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Pseudorotaxane orientational stereoisomerism driven by π-electron density†‡

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Pseudo[2]rotaxane orientational isomers were formed in a stereocontrolled way by exploiting the electron-withdrawing (EW) or electron-donating (ED) effects of *para*-substituted dibenzylammonium axles threaded through the π-electron rich calixarene cavity, which allow the fine tuning of the weak π–π interactions.

Over the past 30 years, supramolecular chemists have learned to build increasingly complex and topologically non-trivial architectures by controlling the secondary forces between molecules.[1] Among them, π–π interactions[2] have played an important role thanks also to the possibility of tuning their strength through substituent effects.[3] These effects have also been exploited to control the relative binding geometries[4] and more peculiar forms of supramolecular isomerism, such as the translational isomerism of catenanes and rotaxanes.[5] However, to the best of our knowledge, no examples of control through aromatic substituent effects of orientational stereoisomerism of (pseudo)-rotaxanes exist so far.

Recently,[6] we have shown that a specific orientational stereoisomer can be obtained when directional alkylbenzylammonium axles (*e.g.*, 2^+) are threaded through a directional calix[6]arene[7] wheel (*e.g.*, **1**) by exploiting the so-called ''*endo*-alkyl rule''. Thus, a neat preference for the *endo*-alkyl-5^+ orientational stereoisomer over the *endo*-benzyl one[6a] (Chart 1) was observed, which was then exploited to construct related rotaxane and catenane architectures.[6c–f] These results prompted us to consider the possibility of controlling orientational stereoisomerism of dibenzylammonium threads **3a–d**$^+$ with calix[6]arene wheel **1**, by exploiting the electron-withdrawing (EW) or electron-donating (ED) effect of a *para* X substituent.

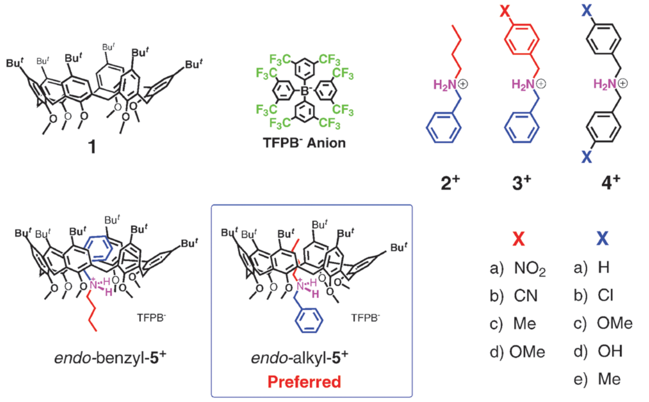
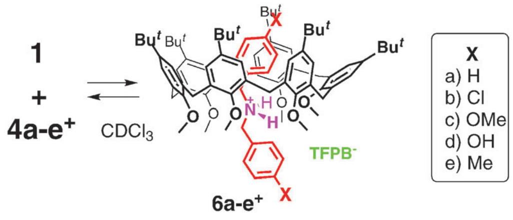


Chart 1 Structures of calix[6]arene wheel **1**, dibenzylammonium axles $\mathbf{2}^+$, **3a–d**$^+$, **4a–e**$^+$, and the $TFPB^-$ anion.

As a preliminary study, we decided to evaluate first the effect of this substituent on the strength of binding of the related disubstituted axles **4a–e**$^+$. In particular, when 1 equiv. of the *p*-chlorosubstituted axle $\mathbf{4b}^+$•$TFPB^-$ was added to a solution of calix[6]arene **1** in $CDCl_3$ the pseudo[2]rotaxane $\mathbf{6b}^+$ (Scheme 1) was formed (Fig. S31, ESI‡) with an apparent association constant of $4.5 \pm 0.4 \times 10^3\ M^{-1}$ (Table 1).[8] This value is higher than that previously observed for the complexation of the simple dibenzylammonium $\mathbf{4a}^+$ (X = H) with the same host **1** ($2.5 \pm 0.2 \times 10^3\ M^{-1}$).[6a] This result, in addition to the modification of the H-bond donating ability of the NH_2^+ group, can be primarily explained in terms of substituent-induced changes in the aryl



Scheme 1 Formation of pseudo[2]rotaxanes **6a–e**$^+$.

