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Cooperative Reactivity in an Extended-Viologen-Based Cyclophane

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Supporting Information

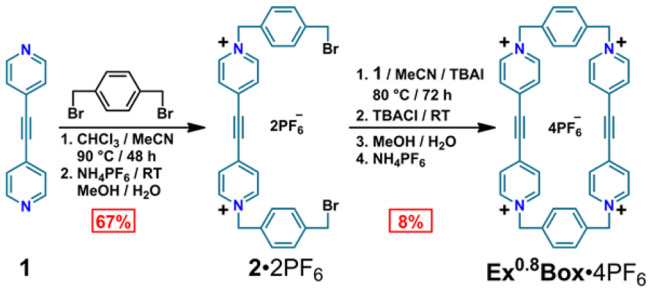
ABSTRACT: A tetracationic pyridinium-based cyclophane with a box-like geometry, incorporating two juxtaposed alkyne functions, has been synthesized. The triple bonds are reactive through cycloadditions toward dienes and azides, promoted by the electron-withdrawing nature of the pyridinium rings, as well as by the strain inherent in the cyclophane. The cycloadditions proceeded in high yields, with the cyclophane reacting faster than its acyclic analogue. While the cyclophane contains two reactive triple bonds, there is no evidence for a stable monofunctional intermediate—only starting material and the difunctional product have been detected by ^{1}H NMR spectroscopy. Molecular modeling of the energy landscape reveals a lower barrier for the kinetically favored second cycloaddition compared with the first one. This situation results in tandem cascading reactions within rigid cyclophanes, where reactions at a first triple bond induce increased reactivity at a distal second alkyne.

The mechanism of action of hemoglobin is remarkable on account of its cooperative response in the binding of oxygen between its four subunits.[1] When these allosteric properties are engineered into wholly synthetic systems, the reactivity of such systems can then be exploited to achieve otherwise difficult transformations, where an initial reaction aids and abets a subsequent reaction. These so-called cascade reactions have been employed[2] with regularity in synthesis; the synthesis of (±)-progesterone is a classic example.[3]

Cycloadditions are one of the most important classes of organic transformations. In one of its simplest forms, the Diels–Alder (DA) reaction embodies[4] the concept of atom efficiency, while generating complexity. The [4+2] cycloaddition between cyclopentadiene and alkynes results in the formation of bicyclo[2.2.1]heptenes, more commonly referred to as norbornenes. Another reaction, the Huisgen 1,3-dipolar cycloaddition, has gained[5] a tremendous amount of attention as a "click" reaction on account of its bioorthogonalilty.[6]

Cationic cyclophanes, referred[7] to as **Ex^{n}Box^{4+}** compounds, created by reacting rigid bipyridyl-based linkers, where n is the number of p-phenylene spacers between the pyridinium rings, with 1,4-bis(bromomethyl)benzene, have been employed toward diverse chemistry[8] on account of their highly strained and π-electron-poor nature. Strained molecules have ample precedent in cycloaddition[9] and cyclophane[10] chemistries, among others,[11] resulting in compounds whose reactivity[12] can be exploited. Herein, we combine the principles of strain and cooperative reactivity to achieve cascade reactions. We report the synthesis of an **Ex^{n}Box^{4+}** cyclophane with strained, electron-deficient triple bonds inserted between pyridinium rings, resulting in the so-called[13] **Ex$^{0.8}$Box^{4+}**, and its subsequent successive cycloadditions with (i) cyclopentadiene and (ii) 1-azidoadamantane. When compared with an acyclic analogue, **Ex$^{0.8}$Box^{4+}** undergoes cycloadditions much more quickly because of the release of strain inherent in the cyclophane. Furthermore, the cycloadditions proceed in the fashion of a tandem cascade,[2b] with no evidence observed for the formation of monofunctional intermediates by ^{1}H NMR spectroscopy, pointing to a situation in which the first cycloaddition increases the reactivity of the cyclophane, rendering the second cycloaddition even faster.

