Selective Synthesis of Two Constitutionally Isomeric Oriented Calix[6]arene-Based Rotaxanes**

Arturo Arduini, Flavio Ciesa, Marcello Fragassi, Andrea Pochini, and Andrea Secchi*

Rotaxanes are key compounds for the construction of synthetic molecular machines.[1,2] In spite of the remarkable achievements in their synthesis, as well as in the control of the movement of the wheel along the dumbbell component,[3] the synthesis of rotaxanes endowed with an unequivocal and predetermined relative orientation of the wheel/dumbbell systems still represents a relatively unexplored field.[4] In fact, the structure of the cyclic component employed is often related to that of a two-dimensional macrocycle, such as a crown ether, or three-dimensional symmetrical hosts, such as cucurbitols,[5] and thus have degenerate properties on the two sides of the wheel that face the two identical[6] or different[7] stoppers of the dumbbell. In the cases where the three-dimensional and nonsymmetrical cyclodextrins are used as the wheel, an axle can thread the cyclodextrin from both rims, thus leading to a mixture of orientational pseudorotaxane isomers[8] in which the orientation of the cyclodextrin along the axle is virtually unpredictable.[9] It could, however, be foreseen that a predetermined orientation of the components within these interlocked systems could endow devices with new properties.

A relatively new type of wheel that can be used in this context is the calix[6]arene platform. We have shown that triphenylureidocalix[6]arene derivatives can act as heteroditopic receptors and form remarkably stabile pseudorotaxanes with dioctylviologen salts ($K_s = 1.3 \times 10^6\,\text{M}^{-1}$)[10] as well as a calixarene-based rotaxane based on this axle/wheel dyad.[11] The binding properties of triphenylureidocalix[6]arene (**1**) were used to address the threading of an asymmetrical dipyridinium axle that threads the wheel exclusively from the upper rim in the apolar solvent C_6D_6 to yield an oriented pseudorotaxane.[12]

Herein it is demonstrated that the binding features of **1** can be exploited to control the orientation of the pseudorotaxane stoppers by using two different stoppers to yield an asymmetric [2]rotaxane having an unequivocal orientation of the wheel with respect to the different stoppers, and that an

---

[*] Prof. Dr. A. Arduini, F. Ciesa, Dr. M. Fragassi, Prof. Dr. A. Pochini, Dr. A. Secchi
Dipartimento di Chimica Organica ed Industriale dell'Università
Parco Area delle Scienze 17/a, 43100 Parma (Italy)
Fax: (+39) 0521-905-472
E-mail: arturo.arduini@unipr.it

[**] This research was partly supported by MIUR (Supramolecular Devices Project) and FIRB (Manipolazione Molecolare per Macchine Nanometriche). We thank the Centro Interdipartimentale di Misure "G. Casnati" for NMR measurements.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

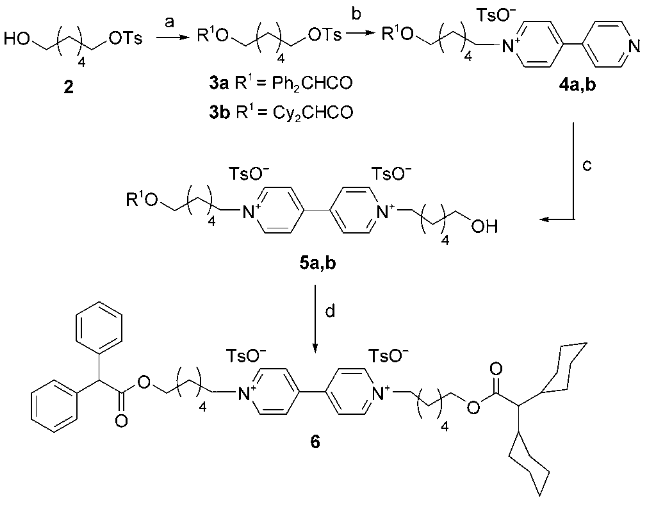
© 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim DOI: 10.1002/ange.200461336

axle based on the 4,4′-bipyridyl group can also thread through the wheel from its lower rim.

