Selectivity access to constitutionally identical, orientationally isomeric calix[6]arene-based [3]rotaxanes by an active template approach†

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Tris(phenylureido)calix[6]arene is endowed with unique properties that make it a valuable macrocyclic component for the synthesis of mechanically interlocked molecules. Its three-dimensional and intrinsically nonsymmetric structure is kinetically selective toward two processes: (i) in apolar media, the threading of bipyridinium based axle-like components takes place exclusively from the upper rim; (ii) \( \text{SN}_2 \) alkylation reactions of a pyridylpyridinium precursor engulfed in the cavity occur selectively at pyridylpyridinium nitrogen atom located at the macrocycle upper rim (active template synthesis). Here we exploit such properties to prepare two series of [3]rotaxanes, each consisting of three sequence isomers that arise from the threading of two identical but nonsymmetric wheels on a symmetric thread differing only for the reciprocal orientation of the macrocycles. The features of the calix[6]arene and the active template synthetic approach, together with a careful selection of the precursors, enabled us to selectively synthesise the [3]rotaxane sequence isomers of each series with fast kinetics and high yields.

Introduction

A challenging task for the bottom-up construction of molecular-level working devices, designed to perform programmed functions, is to organise in space the functional groups and binding sites responsible for their performance with the highest possible precision and in a predetermined manner.1–4 In this context, mechanically interlocked molecules (MIMs) such as rotaxanes are among the most extensively studied platforms.5,5

In typical instances, their synthesis relies on forming a pseudorotaxane precursor between a macrocycle and an axle-type component, guided by molecular recognition. The insertion of bulky substituents (stoppers) at the axle’s termini eventually leads to a rotaxane formation. This threading and capping synthetic strategy, defined as a passive template,5 allows the synthesis of MIMs with sophisticated molecular architectures.7

In more recent times, Leigh and co-workers introduced a new approach, termed as active template approach, in which a metal ion, complexed to the macrocycle, both pivots the organisation of the axle precursors around the macrocyclic cavity and mediates the formation of the covalent bonds between them to create the mechanical link.9 Starting from this seminal work, a growing number of different metal-catalysed reactions have been exploited for the realisation of several otherwise inaccessible MIMs.9–12

It nevertheless appears that the increase of the structural complexity parallels the difficulties in governing/addressing the proper relative position and orientation of their active components. This issue is particularly relevant when the components are nonsymmetric13–15 and heteroditopic,16–18 and constitutes a serious obstacle towards the functional exploitation of such valuable structural features. In this regard, among the plethora of macrocycles so far employed for the construction of molecular devices based on MIMs, calixarenes represent a recent and unusual example of a three-dimensional, nonsymmetric and heteroditopic host.19,20 We have extensively investigated the tris-[N-phenylureido] calix[6]arene (CX) (Fig. 1) as a macrocyclic component for the construction of MIMs.21,22 It was evidenced that, in low polarity media, nonsymmetric \( \text{N,N’-diallylpyridinium} \) (viologen) salts can thread the calix[6]arene annulus exclusively with their shorter alky chain and through the macrocycle upper rim, thus yielding oriented pseudorotaxane complexes. Therefore, by adopting the passive template synthesis, the preparation of rotaxanes characterised by the univocal orientation of the calixarene rims with respect to the dumbbell was achieved (Fig. 1a).23–27
More recently, efficient synthetic routes to pseudorotaxanes and rotaxanes through a metal-free active template approach were devised. In this context, we have exploited the engulfment of positively charged pyridylpyridinium salts inside the π-rich cavity of CX for the selective synthesis of orientational isomers of calix[6]arene-based [2]rotaxanes (Fig. 1b). As a consequence of its inclusion, the bound salt exposing its neutral nitrogen to the upper rim of the calixarene experiences a faster reactivity towards an SN2 reaction, leading to the formation of oriented pseudorotaxanes and rotaxanes with faster kinetics and higher yields compared to the classic threading and capping strategy (passive template approach). This supramolecular-assisted strategy could thus expand the scope for the efficient synthesis of calix[6]arene-based MIMs with strict control on the mutual orientation of their nonsymmetric molecular components (Fig. 1b).