Scheme 1. Synthesis of Ex$^{0.8}$Box·4PF$_6$



The synthesis of **Ex$^{0.8}$Box^{4+}** began (Scheme 1) with the bisalkylation of bis(pyridinyl)acetylene (**1**) by the slow addition of **1** to a solution of 1,4-bis(bromomethyl)benzene in 1:1 $CHCl_3$/MeCN at 90 °C. The solution was stirred for 48 h, cooled to room temperature, and diluted in $CHCl_3$, and then the precipitate was collected by filtration and washed with CH_2Cl_2. The precipitate was dissolved in hot MeOH, followed by the addition of an excess of NH_4PF_6 in H_2O, and subsequent purification by silica gel column chromatography, resulting in the isolation of **2**·2PF$_6$ in 67% yield. To produce **Ex$^{0.8}$Box**·4PF$_6$, a solution of **1**, **2**·2PF$_6$, and catalytic[7] TBAI in dry MeCN was stirred at 80 °C for 72 h. The reaction was quenched, and the

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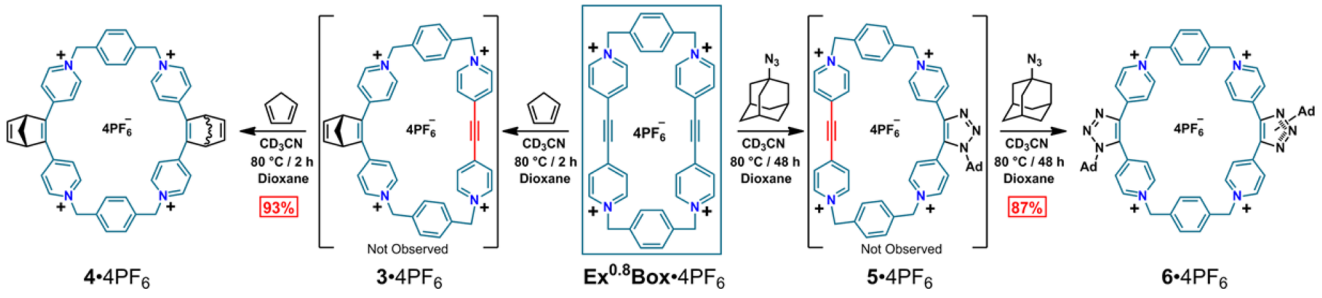
Scheme 2. Reaction of $Ex^{0.8}Box{\cdot}4PF_6$ with Cyclopentadiene (Left) and 1-Azidoadamantane (Right)



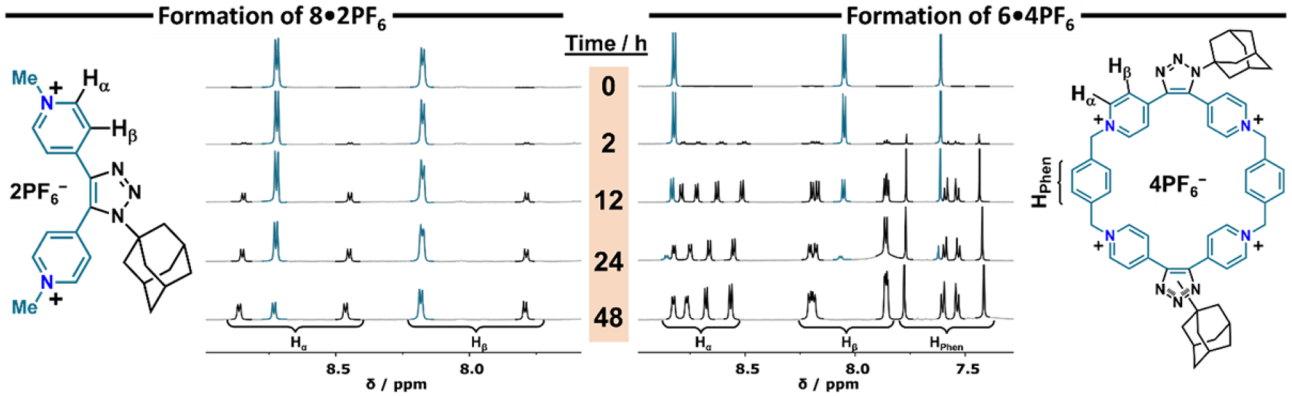


Figure 1. Reaction time points of 1-azidoadamantane with (left) $Ex^{0.8}BIPY\text{-}Me_2{\cdot}2PF_6$ and (right) $Ex^{0.8}Box{\cdot}4PF_6$. The partial ^1H NMR spectra signals corresponding to the starting material are shown in teal and product in black.

