

Selenoureido Calix[6]arenes: A Novel Platform for Pseudorotaxane Synthesis

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Heteroditopic calix[6]arenes are widely employed macrocycles for the synthesis of pseudo-oriented interlocked systems and stimuli-induced molecular machines, among others. Herein, we introduce a new calix[6]arene receptor functionalised with three phenylselenoureido groups. These hydrogen-bonding donor moieties are able to promote the threading of viologen-based

organic axes inside the macrocyclic cavity to form a stable pseudorotaxane species. Preliminary investigations using ¹H-NMR measurements and semi-empirical and DFT studies suggested its further use as a platform for the synthesis of rotaxanes.

Introduction

Calix[6]arenes^[1] are synthetic macrocycles whose use in supramolecular chemistry finds numerous applications, including the synthesis of sensors,^[2] stimuli-responsive devices,^[3,4] and catalysts.^[5,6] With respect to other cavitands, calix[6]arenes are synthetically flexible and non-palindromic. These features have been exploited, for example, for the synthesis of heteroditopic calix[6](thio)urea macrocycles, which are able to work as receptors and transporters for organic ion pairs.^[7–14] Parallely, our group reported the synthesis of a novel family of calix[6]arenes functionalised with three phenyl(thio)ureido groups at the upper, larger rim of the macrocyclic scaffold (TPU and TPT, Figure 1, a).^[15,16] These cavitands were thoroughly studied in the last twenty years and eventually applied to form pseudo-oriented mechanically interlocked molecules. Furthermore, TPU and TPT were exploited to control the directionality of the threading process and as prototypes of stimuli-induced

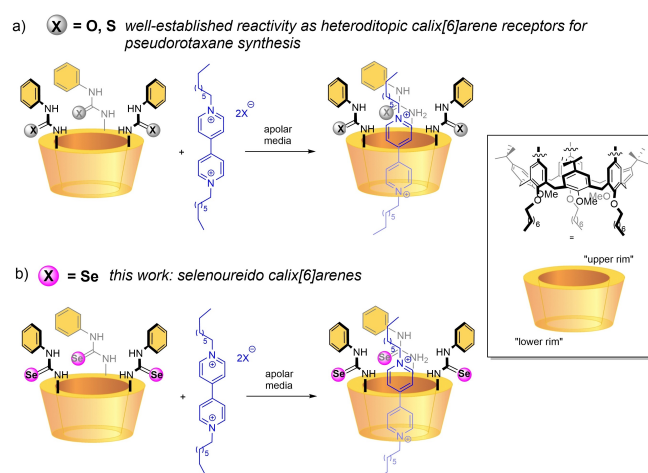


Figure 1. Heteroditopic triphenyl(thio)ureido calix[6]arene receptors TPU ($X = O$) and TPT ($X = S$) (a); triphenylselenoureido calix[6]arene TPSe ($X = Se$) (b).

(light and redox) molecular machines.^[17] Very recently, the ability to control the orientation of bounded guests inside the macrocyclic cavity of TPU was exploited to tune the photo-physical properties of viologen-based organic dyes.^[18,19] It is noteworthy that, for this class of calix[6]arenes, all these functions are made possible by a hydrogen-bonding domain at the upper rim of the macrocycle. In fact, (thio)ureido moieties engage hydrogen-bonding interactions with the counterions of bipyridinium salts, separating the ion-pair associated with these organic salts. This process eventually promotes the unidirectional threading of the axes inside the macrocycle.^[20]

Recently, selenourea-based receptors found widespread application in supramolecular chemistry.^[21–23] Selenium, a metalloid element, presents a nature and thus a reactivity that could be considered both “hard” or “soft” depending on its chemical surroundings. Other features for selenium-containing compounds include a low-oxidation potential [$Se_{(s)} \rightarrow Se_{(aq)}^{2-} = -0.40$ V] that enhances its ability to change its oxidation state and a shift to longer wavelengths for their electronic absorption