Motivated by the general interest in higher-order rotaxanes as prospective nanodevices, and by our expertise in the synthesis of calix[6]arene-based oriented (pseudo)rotaxanes and catenanes, here we report on the preparation and properties of two series of calix[6]arene-based [3]rotaxanes configurational isomers (Fig. 2). Their common structural features are two calix[6]arene wheels threaded by a dumbbell terminating with two identical stoppers, in which a C12 alkyl chain spans two viologen units. The two series are distinguished by the length (C6 or C12) of the linkers connecting each viologen unit to its diphenylacetyl stopper. Within the two series, three distinct orientational isomers characterised by the different reciprocal...
orientation of the two calix[6]arenes that surround the two viologen units of the dumbbell were devised. Orientational isomers indicated as UU and LL present the two calix[6]arene wheels facing each other through their upper or lower rims, respectively. In the UL isomers, the two wheels are instead oriented head-to-tail along with the dumbbell (Fig. 2). Due to their structural complexity, these molecular systems will be hereafter described with apposite labels like R6UU, in which R denotes a rotaxane compound, while the number indicates the length of the alkyl chain linkers between the viologen units and the stoppers, and the subscripts point out the reciprocal orientation of the two wheels as described above (Fig. 2). The synthesis and the complete structural characterisation of the novel six [3]rotaxanes will be discussed, along with their electrochemical properties.

It should be emphasised that our compounds address the problem of sequence isomerism in [3]rotaxanes \(^{44-58}\) by taking advantage of the inherent orientation of the calixarene wheel along the main axis of the rotaxane. \(^{31,32}\) Neri and co-workers recently reported the elegant synthesis of calixarene-based [3]rotaxanes with UU and LL arrangements by a passive template synthesis. \(^{52,53}\) In these systems, a “through annulus” ring inversion of the two wheels, enabled by acid–base stimuli, allowed the observation of all three orientational isomers. In such compounds, however, the three isomers were not isolated. The present study aims at demonstrating that our active template synthesis affords (i) full control of the geometrical arrangement of the calix[6]arene wheels encircling the axle, and (ii) the preparation with high yields of sophisticated interlocked structures, otherwise inaccessible by classic threading and capping strategies (passive template synthesis).

**Results and discussion**

As mentioned in the Introduction (Fig. 1b), we have recently developed a very efficient one-pot synthetic method that allows us to synthesise several types of oriented [2]rotaxane regardless of the length of the arms of the resulting viologen-based dumbbell. \(^{31,32,34}\) The dumbbell is formed inside the calix[6]arene reactor by joining two sub-components: a stoppered pyridylpyridinium precursor and a stoppered alkylating agent. It is important to point out that the sole [2]rotaxane isolated in this one-pot reaction will always have the stopper of the pyridylpyridinium precursor at the calix[6]arene lower rim (red stopper in Fig. 1b). The necessary synthetic precursors for the synthesis of the [3]rotaxanes depicted in Fig. 2 – hereafter indicated as dumbbell components (DC1-5) – were appropriately chosen like pieces of a molecular Meccano by considering that in low polarity solvents: (i) mono-stoppered viologen-based axles always thread the cavity of CX from its upper rim, and (ii) the alkyl chain initially present on the pyridylpyridinium precursors will be in proximity of the lower rim of the wheels in the resulting [3]rotaxane.

