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Threading of Conformationally Stable Calix[6]arene Wheels Substituted at the Methylene Bridges

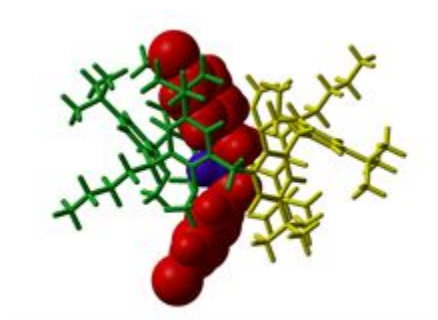
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Threading of Conformationally Stable Calix[6]arene Wheels Substituted at the Methylene Bridges

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ABSTRACT. Calix[6]arenes disubstituted at the methylene bridges, which are stable in the cone or 1,2,3-alternate conformation, form pseudorotaxanes with dialkylammonium axles. The cone-wheel based pseudorotaxanes are 10-100 times more stable than those obtained with the native conformationally-mobile calix[6]arene wheel, as a consequence of their higher degree of preorganization. The threading of conformationally stable 1,2,3-alternate-calix[6]arenes is unprecedented in the literature. Therefore, very peculiar NMR features are

1 here evidenced for this threading process involving the less symmetrical 1,2,3-alternate
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4 calix[6]arene conformation, which implies a peculiar rototranslation motion of the axle.
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19 Introduction

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25 Calixarene¹ macrocycles have a bowl-shaped architecture with an internal cavity of
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27 adjustable shape and dimension depending on the conformation of their skeleton.¹ Thanks to
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29 their synthetic and conformational versatility, calixarenes are considered as one of the most
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31 widespread macrocyclic platform for the design of host molecules.¹ In particular, calixarene
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33 threading has been investigated by us² and by Arduini and coworkers,³ with the aim to obtain
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35 mechanically interlocked molecules (MIMs). In 2010,^{4a} we established that scarcely
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37 preorganized calix[6]arene derivatives (e.g.: **1a,b**) can be threaded by dialkylammonium axles
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39 only when they are associated to the weakly coordinating superweak anion Tetrakis[3,5-
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41 bis(triFluoromethyl)Phenyl]Borate (**TFPB⁻**) (Figure 1). In addition, we observed that the
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43 efficiency of the threading was closely associated to the conformational mobility of the calix-
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wheel.^{4a} Thus, calix[6]-wheel **1b^{cone}**, bearing longer hexyl chains at the lower rim, was threaded by dialkylammonium axles **2a⁺-4⁺**, more efficiently than hexamethoxy-**1a^{cone}** as a result of its higher degree of preorganization.^{4a} Recently, we have focused our attention on the threading of calix[6]-wheels in conformation different than the cone one.

Previously reported data⁵ showed clearly that the most stable conformations for calix[6]arene hexaethers (e.g.: **1a,b**) are the cone (**1a,b^{cone}**) and the 1,2,3-alternate (**1a,b^{1,2,3-alt}**) ones. In particular, we have shown that **1b^{1,2,3-alt}** is threaded faster than **1b^{cone}** in the presence of bis(4-biphenylmethyl)ammonium cation as TFPB⁻ salt.^{5a} The pseudorotaxane initially formed (the kinetic product) shows the calix-wheel in the 1,2,3-alternate conformation^{5a} and is conformationally less stable; therefore, it interconverts to a new one (the thermodynamic product) in which the calix-wheel adopts a cone conformation^{5a}. Very recently,⁶ it was found that the introduction of alkyl groups at the methylene bridges⁷ of the calix[6]arene macrocycle leads to new derivatives (e.g.: **5a** and **6a**) which show a high degree of conformational stability. Thus, derivatives fixed in the 1,2,3-alternate conformation (e.g.: **6a**) have been isolated and characterized both in solution, by 1D and 2D NMR studies, and in the solid state, by X-ray diffractometry.⁶ On this basis, now the question arises as to whether the calix[6]arene bearing alkyl groups at the methylene bridges are also capable of threading with dialkylammonium axles **2⁺-3⁺**.

In addition, we wonder whether the conformational stability of the 1,2,3-alternate calix[6]-wheels could lead to thermodynamically stable pseudorotaxane architectures well observable via NMR.