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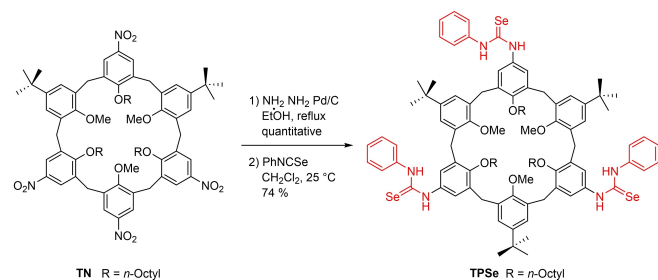
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and emission maxima.^[24] Selenourea compounds have some interesting aspects in this scenario since they could be considered good hydrogen bonding donors and acceptors because of a more delocalised electron density at the larger and polarisable selenium.^[25–28] Based on these considerations and attracted by the scarcity of examples of selenium-containing macrocycles,^[29–35] herein we report the synthesis and characterisation of a new triphenylselenoureido (TPSe) calix[6]arene heteroditopic receptor (Figure 1, b). Preliminary investigations on the complexation ability of this calix[6]arene wheel were also performed, suggesting its further application in the synthesis of interlocked rotaxane systems.

Results and Discussion

The new heteroditopic wheel was synthesised from the known trioctyloxy trinitro calix[6]arene TN.^[36] Reduction of the nitro groups in the presence of hydrazine and catalytic amounts of Pd/C led to the quantitative formation of a triamino analogue that, without further handling, was submitted to the next step. Hence, the reaction with phenyl isoselenocyanate, using CH₂Cl₂ as the solvent, led to the formation of the targeted compound TPSe in 74% yields after purification by column chromatography on silica gel (Scheme 1).

The conformation of the new calix[6]arene wheel TPSe in low polarity solvent was subsequently analysed by ¹H-NMR spectroscopy. In deuterated chlorinated solvents such as chloroform, dichloromethane and tetrachloroethane, at room temperature, the proton resonances of TPSe appear always quite broadened because of the *E/Z* to *Z/E* interconversion of its three selenoureido moieties on the NMR time scale. To confirm this behaviour, some variable temperature NMR experiments were performed. In tetrachloroethane-*d*₂ at 373 K (Figure 2), TPSe is characterised by two sharp peaks at 8.9 and 8.4 ppm for the NH groups of the three selenoureido moieties and an AX system of two doublets at 4.6 and 3.6 ppm related to the bridging axial and equatorial methylene groups (²*J* = 15.4 Hz). A broad, up-field shifted singlet at 2.6 ppm for the three methoxy groups, which point inside the macrocyclic cavity, further suggested a pseudo *cone* conformation for TPSe. Noteworthy, selective ROESY experiments demonstrated the *E/Z* conformation of the selenoureido groups at the upper rim of the macrocycle (Figure S6 of Supporting Information, SI). Further conformational characterisation of the *Z/E* isomerism was accomplished



Scheme 1. Synthetic sequence for triphenylselenoureido calix[6]arene TPSe.

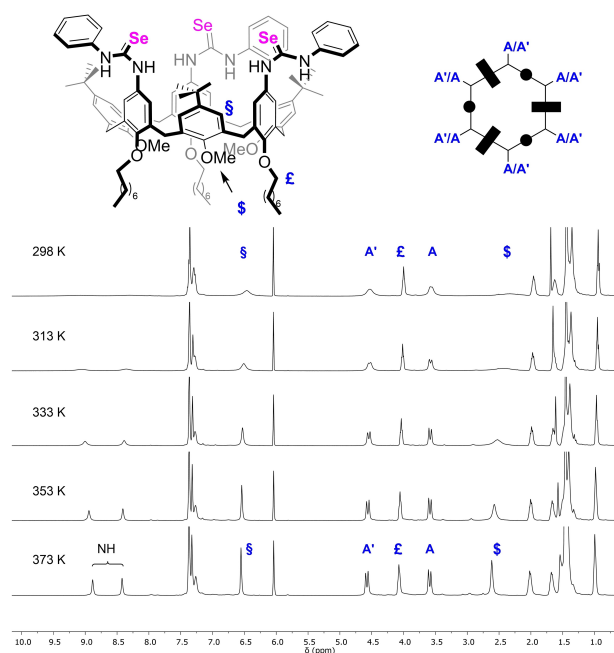


Figure 2. Stacked plot ¹H-NMR (tetrachloroethane-*d*₂, 600 MHz) of TPSe at variable temperatures.

by low-temperature variable NMR experiments on TPSe and its model compound diphenylselenourea DPSeU (Figure S7, SI), a known compound.^[23]

The complexation features of the new wheel were subsequently investigated using a dicationic, bipyridinium-based axle. Hence, a solution in CDCl₃ of TPSe (15 mM) was equilibrated with *N,N*-dioctylviologen ditosylate DOV•2OTs (1:1) at 298 K. A deep yellow solution suggested the formation of a new pseudorotaxane species that was analysed by ¹H-NMR spectroscopy (Figure 3). The formation of two different pseudorotaxane species in a ≈2.1:1 ratio was thus observed in analogy with parental thioureido analogues.^[16] This could be evidenced by the up-field shift of the proton resonances of the aromatic C–H and N–CH₂ bond of the bipyridinium salt that split into two sets of signals. Further, because of the threading, methoxy groups suffer a down-field shift of 1.5 ppm, giving rise to three different signals. A singlet ($\delta^{\#}$) associated with the major *cone* conformer P[TPSe(C)⊃DOV]2OTs and two further singlets, in a 2:1 ratio (δ^* and $\delta^{\#}$) which are typical of a pseudorotaxane species P[TPSe(pC)⊃DOV]2OTs in which the macrocyclic wheel adopts a partial *cone* conformation (pC). This latter conformation is additionally described by the methylene bridging protons A/A' of TPSe that now split into six doublets, with geminal coupling, in a 1:1 ratio. The HSQC spectrum (Figure S9, SI) confirms this feature by revealing a significant shift of the ¹³C resonances for the α/α' couple to $\delta = 35.6$ ppm, suggesting a single inversion point.^[37,38]

To disclose the role of the conformation adopted by TPSe in the pseudorotaxane stabilisation, the structure of the two interwoven complexes P[TPSe(C)⊃DOV]2OTs and P[TPSe(pC)⊃DOV]2OTs was optimised through quantum-chemical methods. Initially, the minimisation was carried out using the PM6-

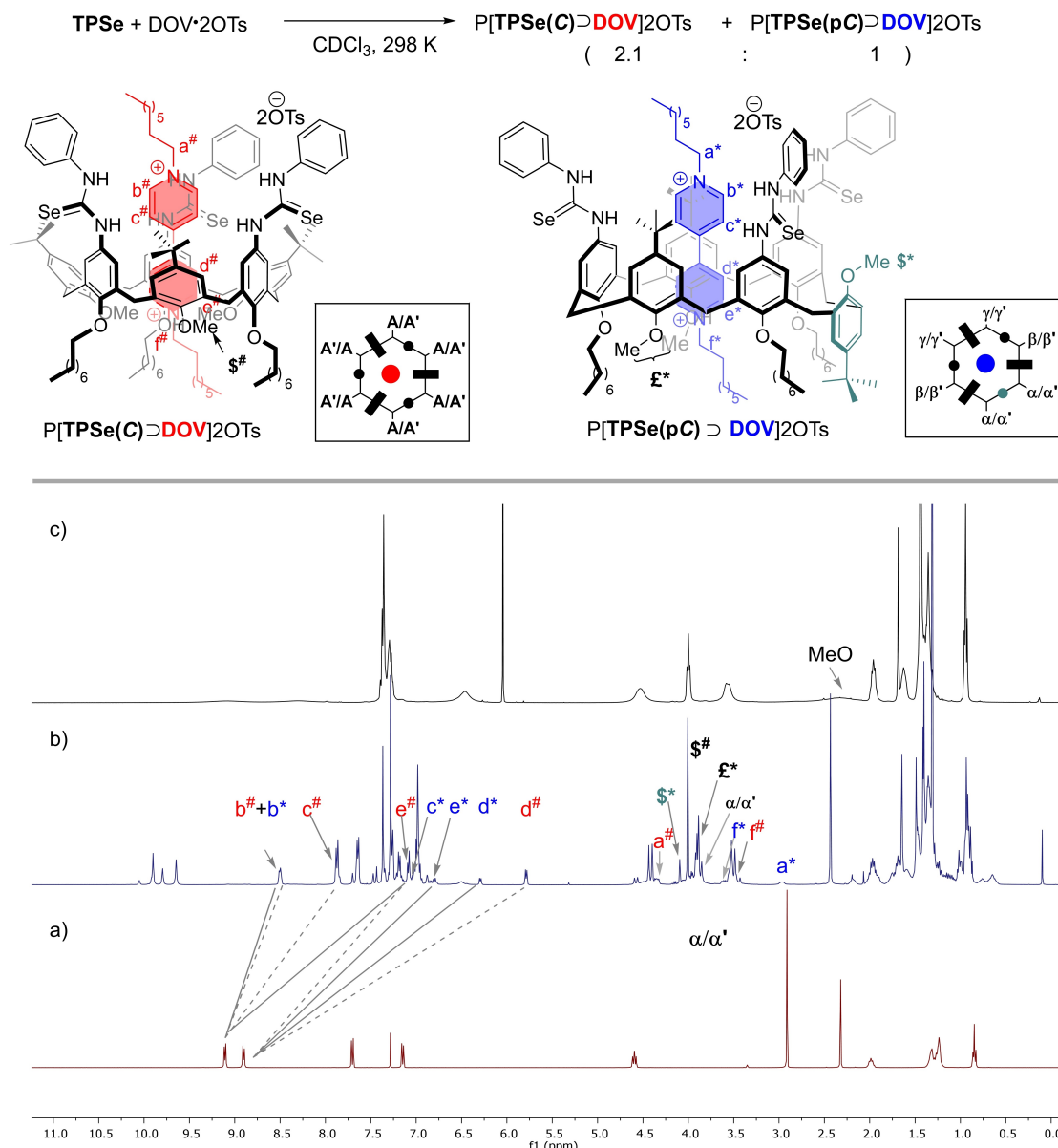


Figure 3. Top, schematic representation of P[TPSe(C)DOV]2OTs and P[TPSe(pC)DOV]2OTs and the assignment of proton resonances. The colour of the ovals/rectangles shows the relative position of the phenolic substituent with respect to the plane defined by the bridging methylene groups (hexagon), i.e., black upward and green downward. The rectangle identifies the phenolic rings substituted with the octyloxy chains, while the circle those with the methoxy group. Bottom, $^1\text{H-NMR}$ spectra (400 MHz, 298 K) of a) TPSe in tetrachloroethane- d_2 ; b) pseudorotaxane P[TPSe(C+pC)DOV]2OTs in CDCl_3 ; c) DOV•2OTs in CD_3CN .

DH+^[39] semi-empirical method that implemented empirical corrections for dispersion and hydrogen-bonding interactions and was used successfully by us to model similar pseudorotaxane systems based on TPT calix[6]arenes.^[16] The resulting minimised structures were then used as a starting guess for further DFT geometrical optimisation using the meta-GGA-TPSS functional^[40] with a def2-SVP basis set.^[41] The final energy of the complexes was then determined with the larger def2-TZPV basis set.^[41] At this level of theory, the total SCF energy calculated for P[TPSe(C)DOV]2T₂O (Figure 4b) was ca. 15 kJ/mol lower than the one calculated for its partial cone pseudorotaxane isomer P[TPSe(pC)DOV]2T₂O (Figure 4a).^[42] In both the minimised structures, one of the axle tosylate anions is

H-bonded with a selenoureido moiety of TPSe, and it remains in intimate contact with the DOV pyridinium ring oriented toward the host upper rim. On the other hand, the other tosylate acts as a bridge between two convergent NHC(Se)NH groups, and it is fully separated from the axle. Considering that DFT studies carried out at TPSS/def2-SVP level on the empty TPSe wheel have shown that the selenoureido moieties prefer to adopt a Z/E configuration (i.e., with one of the NH bonds parallel to the C=Se bond) rather than E/E one as found i.e. in TPU (see SI), this means the pseudorotaxane formation must impose a geometrical rearrangement of the selenoureas to maximise the interaction with the tosylates. This was observed

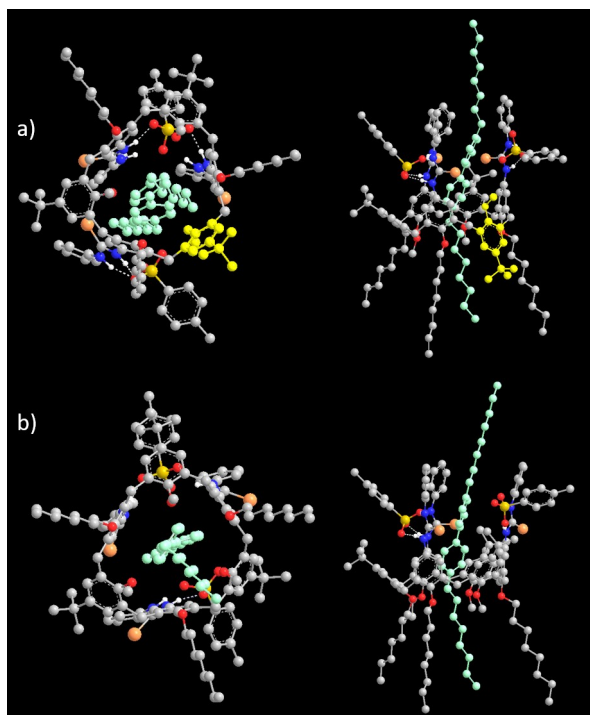


Figure 4. Top and side views of the TPSS/def2-TZVP minimised structures of a) P[TPSe(pC)DOV]2OTs and b) P[TPSe(C)DOV]2OTs pseudorotaxane isomers. All hydrogen atoms except those involved in hydrogen bonding have been omitted for more clarity. The structure of the DOV axle has been depicted in pale green to enhance its visibility; analogously, the inverted phenolic ring of the pseudorotaxane isomer with the host in the partial cone conformation has been highlighted in yellow. H-bondings have been depicted with white dashed lines. Atoms colour scheme: H, white; C, grey; N, blue; O, red; S, yellow; and Se, orange.

regardless of whether the wheel was in a *cone* or a partial *cone* conformation before complexing the DOV axle.

The preliminary results obtained so far suggest that the complexation properties of triphenylselenoureido calix[6]arenes TPSe parallel the ones found for thioureido counterparts TPT. Noteworthy, this process occurs with a loss of the symmetry of the pseudorotaxane system. This manifold is complementary with respect to TPU, in which the threading of dicationic bipyridinium axles takes place, leaving the calix[6]arene macrocycle in its native *cone* conformation. At this stage of the investigation, it seems to be likely that the conformational rearrangement of these heteroditopic calix[6]arene receptors (*cone* vs. partial *cone*), associated with the formation of pseudorotaxane systems, might be a result of the enhanced hydrogen bond donor ability of thio- and selenoureido moieties. This feature, recently discovered by our group while studying the complexation features of sulfonamide calix[6]arene receptors,^[43] demonstrates how complex the interplay of key parameters is in governing the threading process of viologen axles inside calix[6]arene hosts.

To further assess the properties of the newly devised TPSe wheel, the thermodynamic and kinetic parameters of the supramolecular complex were investigated by UV-vis spectroscopy in CH₂Cl₂. The absorption spectrum of TPSe shows an intense band in the UV, with $\lambda_{\text{max}}=278$ nm and $\epsilon=$

36700 M⁻¹cm⁻¹. By comparing the absorption spectrum of a 1:1 mixture of TPSe and DOV•2OTs with the sum of the spectra of the separated components in the same molar ratio, an increase in absorbance in the UV region is observed, together with the appearance of the typical charge transfer band at 450 nm, which can be ascribed to the electron donor-acceptor interaction between the macrocycle and the bipyridinium guest (Figure 5).^[20]

The two different conformers (*cone* and partial *cone*) are not distinguishable with UV-vis spectroscopy; indeed, the absorption changes obtained upon titration of a solution of DOV•2OTs with TPSe are consistent with the formation of only one complex and were fitted with a 1:1 binding model (Figure 5). The association constant is 8.3×10^4 M⁻¹, about two orders of magnitude lower than the parent pseudorotaxane compounds based on TPU and TPT. This difference is not unexpected considering the increased C–N rotational barrier for selenoureas with respect to (thio)urea analogues.^[44] This feature prevents a proper interconversion from a *Z/E* to an *E/E* configuration necessary to establish hydrogen-bonding interactions with the tosylate counterions. It is worth noting that this process is mandatory to promote the threading of the organic axle into the macrocyclic cavity.

Further, kinetic experiments were performed using a stopped-flow apparatus: TPSe and DOV•2OTs were mixed in a 1:1 ratio, and the absorption changes over time were monitored in the UV and visible regions (Figure 6). The kinetic traces were fitted with an equilibrium model by fixing the equilibrium constant at the value determined by titration experiments. The threading rate constant is 4.5×10^2 M⁻¹ s⁻¹, four orders of magnitude smaller with respect to parent ureido derivatives.^[20] Both thermodynamic and kinetic parameters point to a destabilisation of the pseudorotaxane complex (and of the transition state) when O and S are replaced by Se atoms on the upper rim of the wheel.

It is well known that pseudorotaxane complexes based on bipyridinium and calixarene macrocycles are electroactive and

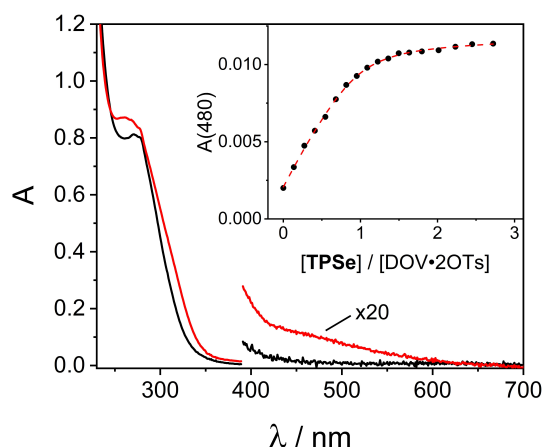


Figure 5. Sum of the absorption spectra (black line) and absorption spectrum of the mixture (red line) of CH₂Cl₂ solutions of DOV•2OTs (3.1×10^{-5} M) and TPSe (3.0×10^{-5} M). Inset: Titration curve (black dots), together with the data fitting (dashed line), obtained upon addition of TPSe to a CH₂Cl₂ solution of DOV•2OTs (3.6×10^{-5} M).

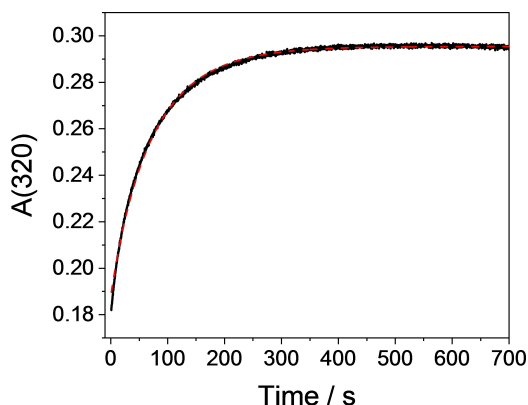


Figure 6. Time-dependent absorption changes recorded upon mixing solutions of DOV•2OTs (3.1×10^{-5} M) and TPSe (3.0×10^{-5} M) in CH_2Cl_2 at 293 K. The dashed line represents the data fitting.

can be disassembled upon reduction of the guest molecule.^[20] Indeed, cyclic voltammetry and differential pulse voltammetry in CH_2Cl_2 were performed on the $\text{P}[\text{TPSe} \supset \text{DOV}]_2\text{TsO}$ complex (Figure 7). The bipyridinium salt is characterised by two mono-electronic and reversible reduction processes ($E_{1/2}^{\prime} = -0.42$ V, $E_{1/2}^{\prime\prime} = -0.87$ V vs SCE); as expected, upon encapsulation, the first cathodic peak is shifted to more negative potential values, on account of the charge transfer interaction between TPSe and DOV•2OTs. The pseudorotaxane disassembles after the first reduction process, as confirmed by the second reduction process, which occurs at the same value as the free bipyridinium. The second anodic process, on its turn, corresponds to the oxidation of the free bipyridinium radical cation. Overall, a similar behaviour to parent calixarene-based pseudorotaxane systems was also demonstrated for TPSe.

Conclusions

In conclusion, we developed a synthetic protocol for heteroditopic calix[6]arenes functionalised at the upper rim with three

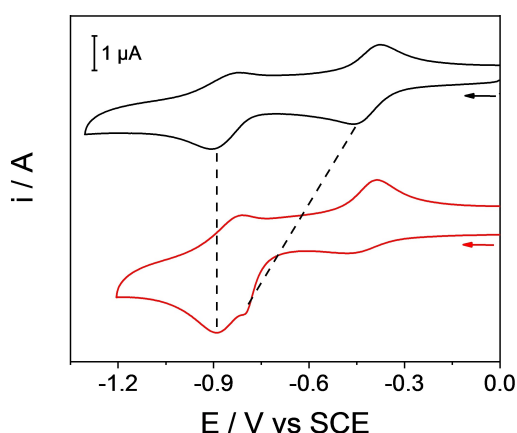


Figure 7. Cyclic voltammetry (scan rate: 100 mV s^{-1} , Argon-purged CH_2Cl_2 , room temperature, TBAOTs 0.01 M) of a solution of DOV•2OTs (1.0×10^{-4} M, black line), and upon addition of TPSe (3.0×10^{-4} M, red line).

selenoureido moieties. Preliminary studies on its complexation properties demonstrated its ability to thread a viologen-based dicationic axle, forming a stable pseudorotaxane complex, despite its enhanced electron delocalisation. Further studies will deal with a more detailed understanding of the ability of selenoureido groups to control the threading process and to evaluate its halogen-bonding donor properties.^[45] The catalytic activity of this novel macrocycle will also be assessed in general Brønsted acid-catalysed reactions.

Experimental Section

Synthesis. Solvents were dried following standard procedures; all other reagents were of reagent-grade quality, obtained from commercial sources and used without further purification. Chemical shifts are expressed in ppm using the residual solvent signal as an internal reference. Mass spectra were determined in ESI mode. TN,^[36] phenylselenocyanate,^[46] DOV ditylate,^[15] and diphenylselenourea (DPSeU)^[23] were synthesised according to reported procedures.

TPSe

In a two-neck flask kept under an inert atmosphere, to a solution of TN (0.3 g, 0.22 mmol) in ethanol (100 mL), hydrazine monohydrate (1.0 g, 13 mmol) and a tip of spatula of 10% Pd/C catalyst were added. The resulting mixture was refluxed for 24 h and then filtered, still warm and under an inert atmosphere, through a celite pad to remove the palladium catalyst. The filtered solution was evaporated to dryness under reduced pressure. The residue was diluted in dichloromethane (50 mL), and the resulting organic phase was washed thrice with water to remove the excess of hydrazine. The separated organic phase was dried over anhydrous CaCl_2 , filtered and evaporated to dryness under reduced pressure. The residue was dissolved in anhydrous dichloromethane (30 mL) and placed in a two-neck flask under an inert atmosphere. To the resulting homogeneous solution, phenyl isoselenocyanate (0.12 g, 0.7 mmol) was added. The reaction mixture was stirred at room temperature for 24 hrs, and then the solvent was removed under reduced pressure. Purification by column-chromatography of the crude mixture (n-Hex: EtOAc = 8:2) afforded TPSe in 74% yield as a tan solid. M. p.: 120–122 °C. ^1H NMR (400 MHz, tetra-chloroethane- d_2) δ = 9.07 (br.s, 3H), 8.30 (br.s, 3H), 7.42–7.22 (m, 21H), 6.46 (br.s, 6H), 4.65–4.37 (m, 6H), 4.00 (t, J = 6.8 Hz, 6H), 3.67–3.46 (m, 6H), 2.65–2.05 (br.s, 6H), 2.02–1.89 (m, 6H), 1.67–1.56 (m, 6H), 1.50–1.28 (m, 57H), 0.98–0.89 (m, 9H). ^{13}C NMR (400 MHz, tetra-chloroethane- d_2) δ = 177.6 (C_q), 154.4 (C_q), 146.8 (C_q), 138.3 (C_q), 137.0 (C_q), 132.8 (C_q), 129.3 (CH), 128.3 (CH), 126.9 (CH), 126.5 (CH), 125.5 (CH), 61.4 (CH₂), 34.3 (C_q), 32.0 (CH₂), 31.7 (CH₃), 30.8 (CH₂), 30.6 (CH₂), 29.7 (CH₂), 29.4 (CH₂), 26.4 (CH₂), 22.8 (CH₂), 14.4 (CH₃). HR-MS (ESI) m/z : = $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{102}\text{H}_{133}\text{N}_6\text{O}_6\text{Se}_3$: 1776.7824 found 1776.7818.

Absorption Spectra

UV-vis absorption spectra were recorded with a Cary 300 (Agilent) spectrophotometer. Unless otherwise specified, measurements were performed on air-equilibrated CH_2Cl_2 (Sigma-Aldrich) solutions at room temperature. Solutions were examined in 1-cm and 0.5-cm spectrofluorimetric quartz cells.

Determination of the Stability Constants from Spectroscopic Titrations

Spectrophotometric titrations were performed by adding a micro-syringe titrant aliquot to the titrand solution. The absorption changes were monitored throughout the titration. The apparent stability constants of the complexes were obtained by fitting the spectra with the software HypSpec,^[47] using a 1:1 association model. The titration experiments were repeated at least 2 times, and the values of the association constants were averaged.

Kinetic Experiments

Reaction's kinetics was investigated by means of a stopped-flow spectrometer (Applied Photophysics SX 18-MV). The experimental data were fitted with the software SPECFIT^[48] using a mixed-order reaction (second order for threading, first order for dethreading), with the constrain that the ratio between the two rate constants has to be equal to the thermodynamic constant determined from titrations. Multiple experiments were fitted, and the values of the kinetic constants were averaged.

Electrochemical Measurements

Cyclic voltammetric (CV) and differential pulse voltammetric (DPV) experiments were carried out in argon-purged solvents with an Autolab 30 multipurpose instrument interfaced to a PC. The working electrode was a glassy carbon electrode (Amel, 0.07 cm²), carefully polished with an alumina-water slurry on a felt surface immediately before use. The counter electrode was a Pt wire, separated from the solution by a frit, an Ag wire was employed as a quasi-reference electrode. Ferrocene was used as an internal standard. Tetrabutylammonium tosylate (TBAOTs) was used as supporting electrolytes, added in a 100-fold proportion with respect to the sample concentration. Cyclic voltammograms were obtained at scan rates varying from 50 to 2000 mV s⁻¹. Differential pulse voltammograms were performed with a scan rate of 20 mV s⁻¹ (pulse height 75 mV). The IR compensation was used, and every effort was made throughout the experiments to minimise the resistance of the solution. The electrochemical reversibility of the voltammetric wave of ferrocene was taken as an indicator of the absence of uncompensated resistance effects.

Quantum Chemical Studies

The geometries of pseudorotaxanes complexes P[TPSe(pC)DOV]2OTs and P[TPSe(C)DOV]2OTs were initially guessed with PM6-DH+ methods^[39] and then fully optimised using the TPSS functional^[40] with the def2-SVP basis set.^[41] The single-point relative energy of the resulting minimised structures was finally calculated using the larger def2-TPZV basis set.^[41] The semi-empirical and quantum chemical calculations were performed using the MOPAC 22.1.0^[49] and ORCA 5.0^[50] program packages, respectively.

Supporting Information

The authors have cited additional references within the Supporting Information.^[51–54]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: calix[6]arenes · selenourea · pseudorotaxane · NMR spectroscopy · Host/Guest chemistry

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