The synthesis of DC1-5 was summarised in Scheme 1 (see ESI† for the experimental details). The free dumbbells 7a,b were also synthesised for comparison. The first [3]rotaxane orientational isomers prepared with the supramolecular-assisted approach were of the UU-type, R6UU and R12UU, which differ for the length of the outer dumbbell arms. In reactions \(\text{[A]}\) of Scheme 1, CX was equilibrated in toluene with the appropriate dumbbell components DC-2 (4a for R6 and 4b for R12) and DC-3 using a CX : DC-2 : DC-3 = 2.5 : 2.4 : 1 stoichiometric ratio. The resulting mixture was heated at 65 °C for at least seven days. In these two runs, [3]rotaxanes R6UU and R12UU were obtained in 62% and 43% yield, respectively, after chromatographic separation. No other orientational isomers were separated from the reaction mixtures. The preparation of the LL-type isomers R6LL and R12LL was carried out similarly, but using the dumbbell components DC-1 (3a for R6 and 3b for R12) and DC-4 as starting reagents (see reactions [C] in Scheme 1). These two [3]rotaxanes were isolated in 50% (R6LL) and 38% (R12LL) yields. Once again, no other orientational isomers were separated from the respective reaction mixtures.

For the synthesis of the third series of [3]rotaxane orientational isomers, R6UL and R12UL, in which both the nonsymmetric calix[6]arene wheels are oriented in the same direction with respect to the thread, a slightly different synthetic sequence was adopted (see reactions [B] in Scheme 1). DC-5 (6a for R6 and 6b for R12) was initially suspended in toluene at 80 °C with a twofold stoichiometric excess of CX to give a [2]
pseudorotaxane orientational isomer in which the stoppered arm of the viologen-based axle is located at the wheel upper rim.‡ The formation of such complex was witnessed by the deep red colour assumed by the now homogeneous solution after a few hours of stirring. The resulting pseudorotaxane complex was not isolated but immediately reacted with DC-2 ($4a$ for $R_6$ and $4b$ for $R_{12}$) for seven days at 80 °C. In this way, the supramolecular-assisted reaction occurs between the protruding $\omega$-bromo termini of DC-5, already confined in CX, and a new complex resulting from the association of DC-2 and the excess of CX already present in the solution. After workup and chromatographic separation, the desired [3]rotaxanes $R_{6uL}$ and $R_{12uL}$ were obtained in 42% and 40% yield, respectively. Analysis of the crude reaction mixture did not allow us to identify unambiguously if any other stereoisomers were formed in the reaction. However, after careful chromatography, only the target geometric isomer was observed in fractions identified as containing [3]rotaxane by LC-MS. As the same eluent system was used to isolate $R_{6uU}$ and $R_{6uL}$, this provides strong evidence for the stereoselectivity of the reaction.

The identity of the isolated compounds was initially investigated through HR-MS measurements. The recorded spectra (Fig. S25–S30†) show molecular peaks (triplly and quadruply charged) with an isotopic distribution in agreement with the structure of the two [3]rotaxanes series. The $^1H$ NMR spectra in CDCl$_3$ of the [3]rotaxanes sharing the same dumbbell 7a and isolated from the reactions {A–C} are shown in the stack plot of Fig. 4. As expected, the spectra of the three [3]rotaxanes are not superimposable. However, the two spectra of $R_{6uU}$ (Fig. 4a) and $R_{6uL}$ (Fig. 4c) have a similar pattern, both showing two well-resolved doublets, with geminal coupling, for the “axial” (4.4 ppm) and “equatorial” (3.5 ppm) diastereotopic protons of the calix[6]arene wheels bridging methylene groups (see black circles in Fig. 4a and c). On the contrary, the spectrum of $R_{6uL}$, isolated from reaction {B}, shows at ~3.5 ppm (see white circles in Fig. 4b) two overlapped doublets suggesting the head-to-tail arrangement of the calixarene macrocycles with respect to the dumbbell.

