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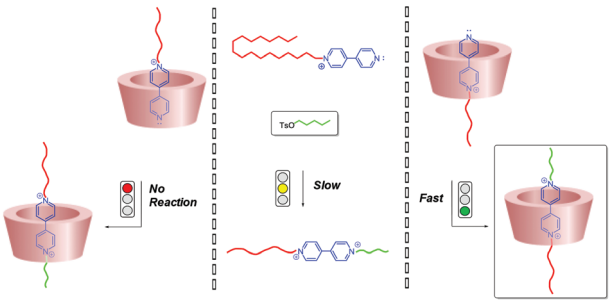
Efficient active-template synthesis of calix[6]arene-based oriented pseudorotaxanes and rotaxanes

Valeria Zanichelli, Giulio Ragazzon, Guido Orlandini, Margherita Venturi, Alberto Credi, Serena Silvi,* Arturo Arduini and Andrea Secchi*

The cavity of a calix[6]arene macrocycle assists the synthesis of oriented rotaxanes by a metal-free active template approach.



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Organic & Biomolecular Chemistry

PAPER

Efficient active-template synthesis of calix[6]arene-based oriented pseudorotaxanes and rotaxanes†

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A substrate can modify its chemical features, including a change of its reactivity, as a consequence of non-covalent interactions upon inclusion within a molecular host. Since the rise of supramolecular chemistry, this phenomenon has stimulated the ingenuity of scientists to emulate the function of enzymes by designing supramolecular systems in which the energetics and selectivity of reactions can be manipulated through programmed host–guest interactions and/or steric confinement. In this paper we investigate how the engulfment of a positively charged pyridinium-based guest inside the π-rich cavity of a tris-(*N*-phenylureido)calix[6]arene host affects its reactivity towards a S_N2 reaction. We found that the alkylation of complexed substrates leads to the formation of pseudorotaxanes and rotaxanes with faster kinetics and higher yields with respect to the standard procedures exploited so far. More importantly, the strategy described here expands the range of efficient synthetic routes for the formation of mechanically interlocked species with a strict control of the mutual orientation of their non-symmetric molecular components.

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Introduction

The formation of a supramolecular complex between a host and a guest is driven by the free energy gain derived from the non-covalent interactions between its components. Particularly in the case where one or both the complementary components of the complex are charged species, an exchange of charge density between the host and its guest takes place, because of attractive Coulombic interactions. This basic physical phenomenon has been extensively exploited for the design and synthesis of efficient and highly selective hosts as ionophores,[1] for highly polar guest recognition and sensing,[2] or for the construction of new functional materials.[3]

Relatively less explored is the possibility to exploit the changes of the chemical features endured by the guest upon its coordination with a host to modify its reactivity. Since the rise of supramolecular chemistry, this phenomenon has stimulated the creativity of chemists in the attempt to emulate the function of enzymes by affecting the energetics and selectivity of reactions of substrates contained in synthetic hosts or cages.[4–7] Supramolecular catalysis in confined environments[8–12] can rely on different strategies, as the role of the host can be either to bring the reactants in close proximity or to function as a platform for the reactions, stabilizing the transition state or increasing the reactivity of the guest. Within this context, calix[*n*]arenes, because of their π-rich concave aromatic cavity and the possibility to insert and orient in space functional groups and binding sites, have been widely used in supramolecular catalysis.[13–18] A most significant issue in host–guest catalysis is the degree of affinity of the product for the host, which can lead to product inhibition, thereby limiting the turnover and decreasing the catalytic efficiency. At worst, if the stability of the complex between the host and the product is large enough, turnover can be totally prevented and the reactions are not catalytic. However, if the host–product complex is a species of interest, the inefficient release of the product is not an issue anymore: indeed the limited turnover, which is normally a drawback for catalysis, can become an advantage from a synthetic point of view.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ob01642e
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We have recently investigated the ability of calix[6]arene derivatives such as **PuCxEt** (Fig. 1), endowed with three *N*-phenylureido (Pu) units at the upper rim and three ethylethoxy (Et) moieties at the lower rim of the calixarene (Cx), to act as heteroditopic hosts for 1,1′-dialkyl-4,4′-bipyridinium ion pairs (dialkylviologen salts). In non-polar solvents, stable oriented pseudorotaxanes are indeed obtained by the threading of the viologen axle into the electron-rich cavity of the calix[6]arene macrocycle (Fig. 1).[19–23] Interestingly, under appropriate conditions the threading takes place with a strict directional control with regard to both the rim of the calixarene and the extremity of the viologen-based thread. This binding process was accurately described, and the studies on the kinetic control on the orientational outcome given by the length of simple alkyl chains appended to the bipyridinium core paved the way for new challenges.[24] Indeed, the total control on the threading/dethreading process of the axle may allow the development of new molecular devices endowed with a wider set of properties and possible applications.

In view of our current interest in understanding whether the stimuli-induced shuttling movement along bipyridinium-based axles can occur in a preferred direction with respect to the two non-equivalent rims of calix[6]arene-based wheels,[19,22,25] it is important to prepare rotaxanes in which the orientation of **PuCxEt** with respect to a non-symmetric axle – *e.g.* a bipyridinium unit bearing alkyl side chains of different lengths – is precisely controlled. So far, the synthesis of this kind of oriented rotaxane was accomplished by means of directional insertion of a 1,1′-dialkyl-4,4′-bipyridinium axle (possibly with one stoppered extremity) in the calixarene, followed by a stoppering (acylation) reaction.[25] The rate determining step of this approach is the alkylation of the bipyridine or pyridylpyridinium ion, which takes 7 days at reflux, with an overall reaction yield of about 70%.[25]

In line with the studies of Rebek and co-workers, who demonstrated the acceleration of the Menschutkin reaction of quinuclidine encapsulated in a cavitand,[26] we recently demonstrated[27] that in these calix[6]arene-based oriented pseudorotaxanes, the engulfment of the positively charged pyridylpyridinium guest inside the π-rich cavity of the host enhances the nucleophilicity of the neutral nitrogen atom towards a S_N2 reaction. The successive alkylation of such a stabilized substrate leads to the accelerated formation of oriented supramolecular complexes or mechanically interlocked molecules. This was the first example of metal-free active template synthesis of rotaxanes.[12] In this paper we investigate the mechanism of this new supramolecularly-assisted synthetic strategy and discuss the results obtained in the preparation of calix[6]arene-based pseudorotaxanes and rotaxanes exhibiting a precise relative orientation of their non-symmetric components.

Results and discussion

To describe the results of this study, we found it useful to label the compounds with explicit descriptors showing (i) the non-symmetric nature of the wheel and axle components and (ii) their relative orientation in (pseudo)rotaxanes (Fig. 1). Hence, the calixarene host (Cx) bearing phenylureido (Pu) units at the upper rim and ethylethoxy (Et) units at the lower rim is denoted as **PuCxEt**. Labels such as $\mathbf{PpyC}_n^{+}$ and $\mathbf{C}_m\mathbf{BpyC}_n^{2+}$ are respectively employed for the pyridylpyridinium (Ppy) and bipyridinium (Bpy) axles, where *m* and *n* are the number of carbon atoms of the side chain(s) connected to the pyridinium nitrogen atom(s). The presence of a terminal stopper in a side chain of the axle is indicated with S. In this study, these salts have been employed as tosylates. In wheel–axle complexes, the calixarene is always denoted as **PuCxEt**, while the order of the side chain(s) in the label of the axle component reflects its (their) positioning with respect to the wheel rims. For example, $[\mathbf{PuCxEt} \supset \mathbf{PpyC}_n]^{+}$ is a pseudorotaxane in which the C_n chain of the pyridylpyridinium guest is oriented

