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Fixed or Invertible Calixarene-Based Directional Shuttles

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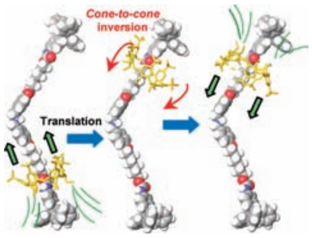
ABSTRACT



The first examples of rotaxanes based on calixarenes threaded by dialkylammonium ions, which also represent the first examples of calixarene-based molecular shuttles, are reported. The base/acid treatment demonstrated that these systems act as molecular shuttles, which move between three sites on the axle. When small OMe groups are appended at the calix[6]arene lower rim an unprecedented inversion of its shuttling direction is observed, which occurs through a *cone-to-cone* inversion of the macrocycle.

Molecular shuttles are mechanically interlocked molecules,[1] more commonly rotaxanes, able to translocate a macrocyclic component (wheel) over two or more sites ("stations") under the influence of an external stimulus.[2] Usually, flat or symmetrical wheels, such as crown ethers[3] or macrolactams,[4] are used, which lead to a nondirectional shuttling component in the presence of a symmetrical thread. Instead, the use of three-dimensional nonsymmetrical wheels, such as cyclodextrins[5] or calixarenes,[6] could give rise to directional shuttles with a determined relative orientation of their components and with new related potential properties. In addition to its basic shuttling, the wheel can also perform a pirouetting motion[7] around the axle component. Furthermore, in the case of directional shuttles, the wheel could also undergo an inversion of its orientation, which is still unprecedented[8] in rotaxane chemistry.

Here, we report on the first examples of rotaxanes based on calixarenes[9] threaded by dialkylammonium ions, which can show this unexplored inversion of the wheel orientation. These systems were synthesized by exploiting our very

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(1) *Molecular Catenanes, Rotaxanes and Knots: A Journey Through the World of Molecular Topology*; Sauvage, J.-P., Dietrich-Buchecker, C., Eds.; Wiley-VCH: Weinheim, 1999.

(2) (a) Saha, S.; Stoddart, J. F. *Chem. Soc. Rev.* **2007**, *36*, 77. (b) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72. (c) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines*, 2nd ed.; Wiley-VCH: Weinheim, 2008.

(3) For recent examples, see: (a) Davidson, G. J. E.; Sharma, S.; Loeb, S. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4938. (b) See also, ref 1, pp 146–152.

(4) For recent examples, see: (a) Panman, M. R.; Bodis, P.; Shaw, D. J.; Bakker, B. H.; Newton, A. C.; Kay, E. R.; Brouwer, A. M.; Buma, W. J.; Leigh, D. A.; Woutersen, S. *Science* **2010**, *328*, 125.

(5) (a) Harada, A.; Hashidzume, A.; Yamaguchi, H.; Takashima, Y. *Chem. Rev.* **2009**, *109*, 5974. (b) Qu, D.-H.; Wang, Q.-C.; Tian, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5296.

(6) To the best of our knowledge, only examples of one-station calix[6]arene-based rotaxane systems in which a calix wheel encircles a viologen axle have been reported so far. In these instances, no shuttling or inversion motion of the calix wheel has been evidenced: (a) Arduini, A.; Bussolati, R.; Credi, A.; Pochini, A.; Silvi, S.; Venturi, M. *Tetrahedron* **2008**, *64*, 8279. (b) Arduini, A.; Ciesa, F.; Fragassi, M.; Pochini, A.; Secchi, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 278. (c) Arduini, A.; Ferdani, R.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3453. For an example of self-threaded calixarene rotaxane, see: (d) Moerkerke, S.; Ménand, M.; Jabin, I. *Chem.—Eur. J.* **2010**, *16*, 11712.