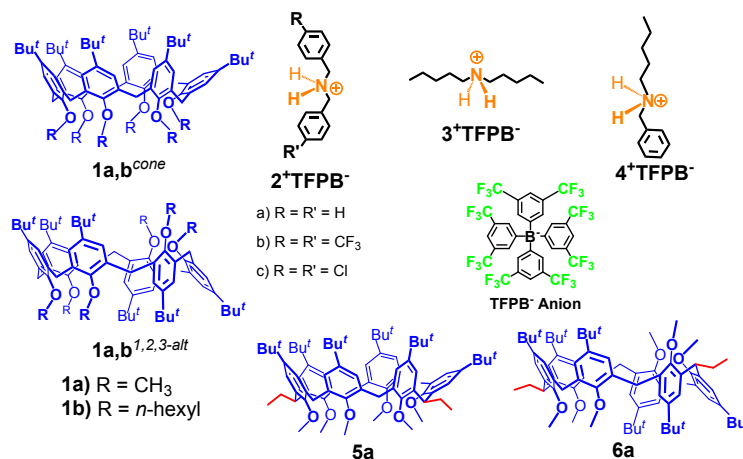


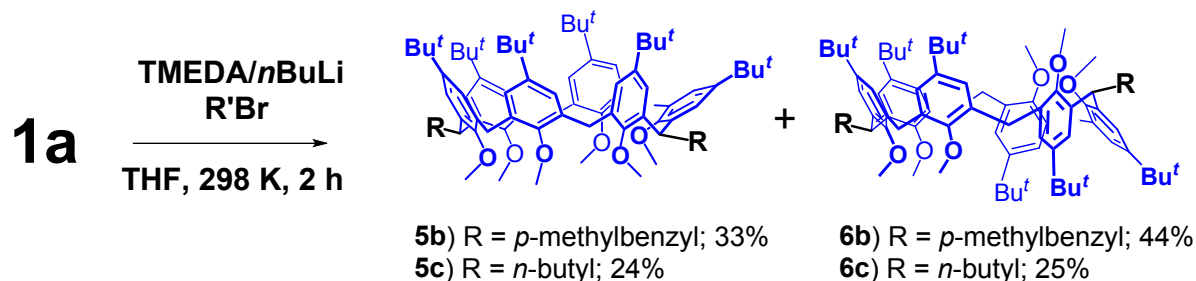
Figure 1. Structures of calix[6]arene wheels **1a,b**, ammonium cations **2⁺**- **3⁺**, and TFPB⁻ anion.

Prompted by these considerations we have investigated the threading ability of methylene-functionalized calix[6]arene macrocycles with dialkylammonium axles and we report here the result of this study.

Results and Discussion

Initially, derivatives **5b/6b** and **5c/6c** were synthesized following the procedure reported by Sing and coworkers.^{6,7} In details, *p*-tert-butylcalix[6]arene hexamethyl ether **1a** was first treated with *n*-BuLi/TMEDA and the anion was then reacted with the corresponding alkyl

halide electrophile, leading to derivatives **5** and **6** fixed in the cone or 1,2,3-alternate conformation, respectively (Scheme 1). Successively, derivatives **5b/6b** and **5c/6c** were characterized by 1D and 2D NMR in accordance with the considerations reported in the literature.^{6,7a} The cone and 1,2,3-alternate structural assignment was confirmed by solid-state X-ray structures of derivatives **6c** and **5c** (Figure 2).



Scheme 1. Synthesis of derivatives **5b/5c** and **6b/6c**.

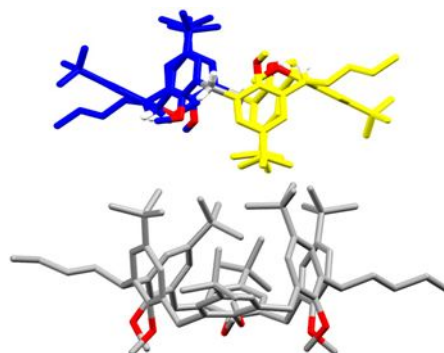


Figure 2. X-ray structures of **6c** (up) and **5c** (down). H atoms have been omitted for clarity.

1 The ^1H NMR spectrum of **5c** in CDCl_3 at 298 K, showed the presence of an AX system at
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4 3.46 and 4.51 ppm, and of a broad triplet at 4.78 ppm, attributable respectively to the
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7 methylene and methine bridges. In addition, two singlets were present at 3.28 and 2.83
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10 attributable to the OMe groups. Lowering the temperature, a broadening for the OMe singlets
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13 was detected at 183 K, and analogously for the aromatic protons of **5c**. In the similar way, the
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17 derivative **5b** showed a broadening of the OMe singlets at same temperature, which can be
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20 attributed to the slowing of the OMe-through-the-annulus passage.⁸
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24 The threading study was started by exploring the complexation ability of cone **5b** with
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27 dibenzylammonium axle **2a**⁺·TFPB⁻. When this salt was added to a CDCl_3 solution of **5b** (1:1
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30 ratio) then significant changes appeared in the ^1H NMR spectrum of **5b** (Figure S11) indicative
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33 of the formation of pseudorotaxane **2a**⁺ \subset **5b**. The cone conformation of the calix-wheel **5b** in
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37 **2a**⁺ \subset **5b** pseudorotaxane was ascertained by 1D and 2D NMR studies (Figure S11, Figure
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40 S12). Regarding the signals of the dibenzylammonium axle in **2a**⁺ \subset **5b** pseudorotaxane, it was
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43 clearly evident the presence of resonances of two different benzylic units: one accommodated
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47 inside the cavity and shielded at 4.48, 5.27, and 5.95 ppm (*ortho*-, *meta*-, and *para*-BnH,
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50 respectively); another outside the calix-cavity, resonating at typical chemical shift value (7.44,
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54 7.58, and 7.44 ppm, *ortho*-, *meta*-, and *para*-BnH, respectively).
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The formation of $2a^+ \subset 5b$ was confirmed by a HR ESI(+) mass spectrum which gave as the base peak a value of 1327.036 *m/z* corresponding to the pseudorotaxane system. The threading of $2a^+$ inside $5b$ reached the equilibrium immediately after mixing. The determination of the apparent association constant of pseudorotaxane $2a^+ \subset 5b$ was carried out by means of a competition experiment^{4a} (Figure S56) with the native hexamethoxycalix[6]arene $1a$. In particular, 1 equiv of $2a^+ \cdot TFPB^-$ was mixed with a 1:1 mixture of $5b$ and $1a$ (in $CDCl_3$) and equilibrated for 15 min at 298 K. The NMR spectrum indicated that pseudorotaxane $2a^+ \subset 5b$ was favored over $2a^+ \subset 1a$ in a 10:1 ratio (Figure S47). From these data an apparent association constant value of $2.6 \pm 0.2 \times 10^5 \text{ M}^{-1}$ was calculated for $2a^+ \subset 5b$, which is significantly higher than that observed for $2a^+ \subset 1a$ ($2.5 \times 10^3 \text{ M}^{-1}$).^{4a} In summary, these initial results indicate that the higher conformational stability of cone $5b$ leads to a dibenzylammonium-based pseudorotaxane with a higher thermodynamic stability with respect to the native, conformationally mobile calix[6]arene-wheel $1a$. A close inspection of the K_{app} values⁹ reported in Figure 3, clearly indicates a general trend within the methylene-functionalized calix[6]arene complexes: the calix-wheels $5b$ and $5c$, fixed in the cone conformation, give pseudorotaxane complexes with ammonium axles $2a^+$ and 3^+ more stable than the analogous obtained by threading the mobile calix[6]arene-wheel $1a$, as a consequence of their higher degree of preorganization. In line with this conclusion, the cone-

