10\,^{\circ}$C, and a barrier of 12.6 kcal mol^{-1} is obtained from this data. Although, in principle, several different situations could be responsible for this behavior,[37] the best explanation is a situation in which the silver cation is placed inside the cavity of the macrocycle, but with a rapid Ag^+-hopping between two different binding sites of the belt-shaped host taking place (Figure 4). This is the first example of metal-hopping in neutral aromatic cyclophanes, a phenomenon that has been the subject of great interest in supramolecular chemistry.[38] The hopping pathway is the one depicted in Figure 4, in which the metal ion hops "between the two (*Z*)-stilbene subunits" and not "between the two DPN subunits", with a hopping barrier of 12.6 kcal mol^{-1}, since the comparison of the ^{1}H NMR spectra of **4** and **4** · Ag^+ (at low temperature) shows that the proton with the lower downfield shift, that is, the proton that remains more separated from the silver cation in the frozen complex, at $-60\,^{\circ}$C, is one of the H6 protons ($\Delta\delta = 0.13$ vs 0.39 ppm, 0.24 and 0.39 ppm, Table 1). A different motion of Ag^+ would lead to a lower downfield shift of one of the H5 protons (motion "between the DPN subunits") or to a more complicated aromatic region at low temperature. The proposed Ag^+-hopping also explains the downfield shift of the H5 and H6 of one of the (*Z*)-stilbene subunits, as the metal ion approximates, and the upfield shift of the other H5 and H6 protons of the (*Z*)-stilbene subunit, more separated from the silver cation, when the ^{1}H NMR spectra of **4** · Ag^+ at 25 °C and $-60\,^{\circ}$C are compared. It is interesting that some peak broadening has been observed in complex **7** · Ag^+ upon lowering the temperature ($T_c = -50\,^{\circ}$C).[15e]

We performed computations in order to gain information about the structure of **4** · Ag^+ and confirm the results obtained by NMR spectroscopy. It has been shown that HF/3-21G* and B3LYP/3-21G* calculations are able to reproduce the geom-

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etries of cyclophane · Ag^+ complexes reasonably well, with omission of the triflate anion in the computation model.[39] The calculated structures are in agreement with those obtained by X-ray structural analysis.

In this study, we used the Gaussian 98 series of programs.[40a] In our case, in order to reduce CPU time, the computations on complex **4** · Ag^+ were carried out starting from the structure of **6**, without the alkyl chains, and with interplanar angles of the phenyl rings of the diphenylmethane moiety frozen at 90° to simulate cofacial arrangement of **4**. In order to find the global minimum, starting structures with the silver ion located inside the diphenylmethane and stilbene subunits were minimized with the RHF/STO-3G method and thereupon with the DFT B3LYP/3-21G method, which includes some aspects of electron correlation.[40b,c] The resulting global minimum energy structure has C_s symmetry (Figure 5). This C_s structure has a dihapto (η^2) interaction, with an Ag–C bond between the metal ion and the C5 carbon atom of each phenyl ring of the (*Z*)-stilbene subunit.

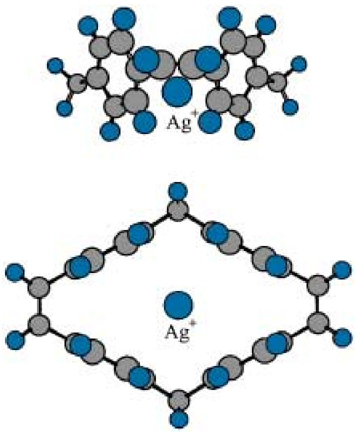

Figure 5. Global minimum energy, C_s symmetry (top), and transition state, D_{2h} symmetry (bottom), of complex **4** · Ag^+ according to the B3LYP/3–21G method. Top: View along the *x* axis. Bottom: View along the *z* axis.

According to these results, the low-temperature ^{1}H NMR spectra should contain eight signals in the aromatic region. However, only four peaks are observed at -60 °C; this indicates a fast racemization of the enantiomeric C_s structures through a C_{2v} transition state (Figure 6). The activation energy between the C_s and C_{2v} structures, according to B3LYP/3-21G calculations, is only 2.38 kcal mol^{-1}. This small energy value

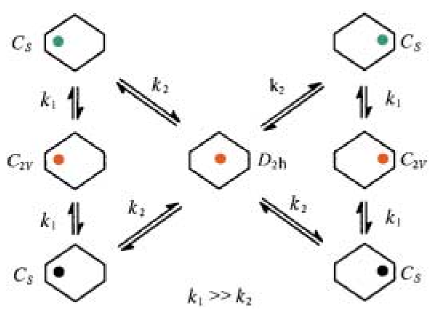

Figure 6. Limiting structures of complex **4** · Ag^+ showing the oscillation of the silver ion inside the cavity of the cyclophane: Ag^+ outside the plane (black point), Ag^+ in the plane (red point) and Ag^+ behind the plane (green point).

explains why only four signals are observable in the ^{1}H NMR spectrum at -60 °C.