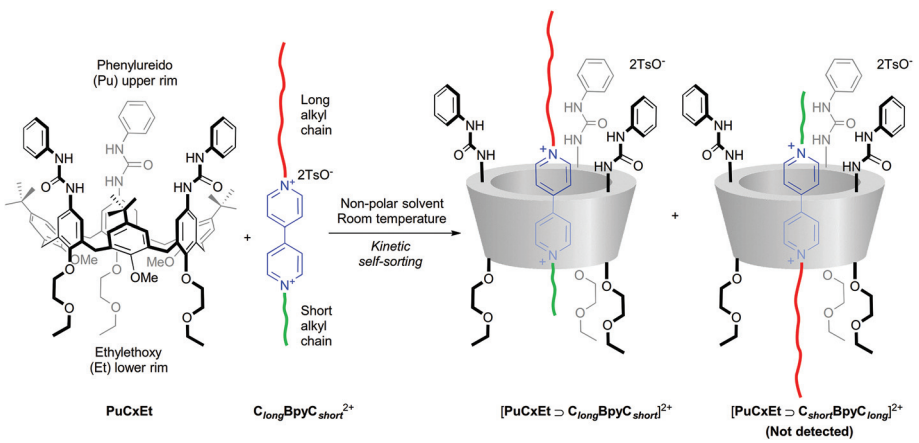


Fig. 1 Upon mixing the heteroditopic calix[6]arene wheel **PuCxEt** with a non-symmetric bipyridinium-based axle bearing two alkyl chains of different lengths ($\mathbf{C}_{long}\mathbf{BpyC}_{short}^{2+}$), two different pseudorotaxane orientational isomers can be formed, but only one of them ($[\mathbf{PuCxEt} \supset \mathbf{C}_{long}\mathbf{BpyC}_{short}]^{2+}$) is afforded in non-polar solvents at room temperature owing to a kinetic self-sorting process. The nomenclature employed to identify the complexes is meant to define the relative orientation of the wheel and axle components (see the text for details).

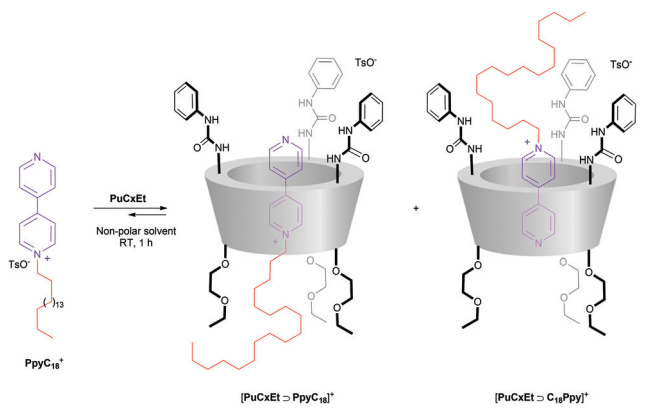
towards the lower rim (Et) of the calixarene, with the pyridyl nitrogen pointing towards the upper rim; $[\mathbf{PuCxEt{\cdot}SC_mBpyC_nS}]^{2+}$ is a rotaxane in which the C_m and C_n chains of the bipyridinium guest are both stoppered and oriented towards the upper (Pu) and lower (Et) rims, respectively.

Initially, 1-octadecyl-4,4′-pyridylpyridinium tosylate $\mathbf{PPyC_{18}}^+$ was selected as a suitable guest to study the ability of **PuCxEt** to form complexes with pyridylpyridinium salts (Scheme 1). The occurrence of the complexation between **PuCxEt** and $\mathbf{PPyC_{18}}^+$ was first hypothesized by the naked-eye observation that, at room temperature, the non-colored suspensions of $\mathbf{PPyC_{18}}^+$ in non-polar solvents such as dichloromethane, chloroform or toluene, became immediately homogeneous and orangish when treated with an equimolar solution of **PuCxEt** in the same solvent. The composition of the 1 : 1 mixture was first investigated through NMR measurements in $CDCl_3$, benzene-d_6 and toluene-d_8. Regardless of the solvent used, all spectra showed a general broadness of the signals (see Fig. S3–S5, ESI†) indicating a high conformational fluxionality of the species in solution. However, the presence of several signals in the high field region of the spectra, in all cases (from 0 to 1 ppm), witness the inclusion of the $\mathbf{PPyC_{18}}^+$ octadecyl chain inside the calix[6]arene cavity. Variable low temperature 1D and 2D NMR experiments in $CDCl_3$ (see Fig. S6–S9, ESI†) finally confirmed that both orientational pseudorotaxane isomers $[\mathbf{PuCxEt} \supset \mathbf{PpyC_{18}}]^+$ and $[\mathbf{PuCxEt} \supset \mathbf{C_{18}Ppy}]^+$ are present (see Scheme 1). The strength of the association was investigated through UV/Vis titrations carried out by adding increasing amounts of **PuCxEt** to a 2.4×10^{-4} M solution of $\mathbf{C_{18}Ppy}^+$ in toluene kept at 60 °C for solubility reasons. During the titration, a new band centered at λ = 370 nm, assigned to charge-transfer (CT) interactions between the electron rich host and the electron poor guest showed up; the fitting of the absorbance data[28] gave an apparent binding constant of 8.1×10^4 M^{-1} (see Fig. S10, ESI†).