1 wheel with the bigger *p*-methylbenzyl substituent **5b** gives pseudorotaxane adducts 10-100
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4 times more stable than **5c**, bearing the smaller *n*-butyl group (Figure 2). At this point, our
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7 attention was turned to the threading of conformationally stable 1,2,3-alternate calix[6]arene
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10 derivatives **6b,c**. While the threading of calix[6]wheels in the cone-conformation is well
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13 documented in the literature,^{4,5} the threading of a stable 1,2,3-alternate-calix[6]arene has
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16 never been described.¹⁰ Consequently, a very limited NMR information has been reported for
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19 the characterization of pseudorotaxanes in which the calix-wheel adopts a 1,2,3-alternate
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22 structure.⁹ The ¹H NMR spectrum of the free calix-wheel **6c** (CDCl₃, 298 K, 600 MHz) in the
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25 1,2,3-alternate conformation, showed the presence of an AB system at 4.06 and 3.65 ppm (8
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28 H) attributable to the unsubstituted ArCH₂Ar groups. As previously described by Biali,^{7a} the
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31 presence of only one AB system for these two different ArCH₂Ar groups is justified on the
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34 basis of a rapid topomerization equilibrium in which the two aromatic rings A and B in Figure 4
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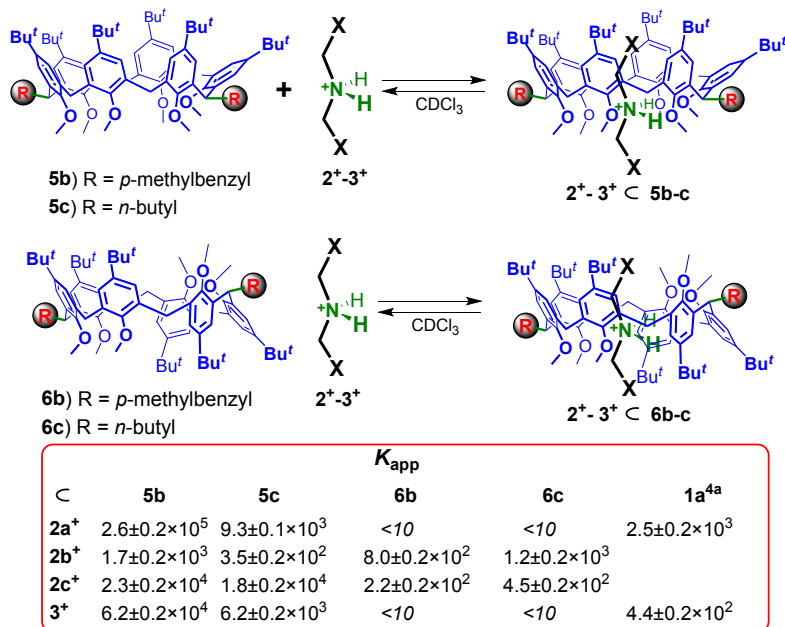


Figure 3. Threading of calix[6]-wheels substituted at the methylene bridges and K_{app} values measured for the formation of the corresponding pseudorotaxanes.

Interestingly, the $\Delta\delta$ value of 0.41 ppm between the two doublets is small, and can also be rationalized by this rapid topomerization (Figure 4).^{7a} Thus, the diastereotopic protons *a* and *e*, which are expected at a very different chemical shifts (AX system), exchange with the isoclinal protons *i* and *i'*, which are expected to display similar chemical shifts (AB system).^{7a} In conclusion, in a fast exchange situation two averaged doublets result with a smaller difference of chemical shift with respect to the values expected for *a* and *e*.^{7a} A ¹H VT NMR study was performed in order to highlight the conformational mobility of derivative **6b,c**. Lowering the temperature, the ¹H NMR spectrum of **6c** in CD₂Cl₂ showed a broadening of the AB system at 4.06 and 3.65 ppm, at 193 K.¹¹