On the other hand, the activation energy between the C_s and D_{2h} structures is 0.51 kcal mol^{-1} according to RHF/3-21G and 6.09 kcal mol^{-1} according to B3LYP/3-21G calculations. The most accurate result is that obtained by the DFT method, the highest level of computation used in this study. The difference between this value and the experimental barrier obtained by DNMR spectroscopy (12.6 kcal mol^{-1}) can be attributed to the influence of the counterion (TfO^-) of the complex, which hinders the oscillation of the metal ion.

We have also studied experimentally the relative stability of complexes **4** · Ag^+ and **6** · Ag^+. The differences observed in the structures of **4** and **6** have very important effects in the binding constants of the corresponding silver complexes, as shown by competition experiments: the same final situation is reached starting both from equimolecular mixtures of **4** and **6** · Ag^+ or **4** · Ag^+ and **6** [Eq. (3)].

$$\mathbf{4} + \mathbf{6}\cdot Ag^+ \rightleftharpoons \mathbf{4}\cdot Ag^+ + \mathbf{6} \quad (3)$$

^{1}H NMR ($CDCl_3$) analysis of these mixtures revealed the presence of signals of complex **4** · Ag^+ and uncomplexed macrocycle **6** only (no evidence of **6** · Ag^+ and uncomplexed **4**). This indicates that equilibrium in Equation (3) is shifted to the right and that complex **4** · Ag^+ is thermodynamically much more stable than **6** · Ag^+. Therefore, the silver cation is bound more strongly to macrocycle **4** than to **6**. The additional stabilization of **4** · Ag^+ is attributed to the higher degree of preorganization and the resulting belt-shaped inner core of **4**. The lack of signals corresponding to **4** and **6** · Ag^+ in the ^{1}H NMR spectra of the mixtures shows that **4** · Ag^+ is, at least, 10^2–10^4 times more stable than **6** · Ag^+ (assuming that the amount of **4** and **6** · Ag^+ in the equilibrium is less than 5–1 %).

Accurate determination of the association constants (k_a) of **4** · Ag^+ and **6** · Ag^+ was not possible: their NMR spectra do not show signals of complexes and cyclophanes separately on account of a rapid equilibrium on the NMR timescale, or because the silver cation is almost completely complexed by **4** and **6**, and the small amount of the hosts in the equilibria is not enough to be detected by the NMR technique. As no appreciable changes in the NMR spectra were observed upon addition of excess AgTfO, it can be concluded that at least 95 % of **4** and **6** form complexes with the silver ion.[14e]

On the other hand, the binding constant of complex **7** · Ag^+ ($k_a = 3700 \pm 300$), one of the most stable complexes between a silver ion and simple arenes described to date, have been measured on the base of the variations of chemical shifts in the ^{1}H NMR spectra of samples of **7** · Ag^+ at different concentrations.[15e] In our case, similar treatment of solutions of **4** · Ag^+ and **6** · Ag^+ in a range of concentrations did not show significant changes in the ^{1}H NMR shifts. This is the situation that is expected with very stable complexes ($k_a > 10^5\,\text{M}^{-1}$) in which the silver cation is almost completely complexed by the host,[41, 42] and clearly shows that, in our complexes, the silver cation is much more strongly bound to **4** and **6** than to **7** (and also the weaker **8** · Ag^+ and **9** · Ag^+, with $k_a = 195$ and $81\,\text{M}^{-1}$ respectively, Figure 4).[15e–g]

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Conclusion

In this paper, we describe the synthesis of two new cyclophane hosts, **4** and **6**. The main difference between them is the higher degree of preorganization of **4** as a result of the inclusion of the 7,7-diphenylnorbornane (DPN) subunit in its structure. X-ray structural analysis shows that the inner cavity of **4** adopts a cofacial belt-shaped structure, while **6** shows a twisted geometry. In the solid state, the molecules of macrocycle **6** are stacked along an axis to form very interesting tubular (nanotubular) structures.

The ability of **4** and **6** to complex silver ions has been tested. The central inner core of the hosts is big enough to allow the incorporation of the silver ion inside the cyclophanes. As a result, these macrocycles form two of the strongest complexes between arene cyclophanes and Ag^+ reported to date. The silver cation is placed inside the cavity of the macrocycle, not outside as in other cyclophane · Ag^+ complexes described in the literature.[15, 39, 43] The NMR spectra of complexes **4** · Ag^+ and **6** · Ag^+ are more similar than those of the neutral hosts **4** and **6**, indicating that, upon complexation, the macrocycles adopt almost the same conformation, although in the case of **6** · Ag^+ it is not as cofacial as in **4** · Ag^+.