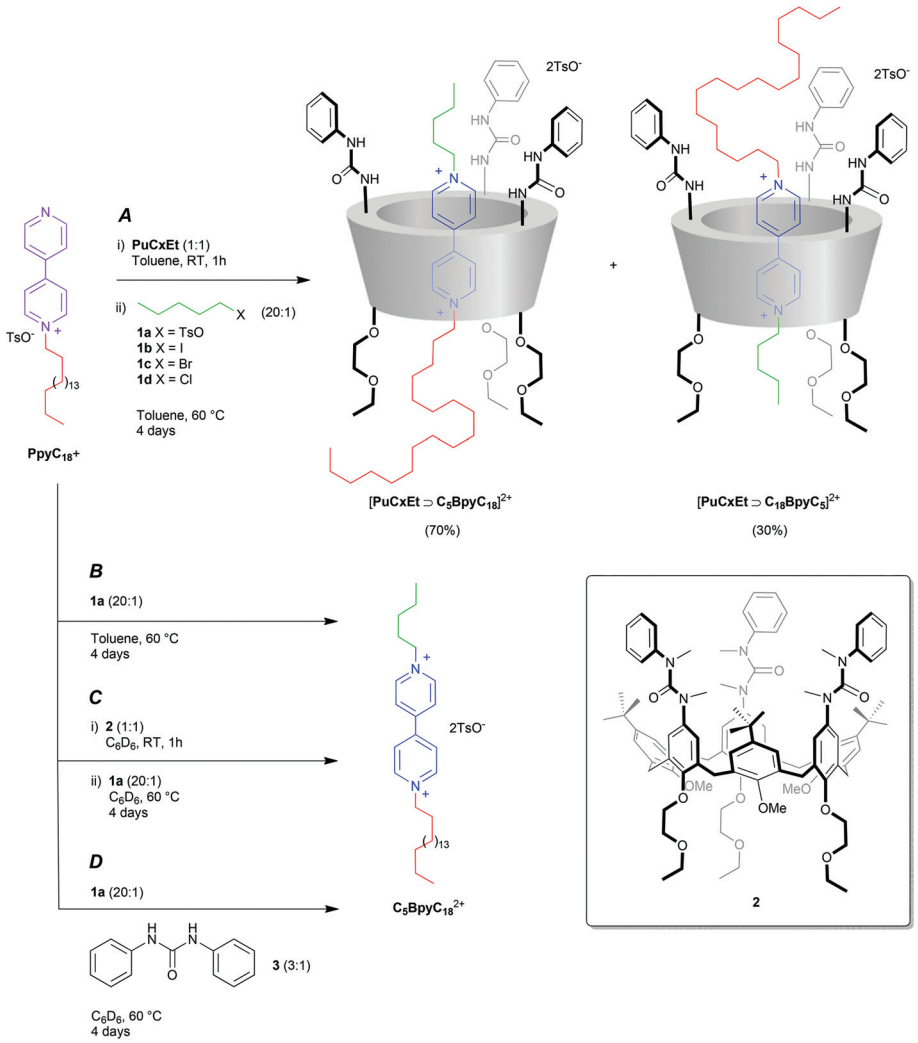
Once the interaction between **PuCxEt** and $\mathbf{PPyC_{18}}^+$ was demonstrated, a simple experiment was devised to verify whether the reactivity of the latter is affected by its inclusion into the aromatic cavity of the former. To this aim, $\mathbf{PPyC_{18}}^+$ was reacted with *n*-pentyl tosylate (**1a**) in a 1 : 20 stoichiometric ratio to yield the 1-pentyl-1′-octadecyl-4,4′-bipyridinium species $\mathbf{C_5BpyC_{18}}^{2+}$ (experiment A in Scheme 2). The alkylation of $\mathbf{PPyC_{18}}^+$ was carried out in toluene at 60 °C in the presence of an equimolar amount of **PuCxEt**. The formation of $\mathbf{C_5BpyC_{18}}^{2+}$ inside the calixarene wheel was confirmed by ^{1}H NMR spectra (see Fig. S11, ESI†) and was directly monitored through UV/Vis measurements (Fig. 2). Indeed, previous studies[24] revealed that such a bipyridinium salt gives rise, with **PuCxEt**, to stable oriented pseudorotaxane isomers $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}$ and $[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$ (Scheme 2), which exhibit typical CT absorption features (a more intense shoulder at around λ = 370 nm and a weaker band at λ = 470 nm), regardless of the orientation of the axle in the calixarene cavity.[19,29,30] Considering a S_N2 mechanism,[26,31,32] the fitting of the absorption data at λ = 470 nm yielded a rate constant of 1.4×10^{-4} M^{-1} s^{-1} (Fig. 2).

A blank experiment (B) was carried out under the same conditions but in the absence of the calixarene host (Scheme 2). In this experiment, the formation of $\mathbf{C_5BpyC_{18}}^{2+}$ could not be directly monitored because it is not appreciably soluble in toluene in its uncomplexed form. Therefore, we set up nine parallel alkylation experiments which were stopped at different and progressive times (from 0 to 100 h). In each of these experiments, the amount of $\mathbf{C_5BpyC_{18}}^{2+}$ formed was evaluated by measuring the absorbance at λ = 370 nm upon addition of **PuCxEt** to the reaction mixture (the CT band at λ = 470 nm was too weak). The increase of the reaction product was less significant than in experiment A; from the fitting of the absorption data according to a S_N2 mechanism, a rate constant of 8.6×10^{-6} M^{-1} s^{-1} was obtained (Fig. 2). The comparison of this value with that determined in experiment A shows evidence of an increment by 16 times of the reaction rate when the alkylation reaction of $\mathbf{PPyC_{18}}^+$ with **1a** is performed in the presence of **PuCxEt**.

To gain more insight into the mechanism of the reaction, we repeated experiment A (Scheme 2) with a series of pentyl derivatives that differ for the leaving group, *n*-$C_5H_{11}X$ (**1b–d**; X = I, Br and Cl). The rate constants determined by fitting the time-dependent absorption data with a second-order mechanism (see Fig. S12, ESI†) are gathered in Table 1. As expected, the tosylate **1a** yielded the highest reaction rate and, in general, the results obtained for the entire series reflect the ability of the leaving groups (TsO > I > Br > Cl) present in the alkylating agent. The rate enhancement measured in this supramolecularly-assisted reaction (experiment A) could be reasonably ascribed to the following factors: (i) *cavity effect*: the encapsulation of $\mathbf{PPyC_{18}}^+$ in the cavity of **PuCxEt** may enhance the nucleophilicity of the neutral nitrogen atom of the former, owing to the charge delocalization of the positive nitrogen induced by the electron-rich cavity of the latter; additionally, the transition state could be stabilized by cation–π interactions with the calixarene cavity;[31–33] (ii) *phenylurea effect*: the phenylurea groups at the upper rim of **PuCxEt** might accelerate the alkylation reaction of $\mathbf{PPyC_{18}}^+$ by binding the leaving groups in the transition state, thereby stabilizing it.



Scheme 1



Scheme 2

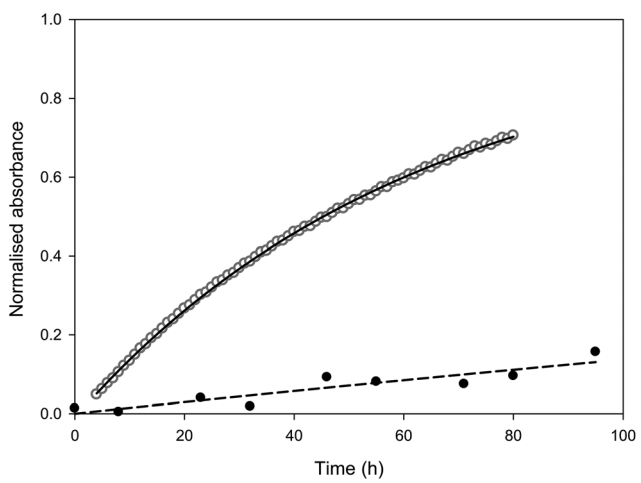


Fig. 2 Normalized absorption changes for experiment A (reaction of $PPyC_{18}^{+}$ in the presence of **PuCxEt**; open circles, solid line, λ = 470 nm) and B (reaction in the absence of **PuCxEt**; full circles, dashed line, λ = 370 nm) using **1a** as the alkylating agent. The lines are the fitting of the data points according to a S_N2 mechanism; see Scheme 2 and the text for details.

Table 1 Kinetic data relative to experiment A in Scheme 2 (toluene, T = 60 °C)

Alkylating agent (n-$C_5H_{11}X$)	k (M^{-1} s^{-1})	Relative rate
1a (X = TsO)	1.4×10^{-4}	26
1b (X = I)	6.6×10^{-5}	12
1c (X = Br)	1.6×10^{-5}	3
1d (X = Cl)	5.4×10^{-6}	1

To investigate the cavity effect, the model reaction was carried out in C_6D_6 at 60 °C in the presence of **1a** and of a calix[6]arene (**2**) derived from **PuCxEt** in which the urea groups are fully *N*-methylated and thus unable to act as hydrogen bonding donors (experiment C in Scheme 2).[34] Only a small amount of $C_5BpyC_{18}^{2+}$ was detected by ^{1}H NMR measurements after four days of reaction (see Fig. S13, ESI†). The complexation of cationic guests by the calixarene cavity, however, is conditioned by the presence of phenylurea moieties which bind the counteranion(s) of the guest.[29] Therefore, it is not possible