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† Dedicated to Prof. Seiji Shinkai on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Synthetic details, 1D and 2D NMR spectra, details of molecular modeling, and relative stability constants K_{rel}. See DOI: 10.1039/c4cc04668d

Table 1 Stability constants (K_a) for the pseudo[2]rotaxane **6a–e**$^+$ and **7a–d**$^+$, and stereoisomeric [*endo*-*p*-X-benzyl-**7**$^+$]/[*endo*-benzyl-**7**$^+$] ratios

	K_a/M^{-1}	σ_{para}[a]	X/H[b]
6a$^+$ (*p*-H)	$2.5 \pm 0.2 \times 10^3$	0.00	—
6b$^+$ (*p*-Cl)	$4.5 \pm 0.4 \times 10^3$	0.24	—
6c$^+$ (*p*-OMe)	$2.2 \pm 0.1 \times 10^2$	−0.27	—
6d$^+$ (*p*-OH)	$2.4 \pm 0.2 \times 10^2$	−0.22	—
6e$^+$ (*p*-Me)	$3.3 \pm 0.2 \times 10^2$	−0.14	—
endo-*p*-NO_2-benzyl-**7a**$^+$	$4.6 \pm 0.3 \times 10^3$	0.78	95/5
endo-benzyl-**7a**$^+$	$2.8 \pm 0.2 \times 10^2$		
endo-*p*-CN-benzyl-**7b**$^+$	$2.1 \pm 0.2 \times 10^3$	0.71	90/10
endo-benzyl-**7b**$^+$	$2.0 \pm 0.2 \times 10^2$		
endo-*p*-Me-benzyl-**7c**$^+$	$2.0 \pm 0.2 \times 10^2$	−0.14	30/70
endo-benzyl-**7c**$^+$	$3.8 \pm 0.2 \times 10^2$		
endo-*p*-OMe-benzyl-**7d**$^+$	53 ± 10	−0.27	15/85
endo-benzyl-**7d**$^+$	$3.0 \pm 0.2 \times 10^2$		

[a] O. Exner, *Correlation Analysis in Chemistry*, Plenum, London, 1978. [b] Stereoisomeric ratio X/H = [*endo*-*p*-X-benzyl-**7**$^+$]/[*endo*-benzyl-**7**$^+$].

π-system according to the electrostatic model of Hunter and Sanders[2a] or the "polar/π" model of Cozzi and Siegel.[3,9,10] Thus, the presence of an EW-substituent (*p*-Cl) at the *para*-position of dibenzylammonium axle **4b**$^+$, lowers the π-electron density on its aromatic rings and increases the affinity toward the π-electron rich calix cavity of **1**.

Unsurprisingly, the stability constants of complexes **6c**$^+$, **6d**$^+$, and **6e**$^+$ ($2.2 \pm 0.1 \times 10^2$, $2.4 \pm 0.2 \times 10^2$, and $3.3 \pm 0.2 \times 10^2$ M^{-1}, respectively, see Table 1) are decreased by the presence of ED-substituents (*p*-OMe, *p*-OH, and *p*-Me), which increase the π-electron density on the aromatic rings of the dibenzylammonium axles **4c**$^+$, **4d**$^+$, and **4e**$^+$.[8]

In analogy to a similar study on the crown ether series reported by Stoddart and coworkers,[11] we have constructed a Hammett-type plot correlating the log[K_{6b-e}/K_{6a}] *vs.* σ values (Fig. S39, ESI‡).[8] Thus, a linear free-energy relationship (LFER) was observed between the K_{6b-e} values and the electronic nature of X (Hammett σ constant). As reported by Stoddart,[11] this correlation may be principally ascribed to the propensity of the substituted aromatic ring of the axles **4b–e**$^+$ to become involved in π–π interactions with the electron-rich aromatic cavity of **1**, which can be modified by the EW or ED nature of its X *para*-substituent.[12]

These π-electron density effects can be visualized by comparing the electrostatic potentials (ESPs) of the pertinent aromatic rings involved in π–π interactions. Thus, for example, the *p*-Cl-benzyl ring has a clear lower π-electron density with respect to the *p*-OMe counterpart (Fig. 1a and b),[8] which explains the better interaction with the electron-rich calixarene cavity (Fig. 1e and f).

These conclusions prompted us to investigate the possibility of driving the threading orientation of unsymmetrical axles **3a–e**$^+$ bearing only one *p*-X-substituted benzyl group. In fact, such threading with calix-wheel **1** can give rise to the two stereoisomeric orientational pseudorotaxanes *endo*-benzyl-**7**$^+$ and *endo*-*p*-X-benzyl-**7**$^+$ (Scheme 2). We envisioned that this isomeric ratio could be influenced by the EW or ED nature of the X *para*-substituent of **3**$^+$, which, by changing the π-electron density of the single *p*-X-benzyl group, could modulate its affinity toward the π-electron-rich aromatic cavity of **1**. On the other hand, the previously mentioned modification of the H-bond donating ability of the NH_2^+ group should be irrelevant in this regard, since equivalent H-bonding interactions could be established for both orientational isomers.

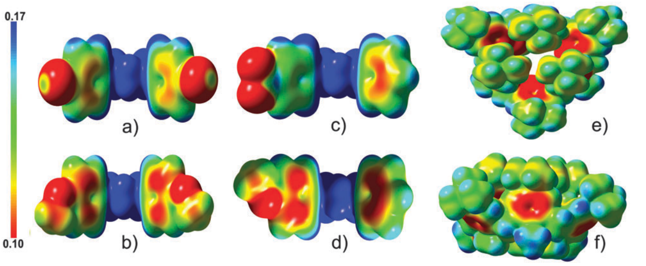
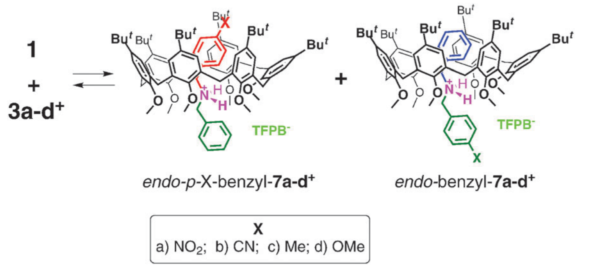


Fig. 1 ESPs mapped onto electron density isosurfaces (ρ = 0.005) for: (a) **4b**$^+$; (b) **4c**$^+$; (c) **3a**$^+$; (d) **3d**$^+$. (e and f) ESPs mapped onto electron density isosurfaces (ρ = 0.005) for calix[6]arene host **1** (drawn in a smaller scale).



Scheme 2 Formation of the two pseudo[2]rotaxane orientational isomers *endo*-*p*-X-benzyl-**7a–d**$^+$ and *endo*-benzyl-**7a–d**$^+$.

As a first step we decided to study the threading of benzyl-*p*-NO_2-benzylammonium **3a**$^+$ with calix-wheel **1**.[8] The ^{1}H NMR spectrum of their 1 : 1 mixture in $CDCl_3$ evidenced the formation of the *endo*-*p*-NO_2-benzyl-**7a**$^+$ (Fig. 2b, a and b red signals) in a 95 : 5 ratio with respect to the *endo*-benzyl-**7a**$^+$ (marked blue signals) isomer. The greater thermodynamic stability of the former isomer was confirmed by the two apparent association constants ($4.6 \pm 0.3 \times 10^3$ M^{-1} and $2.8 \pm 0.2 \times 10^2$ M^{-1}, respectively, Table 1) obtained by integration of their ^{1}H NMR signals.