The stability of **4** · Ag^+ is considerably higher (by a factor of at least $10^2 - 10^4$) than that of **6** · Ag^+. The additional stabilization of **4** · Ag^+ is attributed to the higher preorganization of macrocycle **4** in comparison to **6**. In view of these results, we consider that DPN could find wide application in the design of preorganized supramolecular structures, and should be used instead of other diphenylmethane derivatives.[26, 44]

DNMR experiments carried out with **4** · Ag^+ show evidence of Ag^+-hopping between two different binding sites of the macrocycle, with a barrier of 12.6 kcal mol^{-1}. To the best of our knowledge, this is the first example of this phenomenon described for a complex formed by a neutral arene cyclophane and a metal cation. We believe that these findings are important, since they may contribute to the understanding of cation – π interactions, molecular recognition, or metal transport in biological and artificial systems, and find applications in supramolecular chemistry and areas such as selective recognition of metal cations, design of ion-selective membranes, electrical conductivity of metal complexes, etc. One of the applications based on the regular periodic motion of the silver cation could be the design of molecular clocks. According to a clock based on complex **4** · Ag^+, a second could be defined as the time needed for 371 oscillations of the silver cation inside the cyclophane cavity. Further work on the complexation ability of DPN-phanes and the structure of the corresponding complexes is actually under way.

Experimental Section

7,7-Diphenylnorbornane[29, 30] and macrocycles **4** and **6**[32] were obtained following procedures described in the literature. A standard procedure was used to prepare complexes **4** · Ag^+ and **6** · Ag^+.[15e]

General procedure for the synthesis of cyclophanes 4 and 6: Titanium tetrachloride (1.42 mL, 12.90 mmol) was added to dimethoxyethane (DME, 150 mL) at 0°C, under an argon atmosphere. After 10 min, a Zn/Cu couple (1.69 g, 25.8 mmol) was added, and the mixture was refluxed for 2 h. A solution of the corresponding diketone (**3** or **5**, 0.69 mmol) in DME (30 mL) was slowly added to the blue-violet solution over a period of 24 h. After refluxing for 12 h, saturated $NaHCO_3$ solution (25 mL) was added to the cooled reaction mixture. The precipitate formed during the addition was filtered and redissolved in 10% HCl. Both solutions were then extracted with diethyl ether (3 × 50 mL). The organic solution was washed with water (1 × 50 mL) and dried over $MgSO_4$. After evaporation of the solvent, the corresponding macrocycle was purified by successive chromatography (silica gel/hexane) and recrystallization.

1,2,16,17-Tetrahexyl-9,24-(1,4-cyclohexadiyl)[2.1.2.1]-paracyclophane-1,16-diene (4): M.p. 200.0 – 202.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.99 (d, 8H, J = 8.1), 6.68 (d, 8H, J = 8.1), 2.90 – 2.80 (m, 4H), 2.30 – 2.20 (m, 8H), 1.55 – 1.40 (m, 8H), 1.35 – 1.05 (m, 40H), 0.90 – 0.75 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 142.7, 140.5, 138.3, 128.8, 126.2, 63.5, 42.1, 34.6, 31.7, 29.2, 28.6, 28.1, 22.5, 14.1 ppm; MS (60 eV, EI): m/z (%): 880 (100) $[M]^+$, 865 (10), 809 (40).

1,2,16,17-Tetrahexyl-[2.1.2.1]paracyclophane-1,16-diene (6): M.p. 151.2 – 153.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.77 (s, 16H), 3.70 (s, 4H), 2.62 – 2.50 (m, 8H), 1.42 – 1.20 (m, 32H), 0.95 – 0.80 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 141.0, 38.8, 137.8, 129.7, 127.8, 41.2, 34.1, 31.8, 29.3, 28.6, 22.7, 14.1 ppm; MS (60 eV, EI): m/z (%): 720 (100) $[M]^+$, 705 (5).

General procedure for the synthesis of silver complexes 4 · Ag^+ and 6 · Ag^+: In the absence of light, silver triflate (8 mg, 0.03 mmol) was added to a solution of the corresponding cyclophane (0.03 mmol) in anhydrous THF (20 mL) under an argon atmosphere. After stirring for 30 min, the solvent was evaporated, the residue was dissolved in $CHCl_3$ (20 mL), and the resulting solution was filtered. Evaporation of the solvent gave the corresponding silver complex in quantitative yield.