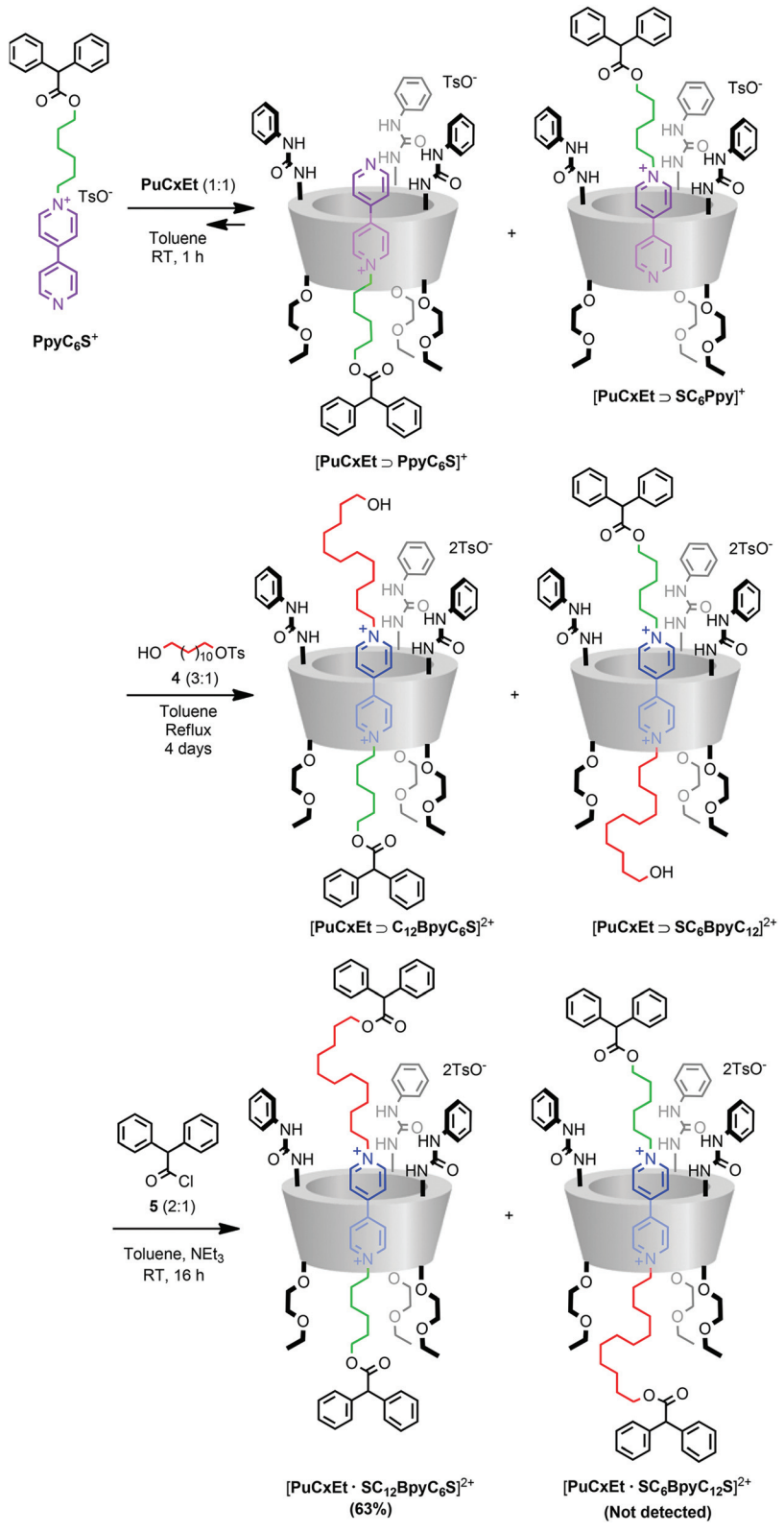
to differentiate the phenylurea effect from that of the calixarene cavity. Nevertheless, experiment D (Scheme 2) was devised in an attempt to reveal a possible phenylurea effect. As in the main experiment A, $\mathbf{PPyC_{18}}^+$ was reacted with **1a** in C_6D_6 at 60 °C in the presence of 3 equivalents of 1,3-diphenylurea (**3**). The latter compound is meant to mimic the role of the three identical *N*-phenylurea units present at the upper rim of **PuCxEt**. After four days calixarene was added to the cooled mixture in order to monitor the amount of $\mathbf{C_5BpyC_{18}}^{2+}$ formed. No traces of the bipyridinium salt were found in the reaction mixture. In fact, the corresponding ^{1}H NMR spectrum shows only signals ascribable to the pseudorotaxane formed between **PuCxEt** and $\mathbf{PPyC_{18}}^+$, and to **3**. From this experiment, it can be thus inferred that the *N*-phenylureido groups not linked to the calixarene host are unable to trigger the S_N2 reaction between $\mathbf{PPyC_{18}}^+$ and **1a**.

Overall, experiments A–D demonstrate that only the presence of both the electron-rich cavity and the phenylureido groups in **PuCxEt** can promote the complexation of $\mathbf{PPyC_{18}}^+$ and, most important, does accelerate the S_N2 reaction to generate $\mathbf{C_5BpyC_{18}}^{2+}$ inside the calixarene cavity. It is worth noting that in this supramolecularly-assisted reaction the anionic leaving group plays a dual role. On the one hand, our experiments (Table 1) show that the rate of S_N2 reactions with RX alkylating agents depends on the ability of the group X to act as a leaving group. On the other hand, the anionic leaving group can contribute to the stabilization of the resulting pseudorotaxane complex by forming hydrogen bonds with the urea moieties present in the receptor. As a matter of fact, the acceleration observed in experiment A is likely to be affected simultaneously by the ability of X to act as a good leaving group and to accept hydrogen bonding by the urea groups as an incipient anionic species in the reaction transition state.

To gain further insights into the supramolecularly-assisted alkylation reaction, we investigated the outcome of experiment A in terms of the distribution of the resulting possible orientational pseudorotaxane isomers $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}$ and $[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$ (Scheme 2). As previously reported, the length of the alkyl chains appended to the bipyridinium core can be exploited as a control element to govern the orientation of the threading of asymmetric axles into **PuCxEt**, to selectively yield oriented pseudorotaxanes.[24] In particular, we have shown that, at room temperature in solvents with low polarity, non-symmetric axles in which the two linear alkyl chains differ in length for at least 7 carbon atoms preferentially thread the wheel from its upper rim with their short alkyl chain. As an example, the threading of $\mathbf{C_5BpyC_{18}}^{2+}$ gives almost exclusively the orientational isomer indicated as $[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$, albeit experiments indicate that the other isomer is equally stable.[24] The kinetic product of threading, $[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$, slowly isomerizes to the other form $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}$ in toluene at reflux, reaching a ratio $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}/[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$ of 3 : 7 after 10 days.[24] Interestingly, a deeper ^{1}H NMR analysis (see Fig. S11, ESI†) of the mixture of orientational isomers resulting from the supramolecularly-assisted experiment A (Scheme 2) gave evidence for the preferential formation of $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}$, that is, the kinetically disfavored isomer resulting from the threading of $\mathbf{C_5BpyC_{18}}^{2+}$ into **PuCxEt**. A ratio $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}/[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$ of 7 : 3 was observed. This finding suggests that among the two possible orientational pseudorotaxane isomers $[\mathbf{PuCxEt} \supset \mathbf{PpyC_{18}}]^+$ and $[\mathbf{PuCxEt} \supset \mathbf{C_{18}Ppy}]^+$ formed upon complexation between **PuCxEt** and $\mathbf{PPyC_{18}}^+$, the former reacts preferentially. This could be either a thermodynamic or a kinetic effect; namely, the selective formation of the orientational isomer $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}$ could be due to (i) a larger population (thermodynamic reason), and/or (ii) a higher reactivity (kinetic reason) of $[\mathbf{PuCxEt} \supset \mathbf{PpyC_{18}}]^+$ with respect to $[\mathbf{PuCxEt} \supset \mathbf{C_{18}Ppy}]^+$. As a matter of fact, the selectivity of the reaction could even be larger, because $[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$ could result from the spontaneous scrambling of $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}$ that occurs upon heating the toluene solution. In other words, it cannot be excluded that $[\mathbf{PuCxEt} \supset \mathbf{C_5BpyC_{18}}]^{2+}$ is the sole product of the alkylation reaction and subsequently, under the experimental conditions of the reaction, its components dethread and rethread to yield the kinetic product of the threading process, $[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$. A minor contribution could also be provided by the alkylation of the uncomplexed salt $\mathbf{PPyC_{18}}^+$ (route B in Scheme 2), affording axle $\mathbf{C_5BpyC_{18}}^{2+}$ which, by taking the faster threading route through calixarene, would lead again to $[\mathbf{PuCxEt} \supset \mathbf{C_{18}BpyC_5}]^{2+}$.[24]