Optimized structures of the *endo*-*p*-NO_2-benzyl-**7a**$^+$ and *endo*-benzyl-**7a**$^+$ stereoisomers were obtained by means of DFT calculations[8] (Fig. 3) at the B3LYP/6-31G(d,p) level of the theory using Grimme's dispersion corrections (IOp(3/124 = 3)).[13] In good accordance with the experimental *endo*-*p*-NO_2-benzyl-**7a**$^+$/*endo*-benzyl-**7a**$^+$ stereoisomeric ratio of 95 : 5, single-point calculations at the M06/6-31+G(d,p)[10] level of theory indicated that the *endo*-*p*-NO_2-benzyl-**7a**$^+$ stereoisomer was more stable than the *endo*-benzyl-**7a**$^+$ one by 3.6 kcal mol^{-1}. A close inspection of the optimized structure (Fig. 3) of the *endo*-*p*-NO_2-benzyl-**7a**$^+$ complex revealed a face-to-face stacked geometry between the *p*-NO_2-benzyl ring of **3a**$^+$ and one anisole ring of **1** (Fig. 3a) to give a favorable π–π interaction. Additional edge-to-face π–π interactions can be seen between the *p*-NO_2-benzyl ring and the wheel Ar rings proximal to the previous one (Fig. 3b).

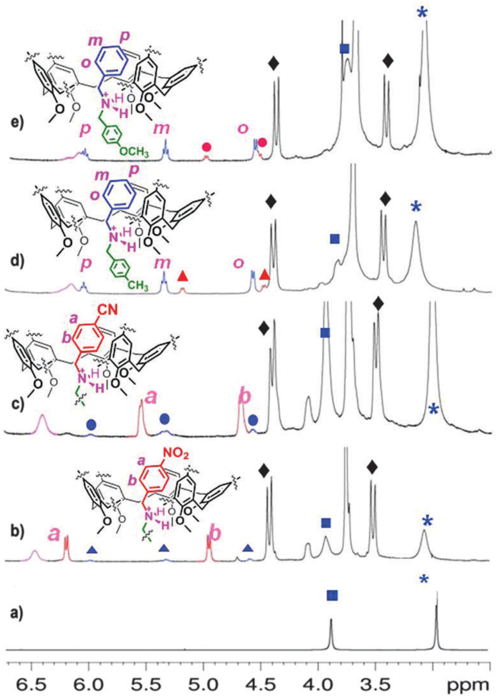


Fig. 2 Significant portions of the ^1H NMR spectra (400 MHz, $CDCl_3$, 298 K) of (a) **1**; (b) 1 : 1 mixture of **1** and **3a**$^+$; (c) 1 : 1 mixture of **1** and **3b**$^+$; (d) 1 : 1 mixture of **1** and **3c**$^+$; (e) 1 : 1 mixture of **1** and **3d**$^+$. The cavity-shielded ArH signals of *endo*-*p*-X-benzyl and *endo*-benzyl **7a–d**$^+$ isomers are reported in red and blue, respectively. Signals marked with circles or triangles correspond to the cavity-shielded ArH protons of the minor stereoisomer. In structure drawings some groups have been removed for clarity. Signals marked with ∗, ■ and ◆ correspond, respectively, to the OMe and $ArCH_2Ar$ protons of the free host **1** and to the $ArCH_2Ar$ protons of the complexed host **1**.

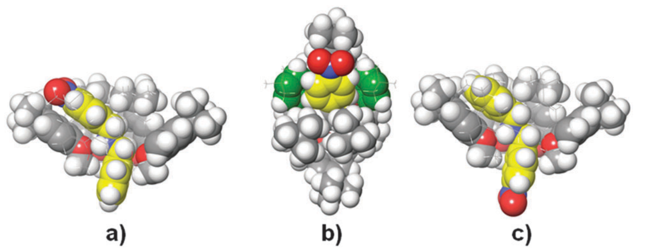


Fig. 3 Side (a) and top (b) view of the optimized structure of the *endo*-*p*-NO_2-benzyl-**7a**$^+$ complex at the B3LYP/6-31G(d,p) level of theory. (c) Side view of the optimized structure of the *endo*-benzyl-**7a**$^+$ complex. A mixed CPK/wireframe representation was used for clarity.