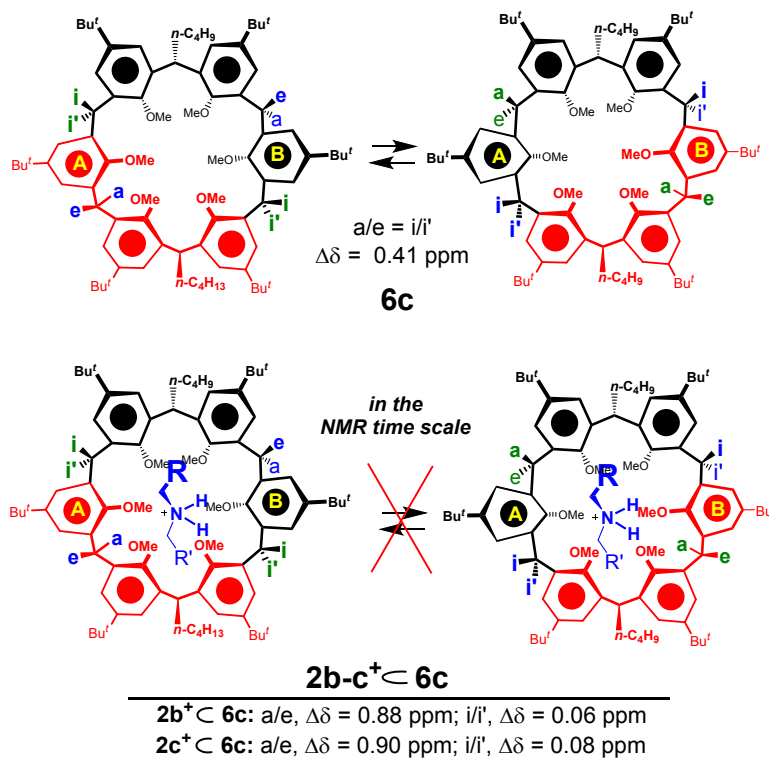


Figure 4. Topomerization equilibrium^{7a} in 1,2,3-alternate **6c** (top). The presence of the axle inside the cavity of **6c**, obstacles the flipping of the aromatic rings A and B in the corresponding pseudorotaxane (bottom).

Analogously the derivative **6b** shows a similar behavior with a broadening at 193 K.¹¹ Interestingly, after addition of **2b⁺·TFPB⁻** to the CDCl₃ solution of **6c**, an AX system was detected at 4.38 and 3.50 ppm (blue in Figure 5b) with a $\Delta\delta$ value of 0.88 ppm significantly higher than that observed in the ¹H NMR spectrum of the free host **6c** ($\Delta\delta = 0.41$ ppm). This AX system showed a correlation in the HSQC spectrum with a carbon resonance at 28.9 ppm indicative of an ArCH₂Ar group between *syn* oriented Ar-rings.¹² Therefore, we confidentially assigned these resonances at the *a* and *e* hydrogen atoms in Figure 4 (bottom). In addition, an

1 AB system was observed at 3.12/3.06 ppm (4H, green in Figure 5b) which correlates in the
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4 HSQC spectrum with a carbon resonance at 34.8 ppm indicative of an ArCH₂Ar system
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7 between *anti* oriented Ar-rings and attributable to isoclinal *i* and *i'* protons (Figure 4, bottom).
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11 These results clearly indicate that after threading of the axle **2b**⁺ through the annulus of **6c**,
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14 the flipping of the two Ar-rings A and B in Figure 4 is blocked with respect to the NMR time
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17 scale (600 MHz). In this way, no exchange can be observed between *a/e* and *i/i'* protons.
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21 Consequently, the AB systems in the ¹H NMR spectrum of free **6c** (8H, Δδ = 0.41 ppm) for the
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24 unsubstituted ArCH₂Ar groups, is splitted, upon threading with **2b**⁺, in one AX system (4H) with
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27 Δδ = 0.88 ppm (*a* and *e* ArCH₂Ar groups in Figure 4) and one AB system (4H) with Δδ = 0.06
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30 ppm (*i* and *i'*, ArCH₂Ar groups in Figure 4). In a similar way, when the *p*-chloro-substituted axle
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34 **2c**⁺ was added to the CDCl₃ solution of **6c**, again the threading of the 1,2,3-alternate-wheel
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37 was evidenced by the appearance of one AX system at 3.50/4.40 ppm (Δδ = 0.90 ppm, blue in
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41 Figure 5c), and an AB system at 3.23/3.15 ppm (Δδ = 0.08 ppm, green in Figure 5c).
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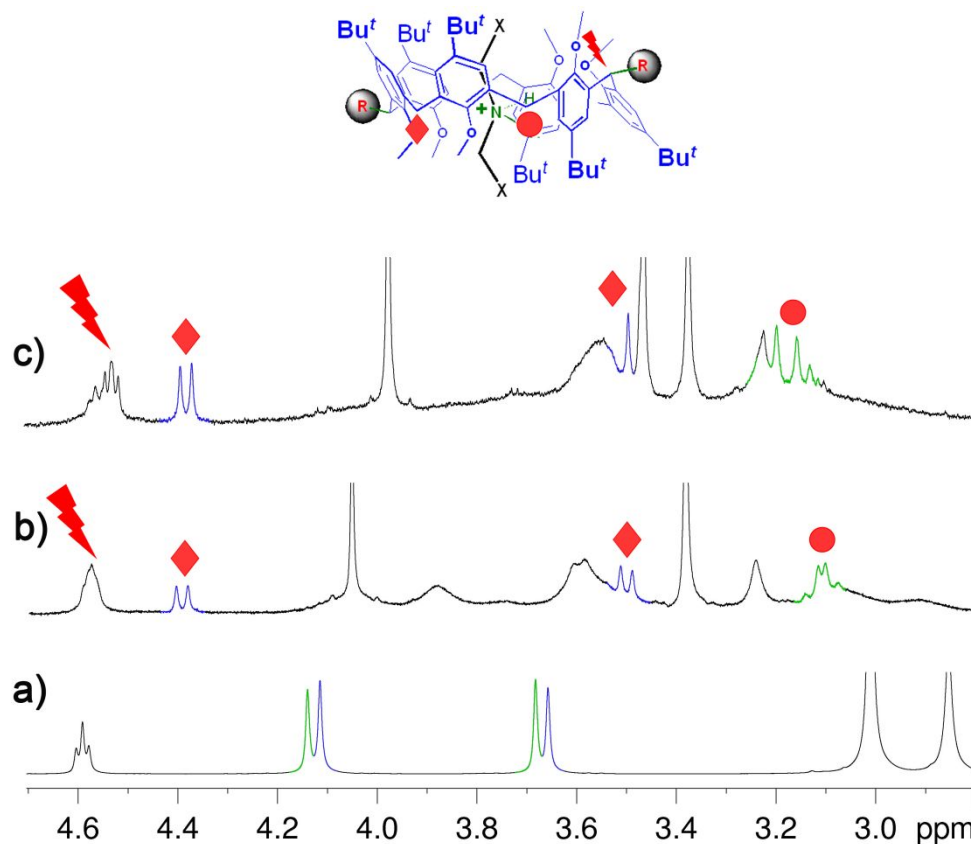