To boost the effect of the supramolecular assistance of **PuCxEt** on the distribution of the orientational isomers, we attempted to reduce the axle scrambling by placing a bulky substituent on the alkyl extremity of the pyridylpyridinium guest in order to hamper the rearrangement of the resulting bipyridinium species into the wheel. It must be recalled here that the threading of a bipyridinium axle into the calixarene wheel in low polarity solvents takes place exclusively through the upper rim, most likely because the dissociation of the guest ion pair, which is a prerequisite for threading, is favored by the binding of the counteranions at the phenylurea groups.[22,24,29] Threading and dethreading from the lower rim are kinetically hampered processes.[22] Therefore, we carried out a new supramolecularly-assisted alkylation experiment using the stoppered pyridylpyridinium salt $\mathbf{PPyC_6S}^+$ as the substrate (Scheme 3).

In analogy with previous results, the complete dissolution of the guest with the formation of an orangish homogeneous solution revealed the formation of a complex between **PuCxEt** and $\mathbf{PPyC_6S}^+$. The solution was analyzed by NMR spectroscopy and, as observed for the formation of the pseudorotaxane between the calixarene and the non-stoppered guest $\mathbf{PPyC_{18}}^+$, the ^{1}H NMR spectrum of the mixture showed very broad signals in all deuterated low-polarity solvents tested. Nevertheless, the presence of two signals in the spectrum in toluene-d_8 at T = 80 °C for the methoxy protons at the lower rim of **PuCxEt**, as well as the presence of two resonances at *ca.* 5 ppm for the methyne proton of the stoppering diphenylacetic group of $\mathbf{PPyC_6S}^+$ (see Fig. S14 and 15, ESI†), could be reasonably ascribed to a mixture of two orientational pseudorotaxane isomers $[\mathbf{PuCxEt} \supset \mathbf{PpyC_6S}]^+$ and $[\mathbf{PuCxEt} \supset$



Scheme 3

$\mathbf{SC_6Ppy}]^+$ (Scheme 3). The observation of both orientational pseudorotaxane isomers when the stoppered axle $\mathbf{PPyC_6S}^+$ is mixed with **PuCxEt** in toluene can only be explained assuming that the pyridylpyridinium guest, unlike bipyridinium homologues,[20] can thread the calixarene through the lower rim. Presumably, the role of the urea moieties in driving the thread-

ing/dethreading of dicationic bipyridinium compounds through the upper rim (*vide supra*) is less significant when the guest bears only one positive charge as in the case of a pyridylpyridinium axle.

Since the relative amount of these species in solution was difficult to determine, and considering the results of the supramolecularly-assisted alkylation reaction (route A in Scheme 2), we tried to confirm the previously hypothesized higher reactivity of the [**PuCxEt** ⊃ **PpyC$_6$S**]$^+$ pseudorotaxane isomer by covalently capturing the corresponding oriented rotaxane derivative through alkylation and stoppering. To this purpose the reaction mixture was treated with an excess of 12-hydroxydodecyl tosylate **4** in refluxing toluene for 4 days, enabling the formation of the two pseudorotaxane isomers [**PuCxEt** ⊃ **C$_{12}$BpyC$_6$S**]$^{2+}$ and [**PuCxEt** ⊃ **SC$_6$BpyC$_{12}$**]$^{2+}$ (Scheme 3). It is worth noting that, for the kinetic reasons described above,[22] [**PuCxEt** ⊃ **C$_{12}$BpyC$_6$S**]$^{2+}$ cannot be formed by the isomerization of [**PuCxEt** ⊃ **SC$_6$BpyC$_{12}$**]$^{2+}$ because the stoppered axle **C$_{12}$BpyC$_6$S**$^{2+}$ would need to thread the cavity through the lower rim of the wheel. Similarly, [**PuCxEt** ⊃ **SC$_6$BpyC$_{12}$**]$^{2+}$ cannot be formed by the isomerization of [**PuCxEt** ⊃ **C$_{12}$BpyC$_6$S**]$^{2+}$, as the stoppered axle should exit from the cavity through the lower rim of the wheel. No attempts to isolate or characterize the pseudorotaxanes were made, and the mixture was directly reacted with diphenylacetyl chloride **5** at room temperature to promote the formation of rotaxane(s) (Scheme 3). It is important to underline that, as observed in our previous work,[25] this kind of stoppering reaction does not cause any isomerization process when performed at RT. Indeed, only the rotaxane isomer [**PuCxEt·SC$_{12}$BpyC$_6$S**]$^{2+}$ was successfully isolated in good yield after chromatographic separation (63%). No trace of the other orientational isomer [**PuCxEt·SC$_6$BpyC$_{12}$S**]$^{2+}$ was found in the mixture.

The ^{1}H NMR characterization in benzene-d_6 of the isolated rotaxane [**PuCxEt·SC$_{12}$BpyC$_6$S**]$^{2+}$ (Fig. 3a) was facilitated by the comparison with the known symmetric rotaxanes [**PuCxEt·SC$_6$BpyC$_6$S**]$^{2+}$ and [**PuCxEt·SC$_{12}$BpyC$_{12}$S**]$^{2+}$, having respectively C_6 and C_{12} alkyl spacers between the bipyridium core and the stoppers.[35] The presence of a sharp singlet at δ = 3.88 ppm for the methoxy groups of the wheel, and only one triplet for each 1′ and 1 methylene groups, at δ = 4.32 and 4.04 ppm, respectively, unequivocally confirmed the hypothesized geometrical arrangement of the axial component of [**PuCxEt·SC$_{12}$BpyC$_6$S**]$^{2+}$ inside the calixarene aromatic cavity.

This remarkable result indirectly confirms that the reaction between **PPyC$_6$S**$^+$ and the alkylating agent **4** must quantitatively take place inside the cavity of **PuCxEt**. In fact, if **PPyC$_6$S**$^+$ were alkylated outside the calix[6]arene cavity, axle **C$_{12}$BpyC$_6$S**$^{2+}$ would have been obtained; as demonstrated in previous studies,[19,20,25] such a species would have threaded the wheel selectively from the upper rim, thereby generating – after the stoppering reaction – the orientational rotaxane isomer [**PuCxEt·SC$_6$BpyC$_{12}$S**]$^{2+}$. Furthermore, the outcome of the reaction also indicates that the supramolecularly-assisted alkylation takes place only on the orientational pseudorotaxane isomer [**PuCxEt** ⊃ **PpyC$_6$S**]$^+$ (Scheme 3): if it had occurred on the other isomer, [**PuCxEt** ⊃ **SC$_6$Ppy**]$^+$, rotaxane [**PuCxEt·SC$_6$BpyC$_{12}$S**]$^{2+}$ would have again been obtained after the stoppering reaction.