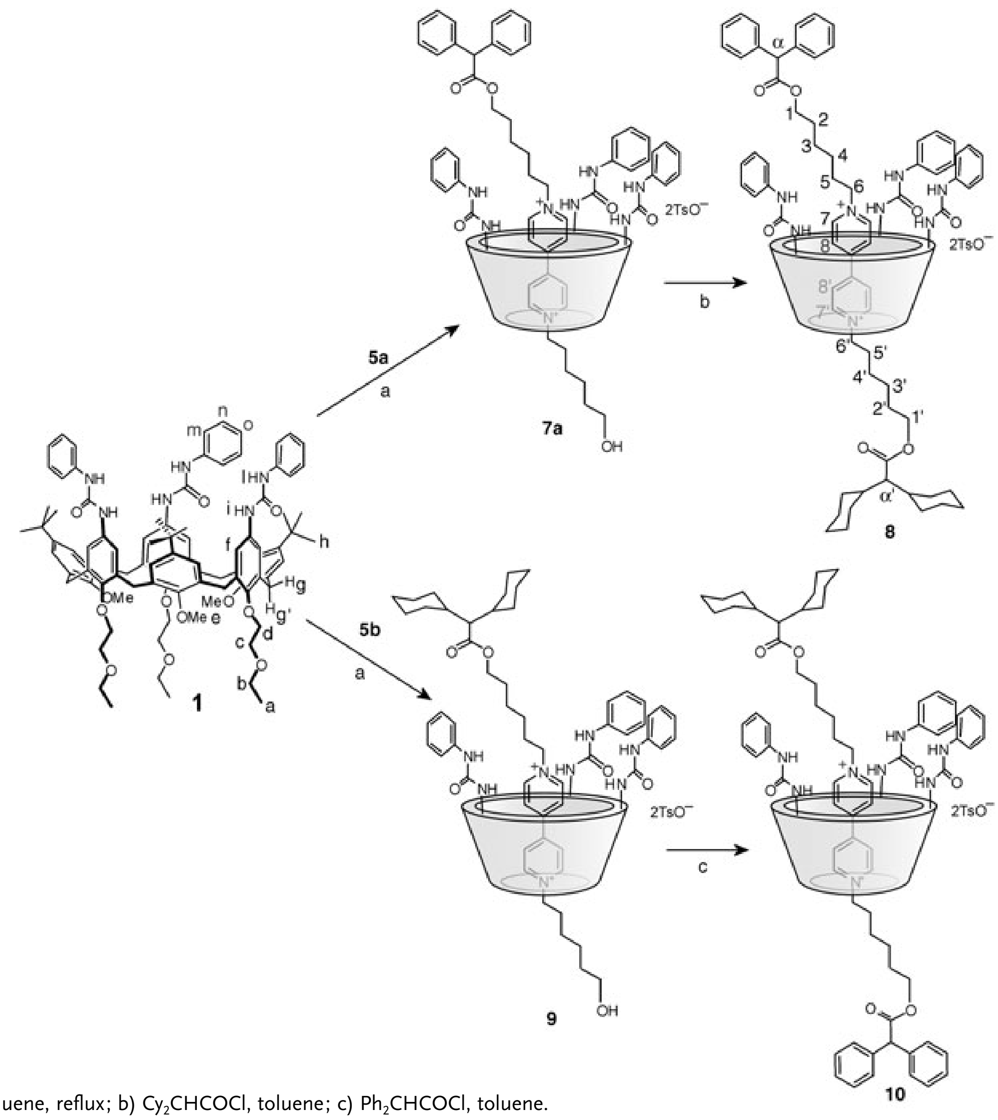
The design of the axial component was based on the observations that the position of the two identical diphenylacetyl stoppers of a calix[6]arene-based rotaxane with respect to the calixarene rims can be established by NMR techniques.[12]

Axle **5a**, in which the 4,4′-bipyridyl unit is functionalized with two C_6 alkyl chains, one of which bears a diphenylacetyl stopper at one side and the other an alcoholic OH group to be used for further stoppering, was synthesized from 6-hydroxyhexyl tosylate **2** in 12% overall yield according to Scheme 1. Wheel **1** was added to a solution of **5a** in toluene to effect the threading reaction. An excess of dicyclohexylacetyl chloride was added to the homogeneous deep red solution thus obtained to stopper the alcoholic OH group of the pseudorotaxane **7a** (Scheme 2). Rotaxane **8** was isolated in 25% yield after chromatographic separation.

Dumbbell **6** was also synthesized for comparison and enable the structure of **8** to be established (Scheme 1). The ^{1}H NMR spectrum of **8** in C_6D_6 shows that the calixarene



Scheme 1. a) R^1Cl, CH_2Cl_2, reflux, 2 h; b) 4,4′-dipyridine, CH_3CN, reflux, 24 h; c) **2**, CH_3CN, reflux, 48 h (11 and 8% overall yield for **5a** and **5b**, respectively); d) **4b**, **3a**, CH_3CN, reflux, 8 h. Cy = cyclohexyl, Ts = toluene-4-sulfonyl.