Figure 5. Methylene region of ^1H NMR spectra (CDCl_3 , 600 MHz, 298 K) of: (a) **6c**; (b) **2b⁺** \subset **6c**; (c) **2c⁺** \subset **6c**.

The above trend is confirmed with the 1,2,3-alternate calix[6]arene **6b**, bearing two *p*-Me-benzyl groups at the methylene bridges, which shows an AB system at 4.94/3.63 ppm, with a $\Delta\delta = 0.41$ ppm, for the unsubstituted ArCH_2Ar groups. Upon addition of **2b⁺**·TFPB⁻ salt, the formation of **2b⁺** \subset **6b** pseudorotaxane is outlined by the appearance of an AX system at 3.45/4.29 ppm with a $\Delta\delta = 0.84$ ppm, and an AB system at 3.06/3.12 ppm with a $\Delta\delta = 0.06$ ppm.

Another interesting feature concerns the signals of the axle. In fact, the ^1H NMR spectrum of dibenzylammonium-based pseudorotaxanes^{4a} in which the calix-wheel adopts a cone conformation, usually evidences the presence two sets of shielded and unshielded benzyl resonances (see above for $2\mathbf{a}^+ \subset 5\mathbf{b}$),^{4a} corresponding to their *endo*- or *exo*-cavity disposition.^{4a} Surprisingly, the ^1H NMR spectrum of the $2\mathbf{b}^+ \subset 6\mathbf{c}$ pseudorotaxane evidences the presence of only one set of benzylic resonances of $2\mathbf{b}^+$ shielded inside the aromatic cavity of the calix-wheel $6\mathbf{c}$. In details, the aromatic H-atoms of $2\mathbf{b}^+$ form an AB system at 6.75/5.96 ppm ($\Delta\delta = \delta_{\text{free}} - \delta_{\text{complex}} = 0.78$ and 1.42 ppm, respectively), while the CH_2 groups in α to the $^+\text{NH}_2$ group form an AB system at 2.56/2.61 ppm ($\Delta\delta = 1.59$ and 1.54 ppm, respectively). In addition, the 2D COSY spectrum of $2\mathbf{b}^+ \subset 6\mathbf{c}$ shows three meta-coupled aromatic signals for $6\mathbf{c}$ at 7.64/7.36, 7.41/6.98, and 7.14/6.95 ppm. This observation clearly indicates than in the $2\mathbf{b}^+ \subset 6\mathbf{c}$ pseudorotaxane the two $\frac{3}{4}$ -cone subcavities (red and blue in Figure 6) are equivalent. This result is unexpected, since the *C*-shape of the axle $2\mathbf{b}^+$ and its H-bonding in pseudorotaxane $2\mathbf{b}^+ \subset 6\mathbf{c}$ (see DFT-optimized structure in Figure 7), should make non-equivalent the two $\frac{3}{4}$ -cones of $6\mathbf{c}$ (see the blue and red color in Figure 6). Thus, the NMR spectra of $2\mathbf{b}^+ \subset 6\mathbf{c}$ can be justified on the basis of the equilibrium highlighted in Figure 6, in which the rototranslation motion of the axle $2\mathbf{b}^+$ between the *anti*-oriented *O*-atoms (red and blue in Figure 6) makes equivalent the two subcavities of $6\mathbf{c}$.