We hypothesize that the selectivity for the [**PuCxEt** ⊃ **PpyC$_6$S**]$^+$ isomer could involve the deeper engulfment of the positive charge into the electron rich cavity of the calixarene, which may result in an increased stabilization and, consequently, in an enhanced nucleophilicity with respect to the [**PuCxEt** ⊃ **SC$_6$Ppy**]$^+$ isomer. Moreover, in the former isomer the pyridine nitrogen atom of the pyridylpyridinium guest is exposed to the bulk and therefore it is more easily accessible, while in the latter isomer the access to the non-alkylated nitrogen is hampered by the presence of the methoxy groups of **PuCxEt**.[20] In the alkylation reaction of the [**PuCxEt** ⊃

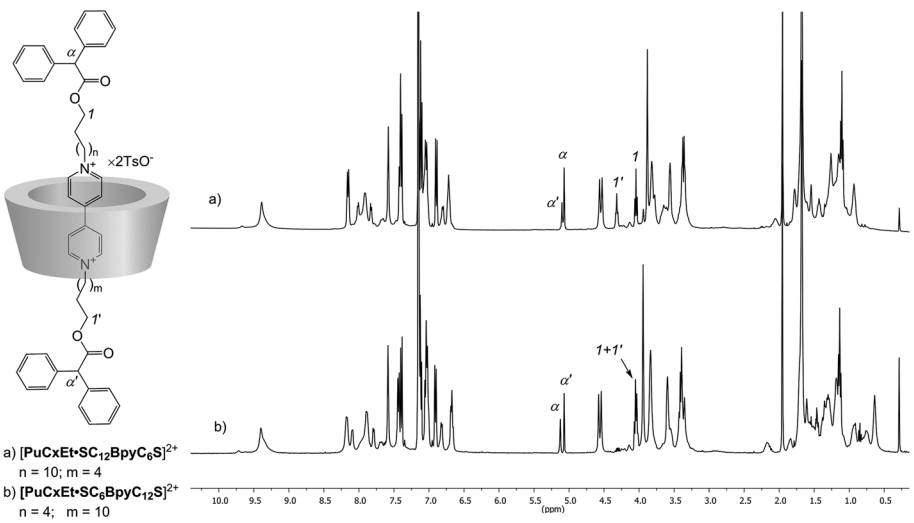
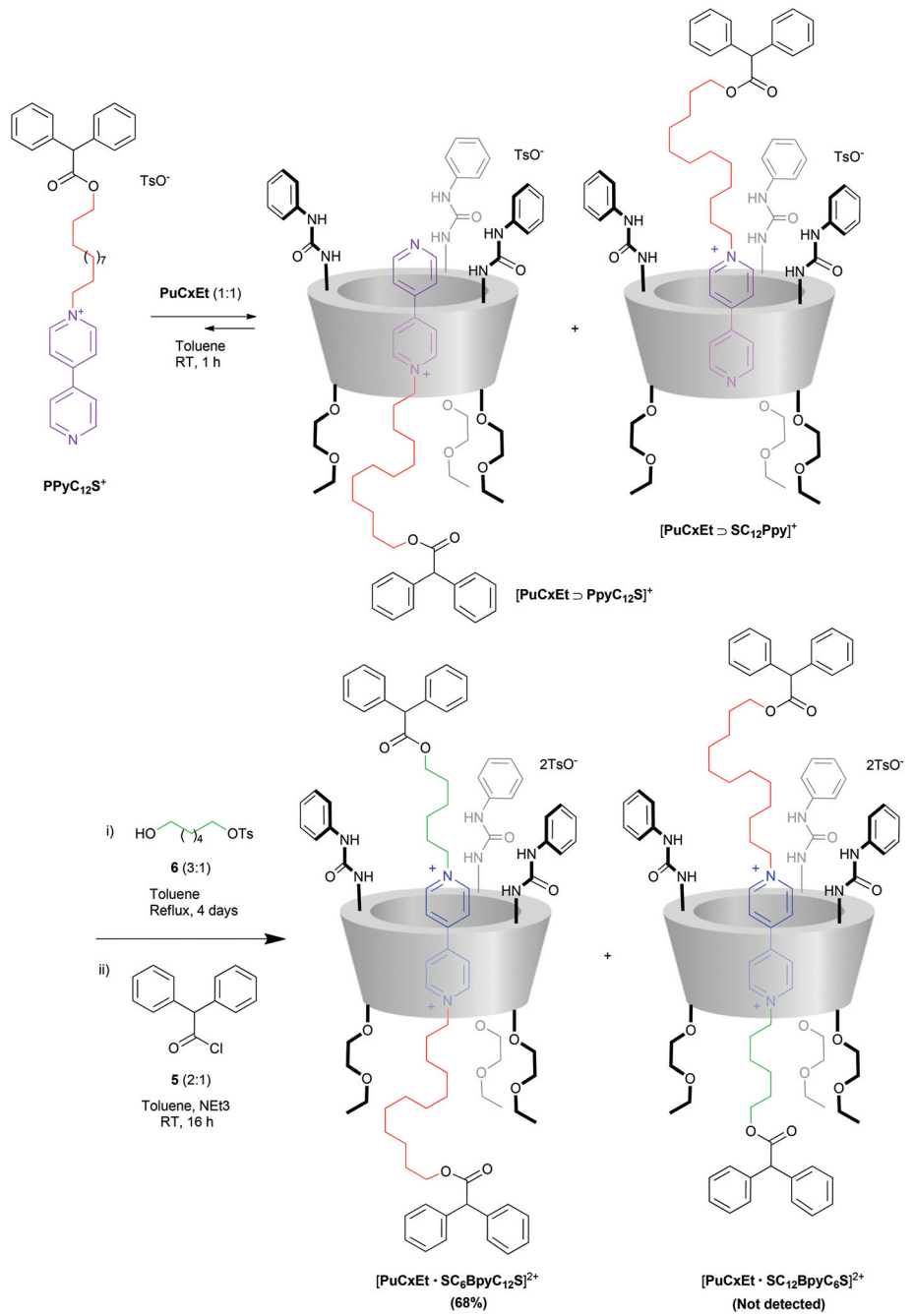


Fig. 3 Stack plot of the ^{1}H NMR spectra (C_6D_6, 400 MHz) of rotaxanes: (a) [**PuCxEt·SC$_{12}$BpyC$_6$S**]$^{2+}$ (see Scheme 3) and (b) [**PuCxEt·SC$_6$BpyC$_{12}$S**]$^{2+}$ (see Scheme 4). See drawing for proton labelling of the axles.

$[\mathbf{PpyC_6S}]^+$ isomer, the proximity of the phenylurea groups of the host could also play a significant role by binding the anionic leaving group of the alkylating agent, particularly when it is a strongly coordinating species such as tosylate. Besides the high selectivity, the most striking observation of the supramolecularly assisted synthesis of rotaxane $[\mathbf{PuCxEt{\cdot}SC_{12}BpyC_6S}]^{2+}$ is that this strategy halves the reaction time and triples the total yield of the reaction in comparison with the threading-and-stoppering approach.