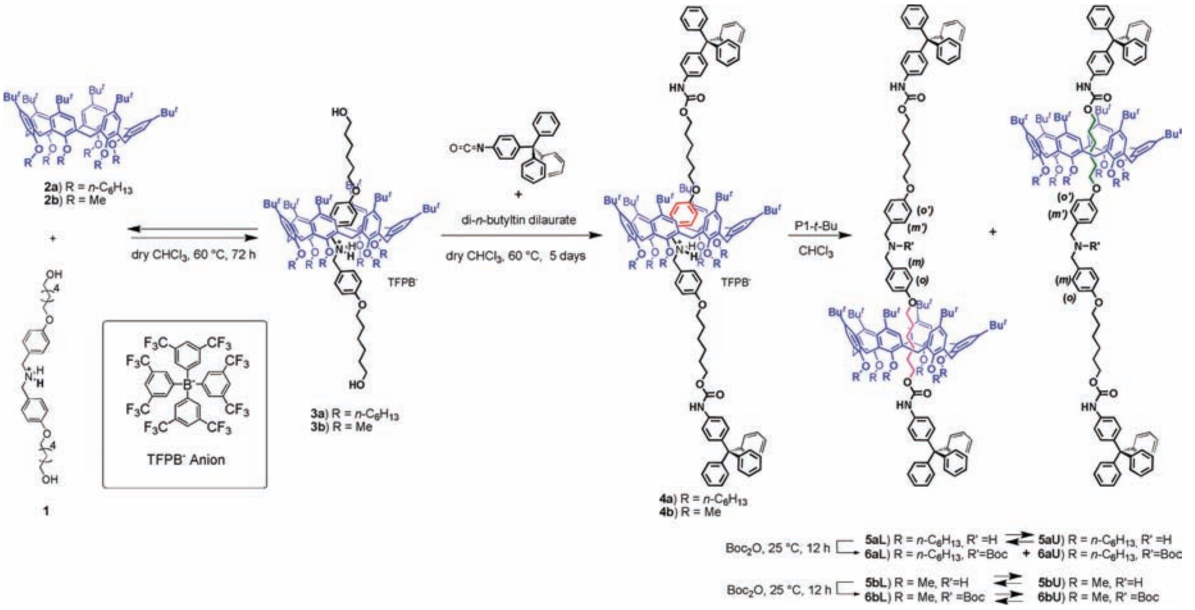
(7) (a) D'Souza, D. M.; Leigh, D. A.; Mottier, L.; Mullen, K. M.; Paolucci, F.; Teat, S. J.; Zhang, S. *J. Am. Chem. Soc.* **2010**, *132*, 9465. (b) Collin, J.-P.; Durola, F.; Mobian, P.; Sauvage, J.-P. *Eur. J. Inorg. Chem.* **2007**, 2420.

(8) A "ring flipping" has been observed for some nondirectional crown ether-based rotaxanes, which cannot be considered as a "truly" inversion of the flat wheel: Iijima, T.; Vignon, S. A.; Tseng, H.-R.; Jarrosson, T.; Sanders, J. K. M.; Marchioni, F.; Venturi, M.; Apostoli, E.; Balzani, V.; Stoddart, J. F. *Chem.—Eur. J.* **2004**, *10*, 6375.

(9) Gutsche, C. D. *Calixarenes, An Introduction*; Royal Society of Chemistry: Cambridge, UK, 2008.

10.1021/ol200753c

Scheme 1



recent observation that the *through-the-annulus* threading of simple calix[6]arene hosts can be obtained through the inducing effect of the weakly coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB) anion[10] that gives free "naked" dialkylammonium cations.[11]

In particular, the TFPB salt of a dibenzylammonium cation bearing two terminal OH groups **1** (Scheme 1) was equilibrated with hexa-*n*-hexyloxy-**2a** or hexamethoxycalix[6]arene **2b** to give threaded complexes **3a**,**b** (Scheme 1). These pseudorotaxanes were then stoppered by reaction with trityl isocyanate to give the first example of dialkylammonium-threaded calixarene rotaxanes **4a**,**b** in 24–32% yield (Scheme 1).[12]