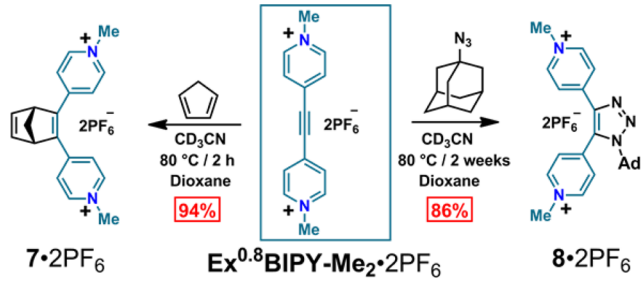
crude product precipitated from solution as its tetrachloride salt using an excess of TBACl, collected by centrifugation, and dissolved in H_2O—to separate the soluble, crude product from insoluble oligomers and polymers—before being precipitated by an excess of NH_4PF_6 and collected. The product was isolated by reverse-phase column chromatography using H_2O (0.1% v/v TFA) and Me_2CO (0 to 10% v/v), with subsequent recrystallization by slow diffusion of iPr_2O vapor into a solution of the crude product in MeCN, to afford pure $Ex^{0.8}Box{\cdot}4PF_6$ in 8% yield. While the product could be isolated (Scheme S5) with ca. 80% purity in 30% yield, its purification proved challenging on account of the cyclophane's innate reactivity.

Single crystals suitable for X-ray diffraction were obtained by the slow vapor diffusion of iPr_2O into a solution of $Ex^{0.8}Box{\cdot}4PF_6$ in MeCN. The solid-state structure reveals (Figure S1) the box-like cyclophane measuring 9.4 Å in length, and 3.3 and 3.8 Å in width at the periphery and center, respectively, after allowing for van der Waals radii. The torsional angles between pyridinium rings are 6° in $Ex^{0.8}Box^{4+}$, compared to ∼30° in $Ex^{1}Box^{4+}$. The former, however, displays a bending in relation to the alkyne of 167°. Armed with the knowledge[14] of the strong interactions between this class of receptor and polycyclic aromatic hydrocarbons, we were able to obtain single crystals by the diffusion of iPr_2O vapors into a solution of $Ex^{0.8}Box{\cdot}4PF_6$ with an excess of pyrene in MeCN. The resulting superstructure was elucidated (Figure S2), revealing that a pyrene molecule resides within the cavity, in contact with both pyridinium binding pockets.[15]

Based on both the π-electron-poor and strained nature of $Ex^{0.8}Box^{4+}$, the cyclophane reacts (Scheme 2) with both (i) cyclopentadiene and (ii) 1-azidoadamantane, passing through intermediates $3{\cdot}4PF_6$ and $5{\cdot}4PF_6$, forming $4{\cdot}4PF_6$ and $6{\cdot}4PF_6$, respectively, in high yields. The acyclic analogue, $Ex^{0.8}BIPY\text{-}Me_2{\cdot}2PF_6$ (Scheme 3), forms $7{\cdot}2PF_6$ and $8{\cdot}2PF_6$ with cyclopentadiene and 1-azidoadamantane, respectively. Both acyclic and cyclic compounds were exposed to the coupling reagents in CD_3CN with dioxane as an internal standard, and the cycloadditions were monitored (Figure 1) by ^1H NMR spectroscopy. For cyclopentadiene, the reaction proceeded rapidly in the case of both $Ex^{0.8}BIPY\text{-}Me_2{\cdot}2PF_6$ and $Ex^{0.8}Box{\cdot}4PF_6$, forming $4{\cdot}4PF_6$ and $7{\cdot}2PF_6$ in 93 and 94% yields, respectively. Under similar conditions, cycloadditions involving 1-azidoadamantane proceeded to completion, albeit more slowly, forming $6{\cdot}4PF_6$ and $8{\cdot}2PF_6$ in 87 and 86% yields, respectively, for the cases of $Ex^{0.8}Box{\cdot}4PF_6$ and $Ex^{0.8}BIPY\text{-}Me_2{\cdot}2PF_6$.