Complex 4 · Ag^+: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.32 (d, 8H, J = 7.5), 6.96 (d, 8H, J = 7.2), 3.00 – 2.90 (m, 4H), 2.35 – 2.25 (m, 8H), 1.50 – 1.40 (m, 8H), 1.35 – 1.05 (m, 40H), 0.95 – 0.80 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 144.4, 141.9, 138.1, 127.7, 126.7, 64.2 (C_7), 41.4, 34.5, 31.6, 29.2, 28.0, 27.9, 22.5, 14.0 ppm.

Complex 6 · Ag^+: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.03 (d, 8H, J = 7.7), 6.93(d, 8H, J = 7.7), 3.76 (s, 4H), 2.55 – 2.45 (m, 8H), 1.40 – 1.20 (m, 32H), 0.95 – 0.80 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 142.3, 141.9, 138.2, 130.8, 125.6, 40.8, 33.8, 31.7, 29.2, 28.3, 22.6, 14.1 ppm.

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[33] X-ray data collection and crystal structure determination of compound **4**: The data collection was carried out on a Bruker Smart CCD diffractometer, $Mo_{K\alpha}$ radiation, graphite monochromator. Crystal data: $M_r = 881.36$, poor crystal, colorless, prismatic, size $0.49 \times 0.47 \times 0.29$ mm^3, monoclinic, $P2_1$, $a = 17.170(2)$, $b = 12.059(1)$, $c = 13.877(1)$ Å, $\beta = 95.193(3)°$, $V = 2861.5(4)$ Å^{-3}, $Z = 2$, $\rho =$

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1.023 $Mg m^{-3}$, $\mu = 0.057$ mm^{-1}, $F(000) = 968$, 18763 reflections collected, independent reflections 7459 [$R(\text{int}) = 0.023$], 4835 observed. Final refinement including 499 parameters, and 19 restraints, converged to $R = 0.089$ for reflections observed and $wR = 0.289$ for all reflections.

[34] X-ray data collection and crystal structure determination of compound **6**: The crystal was mounted on an Enraf-Nonius CAD4 diffractometer, $Mo_{K\alpha}$ radiation, graphite monochromator. Crystal data: $M_r = 721.12$, poor crystal, colorless, thin plate, size $0.4 \times 0.15 \times 0.07$ mm^3, monoclinic, $C2$, $a = 21.281(5)$, $b = 5.545(1)$, $c = 20.858(3)$ Å, $\beta = 104.02(2)°$, $V = 2387.8(9)$ Å^{-3}, $Z = 2$, $\rho = 1.003$ $Mg m^{-3}$, $\mu = 0.056$ mm^{-1}, $F(000) = 792$, 1613 reflections collected, 1562 independent reflections [$R(\text{int}) = 0.023$], 658 observed. Final refinement including 196 parameters and 13 restraints, converged to $R = 0.085$ for reflections observed and $wR = 0.332$ (all data). Both structures **4** and **6** were solved by direct methods and refined using SHELXL-97 software. All non-hydrogen atoms were refined with anisotropic thermal parameter, except the final four atoms of the chains which have been refined fist two cycles isotropically (compound **6**) or anisotropically (compound **4**) and then fixed by using geometrical restraints and variable common carbon – carbon distances. Hydrogen atoms were generated in idealized positions, riding on the carrier atoms. CCDC-190267 (compound **6**) and CCDC-190268 (compound **4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336033; or deposit@ccdc.cam.uk).

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[37] In principle, four different equilibria could explain the coalescence of the ^1H NMR signals: a) metal hopping between two different binding sites placed inside the macrocycle, b) an equilibrium between **4** and **4** · Ag^+ (with the silver cation in the center of the macrocycle), c) an equilibrium between **4** and **4** · Ag^+ (with the silver cation placed outside the macrocycle), and d) intramolecular tunneling of the silver cation through the cavity of **4**, between two equivalent positions outside the macrocycle. Since no variation in the NMR spectra is observable upon dilution, an intermolecular process (options b and c) can be rejected. On the other hand, options c and d consider complexes with the silver ion placed outside the host. Finally, in cases of b and c, the signals of the uncomplexed host **4** should be observed in the spectrum at low temperatures. However, the four signals are shifted downfield, a situation only compatible with option a.

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[43] For a recent example of “inside complexes” of Ag^+ and cyclophanes, see: H.-F. Grützmacher, S. Zorić, C. Wellbrock *Int. J. Mass Spectrom.* **2001**, *210/211*, 311 – 325.

[44] With regard to this, it has been recently described that small variations of the structure of a Ph-X-Ph subunit (X = S, CMe_2 or cyclohexyl) lead to the selective formation of macrocycles, catenanes, or doubly braided[2]catenanes respectively: C. P. McArdle, J. J. Vittal, R. J. Puddephatt, *Angew. Chem.* **2000**, *112*, 3977 – 3980; *Angew. Chem. Int. Ed.* **2000**, *39*, 3819 – 3822.

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