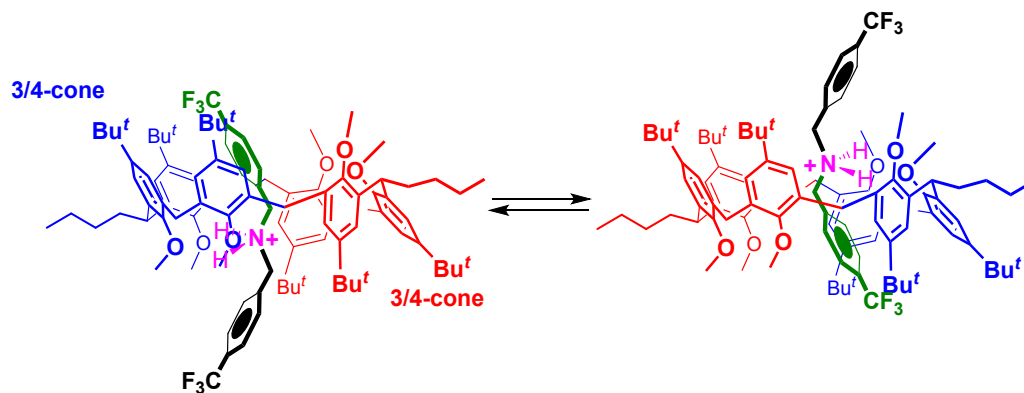


Figure 6. Rototranslation motion of the dibenzylammonium axles $2b^+$ inside the cavity of the calix[6]-wheel $6c$ in 1,2,3-alternate conformation.

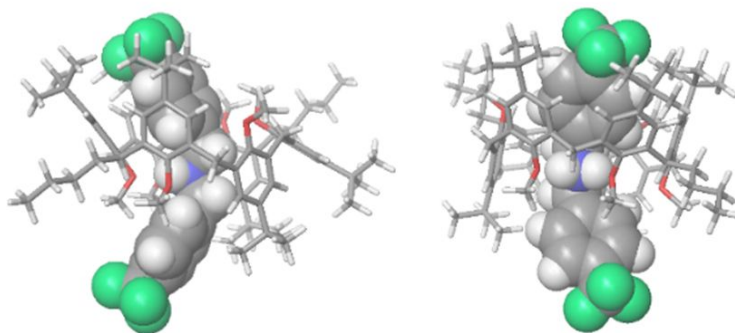


Figure 7. Different views of the DFT-optimized structure of $2b^+ \subset 6c$ pseudorotaxane at the B3lyp/6-31G(d,p) IOp(3/124=3) level of theory. Two H-bonding interactions are present between the ammonium group of the axle and the oxygen atoms of a $\frac{3}{4}$ -cone subcavity, with an average $N^+ \cdots O$ distance of 2.94 Å and a $N-H \cdots O$ angle of 163.5°.

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4 Of course, the equilibrium highlighted in Figure 6 is fast with respect to the NMR time scale
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7 (600 MHz) at room temperature. By lowering the temperature at 223 K, it can be slowed down
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10 thus allowing the detection of the asymmetric enantiomeric pair of Figure 6. Thus, 4 AX
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13 systems attributable to the ArCH₂Ar groups emerged at 4.60/3.54, 4.51/3.48, 4.37/3.52, and
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16 4.24/3.42 ppm. In addition, two sets of aromatic *p*-CF₃-benzylammonium signals for the axle
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19 **2b⁺** (green and black in Figure 6) emerged in the 1D and 2D NMR spectra at 223 K.
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22 Furthermore, 6 AB systems were detected at 7.18/6.50 (6 H), 7.43/6.64 (2H), 7.32/6.80 (2H),
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25 7.30/6.78 (2H), 6.90/6.82 (2H), and 6.72/6.61 (2H) ppm, for the six non-equivalent Ar-rings of
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28 **6c**. By these data and considering the temperature of coalescence at 233 K, (SI) an energy
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31 barrier of 10.2 kcal/mol¹³ was calculated for the rototranslation motion of the
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34 dibenzylammonium axles **2b⁺** inside the cavity of the calix[6]-wheel **6c**.
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44 Conclusions

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47 In conclusion, we have here reported the first examples of pseudorotaxanes obtained by
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50 threading of ammonium axles through calix[6]arene macrocycles substituted at the methylene
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53 bridges. Thanks to their conformational stability, the cone structures **5b** and **5c** form
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56 pseudopseudorotaxane complexes more stable than those obtained by native conformationally
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1 mobile calix[6]arene-wheel **1a**. The NMR features of the threading process between
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4 ammonium axles and calix-wheels in the stable 1,2,3-alternate conformation have been
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7 described in detail, evidencing a rototranslation motion of the axle inside the 1,2,3-alternate
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10 wheel, which could be blocked at low temperatures. These results can be considered useful
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14 reference points for future studies.
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20 21 Experimental Section

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27 **General Information.** Reactions under anhydrous conditions were conducted under an inert
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30 atmosphere (nitrogen) using dry solvents. The commercial reagents were purchased by
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34 Aldrich and Fluka and were used without further purification. The reactions were controlled by
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37 thin-layer chromatography (TLC) with Macherey-Nagel plates coated with silica gel (0.25 mm)
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40 with fluorescence indicator UV254 and visualized using UV light and nebulisation with an
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43 indicator solution of H₂SO₄-Ce(SO₄)₂. The reaction temperatures were measured externally
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46 using electronic thermometers. The reaction products were purified by Macherey-Nagel silica
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49 gel chromatography (60, 70-230 mesh). NMR spectra were recorded on Bruker Avance-600
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52 spectrometer [600 (¹H) and 150 MHz (¹³C)], Bruker Avance-400 spectrometer [400 (¹H) and
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55 100 MHz (¹³C)]. Chemical shifts are reported relative to the residual solvent peak (C/Cl₃: δ
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7.26, CDCl_3 : δ 77.16) Standard pulse programs, provided by the manufacturer, were used for 2D NMR experiments. High-resolution Mass spectra were acquired with a Bruker Solarix spectrometer equipped with a Tesla magnet. It was used a MALDI as methods of sample ionization. DHB was used as matrix. Samples were prepared in CHCl_3 (1 mg / mL).