To assess the structure of these MIMs, extensive NMR experiments were carried out to identify the isolated spin systems of the inner chain and external arms and their position with respect to the rims of the calix[6]arene macrocycles. The proton signals arising from the internal (a to z) and external (1 to 6) alkyl chains of the dumbbell in $R_{6uU}$ were unequivocally

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Fig. 3 $^1H$ NMR stack plot (400 MHz, CDCl$_3$) of (a) wheel CX, (b) [3]rotaxane $R_{6uU}$, and (c) dumbbell 7a. For solubility reasons, spectrum (c) was taken in CD$_3$OD. The most representative resonances are labelled according to the molecular sketches placed above the stack plot, while their complexation induced shifts are indicated with solid lines; the unlabeled signals marked with an asterisk in the spectrum (b) belong to a rotamer of $R_{6uU}$ in the partial cone (paCo) conformation; see text and ESI† for further details.
assigned through a series of 1D and 2D NMR experiments. Initially, the $^1$H NMR spectra of R6UU, the empty wheel CX, and the free dumbbell 7a were gathered in the stack plot of Fig. 3 (for the protons labelling, see the molecular sketches in Fig. 3 and 4). From previous studies carried out on calix[6]arene-based [2]rotaxanes, it is known that the methine proton (labelled as 0) of the diphenylacetic stoppers yields a diagnostic singlet at ca. 5 ppm. In R6UU, this signal is found at 5.07 ppm (see Fig. 3b and 4a). In the rotaxanes, several signals of the dumbbell are upfield-shifted (cf. Fig. 3b and c) because of its inclusion inside the cavities of CX. Through a 2D HSQC experiment (Fig. S3†), we were able to identify the resonance of the methylene groups (1) adjacent to the diphenyl acetic stopper. Starting from this signal and thanks to a 2D TOCSY experiment (Fig. S5†), the whole spin system of the external C6 alkyl chain in R6UU was recognised. The same approach allows us to identify the signals from the free dumbbell 7a, the tosylate counterions have been omitted for clarity. Because of the symmetry, in the spectrum of the free 7a (Fig. 3c), the signals of these protons’ pairs are overlapped. However, in R6UU, these viologen units experience an anisotropic magnetic environment exerted by the nonsymmetric calixarene cavities. Thus, their signals are split into four upfield-shifted resonances at 7.67 (¥), 7.32 (§), 6.67 ($) and 6.17 ($) ppm (see purple lines in Fig. 3b and c).

Moving forward along the dumbbell’s internal and external alkyl chains, up to the methylene groups (ð) and (2), different but very diagnostic shielding effect of the calixarene cavities could be detected. The shielding effect is still very significant for the methylene protons of the internal C12 alkyl chain ($\Delta$δ = +1.4, +0.6, and +0.4 ppm for β, γ and δ, respectively, see the red-shaded box in Fig. 3). In comparison, it is negligible for the methylene protons (5) [$\Delta$δ = +0.05 ppm] of the C6 external chains. A small deshielding effect was instead observed for the methylene (4) to (2) of the same chain (see the blue-shaded box in Fig. 3). Such an effect can be accounted for by considering that, in the postulated structure of R6UU, the methylene group (5), with the rest of the chain, protrudes from the macrocycles lower rim. Thus, the dumbbell external alkyl chains suffer the deshielding effect of ethylethyloxy alkyl chains present on the calix[6]arenes lower rim. To confirm these findings, we also carried out a 2D ROESY experiment that, through the analysis of the resulting cross-peaks, revealed the spatial proximity between the protons of the inner alkyl spacer (α to δ) and the aromatic protons (b and c) of the phenylureas at the macrocycles upper rim (Fig. 5). Analogous results were obtained for

![Fig. 4](image-url)  