Building upon these results, we envisaged to exploit this straightforward procedure to synthesize rotaxanes bearing the longer alkyl chain of the axle oriented toward the calixarene lower rim, such as $[\mathbf{PuCxEt{\cdot}SC_6BpyC_{12}S}]^{2+}$. This rotaxane cannot be obtained by the kinetically controlled threading of a $\mathbf{C_6BpyC_{12}}^{2+}$-type guest into **PuCxEt** and subsequent stoppering of the axle extremities; it could only be prepared through the complexation of a stoppered axle like $\mathbf{SC_6BpyC_{12}}^{2+}$ by the calixarene (only the orientational isomer $[\mathbf{PuCxEt} \supset \mathbf{SC_6BpyC_{12}}]^{2+}$ is obtained because, as discussed above, lower rim threading of a doubly alkylated 4,4′-bipyridine is not possible) and capping at the C_{12} terminus. Thus, according to the protocol followed for $[\mathbf{PuCxEt{\cdot}SC_{12}BpyC_6S}]^{2+}$, we carried out a further



Scheme 4

supramolecularly-assisted reaction exploiting salt $\mathbf{PPyC_{12}S^+}$ (Scheme 4) that bears a C_{12} alkyl chain.

This compound was first equilibrated with **PuCxEt** in toluene at room temperature and then refluxed with 6-hydroxyhexyl tosylate **6** for 4 days. After the usual stoppering reaction with diphenylacetyl chloride at room temperature, the desired rotaxane $[\mathbf{PuCxEt{\cdot}SC_6BpyC_{12}S}]^{2+}$ was isolated in 68% yield after chromatographic separation. A ^{1}H NMR analysis in benzene-d_6 (Fig. 3b) confirmed the exclusive formation of the target orientational isomer. In particular, the presence of a sharp singlet at δ = 3.94 ppm for the wheel methoxy groups is in agreement with the presence of a C_{12} alkyl chain in proximity to the lower rim of the calixarene cavity. The chemical shift of the multiplet assigned to the 1 and 1′ methylene groups (4.4 ppm) and the two singlets at 5.12 ppm and 5.07 ppm relative to the α and α′ methyne protons of the diphenylacetic stoppers confirmed the univocal arrangement of the axle relatively to the macrocycle. Also in this case no traces of the opposite orientational isomer were observed, and both the rate and yield of the reaction increase with respect to standard synthetic procedures.[25] These results highlight the general validity of the investigated supramolecularly-assisted procedure, which can be applied to different pyridylpyridinium salts while maintaining a predictable and quantitative selectivity on the resulting rotaxane orientation, regardless of the length of the alkyl chains appended to the axle.

Conclusion

We have demonstrated that tris(*N*-phenylureido)calixarene **PuCxEt** forms stable host–guest complexes with 1-alkyl-4,4′-pyridylpyridinium salts in solvents of low polarity, and that these complexes undergo a S_N2 alkylation reaction to afford 1,1′-dialkyl-4,4′-bipyridinium-type pseudorotaxanes and rotaxanes. We have found that the engulfment of the pyridylpyridinium substrates into the calixarene cavity results in an enhancement of their apparent nucleophilicity that leads to an increase of up to 16 times the alkylation reaction rate. This effect was ascribed both to the stabilization of the positively charged pyridinium ring by the electron-rich calixarene cavity and to the presence of the phenylurea moieties at the upper rim of **PuCxEt** which can bind the anionic leaving group of the alkylating agent. Therefore, **PuCxEt** not only preorganizes the reactants inside its cavity, but it enhances the reactivity of the pyridylpyridinium substrate. In this regard, the calix[6]arene host is an active template. The process is intrinsically stoichiometric, as the template is a component of the final product, and it does not require the use of metals.

Moreover, we took advantage of such a supramolecular reactivity enhancement in combination with the non-symmetric structure of the wheel and axle to synthesize mechanically interlocked molecules (rotaxanes) with full control of the relative orientation of the components. Using stoppered pyridylpyridinium axles we have proved that both orientational pseudorotaxane isomers are formed, indicating that these guests – unlike bipyridinium-type axles – can pierce the calixarene cavity also from the lower rim. Interestingly, our results show that only the pseudorotaxane bearing the neutral pyridine nitrogen atom pointing towards the urea-decorated upper rim of the calixarene exhibits a higher reactivity in the S_N2 alkylation reaction. Such a behavior has been rationalized considering the fact that in this orientational isomer: (i) the pyridinium charge is more deeply engulfed into the electron rich cavity of **PuCxEt**, resulting in an increased stabilization and an enhanced nucleophilicity, (ii) the pyridine nitrogen atom is more exposed to the bulk and therefore more easily accessible, and (iii) the urea groups of the calixarene are proximal to the reactive site and may bind the anionic leaving group of the alkylating agent, thereby accelerating the S_N2 reaction. Indeed, in the opposite orientational isomer the access to the non-alkylated nitrogen of the pyridylpyridinium axle is hampered by the presence of the methoxy groups at the narrower calixarene rim.

The described supramolecularly-assisted strategy was proved to be effective with different pyridylpyridinium axles and allowed the preparation of rotaxanes whose axles bear longer or shorter alkyl chains at either rims of the calixarene. Overall, the most striking outcome is that this new procedure allowed the formation of oriented rotaxanes as single orientational isomers in significantly higher yields and much shorter reaction times compared to traditional sequential procedures.[25] The methodology investigated here can enable the design and synthesis of more complex mechanically interlocked structures containing oriented components in a predetermined and univocal arrangement, which in turn could lead to the development of novel molecular machines exhibiting directionally controllable movements.

Experimental part

General

All solvents were dried using standard procedures; products **1b–d** and **3** and all other reagents were of reagent grade quality obtained from commercial suppliers and were used without further purification. Chemical shifts are expressed in ppm (δ) using the residual solvent signal as an internal reference (7.16 ppm for C_6H_6; 7.26 ppm for $CHCl_3$ and 3.31 for CH_3OH). Mass spectra were recorded in the ESI mode. Products **PuCxEt**,[19] **2**,[34] **3a**,[21] **4**,[36] **6**,[35] $\mathbf{PPyC_6S^+}$,[20] and **10** [22] were synthesized according to published procedures. Toluene for UV-Vis absorption spectra was of spectroscopic grade quality obtained from commercial suppliers and was used without further purification. Absorption spectra, spectroscopic titrations and kinetic experiments were recorded at 60 °C with a Varian Cary 50 Bio. Spectroscopic titrations were performed by adding small aliquots of a concentrated solution of **PuCxEt** to a dilute solution of $\mathbf{PPyC_{18}^+}$. The titration curve was fitted according to a 1 : 1 association model by using the SPECFIT software.[28] Kinetic experiments for the catalyzed reaction were performed by adding an excess of **1a** to a solution of **PuCxEt** and $\mathbf{PPyC_{18}^+}$. In the case of the uncatalyzed reaction, a solution

of **PPyC$_{18}$**$^+$ and **1a** was subdivided into several vials that were kept at 60 °C. At different times, a stoichiometric amount of **PuCxEt** with respect to **PPyC$_{18}$**$^+$ was added (the volume of the solution tripled in this step), and the absorption spectra were recorded after an equilibration time of 20 min at 60 °C. Kinetic traces were evaluated at 470 or 370 nm and fitted to a second order reaction according to a S_N2 model, by using the SPECFIT software.[28]

Synthesis of PPyC$_{18}$$^+$

In a 100 ml round-bottomed flask, octadecyl 4-methylbenzenesulfonate (1.0 g, 2.4 mmol) and 4,4′-dipyridyl (1.1 g, 7.1 mmol) were dissolved in CH_3CN (50 ml) and the solution was refluxed for 24 h. Then the solvent was evaporated at reduced pressure and the residue was triturated with EtOAc (3 × 20 ml) until the product precipitated as a solid compound and was recovered by suction filtration to afford 1.0 g of **2** as a white solid (64%). M.p. = 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD): δ = 9.02 (d, J = 6.4 Hz, 2H), 8.82 (d, J = 6.4 Hz, 2H), 8.40 (d, J = 6.4 Hz, 2H), 7.99 (d, J = 6.4 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.63 (t, J = 7.6 Hz, 2H), 2.28 (s, 3H), 2.0–1.9 (m, 2H), 1.2–1.3 (m, 30H), 0.81 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$/MeOD): δ = 152.6, 148.6, 145.3, 144.1, 142.0, 140.2, 128.8, 126.3, 125.6, 123.2, 62.1, 31.8, 31.5, 29.6 (2 res), 29.5, 29.4, 29.3 (2 res), 28.9, 26.0, 22.6, 21.1, 14.0 ppm; ESI-MS(+): m/z (%) = 409.4(100), 410.4(30); elemental analysis calculated for $C_{35}H_{52}N_2O_3S$: C, 72.37; H, 9.02; N, 4.82; S, 5.52; found: C, 72.01; H, 9.39; N, 4.71; S, 4.99.