The interlocked [2]rotaxane nature of **4a**,**b** was confirmed by ESI(+) MS spectra, by the expected ^{1}H and ^{13}C NMR resonances of all components, and by a typical upfield AX system between 4.0 and 5.0 ppm (Figure 1a) for ArH protons of the shielded *endo*-cavity benzylammonium unit of the axle, similar to those observed for the related pseudorotaxane complexes.[11,12] In addition, these upfield signals demonstrate that the calix[6]arene macrocycle is located at the middle of the axle component and is held in place by hydrogen bonds between its ethereal OR atoms and the ammonium $^+NH_2$ group.[12]

This positioning was fully confirmed by Monte Carlo searches and MM3 calculations[13] which indicate that two N–H···O hydrogen bonds strongly contributed to stabilize this site.[12] In addition, this H-bonding contributes to fix the calix[6]arene macrocycle in a cone conformation as demonstrated by well-spaced AX systems for $ArCH_2Ar$ protons. Interestingly, these spectral did not change significantly either by changing the temperature or by adding anions (Cl^-) or polar solvents (CH_3CN) that usually cause decomplexation for the corresponding pseudorotaxanes.[12]

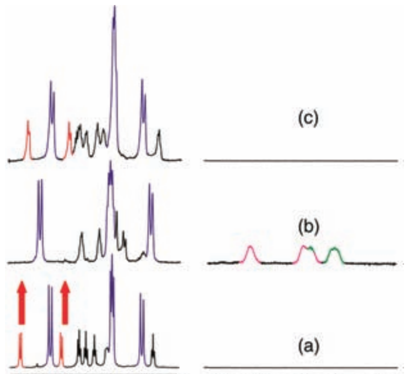


Figure 1. Relevant portions of the ^{1}H NMR spectra (400 MHz, $CDCl_3$) of (a) [2]rotaxane **4a** at 298 K; (b) [2]rotaxane **4a** upon addition of 1.6 equiv of P_1-*t*-Bu base, at 263 K; (c) the original spectrum (a) regenerated upon addition of 1.6 equiv of TFA. The coloring corresponds to the portion of the axle (station) hosted inside the cavity of the calix shuttle, as indicated in Scheme 1.

Deprotonation of hexyloxy-bearing [2]rotaxane **4a** by addition of 1.5 equiv of phosphazene base P1-*t*-Bu (*N*-*tert*-butyl-*N'*,*N'*,*N''*,*N''*,*N'''*,*N'''*-hexamethylphosphorimidic triamide) caused dramatic changes in its ^{1}H NMR spectrum, which involved the displacement of the shielded benzylic

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[10] (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927. (b) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600. For a recent review on counterion effects in supramolecular chemistry, see: (c) Gasa, T. B.; Valente, C.; Stoddart, J. F. *Chem. Soc. Rev.* **2011**, *40*, 57.

[11] (a) Gaeta, C.; Troisi, F.; Neri, P. *Org. Lett.* **2010**, *12*, 2092. (b) Talotta, C.; Gaeta, C.; Pierro, T.; Neri, P. *Org. Lett.* **2011**, *13*, 2098.

[12] See the Supporting Information for further details.

[13] MacroModel-9.0/Maestro-4.1 program: Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

ArH protons (Figure 1a,b) to normal values (6.8−7.2 ppm) and the appearance in the upfield negative region of the spectrum (from −0.5 to −1.5 ppm) of CH_2 signals corresponding to an aliphatic chain (Figure 1b), as confirmed by a COSY spectrum.[12] This result clearly indicates that upon deprotonation of **4a** to give **5a**, the calix[6]arene wheel moves from the previous dibenzylammonium station (or middle station in Figure 2) to a new position in which an aliphatic chain is inside the calix cavity. Because of the unsymmetrical nature of the calix[6]arene wheel there are two nonequivalent aliphatic sites along the axle which can be occupied by a calix shuttle: the upper and lower stations in Figure 2. This should lead, in principle, to two translational isomers (coconformers), **5aL** or **5aU**, in which the alkoxy moieties at the lower rim or the *tert*-butyl groups at the upper rim are facing the trityl stopper, respectively (Figure 2).