**Fig. 4**  $^1$H NMR stack plot (400 MHz, CDCl₃) of the [3]rotaxanes sharing dumbbell 7a, isolated from the supramolecular-assisted reactions (A–C) of Scheme 1, and corresponding to (a) R6UU, (b) R6UL and (c) R6LL, respectively. The U and L subscript labels of the spectrum (b) indicate that the corresponding protons’ chemical shifts coincide with those found for the UU and LL orientational isomers, respectively. In the sketch of the three [3]rotaxanes on the left, the tosylate counteranions have been omitted for clarity.
samples of the endure the shielding e protons of methylene (6) in more up isomers, the signals of the external alkyl chains are signiﬁcantly more separated resonances because of the two wheels’ head-to-tail arrangement. In this regard, the splitting of the signals relative to the wheels bridging methylene groups was briefly discussed. The spectra of these compounds also show two distinct resonances for the N’CH$_3$ groups sitting at the upper rim of the wheels. Thanks to a series of 1D TOCSY experiments (Fig. S20†), it was possible to assign the signal resonating at 3.25 ppm to the methylene a$_{UL}$ while the one resonating at 3.13 ppm to e$_{L}$ (Fig. 4b). Indeed, the external alkyl chain spin system starting from e$_{L}$ unequivocally leads to a signal resonating at 4.09 ppm and relative to the OCH$_2$ group 1$_{UL}$. Similarly, a second C$_6$ alkyl chain starting from the OCH$_2$(1$_{UL}$) resonating at 4.36 ppm and leading to (6$_{UL}$) at 3.85 ppm was identified.

UV-visible spectroscopic and electrochemical measurements

The UV-visible spectroscopic characterisation of the six [3]rotaxanes was performed in CH$_2$Cl$_2$. All the compounds show the typical absorption features of calixarene–bipyridinium based rotaxanes,$^{26,55}$ i.e., an intense band in the UV region and a weak broad band in the visible region of the absorption spectrum around 450 nm (Fig. S32†). As expected, the molar absorption coefficients of these two bands are roughly doubled with respect to parent [2]rotaxanes on account of the presence of twice as many chromophoric units. The spectral shapes are very similar and almost superimposable, regardless of the length of the alkyl chains and the orientation of the calixarene rings (Fig. S32◊).

By a closer inspection of the UV band maximum, however, a slight shift can be observed for the R6 series (Fig. S33†). The band is red-shifted moving from the UU to the UL and LL isomers. This behaviour would suggest an effect of the relative orientation of the calixarene wheels, which can be detected only for the series with the shorter axle. Indeed, the band is at higher energy when the three urea moieties face each other and at lower energy when they point toward the stopper units. As the wavelength shift is comparable with the resolution of our instrument, we prefer not to speculate on this observation. However, it cannot be excluded that in the shorter rotaxanes, the bipyridinium encapsulation is slightly dependent on the wheel orientation because of the presence of a nearby stopper. For comparison, the absorption spectra of the model dumbbells 7$_{a,b}$ were collected (Fig. S34†): unfortunately, these two compounds are mostly insoluble in CH$_2$Cl$_2$, and their absorption coefficient could not be measured. Nevertheless,
a comparison of the shape of the spectra confirms that the
length of the chains has no effect on the optical properties of
these compounds.

The electrochemical characterisation of the rotaxanes and
the dumbbell model compounds was performed by cyclic vol-
tammetry (CV) and differential pulse voltammetry (DPV) in
CH2Cl2; the data are gathered in Table S2. Compounds 7a and
7b show two reduction processes, respectively assigned to the
first and second monoelectronic reduction of the two bipy-
rnidium units, thus suggesting that they are independent and
non-interacting. Both processes are slightly shifted to more
negative potential values (ca. 50 mV) with respect to parent
bipyridinium-based axle compounds. This observation could
be related to the scarce solubility of the compounds and the
formation of small aggregates: indeed, the quality of the CV
curves is poor, showing the presence of spurious peaks, possibly
related to partial precipitation of the compounds during the
measurements.