Synthesis of derivatives 5b and 6b. In a dry round flask, under N_2 , hexamethoxycalix[6]arene **1** (0.502 g, 0.45 mmol) was dissolved in freshly distilled THF (50 mL). Subsequently, TMEDA (0.57 mL, 3.59 mmol) and *n*-BuLi (1.50 mL of a solution 2.5 M in hexane, 3.59 mmol) were added at room temperature. A persistent blood red colored anion was generated. Afterwards, a solution of *p*-methylbenzyl bromide (0.724 g, 3.59 mmol) in THF dry (20 mL) was added dropwise to the reaction mixture. It's observed a gradually change color of mixture, first to green and later to pale yellow. Stirring was continued for an hour at room temperature. After the reaction was stopped by addition of 1 N HCl and the solution was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 , filtered and evaporated of the solvent. The raw was purified through chromatography column on silica gel and using solvent mixture 74 % hexane / 21 % chloroform / 5 % ethyl acetate as eluens. *cone* **5b** was isolated with 25 % yield, and *1,2,3-alternate* **6b** conformer with 22 % yield. Derivative **5b**: $^1\text{H NMR}$ (600 MHz, CDCl_3 , 298 K) δ : 7.16 (s, 4H, ArH), 7.04 (d, $J = 7.6$ Hz, 4H, ArH), 7.02 (s, 4H, ArH), 6.96 (d, $J = 7.6$ Hz, 4H, ArH), 6.86 (s, 4H, ArH), 5.13 (bt, 2H, ArCH(*p*-MeBn)Ar), 4.41 and 3.45 (AX

system, $J = 15.3$ Hz, 8H, ArCH_2Ar), 3.23-3.19 (overlapped, $-\text{CH}_2\text{Ph}$, 16H, $-\text{OCH}_3$), 2.70 (s, 6H, $-\text{OCH}_3$), 2.23 (s, 6H, $-\text{BnCH}_3$), 1.16 (s, 18H, $-\text{C}(\text{CH}_3)_3$), 1.07 (s, 36H, $-\text{C}(\text{CH}_3)_3$). ^{13}C NMR (150 MHz, CDCl_3 , 298 K): δ 154.0, 153.6, 145.7, 145.2, 137.9, 136.5, 135.0, 133.1, 133.1, 128.9, 128.7, 126.3, 125.3, 123.9, 60.2, 60.0, 41.9, 34.2, 34.1, 31.4, 31.4, 29.9, 20.9. HRMS (m/z) calcd for $\text{C}_{88}\text{H}_{112}\text{NaO}_6$ 1287.8351 found 1287.8378. Derivative **6b**: ^1H NMR (600 MHz, CDCl_3 , 298 K): δ 7.12 (s, 4H, ArH), 7.02-7.02 (overlapped, 8H, ArH), 6.96-6.94 (overlapped, 8H, ArH), 4.89 (bt, 2H, $\text{ArCH}(\text{p-MeBn})\text{Ar}$), 4.05 and 3.64 (AX system, $J = 14.8$ Hz, 8H, ArCH_2Ar), 3.25 (d, $J = 7.3$ Hz, 4H, $-\text{CH}_2\text{Ph}$), 2.96 (s, 12H, $-\text{OCH}_3$), 2.80 (s, 6H, $-\text{OCH}_3$), 2.22 (s, 6H, $-\text{BnCH}_3$), 1.17 (s, 18H, $-\text{C}(\text{CH}_3)_3$), 1.15 (s, 36H, $-\text{C}(\text{CH}_3)_3$). ^{13}C NMR (150 MHz, CDCl_3 , 298 K): δ 154.2, 154.1, 145.7, 145.3, 137.9, 136.7, 135.0, 133.5, 133.1, 128.9, 128.7, 126.3, 125.8, 124.4, 69.0, 60.1, 59.6, 40.9, 34.2, 34.1, 31.4, 20.9. **Elemental Analysis**: Calcd for $\text{C}_{88}\text{H}_{112}\text{O}_6$ C, 83.50; H, 8.92; O, 7.58, Found: C, 83.48; H, 8.93; O, 7.59.

