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Synthesis of Ex^{n}Box Cyclophanes

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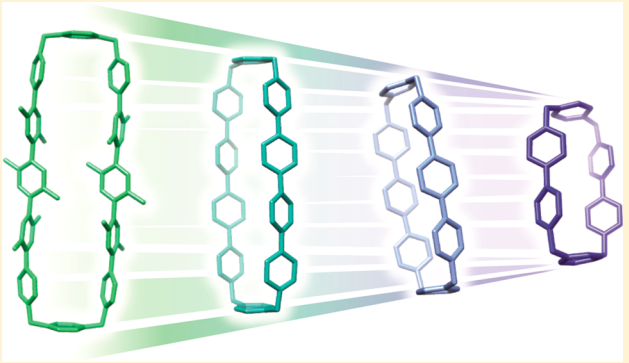
Supporting Information

ABSTRACT: A rapid and efficient synthesis of the extended bipyridinium-based class of cyclophanes—that is, **Ex^{n}Box**$^{4+}$ (n = 0−3), where n is the number of p-phenylene rings inserted between the pyridinium rings—is demonstrated, resulting in much higher yields of products along with a reduced output of oligomeric byproducts. Although each cyclophane can be synthesized readily without the use of a precise stoichiometric amount of template, **ExBox**$^{4+}$ can be prepared in 66% yield (following crystallization) using six equivalents of pyrene in a template-directed protocol. This new methodology has been employed to synthesize, in modest yield, a nearly 2.5 nm long cyclophane consisting of 12 aromatic rings.



INTRODUCTION

Cyclophanes[1] represent an important class of compounds in host−guest chemistry,[2] on account of their ability to function as molecular receptors utilizing a range of different noncovalent bonding interactions. In particular, tetracationic cyclophanes, consisting of two π-electron-poor bipyridinium units, are capable[3,4] of entering into strong donor−acceptor interactions with π-electron-rich guests to form either 1:1 or 1:2 host−guest complexes depending on the size of the host's cavity. One of the most ubiquitous[5] tetracationic cyclophanes—in terms of the central role it plays in mechanically interlocked molecules[6]—is cyclobis(paraquat-p-phenylene),[5] herein referred to as **Ex^{0}Box**$^{4+}$. This cyclophane is comprised of two π-electron-deficient 4,4′-bipyridinium units connected end-to-end by two p-xylylene linkers so as to afford an inner cavity geometry of ∼7 Å in width and ∼11 Å in length, which is a suitable size for the encapsulation of π-electron-rich guests such as 1,5-dioxynaphthalene[7] and tetrathiafulvalene[8] derivatives. Recently, we have described[9,10] the synthesis and binding properties of two other cyclophanes—namely, **ExBox**$^{4+}$ and **Ex^{2}Box**$^{4+}$—which possess one and two p-phenylene bridges, respectively, between the pyridinium rings of each extended bipyridinium unit. These constitutional modifications result in larger cavities which make it possible to bind[1,11] larger polycyclic aromatic hydrocarbons (PAHs)—even in H_2O as their chloride salts[9]—and, in the case of **Ex^{2}Box**$^{4+}$, two guests simultaneously. As the number of potential applications of these cyclophanes continues to grow, a more practical synthetic protocol is required in order to be able to prepare each cyclophane more rapidly and efficiently in high purity.

Here, we report the implementation of Baker's rigid-group principle[12]—where double bonds or aromatic rings are incorporated into the open-chain precursor prior to ring closure in order to decrease the degree of bond rotation and so curtail the production of linear oligomers—and Ziegler's high-dilution technique[13] in combination with high temperatures and catalytic amounts of tetrabutylammonium iodide[14−16] (TBAI) to synthesize this class of tetracationic bipyridinium-based cyclophanes in a quick and practical manner. The syntheses of the three cyclophanes illustrated in Scheme 1 (where n = 0−2) start with their respective previously reported open-chain dibromo-precursors[9,10,17] (**Ex^{n}DB**·2PF$_6$), all of which have been prepared in high yields (72−92%).

Previous protocols for completing the final cyclization steps have consisted of using an excess of a template[7b,7c,18] (usually a π-electron-rich guest molecule, such as 1,5-bis[2-(2-hydroxyethoxy)ethoxy]naphthalene[18b] in the case of n = 0, pyrene[9] in the case of n = 1, and 1,4-bis(3-methoxyphenyl)-1H-1,2,3-triazole[10] in the case of n = 2) in order to stabilize the transition states leading to ring closure and thus improve the yields of the reactions. Moreover, these protocols were usually carried out at room temperature and required no less than 2 weeks to complete from start to finish. During the course of these reactions, many different oligomers were formed and the crude material had to be subjected to chromatography on silica gel (SiO_2), followed by one or two crystallizations, involving slow vapor diffusion of i-Pr$_2$O into concentrated solutions of MeCN to obtain up to 42% yields in the cases of **Ex^{0}Box**·4PF$_6$ and **ExBox**·4PF$_6$ and a 20% yield for **Ex^{2}Box**·4PF$_6$. When templates were not employed, the isolated yields dropped, in our hands, to 4−5% for **Ex^{0}Box**·4PF$_6$, 19% for **ExBox**·4PF$_6$, and 10% for **Ex^{2}Box**·4PF$_6$.