The electrochemical behaviour of the six [3]rotaxanes is very
similar (Fig. 6): all the compounds show two reduction
processes, at more negative potential values with respect to
model bipyridinium dumbbells and in analogy to parent [2]
rotaxanes. The presence of only two processes, like in the
dumbbell model compounds, suggests that the two bipy-
rnidium units are equivalent and non-interacting with each other.
The shift of the first process is ascribed to the charge
transfer interaction between the bipyridinium units and the
calixarene macrocycles, which stabilises the dicaticonic bipy-
rnidium moieties. The shift of the second reduction process
suggests that the calixarenes and the monoreduced bipy-
rnidium sites are still interacting, as observed for related [2]
rotaxanes. In cyclic voltammetric experiments, both reduc-
tion curves show some degree of electrochemical irreversibility,
with peak-to-peak separation >100 mV at the explored scan rates
(from 0.1 to 1 V s⁻¹). Overall, the [3]rotaxanes show the same
electrochemical features as the parent [2]rotaxanes. Apparently,
no effect of the chain length and the relative orientation of the
wheels could be detected. Small effects, like those observed in
the absorption spectra, could be expected, but unfortunately,
the poor reversibility of the processes prevented a more detailed
analysis.

Conclusions

We have described a methodology to prepare [3]rotaxanes
comprising two identical heteroditopic nonsymmetric calix[6]
arene macrocycles with full control of their mutual orientation.
The method, based on an active template effect exerted by the
calixarene cavity on the axle subcomponents, ensures large
flexibility to the axle structure. Sets of three isomeric [3]rotax-
anes that are constitutionally identical but structurally non-
equivalent, owing to the different relative orientations of the
calixarene wheels, have been prepared and characterised for the
first time. Two series of [3]rotaxanes that differ for the length
of the axle components have been synthesised, demonstrating the
versatility of the approach. Its success stems from the fact that
the programmed isomer is obtained selectively and efficiently,
thus avoiding the need for isolation procedures that, according
to our observations, would be particularly problematic. To the
best of our knowledge, this is the only example in which the
three sequence isomers of [3]rotaxanes made of identical axle
and wheel components originating from the intrinsic asym-
metry of the wheel were selectively synthesised and isolated.

The development of made-to-order synthetic approaches to
MIMs that contain nonsymmetric components assembled with
a predetermined mutual orientation is key to explore the
virtually unlimited possibilities that the mechanical bond can
offer to stereochemistry and its applications. The realisation of
directional motion in molecular machines and the use of
sequences of threaded molecular wheels to store information at
the nanoscale are only two examples of this kind. Various
functional elements – e.g., stoppers, spacers and recognition
sites – can be introduced in the dumbbell-shaped component.
In principle, the strategy discussed here could also be extended
to make higher-order rotaxanes with more than two identical
nonsymmetric wheels threaded in any desired sequence of
relative orientations.

Author contributions

M. B. – investigation, data interpretation, writing & review; L. A.
– investigation, data interpretation, & writing; S. S. – data
interpretation, writing, review, supervision & editing; A. C. –
review, supervision & funding acquisition; G. C. – writing &
review; A. S. – data interpretation, original draft, writing, review,
supervision & editing; A. A. – conceptualization, writing, review,
supervision & funding acquisition.

Conflicts of interest

There are no conflicts to declare.
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Notes and references

[1] In weakly polar solvents, monostoppered viologen-based axles like 6a,b always thread the cavity of CX from its upper rim giving rise to orientational [2]pseudo-roxtanexes, see e.g. ref. 56.

[2] In a recent study, we demonstrated that the spontaneous threading of a ω-hydroxy endings tetracationic dumbbell inside two wheels, followed by a stoppering reaction, lead to the formation of R6Cu from the active template synthesis (A) indirectly confirmed the goodness of the active template approach to obtain calix[n]arene-based [n]rotaxane structures with full control of the geometry of the components; M. Bazzoni, G. Orlandini, G. Cera, A. Secchi and A. Arduini, unpublished results.

[3] The formation of pucro rotamers in calix[6]arene-based [2]pseudo-roxtanexes was already verified using both trisulfonamidocalix[6]arenes (see ref. 46) and CX (M. Bazzoni, G. Cera, A. Secchi and A. Arduini, unpublished results).

[4] For the full NMR characterisation of R6Ca, see ESI.†

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