While $7{\cdot}2PF_6$ retains a high degree of symmetry, and hence the ^1H NMR spectrum remains relatively simple, $4{\cdot}4PF_6$ exists as a mixture of the *cis* and *trans* isomers, arising from the two products having either a time-averaged plane of symmetry or a C_2 axis of symmetry, respectively, with coincidental overlap of the different ^1H NMR signals. In the case of 1-azidoadamantane $8{\cdot}2PF_6$, the desymmetrization is more pronounced by the orientation of the large adamantyl group. This lack of symmetry results in four sets

Scheme 3. Control Pericyclic Reactions



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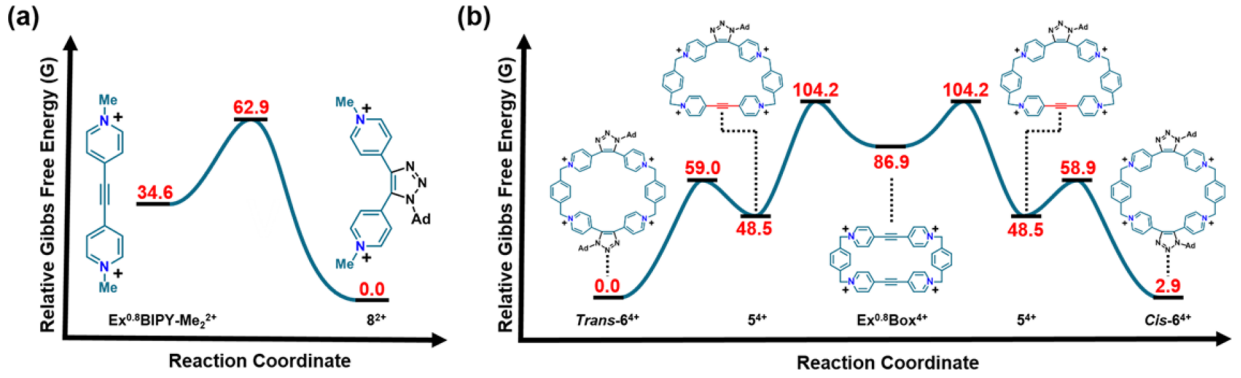

Figure 2. Computed relative energies (kcal/mol) of compounds and transition states in the reaction coordinate diagram of 1-azidoadamantane with (a) $\mathbf{Ex^{0.8}BIPY\text{-}Me_2}^{2+}$ and (b) $\mathbf{Ex^{0.8}Box}^{4+}$ at B3LYP/6-311G**++ level of DFT.

of signals (excepting the adamantyl groups, Scheme S7b) in the ^{1}H NMR spectrum, with roughly 1:1.1 relative intensities in the case of **6**·4PF$_6$, resulting from the near-statistical generation of *cis* and *trans* isomers.

The reaction was complete for both alkynylpyridinium compounds with cyclopentadiene within 2 h at 80 °C. By comparison, the reaction with 1-azidoadamantane took on the order of days to weeks. While the reaction with cyclopentadiene proceeded too rapidly to show meaningful differences in the reaction rates, 1-azidoadamantane provides a good substrate for probing (Figure 1) the differences by ^{1}H NMR spectroscopy. Both $\mathbf{Ex^{0.8}Box}$·4PF$_6$ and $\mathbf{Ex^{0.8}BIPY\text{-}Me_2}$·2PF$_6$ were mixed separately with 1-azidoadamantane in CD$_3$CN, with dioxane as an internal standard, and heated to 80 °C. $\mathbf{Ex^{0.8}Box}$·4PF$_6$ showed nearly 66% conversion to product after 12 h, with the reaction being complete after 48 h. In contrast, $\mathbf{Ex^{0.8}BIPY\text{-}Me_2}$·2PF$_6$ showed partial (20%) product formation after 12 h, with only ∼50% conversion after 48 h and the reaction reaching completion after 2 weeks. The electron-deficient nature of the triple bonds promotes reactivity in both instances, but it appears that the major difference in structure, specifically the strain inherent in the cyclophane, leads to an increase in its reactivity. Since no monofunctional intermediate is observed on addition of 1-azidoadamantane to $\mathbf{Ex^{0.8}Box}$·4PF$_6$, the intermediate is presumably more reactive than the starting material.