Naturally, stabilizing H-bonds were observed between the $^+NH_2$ protons of **3a**$^+$ and ethereal-oxygen atoms of **1** with an average $N^+\cdots O$ distance of 3.2 Å (see Fig. S40 left, ESI‡).[7] Interestingly, C–H⋯π interactions were also evidenced between the methylene $PhCH_2{}^+NH_2CH_2C_6H_4$-*p*-NO_2 protons of **3a**$^+$ (Fig. S40 right, ESI‡) and two Ar rings of **1**. Overall comparable interactions were observed in the optimized structure of the isomeric *endo*-benzyl-**7a**$^+$ complex (Fig. 3c and Fig. S41 and S42, ESI‡).

Again the stereoselectivity observed can be justified on the basis of the greater aptitude of the *p*-NO_2-substitued aromatic ring of axle **3a**$^+$ to become involved in π–π interactions with the electron-rich aromatic cavity of **1**. In fact, the electrostatic potential surface (ESP) of **3a**$^+$ shows that the *p*-NO_2-benzyl ring (Fig. 1c, left ring) has a lower π-electron density with respect to the benzylic counterpart (Fig. 1c, right ring).

Interestingly, when benzyl-*p*-CN-benzylammonium thread **3b**$^+$ was used the pseudorotaxane *endo*-*p*-CN-benzyl-**7b**$^+$ was formed in a 90 : 10 ratio with respect to the *endo*-benzyl-**7b**$^+$ isomer (Fig. 2c, Table 1). Thus the presence of an EW-substituent (X = CN) with a Hammett σ constant smaller than the nitro group (σ_{CN} = 0.71, σ_{NO_2} = 0.78) lowers the stereoselectivity of the threading process.

In agreement with our prediction, the presence of ED-groups with a negative Hammett σ constant reverses the above observed preferences for *endo*-*p*-X-benzyl-**7**$^+$ stereoisomers. In fact, when benzyl-*p*-Me-benzylammonium thread **3c**$^+$ was mixed in a 1 : 1 ratio with calix-wheel **1** in $CDCl_3$ the pseudorotaxane *endo*-benzyl-**7c**$^+$ was favored with respect to the *endo*-*p*-Me-benzyl-**7c**$^+$ one (σ_{Me} = −0.14) with a stereoisomeric ratio of 70 : 30 (Fig. 2d, Table 1).[8] Finally, the presence of the OMe group in **3d**$^+$ with a more negative Hammett σ_{para} constant (σ_{OMe} = −0.27) increases the stereoisomeric ratio (85 : 15) in favor of the *endo*-benzyl-**7d**$^+$ stereoisomer (Fig. 2e, Table 1).[8]

The ESP of **3d**$^+$ clearly shows that the *p*-OMe-benzyl ring (Fig. 1d, left ring) has a higher π-electron density than the benzylic counterpart (Fig. 1d, right ring) thus justifying its lower aptitude to interact with the electron-rich aromatic cavity of **1** (Fig. 1e and f).

In conclusion, we have successfully demonstrated that pseudorotaxane orientational stereoisomerism can be effectively controlled by changing the π-electron density of the thread through EW or ED aromatic substituent effects. This approach can be extended to more complex interpenetrated architectures leading to a fine stereochemical control through the weak π–π interactions.

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12 In principle, the CH–π interactions between the calix *t*-Bu groups and the guest Ar ring could also play a role in this regard. However, in our case this should be even detrimental because it is well known that their strength is increased by increasing the π–electron density of the Ar ring. The presence of EW-substituents (*e.g.*, $-NO_2$) at the calix *p*-positions should give opposite stabilities for pseudorotaxanes **6a–e**$^+$. Unfortunately, in such instances no threading was observed (Fig. S43, ESI‡).

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