Synthesis of derivatives 5c and 6c. In a dry round flask, under N_2 , hexamethoxycalix[6]arene **1** (1.575 g, 0.94 mmol) was dissolved in freshly distilled THF (150 mL). Subsequently, TMEDA (1.73 mL, 7.52 mmol) and $n\text{-BuLi}$ (4.50 mL of a solution 2.5 M in hexane, 7.52 mmol) were added at room temperature. A persistent blood red colored anion was generated. Afterwards, a solution of 1-bromobutane (1.23 mL, 7.60 mmol) in THF dry (60 mL) was added dropwise to the reaction mixture. It's observed a gradually change color of mixture, first to green and later

1 to pale yellow. Stirring was continued for an hour at room temperature. After the reaction was
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4 stopped by addition of 1 N HCl and the solution was extracted with ethyl acetate. The organic
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7 phase was dried over anhydrous Na₂SO₄, filtered and evaporated of the solvent. The raw was
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10 purified through chromatography column on silica gel and using solvent mixture 74 % hexane /
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13 21 % chloroform / 5 % ethyl acetate as eluens., *cone* **5c** was isolated with 27 % yield and
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16 *1,2,3-alternate* **6c** conformer with 10 % yield. Derivative **5c**: ¹H NMR (600 MHz, CDCl₃, 298 K):
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18 δ 7.06 (s, 4H, ArH), 7.01 (s, 4H, ArH), 6.92 (s, 4H, ArH), 4.78 (t, $J_{ab} = 7.6$ Hz, 2H,
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20 ArCH(*n*Bu)Ar), 4.51 and 3.46 (AX system, $J = 15.3$ Hz, 8H, ArCH₂Ar), 3.28 (s, 12H, OCH₃),
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22 2.83 (s, 6H, OCH₃), 1.92 (q, $J_{ba} = 7.6$ Hz, $J_{bc} = 14.7$, 4H, -CH₂CH₂CH₂CH₃), 1.34 - 1.28 (m,
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24 8H, -
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26 CH₂CH₂CH₂CH₃), 1.13 (s, 18H, -C(CH₃)₃), 1.06 (s, 36H, -C(CH₃)₃), 0.86 (t, -CH₂CH₂CH₂CH₃,
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28 $J = 7.1$ Hz, 6H). ¹³C NMR (150 MHz, CDCl₃, 298 K): δ 153.8, 153.5, 145.7, 145.4, 137.4,
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31 133.2, 133.1, 126.1, 125.2, 123.4, 69.0, 60.3, 60.1, 36.9, 36.4, 34.2, 34.1, 31.4, 30.5, 29.8,
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34 22.7, 14.0. HRMS (*m/z*) clcd for C₈₀H₁₁₂O₆Na 1191.8351 found 1191.8399 Derivative **6c**: ¹H
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37 NMR (600 MHz, CDCl₃, 298 K): δ 7.08-7.02 (overlapped, 12H, ArH), 4.58 (t, $J_{ab} = 7.6$ Hz, 2H,
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40 ArCH(*n*Bu)Ar), 4.11 and 3.66 (AX system, $J = 15.0$ Hz, 8H, ArCH₂Ar), 3.00 (s, 12H, OCH₃),
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43 2.84 (s, 6H, OCH₃), 1.93 (q, $J_{ba} = 7.6$ Hz, $J_{bc} = 14.9$, 4H, -CH₂CH₂CH₂CH₃), 1.34 - 1.28 (m,
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46 8H, -CH₂CH₂CH₂CH₃), 1.19 (s, 54H, -C(CH₃)₃), 0.86 (t, $J = 7.1$ Hz, 6H, -CH₂CH₂CH₂CH₃). ¹³C
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1 **NMR** (150 MHz, CDCl₃, 298 K): δ 154.5, 154.3, 145.8, 145.6, 137.5, 133.7, 133.4, 126.6,
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4 126.0, 124.0, 60.3, 59.8, 38.0, 35.7, 34.4, 34.3, 32.2, 31.6, 30.7, 22.9, 14.2. **Elemental**
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7 **Analysis:** Calcd for C₈₀H₁₁₂O₆ C, 82.14; H, 9.65; O, 8.21, Found: C, 82.13; H, 9.67; O, 8.20.
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10 For further detail about determination of the crystallographic structures of derivative **5c** and
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13 **6c** see Supporting Information.
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16 ASSOCIATED CONTENT

17 Supporting Information

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20 The Supporting Information is available free of charge on the ACS Publications website at
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26 xxxx. Detail on 1D and 2D NMR spectra, HR mass spectra and. Crystallographic details for
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30 derivate reported.
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(9) Regarding the complexes $2\text{b}^+ \subset 6\text{b}$, $3^+ \subset 5\text{b}$, $2\text{a}^+ \subset 5\text{c}$, $2\text{c}^+ \subset 5\text{c}$ and $3^+ \subset 5\text{c}$, the calculation of the apparent association constants has been performed by integration of the ^1H

1 NMR signals of the complexes and free hosts (SI). For the complexes $2b^+ \subset 5b$, $2c^+ \subset 5b$, $2c^+$
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4 $\subset 6b$, $2b^+ \subset 5c$, $2b^+ \subset 6c$ and $2c^+ \subset 6c$, the K_{app} have been calculated by qNMR.
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8 (10) The formation of pseudorotaxanes in which the calix-wheel adopts a 1,2,3-alternate
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11 structure has been described in refs. 5a,b. In these cases, the 1,2,3-alternate
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14 pseudorotaxanes were the kinetic species which evolved towards the more stable cone
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17 conformation.
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22 (11) Probably, the broadening of the ArCH₂Ar signals is attributable to the slowing of the
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25 flipping motion represented in figure 4 (top). Due to the instrumental limitations, it was not
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28 possible to lower the temperature below 183 K, and consequently we were not able to detect
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31 the freezing of the flipping motion.
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