In an attempt to gain a better understanding of the energy landscape as $\mathbf{Ex^{0.8}Box}^{4+}$ proceeds through $\mathbf{5}^{4+}$ to $\mathbf{6}^{4+}$, we investigated[16] the starting materials, transition states, and products associated with both $\mathbf{Ex^{0.8}Box}^{4+}$ and the acyclic $\mathbf{Ex^{0.8}BIPY\text{-}Me_2}^{2+}$ (Figure 2) computationally (see the SI). The structures were optimized at the B3LYP/6-31G** level of DFT, while single-point calculations were run using a larger basis set at the B3LYP/6-311G**++ level.

Computationally, the reaction coordinates for $\mathbf{Ex^{0.8}Box}^{4+}$ reveal (Figure 2b) a difference between the relative energies for *cis*-$\mathbf{4}^{4+}$ and *trans*-$\mathbf{4}^{4+}$, in agreement with the integration of the different isomers in the ^{1}H NMR spectrum, with an overall ΔG = −86.9 and −84.0 kcal/mol, respectively. The control compound $\mathbf{Ex^{0.8}BIPY\text{-}Me_2}^{2+}$ is associated (Figure 2a) with an energy barrier ($\Delta G^{\ddagger}$) of 28.3 kcal/mol and ΔG = −34.6 kcal/mol upon proceeding to $\mathbf{8}^{2+}$. $\mathbf{Ex^{0.8}Box}^{4+}$ proceeds to $\mathbf{5}^{4+}$—associated with ΔG = −38.4 kcal/mol—over an energy barrier of 17.3 kcal/mol. The intermediate passes through a second transition state where $\Delta G^{\ddagger}$ = 10.4/10.5 kcal/mol toward *cis*-$\mathbf{6}^{4+}$/*trans*-$\mathbf{6}^{4+}$, with ΔG = −45.6/−48.5 kcal/mol, respectively.

The computation provides (Figure 2) some insight into the reason why $\mathbf{5}^{4+}$ is not observed, as well as into the difference in reaction rates of the box-like versus acyclic compounds. The minimized structure of $\mathbf{Ex^{0.8}Box}^{4+}$ reveals an angle of 158° between pyridinium units, indicating not only that the triple bonds are in an activating, electron-deficient environment, but also that a considerable element of strain exists that is not experienced by the linear $\mathbf{Ex^{0.8}BIPY\text{-}Me_2}^{2+}$. The large disparity in relative activation energies between $\mathbf{Ex^{0.8}BIPY\text{-}Me_2}^{2+}$ and $\mathbf{Ex^{0.8}Box}^{4+}$—28.3 versus 17.3 kcal/mol, respectively—is supported by the difference in observed reaction rates and in accordance with the strain effect.

The formation of the carbon−nitrogen bonds in the triazole scaffold provides the drive to move the reaction coordinate, but in reacting with the first alkyne—resulting in a bond angle lowering from 157 to 145° (Figure 3)—the second alkyne is

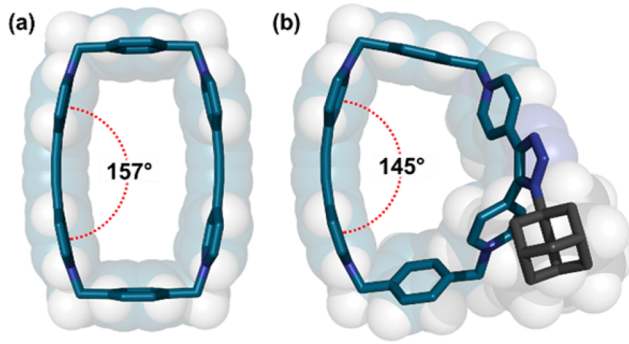

Figure 3. Computed geometry of (a) $\mathbf{Ex^{0.8}Box}^{4+}$ and (b) $\mathbf{5}^{4+}$, revealing alkynes strained to 157 and 145°, respectively.

strained even more. This deformation leads to a structure closer to that of the transition state (Figure S8) necessary for the second cycloaddition reaction, lowering the activation energy to only 10.4/10.5 kcal/mol for *cis*-$\mathbf{4}^{4+}$/*trans*-$\mathbf{4}^{4+}$, respectively. The first reaction, while slower, functions to prime the second alkyne for a much faster, strain-promoted cycloaddition, with the ensuing structure containing a cavity that is distorted greatly compared[17] to the starting cyclophane. The reaction between $\mathbf{Ex^{0.8}Box}^{4+}$ and cyclopentadiene was also explored (Figures S7 and S8) computationally, resulting in a similar relative free energy profile accompanied by a decrease in the angle of the triple bond in $\mathbf{3}^{4+}$.

The $\mathbf{Ex^{0.8}Box}^{4+}$ cyclophane provides a platform on which the electronic, strained nature engineered into the molecule is exploited such that the triple bonds can be modified as a consequence of different pericyclic reactions. While the reported experiments explore the energetics of this cooperative reactivity

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in tandem cascade reactions, the difference in reactivity between analogous juxtaposed triple bonds could be harnessed in more complex molecules.[18] Alternatively, the first reaction could be thought of as a primer that can promote a second reaction with an otherwise less reactive substrate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01368.

Synthetic procedures, crystallographic and spectroscopic characterization data, and computational methods (PDF)
JMol files for 1-azidoadamantane and cyclopentadiene (ZIP)
X-ray crystallographic data (CIF)

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Author Contributions

‖E.J.D. and D.P.F. contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Epstein, F. H.; Hsia, C. C. W. *N. Engl. J. Med.* **1998**, *338*, 239.

(2) (a) Ho, T. *Tandem Organic Reactions*; Wiley & Sons: New York, 1992. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (d) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243. (e) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (f) Wzorek, J. S.; Knöpfel, T. F.; Sapountzis, I.; Evans, D. A. *Org. Lett.* **2012**, *14*, 5840. (g) Catino, A. J.; Sherlock, A.; Shieh, P.; Wzorek, J. S.; Evans, D. A. *Org. Lett.* **2013**, *15*, 3330. (h) Foster, R. A. A.; Willis, M. C. *Chem. Soc. Rev.* **2013**, *42*, 63. (i) Felix, R. J.; Munro-Leighton, C.; Gagné, M. R. *Acc. Chem. Res.* **2014**, *47*, 2319. (j) *Catalytic Cascade Reaction*; Xu, P.-F., Wang, W., Eds.; Wiley: Hoboken, NJ, 2014. (k) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832. (l) Lohr, T.; Marks, T. *Nat. Chem.* **2015**, *7*, 477.

(3) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332.

(4) Diels, O.; Alder, K. *Liebigs Ann.* **1928**, *460*, 98.

(5) (a) Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967**, *100*, 2494. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (d) Moynihan, L.; Chadda, R.; McArdle, P.; Murphy, P. V. *Org. Lett.* **2015**, *17*, 6226.

(6) (a) Prescher, J. A.; Bertozzi, C. R. *Nat. Chem. Biol.* **2005**, *1*, 13. (b) Agard, N. J.; Baskin, J. M.; Prescher, J. A.; Lo, A.; Bertozzi, C. R. *ACS Chem. Biol.* **2006**, *1*, 644. (c) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 16793. (d) Pretzel, D.; Sandmann, B.; Hartlieb, M.; Vitz, J.; Hölzer, S.; Fritz, N.; Moszner, N.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2015**, *53*, 1843.

(7) (a) Barnes, J. C.; Juríček, M.; Vermeulen, N. A.; Dale, E. J.; Stoddart, J. F. *J. Org. Chem.* **2013**, *78*, 11962. (b) Barnes, J. C.; Juríček, M.; Strutt, N. L.; Frasconi, M.; Sampath, S.; Giesener, M. A.; McGrier, P. L.; Bruns, C. J.; Stern, C. L.; Sarjeant, A. A.; Stoddart, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 183. (c) Juríček, M.; Strutt, N. L.; Barnes, J. C.; Butterfield, A. M.; Dale, E. J.; Baldridge, K. K.; Stoddart, J. F.; Siegel, J. S. *Nat. Chem.* **2014**, *6*, 222.