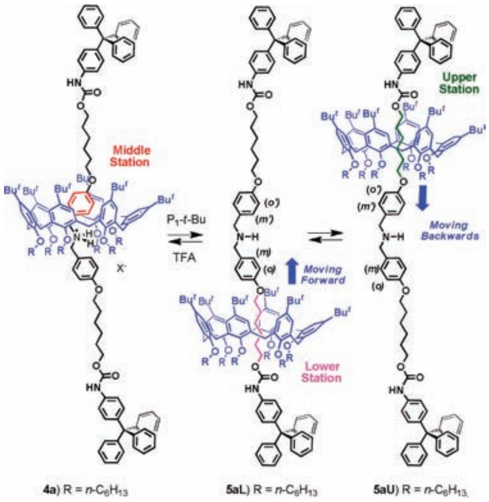

Figure 2. Directional shuttling motion in cationic/neutral calix[6]arene-based [2]rotaxanes **4a**/**5a**.

The presence of both translational isomers **5aL** and **5aU** was confirmed by means of a combined study of 2D COSY and ROESY spectra of neutral **5a** in $CDCl_3$ at 263 K that allowed us to obtain the complete assignments of two distinct shielded alkyl chains corresponding to the two isomers.[12] In particular, the two sets of signals evidenced a 6:4 ratio for the two isomers **5aL**/**5aU**. In good accordance, MM3 calculations indicated that **5aL** was only slightly more stable than **5aU** by a small energy difference of 0.18 kcal/mol.[12] Obviously, the acidic treatment[12] of **5a** fully restored the spectrum of cationic **4a** (Figure 1c) demonstrating that this system acts as a molecular shuttle, which moves along a three-station track. In fact, under acidic condition the calix shuttle encircles the benzylammonium unit (middle station) of **4a**, while in neutral **5a** it travels back and forth between the lower and the upper station.[5b] Exchange cross-peaks were also observed in the EXSY spectrum of **5a** (400 MHz, $CDCl_3$, 263 K) that allowed us to evaluate as 0.38 s^{-1} the rate constant[14] for the **5aL** → **5aU** direct travel (Scheme 1) corresponding to a free energy of activation of 15.8 kcal mol^{-1}, while a rate constant of 0.57 s^{-1} was evaluated for the **5aU** → **5aL** inverse run ($\Delta G^{\ddagger}$ = 15.6 kcal mol^{-1}).

The shuttling of calix[6]arene wheel in neutral **5a** could be stopped by introducing a bulky group on the axle component. Therefore, **5a** was converted to its *N*-Boc derivative by treatment with Boc_2O in the presence of 2.5 equiv of P1-*t*-Bu (Scheme 1).[12] As expected, two compounds could be isolated by chromatography which correspond to the directional isomers **6aL** (29%) and **6aU** (14%) (Scheme 1).[12]

The position of the calix wheel along the axle in the most abundant isomer **6aL** was assigned by means of a 2D ROESY experiment (400 MHz, $CDCl_3$, 298 K). In particular, a diagnostic cross-peak was present between the aromatic H_o signal (Scheme 1) of the axle at 6.29 ppm and the *t*-Bu singlet of the calix wheel at 1.14 ppm.[12] Obviously, **6aL** and **6aU** isomers cannot be mutually interconverted by simple heating, and an acidic Boc-deprotection is required to restore the wheel shuttling (Scheme 1).