Scheme 2. a) Toluene, reflux; b) $Cy_2CHCOCl$, toluene; c) $Ph_2CHCOCl$, toluene.

wheel rearranges and assumes a more-stiffened cone structure. The downfield shift of almost $\Delta\delta = 2$ ppm of the resonances of the six NH protons indicates their involvement in hydrogen bonding with the two tosylate anions of **5a**, as also shown by X-ray structural data.[13] The position of the calixarene along the axle was established by looking at the variation in the chemical shifts of the protons of the dumbbell portion between C1 and C1′ relative to those of **6** (see Scheme 2 for numbering). In particular, the protons from C2 to C6′ in **8** undergo a substantial upfield shift, while those from C5′ to α′ are downfield shifted to a much smaller extent. The relative orientation of the dumbbell C_6 spacers with respect to the calixarene rims were established through ROESY experiments, which showed cross peaks between protons 4 and 5 of the axle and protons m, n, and o of the wheel (see Supporting Information).

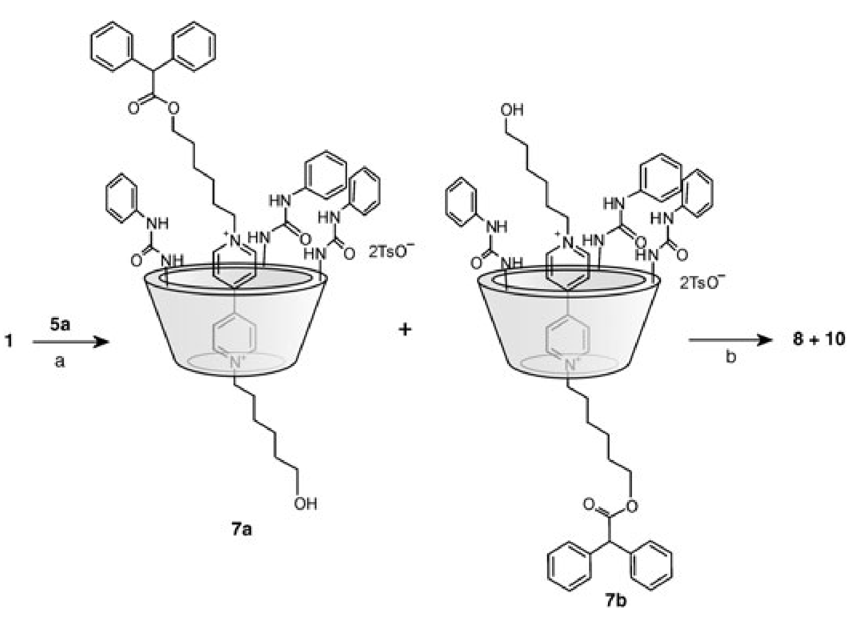
The lack of ROE cross peaks between the two different stoppers and the corresponding hexyl chains, or with protons of the wheel, precluded the existence of equivalent matching spacer—stopper groups. Nevertheless, the presence of only one signal for proton α at $\delta = 5.24$ ppm in the NMR spectrum of **8**[12] enables it to be assumed that the diphenylacetyl stopper is positioned at the upper rim of the wheel, while the dicyclohexyl one points toward the lower rim of the calixarene.

To confirm the structure of **8**, and also to exclude the presence of other rotaxanes in the reaction mixture, the rotaxane isomer **10** (see Scheme 2) was also synthesized (in 18% yield) by employing the new axle **5b**, which is characterized by the presence of a dicyclohexylacetic stopper (see Scheme 1). As expected, the ^{1}H NMR spectrum of **10** shows that the conformation of the calix[6]arene is almost exactly the same as that observed in **8**. However, the protons of the dumbbell portion between C3′ to C6 in **10** are substantially shifted upfield, while those from C5 to C1 are shifted downfield. The presence of only one singlet at $\delta = 5.23$ ppm strongly suggests that the diphenylacetyl stopper is in proximity to the lower rim in **10**, while the dicyclohexyl stopper is oriented toward the upper rim of the calixarene (see the Supporting Information).

These data can be tentatively explained if it is considered that axles **5a** and **5b** are present as tight ion pairs during the initial formation of the pseudorotaxane in toluene and as such can not fit into the calixarene cavity. These conditions maximize the hydrogen-bonding ability of the ureido NH groups toward the axle counteranion(s) that thus pivot the cationic portion of the axles to thread through the wheel exclusively from the upper rim. The high kinetic stability of the oriented pseudorotaxane that forms favors the stoppering of the OH group that protrudes from the lower rim of the wheel, without any detectable axle–wheel isomerization.

At this point a question came apparent: are these results sufficient to exclude the threading of some of the axles **5a** or **5b** from the lower rim, or is this direction of threading prevented because of the insufficient size of the calix[6]arene annulus for these guests? Acetonitrile should decrease the extent of ion pairing of the axle and hence limit the magnitude of the pivoting role exerted by the ureido groups of the wheel during threading.