(8) Dale, E. J.; Vermeulen, N. A.; Juríček, M.; Barnes, J. C.; Young, R. M.; Wasielewski, M. R.; Stoddart, J. F. *Acc. Chem. Res.* **2016**, *49*, 262 and references therein.

(9) (a) Alder, K.; Stein, G. *Liebigs Ann.* **1933**, *501*, 1. (b) Wittig, G.; Krebs, A. *Chem. Ber.* **1961**, *94*, 3260. (c) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046. (d) Schoenebeck, F.; Ess, D. H.; Jones, G. O.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 8121. (e) Knall, A.-C.; Slugovc, C. *Chem. Soc. Rev.* **2013**, *42*, 5131.

(10) (a) Kawase, T.; Darabi, H. R.; Oda, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2664. (b) *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 81−102 and references therein. (c) Bogdan, A. R.; Jerome, S. V.; Houk, K. N.; James, K. *J. Am. Chem. Soc.* **2012**, *134*, 2127. (d) Evans, P. J.; Darzi, E. R.; Jasti, R. *Nat. Chem.* **2014**, *6*, 404. (e) Matsui, K.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2014**, *136*, 16452.

(11) (a) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Gulder, T.; Baran, P. S. *Nat. Prod. Rep.* **2012**, *29*, 899. (c) Zou, L.; Paton, R. S.; Eschenmoser, A.; Newhouse, T. R.; Baran, P. S.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 4037. (d) Chiu, M.; Tchitchanov, B. H.; Zimmerli, D.; Sanhueza, I. A.; Schoenebeck, F.; Trapp, N.; Schweizer, W. B.; Diederich, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 349. (e) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. *Science* **2016**, *351*, 241.

(12) (a) Misumi, S. *Pure Appl. Chem.* **1987**, *59*, 1627. (b) Dosa, P. I.; Erben, C.; Iyer, V. S.; Vollhardt, K. P. C.; Wasser, I. M. *J. Am. Chem. Soc.* **1999**, *121*, 10430. (c) Bodwell, G. J.; Fleming, J. J.; Mannion, M. R.; Miller, D. O. *J. Org. Chem.* **2000**, *65*, 5360. (d) Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res.* **2011**, *44*, 666. (e) Debets, M. F.; van Berkel, S. S.; Dommerholt, J.; Dirks, A. T. J.; Rutjes, F. P. J. T.; van Delft, F. L. *Acc. Chem. Res.* **2011**, *44*, 805.

(13) The length of this class of compound is described by the number *n* of *p*-phenylene spacers between two pyridinium rings. This definition leads to $\mathbf{Ex^1Box^{4+}}$ with a length of ∼11.3 Å, whereas the reported compound measures only ∼9.5 Å, hence $\mathbf{Ex^{0.8}Box^{4+}}$.

(14) The shape of the binding cavity, particularly the near-optimal height for $\pi-\pi$ stacking, lends itself toward strong interactions with PAHs. ^{1}H NMR titration of pyrene in CD_3CN into a solution of $\mathbf{Ex^{0.8}Box^{4+}}$ in CD_3CN at 25 °C was performed, resulting in a calculated association constant $K_a = 480 \pm 24\ M^{-1}$ (Figures S5 and S6).

(15) Additional unbound pyrene molecules are present in the lattice since sheets of pyrene⊂$\mathbf{Ex^{0.8}Box}$·4PF_6 are separated by sheets of pyrene along the *b*-axis. See Figure S2.

(16) Harmonic zero-point energy and thermochemical corrections (calculated at B3LYP/6-31G** level) were added to all relative energies to obtain relative (Gibbs) free energies.

(17) Upon reaction of $\mathbf{Ex^{0.8}Box^{4+}}$ with cyclopentadiene, its global geometry, determined computationally at the B3LYP/6-31G** level, changes dramatically, exchanging its box-like cyclophane form for one with a hexagonal cavity.

(18) Although an analogue to $\mathbf{Ex^{0.8}Box^{4+}}$ has been synthesized, containing four internal triple bonds in a strained ring (Scheme S9 and Figures S3 and S4), the reactivity profile has not yet been explored.

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