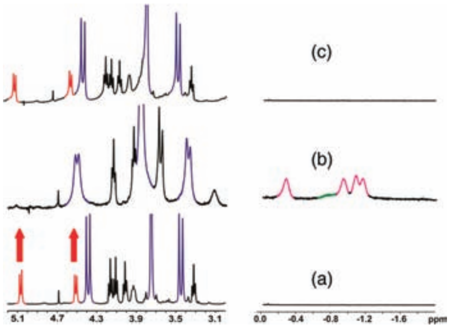

Figure 3. Relevant portions of the ^1H NMR spectra (400 MHz, $CDCl_3$) of (a) [2]rotaxane **4b** at 298 K; (b) [2]rotaxane **4b** upon addition of 1.6 equiv of P_1-*t*-Bu base, at 253 K; (c) the original spectrum (a) regenerated upon addition of 1.6 equiv of TFA. The coloring corresponds to the portion of the axle (station) hosted inside the cavity of the calix shuttle, as indicated in Scheme 1.

An unexpected different behavior was observed for methoxy-bearing [2]rotaxane **4b** which upon deprotonation gives a broad ^1H NMR spectrum for **5b**.[12] At a first glance, this could be simply ascribed to a **5bL**/**5bU** shuttling, as described above for neutral **5a**, which should be faster because of the smaller dimension of OMe groups. The ^1H NMR spectrum of neutral **5b** in $CDCl_3$ at 253 K shows two sets of signals in a 97:3 ratio that can be attributed to the two translational isomers **5bL** and **5bU** (Figure 3b). Diagnostic ROESY correlations clearly indicated that the most abundant isomer was coconformer **5bL** bearing the calix wheel at the lower station close to the urethane function. This high preference can be explained by the formation of a strong H-bond between the urethane NH at the lower station and the calixarene oxygens, as confirmed by MM3 calculations that favored **5bL** by 2.3 kcal/mol with respect to **5bU**.[12] Interestingly, ^1H VT-NMR studies on **5b** clearly evidenced a coalescence for calixarene $ArCH_2Ar$ signals at

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(14) Perrin, C. L.; Dwyer, T. J. *Chem. Rev.* **1990**, *90*, 935.

328 K (400 MHz, $CDCl_3$), which indicates the inversion of calix[6]arene cone conformation.[11]

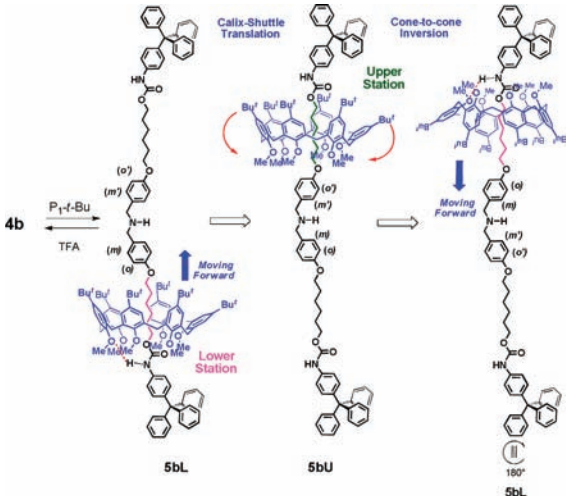

Figure 4. Combined translation/inversion motion of calix[6]-wheel in [2]rotaxane **5b**.

This implies that the axle component is not enough encumbering to impede the *O-through-the-annulus* passage of the small OMe group. This coalescence can be justified only if the shuttling process takes place between two identical stations, which are characteristics of a degenerate rotaxane system. In our instance this degeneration is the result of a combined motion of translation followed by a *cone-to-cone* inversion of the calix shuttle, as represented in Figure 4. From the above measurement, a barrier of ca. 14.8 ± 0.3 kcal mol^{-1} can be calculated for this degenerate combined motion. A further confirmation of this motion can be obtained by the two H_o and $H_{o'}$ signals of the dibenzylamino central core of the axle, which also exhibit a coalescence at 318 K due to the same combined dynamic process. Also in this instance an identical energy barrier of 14.8 ± 0.3 kcal mol^{-1} can be estimated. This barrier was also confirmed by EXSY experiments that gave a rate of exchange of $0.77 \pm 0.04\ s^{-1}$ corresponding to a free energy of activation of 14.9 ± 0.2 kcal mol^{-1}.

In order to evaluate the influence of the H-bond at the urethane NH (Figure 4) on the shuttling rate of the calix wheel in **5b** we performed a dynamic NMR study in a competitive hydrogen bond acceptor solvent such as THF-d_8. Thus, in this solvent a coalescence at 303 K was ascertained for calixarene $ArCH_2Ar$ signals of **5b**, which led to a $\Delta G^{\ddagger} = 13.6$ kcal mol^{-1}, significantly lower with respect to that obtained in $CDCl_3$ ($\Delta T_c = 25$ K, $\Delta\Delta G^{\ddagger} = 1.2$ kcal mol^{-1}). Thus, in THF-d_8, the translation/inversion combined motion of the calix shuttle is faster than in $CDCl_3$, likely because in apolar solvent the urethane NH acts as a "H-bond brake".

The translational component of the combined movement of calix shuttle of **5b** can be stopped by conversion to its *N*-Boc derivative **6b** (Scheme 1). However, in contrast to hexyloxy-bearing **5a**, in this instance only one compound could be isolated after the usual workup, which still shows a broad ^1H NMR spectrum. This means that the initially formed directional isomers **6bL** and **6bU** undergo a mutual interconversion through a *cone-to-cone* inversion of calix[6]arene macrocycle. In fact, VT-NMR studies[12] evidenced sharp signals for **6bL** and **6bU** at low temperatures and a broadening for calixarene $ArCH_2Ar$ resonances at higher temperatures in accordance with the calixarene inversion between two nonequivalent states. In addition, the low-temperature ^1H NMR spectrum of **6b** (400 MHz, $CDCl_3$, 253 K) shows that **6bL** is the most abundant isomer with respect to **6bU** (98/2 ratio). This can be again ascribed to the formation of a strong H-bond between the urethane NH proton and the oxygen atoms of the calix wheel, as indicated by MM3 calculations.[12] Dynamic data relative to the *cone-to-cone* inversion process of **6b** were obtained by 2D EXSY spectroscopy (400 MHz, $CDCl_3$, 233 K). These measurements gave a rate of exchange of 0.02 and 0.54 s^{-1}, corresponding to free energies of activation of 15.3 and 13.8 kcal mol^{-1}, for the **6bL** → **6bU** and **6bU** → **6bL** conversions, respectively. These data are higher with respect to the analogous *cone-to-cone* inversion of free hexamethoxycalix[6]arene **2b** (12.4 kcal mol^{-1}) due to the effects of H-bonding and axle steric encumbrance.[11,15] In addition, the comparison of above energy barriers suggests that the translation/inversion combined motion of **5b** should preferentially occur via a *cone-to-cone* inversion of **5bU** → **5bL** followed by a calix shuttle translation of **5bL** → **5bU**, with this latter as the slowest rate-determining step.[16]

To the best of our knowledge, the first examples of calixarene-based molecular shuttles here reported also represent the first examples of wheel inversion in a directional rotaxane. This can be considered as a new kind of motion that a molecular shuttle can perform and whose control could allow the design of molecular machines with expanded properties or functions.

Acknowledgment. Thanks are due to Dr. Patrizia Iannece (Dipartimento di Chimica e Biologia, Università di Salerno) for ESI-MS measurements.

Supporting Information Available. Synthetic details, 1D, 2D, EXSY, and VT NMR spectra, details on molecular on molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) It is interesting to point out that the coalescence of calixarene $ArCH_2Ar$ signals of [2]rotaxane **4b** occurs at temperatures surely higher than 403 K in TCDE. Therefore, an energy barrier surely higher than 18.4 kcal/mol can be estimated for the *cone-to-cone* inversion of the calix wheel in [2]rotaxane **4b**.

(16) For comparison, the difficulty associated with the passage of a *p*-xylylene spacer through the cavity of a dibenzo[24]crown-8 macroring has been highlighted: Cao, J.; Fyfe, M. C. T.; Stoddart, J. F. *J. Org. Chem.* **2000**, *65*, 1937.