Synthesis of PpyC$_{12}$S$^+$

In a sealed glass reactor, 12-(tosyloxy)dodecyl 2,2-diphenylacetate (0.25 g, 0.45 mmol) and 4,4′-dipyridyl (0.21 g, 1.36 mmol) were dissolved in 20 mL of CH_3CN and heated at 80 °C overnight. After cooling at room temperature, the solvent was removed under reduced pressure, and the crude product was purified by precipitation from cold EtOAc (20 mL). The product was collected by Buchner filtration as a white solid (0.28 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (d, J = 6.4 Hz, 2H), 8.78 (d, J = 6.4 Hz, 2H), 8.25 (d, J = 6.4 Hz, 2H), 7.76 (d, J = 6.4 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.6–7.5 (m, 2H), 7.3–7.2 (m, 8H), 7.11 (d, J = 8.0 Hz, 2H), 4.73 (t, J = 7.2 Hz, 2H), 4.14 (t, J = 6.8 Hz, 2H), 2.29 (s, 3H), 2.0–1.90 (m, 2H), 1.6–1.5 (m, 2H), 1.3–1.1 (m, 16H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 153.0, 151.2, 145.8, 143.9, 141.0, 139.4, 138.8, 128.8, 127.2, 125.9, 121.5, 120.6, 65.3, 61.6, 57.2, 31.7, 29.5, 29.1, 28.5, 26.1, 25.8, 21.2 ppm; ESI-MS(+): m/z (%) = 535.3 (100), 536.4 (40); elemental analysis calculated for $C_{43}H_{50}N_2O_5S$: C, 73.06; H, 7.13; N, 3.96; S, 4.54; found: C, 72.84; H, 7.26; N, 3.81; S, 4.19.

General procedure for the supramolecularly-assisted rotaxanes synthesis

To a solution of wheel **PuCxEt** (0.07 mmol) in toluene (20 mL), an equimolar ratio of stoppered salt (**PPyC$_6$S**$^+$ or **PpyC$_{12}$S**$^+$, 0.07 mmol) and an excess of ω-hydroxy alkyltosylate (**4** or **6**, 0.21 mmol) was added. The orangish resulting solution was refluxed for four days; afterwards, the mixture was cooled to room temperature and diphenylacetyl chloride (0.14 mmol) and triethylamine (0.14 mmol) were added. The solution was stirred at room temperature for 16 hours. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography (dichloromethane : methanol = 95 : 5) to afford the pure rotaxane.

[**PuCxEt·SC$_{12}$BpyC$_6$S**]$^{2+}$ as ditosylate (0.12 g, 63% yield): ^{1}H NMR (400 MHz, C_6D_6): δ = 9.4 (br.s, 6H), 8.16 (d, J = 7.6 Hz, 4H), 8.1–7.8 (m, 8H), 7.83 (d, J = 6.0 Hz, 2H), 7.58 (s, 6H), 7.5–7.3 (m, 10H), 7.2–7.1 (m, 10H), 7.1–7.0 (m, 10H), 6.90 (d, J = 8.0 Hz, 4H), 6.81 (d, J = 6.0 Hz, 2H), 6.8–6.6 (m, 5H), 5.10 (s, 1H), 5.07 (s, 1H), 4.56 (d, J = 14.8 Hz, 6H), 4.33 (t, J = 6.2 Hz, 2H), 4.04 (t, J = 6.6 Hz, 2H), 3.88 (s, 9H), 3.8 (br.s, 6H), 3.7–3.5 (m, 10H), 3.5–3.2 (m, 12H), 2.1 (br.s, 2H), 1.95 (s, 6H), 1.9–0.6 (m, 83H); ^{13}C NMR (100 MHz, C_6D_6): δ = 172.0, 171.9, 153.5, 152.9, 148.1, 147.9, 144.4, 143.3, 143.0, 141.3, 139.4, 139.3, 139.0, 137.5, 133.8, 132.2, 129.3, 128.7, 128.6, 128.5, 127.8, 127.6, 127.3, 127.1, 126.5, 125.6, 124.8, 121.1, 118.1, 116.7, 72.4, 69.9, 66.3, 64.9, 61.3, 61.0, 60.7, 57.3, 34.6, 31.5, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 28.8, 28.6, 27.8, 26.1, 26.0, 25.8, 22.8, 20.8, 15.2, 14.0; ESI-MS(+): m/z (z = 2, %): 1147.7 (58), 1148.3 (100), 1148.6 (85), 1149.1 (40); elemental analysis calculated for $C_{160}H_{188}N_8O_{22}S_2$: C, 72.81; H, 7.18; N, 4.25; S, 2.43; found: C, 72.34; H, 7.26; N, 4.07; S, 2.21.

[**PuCxEt·SC$_6$BpyC$_{12}$S**]$^{2+}$ as ditosylate (0.13 g, 68% yield): ^{1}H NMR (400 MHz, C_6D_6): δ = 9.4 (br.s, 6 H), 8.3–8.0 (br.s, 6 H), 8.0–7.7 (m, 10 H), 7.59 (s, 6 H), 7.45 (d, J = 7.6 Hz, 4H), 7.41 (d, J = 7.2 Hz, 4 H), 7.2–7.1 (m, 6H), 7.1–7.0 (m, 10H), 6.92 (d, J = 8.0 Hz, 4H), 6.83 (d, J = 6.0 Hz, 2H), 6.68 (t, J = 6.8 Hz, 6H), 5.13 (s, 1H), 5.08 (s, 1H), 4.58 (d, J = 15.2 Hz, 6H), 4.1–4.0 (m, 4 H), 3.95 (s, 9H), 3.9–3.7 (m, 8H), 3.7–3.5 (m, 8H), 3.5–3.2 (m, 12H), 2.2 (br.s, 2H), 1.96 (s, 6H), 1.8 (br.s, 2H), 1.8–1.5 (m, 70H); ^{13}C NMR (100 MHz, C_6D_6): δ = 172.0, 171.9, 153.5, 152.8, 148.2, 147.9, 144.4, 142.9, 141.2, 139.2, 139.2, 137.5, 133.8, 132.1, 129.3, 128.7, 128.7, 128.6, 128.6, 128.5, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 127.1, 127.0, 126.5, 125.7, 124.7, 121.2, 118.1, 116.7, 72.4, 70.0, 66.3, 64.7, 60.9, 60.5, 57.4, 57.3, 34.6, 31.5, 30.0, 29.7, 29.2, 28.6, 28.3, 25.8, 25.5, 24.9, 20.8, 15.2; ESI-MS(+): m/z (z = 2, %): 1147.7 (60), 1148.2 (100), 1148.7 (80), 1149.2 (35); elemental analysis calculated for $C_{160}H_{188}N_8O_{22}S_2$: C, 72.81; H, 7.18; N, 4.25; S, 2.43; found: C, 72.31; H, 7.41; N, 4.21; S, 2.19.

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