Pseudorotaxane formation in CD_3CN was thus studied by ^{1}H NMR spectroscopy by equilibrating **1** and **5a** in a 1:1 molar ratio. In the spectrum of the solution thus obtained, most of the signals appeared as broad peaks and this prevents accurate assignment. However, the presence of three singlets at $\delta = 5.11$, 5.13, and 5.14 ppm (relative ratio 9:59:32) in the region where the proton α of the diphenylacetyl moiety resonates suggested that this proton existed in three different environments. In particular, the signal at $\delta = 5.11$ ppm was easily assigned to the free axle while the other two were tentatively assigned to the two isomeric pseudorotaxanes **7b** and **7a**. A similar distribution of products was also observed by dissolving the oriented pseudorotaxane **7a** that had formed in C_6D_6 in CD_3CN. This observation shows that the oriented pseudorotaxane **7a** can dissociate into its components in acetonitrile and that the threading/dethreading processes can occur from both calix[6]arene rims, thus yielding both pseudorotaxanes isomers (see the Supporting Information). This result clearly indicates that the calix[6]arene annulus is also large enough to thread on to the axle from the lower rim, and that indeed, in acetonitrile, the control elements governing the exclusive threading from the upper rim operate—if at all—only to a limited extent. Both rotaxanes **8** and **10** were obtained in 24% yield as unique chromatographic fractions by treating **1**, axle **5a**, and dicyclohexylacetyl chloride in acetonitrile (Scheme 3). Their ^{1}H NMR spectra in C_6D_6 correspond exactly to the sum of rotaxanes **8** and **10**, and thus indirectly demonstrate that only



Scheme 3. a) CH_3CN, reflux; b) $Cy_2CHCOCl$.

one of the two constitutionally isomeric rotaxanes had formed in the apolar toluene (see the Supporting Information).

The study of the unidirectional movement of the wheel along the axle of the new oriented calix[6]arene-based rotaxanes under the action of electrochemical stimuli is under investigation.

Received: July 16, 2004

Keywords: calixarenes · rotaxanes · self-assembly · solvent effects · supramolecular chemistry

---

[1] V. Balzani, A. Credi, M. Venturi, *Molecular Devices and Machines—A Journey into the Nano World*, VCH, Weinheim, **2003**.
[2] V. Balzani, A. Credi, F. M. Raymo, J. F. Stoddart, *Angew. Chem.* **2000**, *112*, 3486; *Angew. Chem. Int. Ed.* **2000**, *39*, 3348.
[3] J. D. Badjic, V. Balzani, A. Credi, S. Silvi, J. F. Stoddart, *Science* **2004**, *303*, 1845.
[4] H. R. Tseng, S. A. Vignon, P. C. Celeste, J. F. Stoddart, A. J. P. White, D. Williams, *Chem. Eur. J.* **2003**, *9*, 543.
[5] J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621.
[6] H. R. Tseng, S. A. Vignon, P. C. Celeste, J. Perkins, J. O. Jeppesen, A. Di Fabio, R. Ballardini, M. T. Gandolfi, M. Venturi, V. Balzani, J. F. Stoddart, *Chem. Eur. J.* **2004**, *10*, 155.
[7] a) G. W. H. Wurpel, A. M. Brouwer, I. H. M. Stokkum, A. Farran, D. A. Leigh, *J. Am. Chem. Soc.* **2001**, *123*, 11327; b) J. O. Jeppesen, K. A. Nielsen, J. Perkins, S. A. Vignon, A. Di Fabio, R. Ballardini, M. T. Gandolfi, M. Venturi, V. Balzani, J. Becher, J. F. Stoddart, *Chem. Eur. J.* **2003**, *9*, 2982.
[8] B. C. Gibb, *J. Supramol. Chem.* **2002**, *2*, 123.
[9] For examples of cyclodextrin-based oriented pseudorotaxanes, see: a) H. Yonemura, M. Kasahara, H. Saito, H. Nakamura, T. Matsuo, *J. Phys. Chem.* **1992**, *96*, 5765; b) M. R. Craig, M. G. Hutchings, T. D. W. Claridge, H. L. Anderson, *Angew. Chem.* **2001**, *113*, 1105; *Angew. Chem. Int. Ed.* **2001**, *40*, 1071; c) R. Isnin, A. E. Kaifer, *J. Am. Chem. Soc.* **1991**, *113*, 8188.
[10] A. Credi, S. Dumas, S. Silvi, M. Venturi, A. Arduini, A. Pochini, A. Secchi, *J. Org. Chem.* **2004**, *69*, 5881.
[11] A. Arduini, R. Ferdani, A. Pochini, A. Secchi, F. Ugozzoli, *Angew. Chem.* **2000**, *112*, 3595; *Angew. Chem. Int. Ed.* **2000**, *39*, 3453.
[12] A. Arduini, F. Calzavacca, A. Pochini, A. Secchi, *Chem. Eur. J.* **2003**, *9*, 793.
[13] F. Ugozzoli, C. Massera, A. Arduini, A. Pochini, A. Secchi, *CrystEngComm* **2004**, *6*, 227.

© 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim