

TetrazineBox: A Structurally Transformative Toolbox

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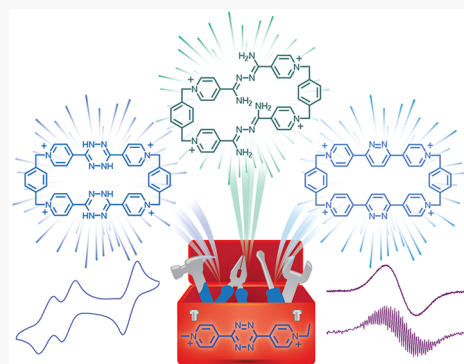


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ABSTRACT: Synthetic macrocycles capable of undergoing allosteric regulation by responding to versatile external stimuli are the subject of increasing attention in supramolecular science. Herein, we report a structurally transformative tetracationic cyclophane containing two 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine (4-bptz) units, which are linked together by two *p*-xylylene bridges. The cyclophane, which possesses modular redox states and structural post-modifications, can undergo two reversibly consecutive two-electron reductions, affording first its bisradical dicationic counterpart, and then subsequently the fully reduced species. Furthermore, one single-parent cyclophane can afford effectively three other new analogs through box-to-box cascade transformations, taking advantage of either reductions or an inverse electron-demand Diels–Alder (IEDDA) reaction. While all four new tetracationic cyclophanes adopt rigid and symmetric box-like conformations, their geometries in relation to size, shape, electronic properties, and binding affinities toward polycyclic aromatic hydrocarbons can be readily regulated. This structurally transformative tetracationic cyclophane performs a variety of new tasks as a result of structural post-modifications, thus serving as a toolbox for probing the radical properties and generating rapidly a range of structurally diverse cyclophanes by efficient divergent syntheses. This research lays a solid foundation for the introduction of the structurally transformative tetracationic cyclophane into the realm of mechanically interlocked molecules and will provide a toolbox to construct and operate intelligent molecular machines.



INTRODUCTION

The design and preparation of functional macrocycles have been key driving forces in promoting major advances in supramolecular chemistry,¹ which was pioneered by Pedersen,² Cram,³ and Lehn.⁴ The subsequent decades have witnessed the emergence of plentiful supplies of macrocyclic compounds, including, but not limited to, cyclodextrins,⁵ calixarenes,⁶ cucurbiturils,⁷ expanded porphyrins,⁸ pillararenes,⁹ and cationic cyclophanes,¹⁰ such as cyclobis(paraquat-*p*-phenylene) (CBPQT⁴⁺) or the so-called **Blue Box**.¹¹ All these macrocycles offered good models for investigating the nature of non-covalent bonding interactions.¹² Meanwhile, they also served as primary building blocks for the construction of advanced (supra)molecular assemblies^{6c,7c,13} and functional materials.^{7f,14} In particular, the successful landmarks in synthetic macrocyclic chemistry enabled chemists to construct^{7c,15} artificial molecular machines and investigate¹⁶ the relative motions of their component parts on the molecular scale.

While the properties of these classic macrocycles are well-known, the structural diversity and host–guest chemistry³ of synthetically novel macrocycles continue to be the subjects of investigations¹⁷ in an attempt to unleash new research directions in chemistry and materials science. Typically, most of these synthetic macrocycles, however, are structurally well-defined with rigid stereoelectronic constitutions. Recently, the applications of the so-called post-macrocyclization modifica-

tion and covalent post-assembly modification (PAM) strategies employing synthetic macrocycles containing tetrazine units, which were pioneered by Wang¹⁸ and Nitschke,¹⁹ offered straightforward ways to fabricate complex and functional macrocycles. Here, we report (Scheme 1) a structurally transformative tetrazine-containing tetracationic cyclophane,²⁰ namely **TetrazineBox** (**TzBox**⁴⁺), which possesses modular redox states that lead to versatile and modifiable structures. The three reversible redox states of **TzBox**⁴⁺ can be manipulated simply by the application of redox chemistry, and their properties have been revealed fully by cyclic voltammetry (CV), as well as by UV–vis–NIR and EPR spectroscopies. Moreover, **TzBox**⁴⁺ undergoes box-to-box cascade transformations through either reductions or an inverse electron-demand Diels–Alder (IEDDA) reaction, affording three new cyclophanes. Single-crystal X-ray crystallographic analysis on crystalline samples of these cyclophanes demonstrates that the dimensions of their cavities can be regulated. Finally, as a proof of principle, we show that their

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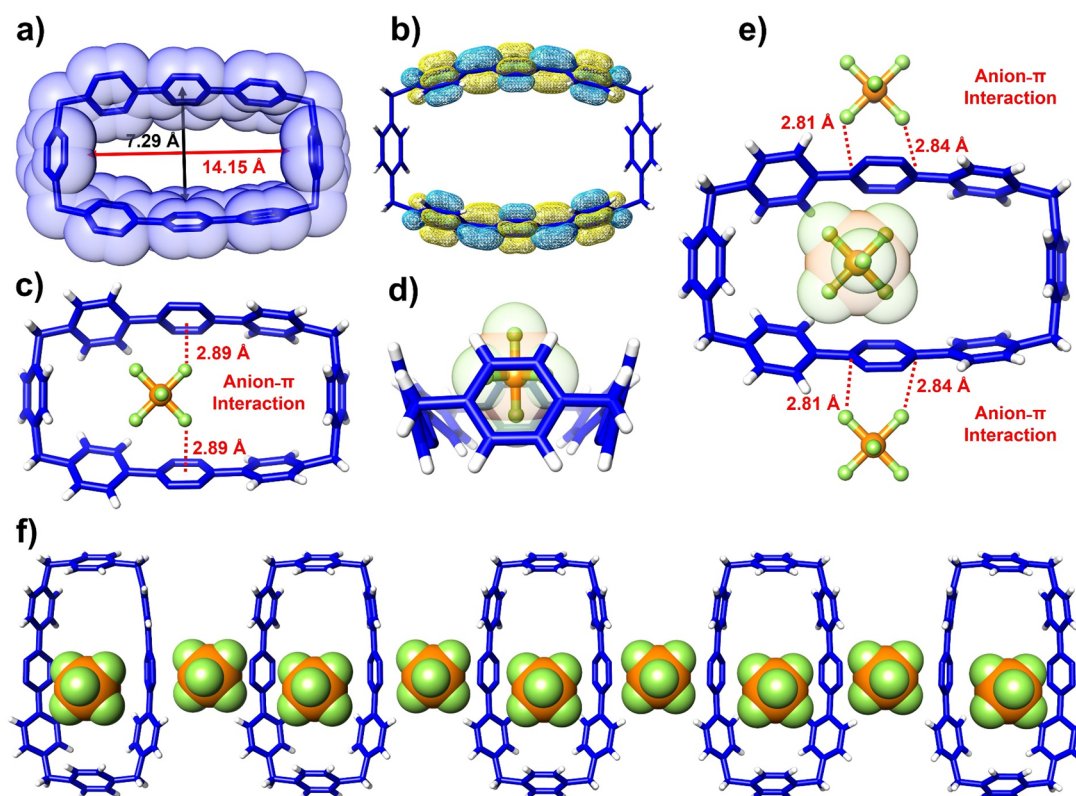
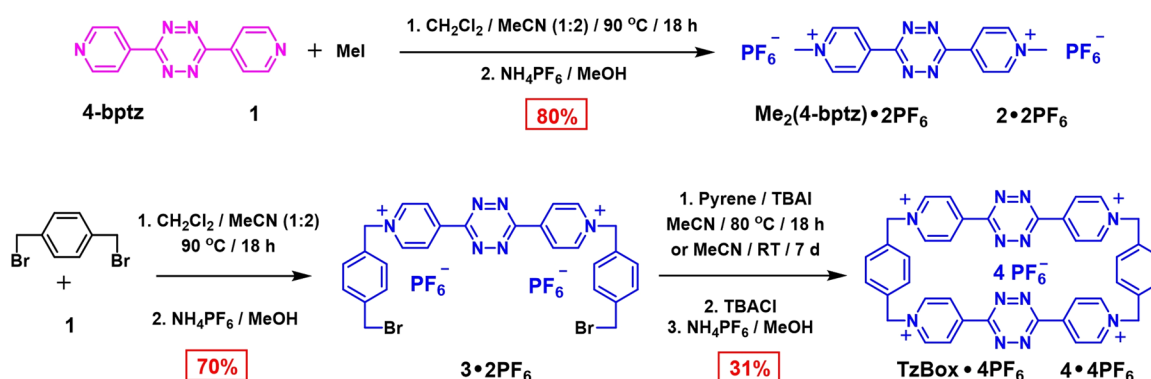
Scheme 1. Synthesis of the Reference Compound $\text{Me}_2(4\text{-bptz})\cdot 2\text{PF}_6$ and $\text{TzBox}\cdot 4\text{PF}_6$ 

Figure 1. X-ray single-crystal (super)structures of TzBox^{4+} . Atom colors: the organic skeletons are illustrated as stick representations in blue; P, yellow; F, green. The anion- π interactions are depicted as red dashed lines. (a) Top-down view of TzBox^{4+} as a stick representation with the corresponding semitransparent space-filling representation superimposed upon it. The dimensions of the cavity are highlighted by black and red arrows. (b) Graphical representation of the DFT-calculated lowest unoccupied molecular orbital (LUMO) of TzBox^{4+} . (c) A PF_6^- counterion located inside the cavity of TzBox^{4+} as a result of synergistic anion- π interactions. The PF_6^- anion is shown as a ball-and-stick representation. (d) Side-on view of the PF_6^- counterion situated inside the cavity of TzBox^{4+} . (e) Anion- π interactions occurring both on the exterior and in the interior of the cavity. The exterior PF_6^- counterions are shown as ball-and-stick representations. The interior PF_6^- counterion is shown as a ball-and-stick representation with the corresponding semitransparent space-filling representation superimposed upon it. (f) The multiple anion- π interactions assembling TzBox^{4+} and PF_6^- counterions into an ordered 1D superstructure. The PF_6^- counterions are shown as space-filling representations.

binding affinities toward polycyclic aromatic hydrocarbons (PAHs) can be modulated as a consequence of the variable electronic features of TzBox^{4+} and its analogs.

RESULTS AND DISCUSSION

Synthesis and Structure of the TetrazineBox. We chose 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine (4-bptz) **1** as a key building block in making TzBox^{4+} on account of its redox and IEDDA reactions in macrocyclic compounds¹⁸ and coordina-

tion chemistry.^{19b,21} The incorporation of 4-bptz into a tetracationic cyclophane could be expected to result in a plethora of outcomes. The synthesis of $\text{TzBox}\cdot 4\text{PF}_6$ is illustrated²² in Scheme 1. Treatment of **1** with 10 equiv of 1,4-bis(bromomethyl)benzene in $\text{CH}_2\text{Cl}_2/\text{MeCN}$ (1:2), while heating at 90 °C for 18 h, followed by counterion exchange ($\text{NH}_4\text{PF}_6/\text{MeOH}$), afforded $3\cdot 2\text{PF}_6$ in 70% yield. In the presence of 6 equiv of pyrene as a template, with 30 mol% of tetrabutylammonium iodide (TBAI) as a catalyst, the reaction

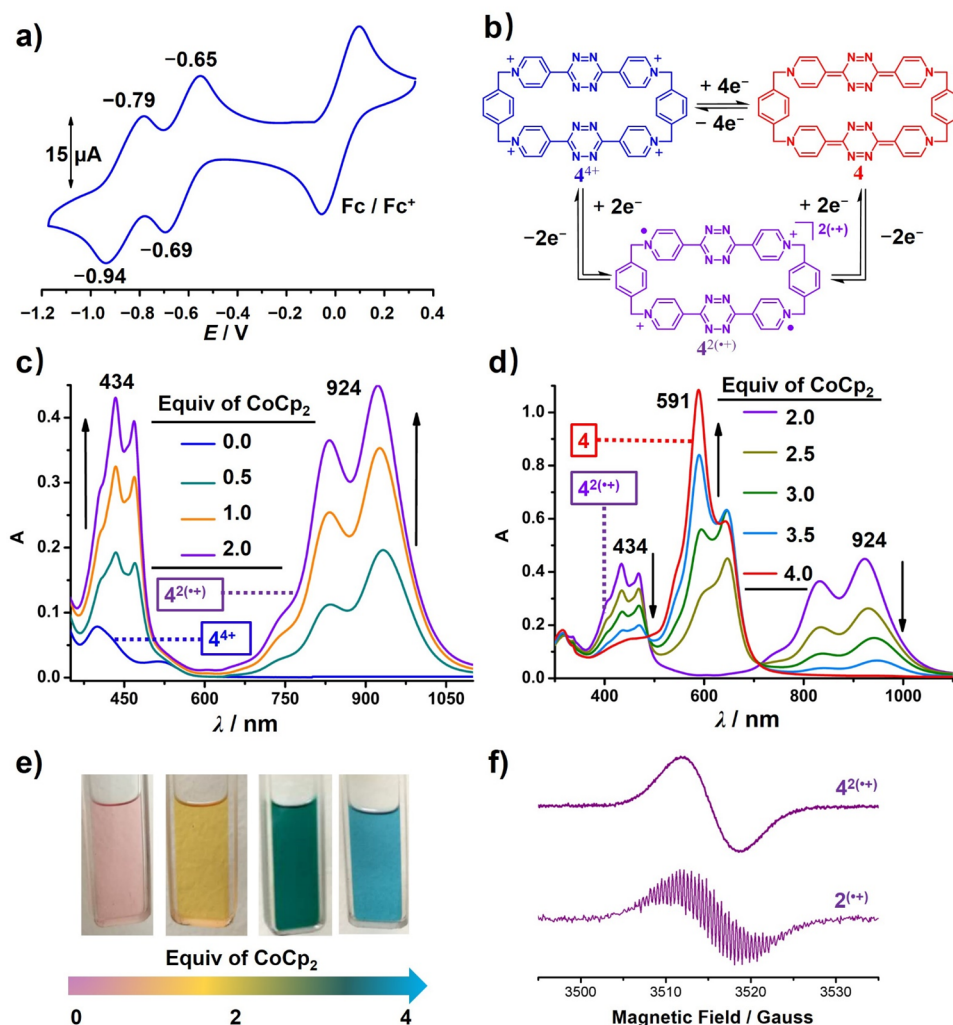


Figure 2. Manipulation and characterization of the redox states of **TzBox**·4PF₆. (a) Cyclic voltammogram (CV) of **TzBox**·4PF₆ recorded (scan rate 100 mV s⁻¹) with a glassy carbon electrode. The experiment was performed at 298 K in an Ar-purged DMF solution (1 mM) with 0.1 M TBAPF₆ as the supporting electrolyte and ferrocene as internal standard. (b) Structural formulas of the three reversible redox state of **TzBox**⁴⁺. (c, d) UV-vis-NIR absorption spectra of **TzBox**^{4+/2(•+)}, which were obtained by stepwise addition of 0, 0.5, 1.0, 2.0, 2.5, 3.0, 3.5, and 4.0 equiv of CoCp₂. All spectra were recorded in Ar-purged DMF solutions at 298 K. (e) Change of the color of DMF solutions from light pink to yellow to green and finally to blue on stepwise addition of CoCp₂. (f) CW-EPR spectra of **4**^{2(•+)} and **2**^(•+).

of **3·2PF₆** in MeCN with 4-bptz at 80 °C for 18 h—or at room temperature for 7 days—followed by precipitation of the product with tetrabutylammonium chloride (TBACl), furnished crude **pyrene**C**TzBox**·4Cl. The complex, which was subjected to counterion exchange (NH₄PF₆/MeOH), afforded crude **pyrene**C**TzBox**·4PF₆. The template (**pyrene**) was removed by reverse-phase column chromatography, and the desired product **TzBox**·4PF₆ was isolated as a red solid in 31% yield. Without the use of **pyrene** as a template in this reaction, the cyclophanes cannot be prepared.

Further atomic-level (super)structural information was obtained (Figure 1) from single-crystal X-ray diffraction (SCXRD) experiments. Orange plate-like single crystals, suitable for SCXRD, were obtained by slow vapor diffusion of *i*Pr₂O into an MeCN solution of **TzBox**·4PF₆ during 1 day. In the solid state, **TzBox**⁴⁺ adopts (Figure 1a) a symmetrical box-like conformation, with average dimensions of 14.1 × 7.3 Å. Density functional theory (DFT) calculations²³ reveal (Figure 1b) that the LUMO of **TzBox**⁴⁺ is highly delocalized on the 4-bptz²⁺ subunits. Superstructural analyses show that

anion-π interactions exist between the PF₆⁻ counterions and **TzBox**⁴⁺. One PF₆⁻ counterion is situated (Figure 1c,d) close to centrosymmetrically inside the cavity of **TzBox**⁴⁺ and interacts synergistically with two 4-bptz²⁺ walls through utilizing anion-π interactions. The distances between the included PF₆⁻ ion and the centroids of the tetrazine units are both 2.89 Å, i.e., well within the typical distances of 2.80–3.50 Å for anion-π interactions recorded in the literature.^{17d,24} Meanwhile, anion-π interactions also occur (Figure 1e) outside of the box cavity between the two 4-bptz²⁺ units and associated PF₆⁻ counterions, with distances of 2.81 and 2.84 Å. Finally, multiple anion-π interactions enable the assembly (Figure 1f) of the PF₆⁻ ions and **TzBox**⁴⁺ into a 1D superstructure.²⁵ Although similar anion-π interactions are also present (Figure S1) in the superstructures of **2·2PF₆**, they have never been observed in the solid-state superstructures of other tetracationic cyclophanes,^{17a} thus highlighting the highly π-electron-deficient nature of the 4-bptz²⁺ units in these two compounds.

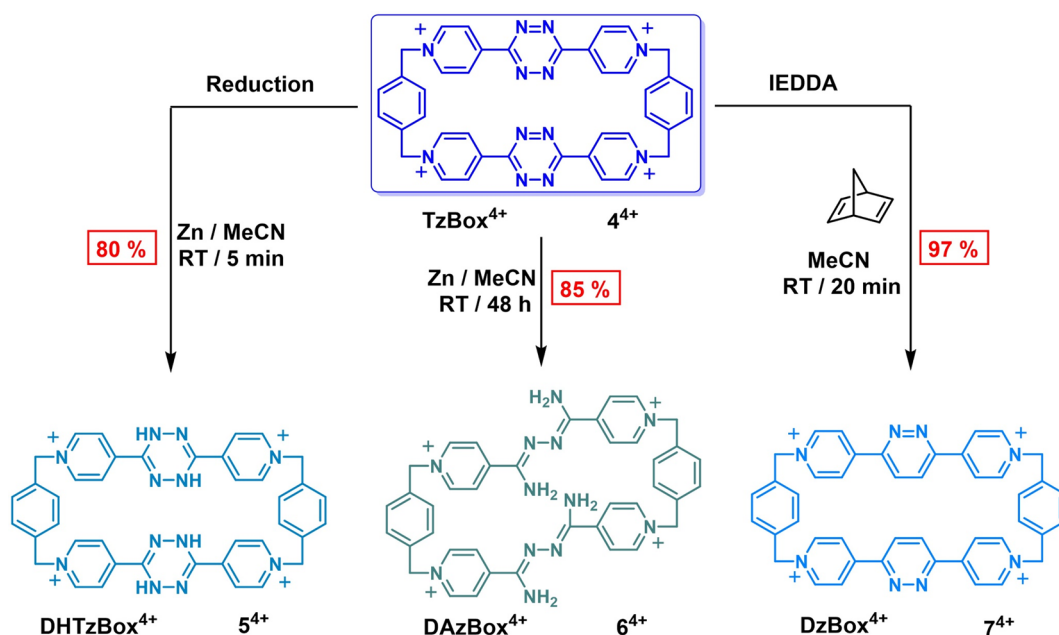


Figure 3. Box-to-box transformations. The parent **TzBox**⁴⁺ is transformed to **DHTzBox**⁴⁺ (5⁴⁺), **DAzBox**⁴⁺ (6⁴⁺), and **DzBox**⁴⁺ (7⁴⁺) by reductions and an inverse electron-demand Diels–Alder (IEDDA) reaction.

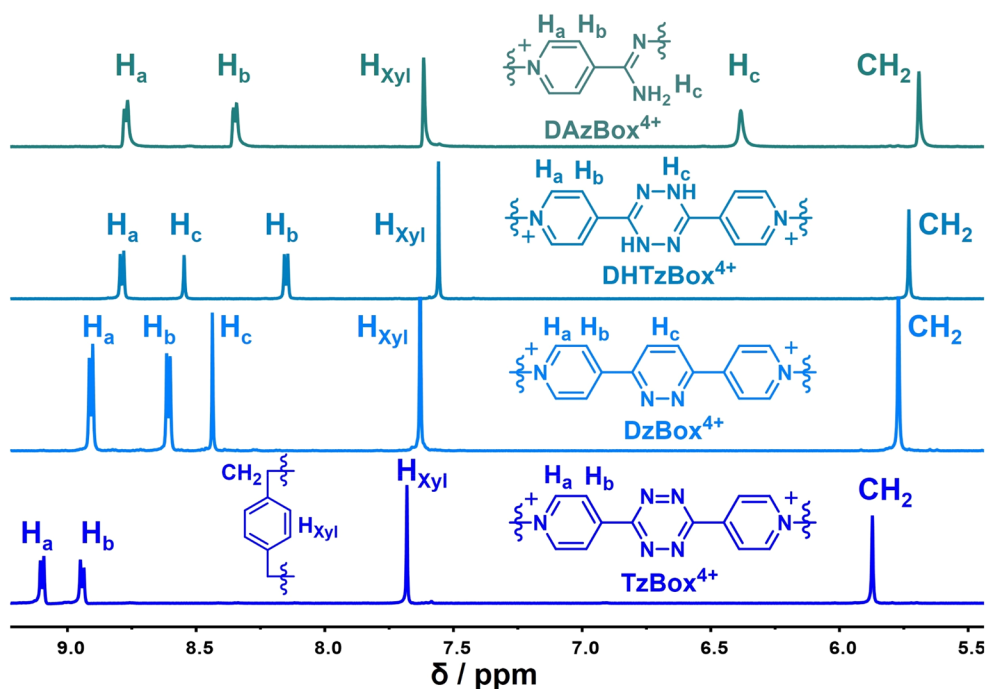


Figure 4. ¹H NMR spectra of **DAzBox**⁴⁺, **DHTzBox**⁴⁺, **DzBox**⁴⁺, and **TzBox**⁴⁺. All their ¹H NMR spectra recorded in CD₃CN at 298 K reveal single sets of resonances, in keeping with their average molecular symmetry.

Redox Chemistry. Cyclic voltammetry (CV) was performed on **TzBox**·4PF₆ and the reference compound 2·2PF₆ in order to shed light on the electrochemical behavior of the rigid cyclophane. **TzBox**·4PF₆ consists (Figure 2a) of two well-separated two-electron redox couples, observed at −0.69 and −0.94 V vs Fc/Fc⁺ in DMF, corresponding to (Figure 2b) the formation of the bisradical dicationic **TzBox**^{2(•+)} and the fully reduced neutral species, **TzBox**, respectively. The fact that this transformational process is reversible is supported by the overlapping of the CV curves of 10 repeated cycles. These observations highlight the fact that the three reversible

oxidation states of tetracationic **TzBox**⁴⁺ can be manipulated by simply applying redox chemistry.

In addition, UV–vis–NIR and EPR spectroscopies were used to probe the physicochemical properties of the **TzBox**⁴⁺ cyclophane and its different redox states in DMF solution by titrating with a one-electron reductant, cobaltocene²⁶ (CoCp₂), under an Ar atmosphere. Upon stepwise addition of CoCp₂ to a solution of **TzBox**·4PF₆, the characteristic absorbances (Figure 2c) of the bisradical dicationic **TzBox**^{2(•+)}, i.e., two sets of absorption bands at around 434 and 924 nm, increase in their intensities gradually in the

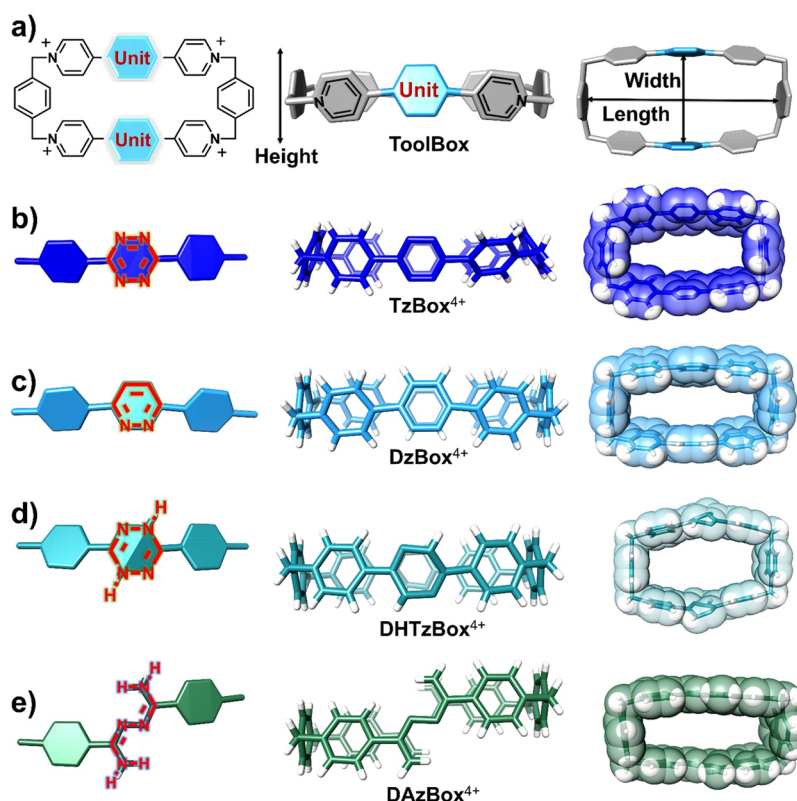


Figure 5. Illustration of box cavities of the tetracationic cyclophane analogs in solid state. (a) Schematic diagrams showing the box-like conformations and the dimensions of the cavities, related to their heights, widths, and lengths. Different representations of the single-crystal structures of (b) TzBox^{4+} , (c) DzBox^{4+} , (d) DHTzBox^{4+} , and (e) DAzBox^{4+} . Left, graphical representations of the structures of the spacers. Middle, stick representations of box-like cavities. Right, stick representations with the corresponding semitransparent space-filling representations superimposed upon them.

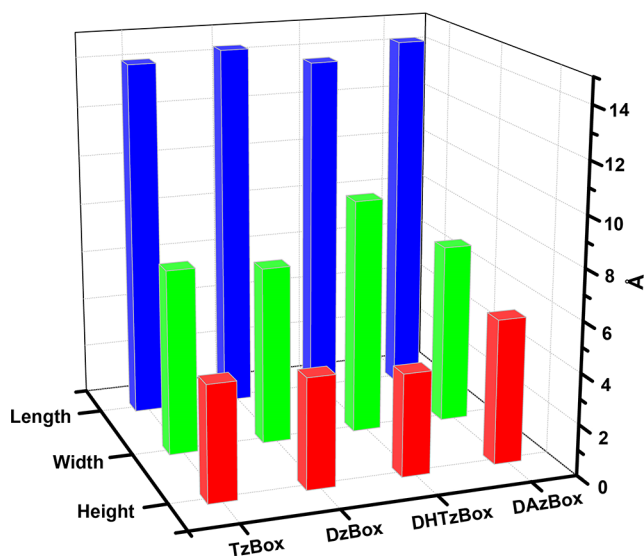


Figure 6. Histogram comparing the cavities in TzBox^{4+} , DzBox^{4+} , DHTzBox^{4+} , and DAzBox^{4+} in relation to the dimensions of heights, widths, and lengths.

spectrum. The TzBox^{4+} was converted quantitatively to the bisradical dication $\text{TzBox}^{2(\bullet+)}$ on addition of 2 equiv of CoCp_2 . When more than 2 equiv of the reductant were added, the intensities of the bands around at 434 and 924 nm both decreased (Figure 2d), while a new absorption band centered at 591 nm appeared. This new band, which was attributed to

the formation of the fully reduced cyclophane TzBox in quantitative yield by employing 4 equiv of CoCp_2 , was evidenced by the concomitant disappearance of the absorption bands of the bisradical dication and the maximal absorption intensity of the band at around 591 nm. The continuous shifts of the absorption bands are exactly in line with the heterochromatic changes (Figure 2e) of the solutions. The colors of the solutions changed from light pink to yellow to green and then finally to blue. Furthermore, $\text{TzBox}^{2(\bullet+)}$ and TzBox can also be obtained (Figure S22) by reducing TzBox^{4+} with Zn powder in Ar-purged dry MeCN and DMF solutions, respectively.

Continuous-wave EPR spectra provide (Figure 2f) further evidence for the formation of radical cations. The spectrum of reference compound 2·2PF₆ exhibits multiple peaks as a result of the hyperfine splitting from the protons and nitrogen, an observation which is consistent with the EPR signal reported in the literature.²⁷ The EPR spectrum of $\text{TzBox}^{2(\bullet+)}$ shows a complete absence of hyperfine structure, most likely because of intramolecular spin-exchange interactions between the unpaired electrons from the dimeric 4-bptz^(•+) units, which are isolated about 7 Å apart as a result of bridging by a pair of p-xylylene linkers.²⁸

Box-to-Box Transformations. The facile and reversible redox chemistry of TzBox^{4+} encouraged us to grow single crystals of the bisradical dicationic $\text{TzBox}^{2(\bullet+)}$ and the neutral TzBox . Unexpectedly, reducing TzBox^{4+} in a glovebox with an excess of Zn powder for 5 min and 48 h, respectively, led to (Figure 3) two different products, namely, Dihydro-tetrazine-

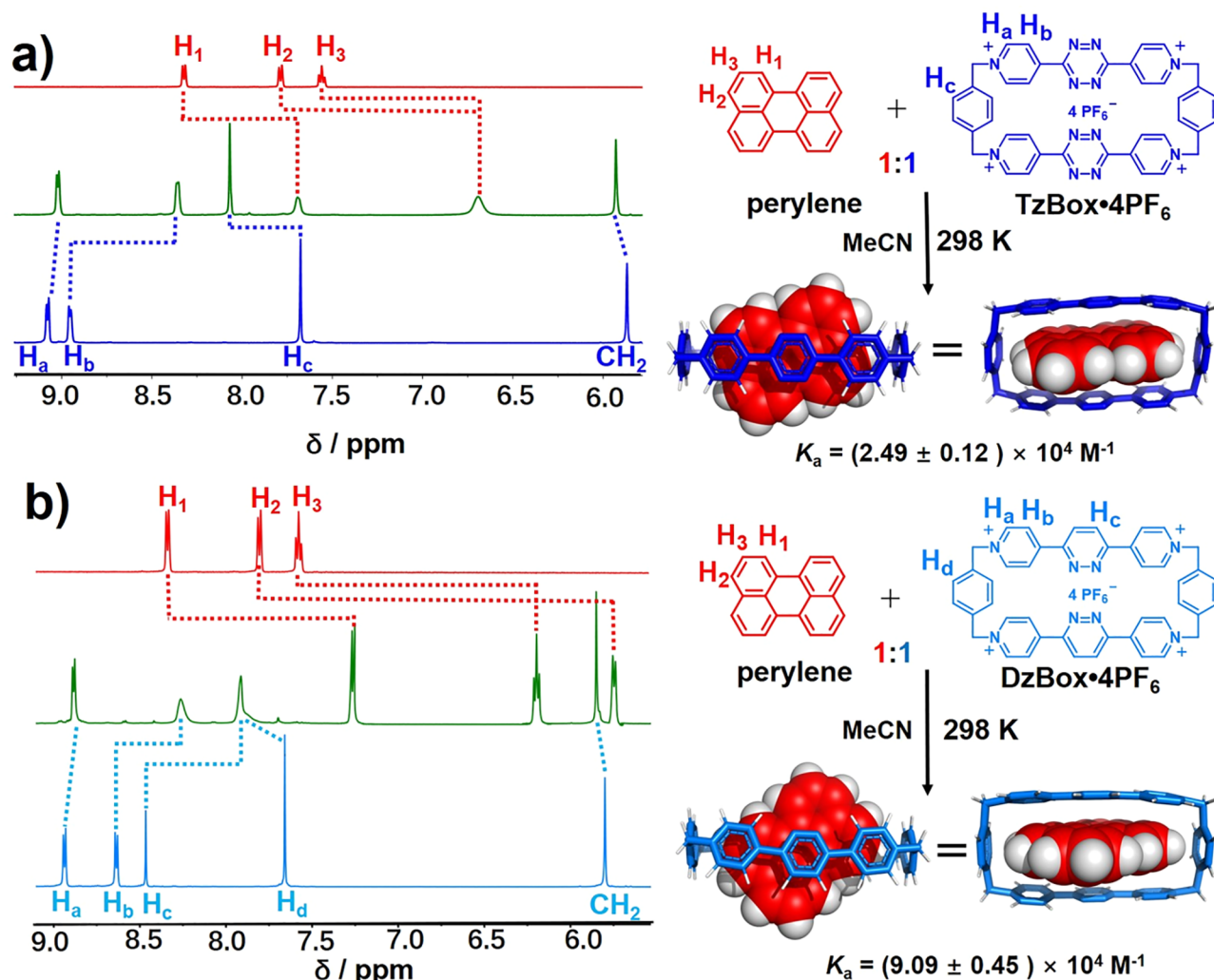


Figure 7. Binding affinities of **TzBox** and **DzBox** toward **perylene**. (a) ^1H NMR spectra of **perylene**, **TzBox**, and their 1:1 mixture recorded in CD_3CN solution as well as the single-crystal structure of the inclusion complex. The **perylene** is highlighted as a space-filling representation in red. The organic skeleton of **TzBox** is illustrated as a stick representation in blue. (b) ^1H NMR spectra of **perylene**, **DzBox**, and their 1:1 mixture in CD_3CN solution as well as the single-crystal superstructure of the inclusion complex. The **perylene** is highlighted as a space-filling representation in red. The organic skeleton of **DzBox** is illustrated as a stick representation in light blue.

Box (**DHTzBox** $^{4+}$) and **DiaminoazineBox** (**DAzBox** $^{4+}$). We speculate that both **TzBox** $^{2(+)}$ and **TzBox** are extremely reactive and sensitive toward protons, oxygen, and other electrophiles in solution. In the presence of Zn powder and a small amount of H_2O in MeCN, a reductive hydrogenation involving two consecutive single-electron reductions, followed by protonation, transforms (Scheme S7a) the aromatic tetrazine into the nonplanar 1,4-dihydro-tetrazine, producing **DHTzBox** $^{4+}$. On prolonging the reduction time (48 h), a ring-opening reaction subsequently converts 1,4-dihydro-tetrazine to the acyclic product, diaminoazine. The intermediate **DHTzBox** $^{4+}$ was converted finally to **DAzBox** $^{4+}$. While reducing tetrazine has been reported²⁹ in metal-coordination chemistry literature, to the best of our knowledge, the structures presented here are the first examples of exploring both reactions in the context of organic molecules. The mechanisms of the reductions and box-to-box transformations are summarized in Scheme S7. In comparison with the traditional stepwise syntheses of macrocycles, this box-to-box transformation, not only demonstrates the versatile nature of the parent macrocycle, but also enables us to introduce various

functional groups—such as a secondary amino group into **DHTzBox** $^{4+}$ and a primary amino group into **DAzBox** $^{4+}$ —that would otherwise be incompatible with the conditions of forming the parent **TzBox** $^{4+}$. In order to expand the scope of the box-to-box transformation, the preparation³⁰ of **Diazine-Box** (**DzBox** $^{4+}$) in 97% yield employing an IEDDA reaction was also demonstrated. All these tetracationic cyclophane analogs were fully characterized by recording their ^1H and ^{13}C NMR spectra (Figures S12–S21) in addition to their high-resolution mass spectra. All the ^1H NMR spectra reveal (Figure 4) single sets of resonances on account of their symmetric conformations in solution.

Regulatable Cavities and Binding Affinities. X-ray crystallography reveals unambiguously the conformations of the cyclophane analogs in the solid state. Ignoring the influence of the spacers between the pyridinium units, all these analogs adopt (Figure 5) a box-like geometry. The dimensions of the cavities of these tetracationic cyclophanes, related to (Figures 5 and 6, and Table S1) their heights, widths, and lengths,³¹ are regulatable. **TzBox** $^{4+}$ and **DzBox** $^{4+}$ share similar shapes with ca. 4.4, 7.1, and 14.3 Å characterizing

their heights, widths, and lengths, respectively, since the spacers in these two boxes are both rigid six-membered aromatic rings, namely tetrazine and diazine. The characteristic curve-shape of **DHTzBox**⁴⁺ has the smallest height and length, while possessing the largest width as a consequence of its flexible spacers, namely dihydro-tetrazine. The largest height of **DAzBox**⁴⁺, accompanied by average values of width and length, is attributed to the relaxed conformation of the spacer with ring-opening structures.

These regulatable geometries of progenitor and analogs hold out the prospect of modulating their binding abilities toward a myriad of guests. In order to give some substance to this hypothesis, we chose ³² **TzBox**·4PF₆ and **DzBox**·4PF₆ to probe their binding abilities toward both **pyrene** and **perylene**. The dramatic shifts in the proton resonances in the ¹H NMR spectra associated with the hosts, guests and mixtures indicate (Figure 7) the formation of inclusion complexes. In addition, all the 1:1 host–guest mixtures show (Figures S4–S7) characteristic charge-transfer (CT) bands in the UV–vis absorption spectra. Job's plots confirm (Figures S4–S7) their 1:1 stoichiometries. On the basis of the UV–vis titration data, the binding constants (*K*_a) were calculated (Figure 7 and Figures S4–S7) to be $(1.54 \pm 0.08) \times 10^4$ (**pyrene**·**TzBox**⁴⁺), $(2.49 \pm 0.12) \times 10^4$ (**perylene**·**TzBox**⁴⁺), $(1.62 \pm 0.08) \times 10^4$ (**pyrene**·**DzBox**⁴⁺), and $(9.09 \pm 0.45) \times 10^4$ M^{−1} (**perylene**·**DzBox**⁴⁺). Both **TzBox**·4PF₆ and **DzBox**·4PF₆ exhibit similar and weak binding affinities toward **pyrene** because of the mismatched sizes of the hosts and guests, while their binding affinities toward **perylene** are quite different. The binding constant between **DzBox**⁴⁺ and **perylene** is almost 5 times larger than that between **TzBox**⁴⁺ and **perylene**. The difference in binding constants can be ascribed to the different electronic properties present in **TzBox**⁴⁺ and **DzBox**⁴⁺. CV and differential pulse voltammetry (DPV) show (Figure S8) the more positive reduction potentials of **TzBox**⁴⁺, revealing its more electron-deficient environment which is favorable for the inclusion of PF₆[−] ions in the cavity as a result of anion– π interactions, as also evidenced in the single crystal structure of **TzBox**·4PF₆. The presence of PF₆[−] ions, however, prevents guests from entering the cavity, resulting in an inferior association constant.³³

Concrete evidence for the formation of 1:1 inclusion complexes and their binding models are evaluated from their solid-state superstructures.³⁴ The X-ray superstructural analysis reveals (Figure S9) that the guests sit inside the cavity of the hosts in order to achieve the maximum face-to-face π -surface overlaps. The stacking distances between the guests and the tetracationic cyclophanes are ca. 3.5 Å, a typical distance for strong [$\pi \cdots \pi$] interactions. In comparison with **pyrene**, **perylene** has a larger π surface which is more favorable for inclusion in the cavities of **TzBox**⁴⁺ and **DzBox**⁴⁺. Moreover, this larger size also enhances the [C–H $\cdots\pi$] interactions in the complexes, an observation which is reflected by the shorter distances between the protons of the guests and the π surfaces of *p*-xylylene units.

CONCLUSIONS

In summary, a structurally transformative tetracationic cyclophane has been designed and synthesized. The cyclophane exists in three different reversible redox states which can be manipulated and visited by delicately controlled redox chemistry. The parent cyclophane can also be transformed into three new cyclophane analogs by use of efficient box-to-

box transformations. All four tetracationic cyclophanes adopt rigid box-like conformations. Their cavity geometries, electronic properties, and binding abilities toward PAHs, are regulatable. Our investigation demonstrates that one specially designed tetracationic cyclophane can perform a variety of tasks, thus serving as a toolbox for probing the radical chemistry and generating libraries of analogs with more intricate box-like structures. The incorporation of such a structurally transformative tetracationic cyclophane into mechanically interlocked molecules will provide a way of controlling and manipulating the behavior of artificial molecular machines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c01114>.

Detailed information regarding the experimental methods and procedures, X-ray crystallographic data, and supporting figures and tables (PDF)

X-ray crystallographic data for 4-PF₆ (CIF)

X-ray crystallographic data for 5-PF₆ (CIF)

X-ray crystallographic data for 2-PF₆ (CIF)

X-ray crystallographic data for 6-PF₆ (CIF)

X-ray crystallographic data for 7-PF₆ (CIF)

X-ray crystallographic data for 4-pyrene (CIF)

X-ray crystallographic data for 4-perylene (CIF)

X-ray crystallographic data for 7-pyrene (CIF)

X-ray crystallographic data for 7-perylene (CIF)

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Notes

The authors declare no competing financial interest.

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