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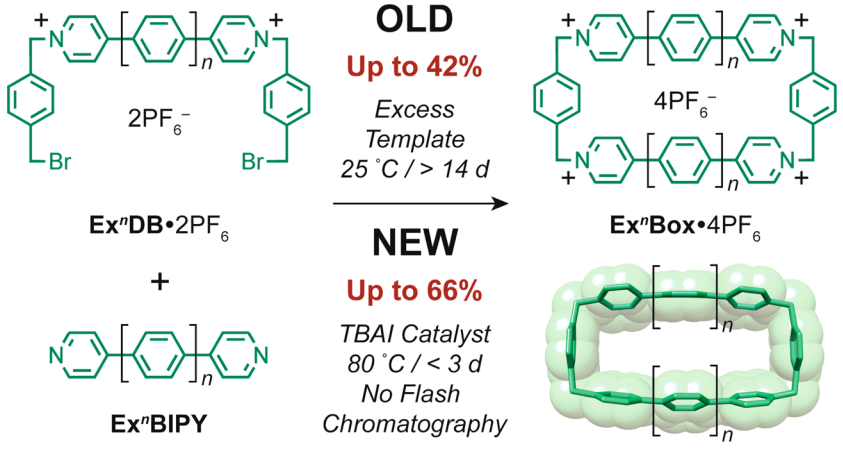
Scheme 1. OLD and NEW Syntheses of Extended Bipyridinium Cyclophanes Ex^{n}Box·4PF$_6$ (n = 0−2) Starting from Ex^{n}DB·2PF$_6$ and Ex^{n}BIPY Precursors



RESULTS AND DISCUSSION

In an effort to increase product formation, we have investigated systematically the effect of altering common synthetic practices and conditions—namely, temperatures, templates, and catalysts—in the formation of **Ex^{n}Box**·4PF$_6$. Using analytical reverse-phase (RP) HPLC—where all samples were converted to TFA salts prior to injection—and **ExBox**·4PF$_6$ as a chemical holotype, we have investigated the effects of (i) varying temperatures, (ii) use of a well-suited template (pyrene), and (iii) addition of a catalyst (TBAI) upon the product formation. Starting with a 1:1 mixture (2 mM in dry MeCN) of **ExDB**·2PF$_6$ and **ExBIPY** at 25 °C, only trace amounts of the cyclophanes are formed (Figure 1a, trace 3, 12.7 min) after 48 h accompanied by a significant production of, presumably, the monoalkylated intermediate (Figure 1a, trace 3, 15−16 min). This observation is consistent with the long reaction times reported[9] previously. The addition of catalytic amounts (0.2 equiv) of TBAI accelerates the reaction and leads to an increase in product formation (Figure 1a, trace 4, 12.7 min) after 48 h at 25 °C. A slight improvement can be observed (Figure 1a, trace 6, 12.7 min) when the pyrene template is used in conjunction with TBAI at 25 °C. When the temperature is increased—of a reaction mixture containing both pyrene and TBAI—from 25 to 80 °C, the starting material is consumed completely and the desired **ExBox**·4PF$_6$ is the major product (Figure 1a, trace 7, 12.7 min) after 48 h. It should be noted that although pyrene has a very significant positive effect on cyclophane formation it most likely will not function as an efficient template in the formation of other extended cyclophanes.

Using only catalytic amounts (0.2 equiv) of TBAI at 80 °C (Figure 1b, traces 1−5), complete conversion of starting materials and formation of **ExBox**·4PF$_6$ is observed after 72 h. This general procedure can be applied to the synthesis of any **Ex^{n}Box**$^{4+}$, despite the lack of an inexpensive and readily removable template. In the specific instance of **ExBox**·4PF$_6$, pyrene can be used to drive the reaction to completion (Figure 1b, traces 6 and 7) within only 18 h and represents the optimum situation for the preparation of this particular cyclophane.

After establishing (Scheme 1, NEW) the optimal synthetic conditions—i.e., 2 mM in dry MeCN in the presence of pyrene (6 equiv) and catalytic amounts (0.2 equiv) of TBAI at 80 °C for 72 h—the reaction was quenched by adding concentrated HCl (2−3 mL) to the crude reaction mixture, precipitating the crude product as the chloride salt **ExBox**·4Cl, which is orange as a consequence of the charge-transfer interactions between the tetracationic host and the template. Subsequent washing with CH_2Cl_2 removes any excess of (uncomplexed) pyrene prior to dissolution of the orange solid in H_2O, which results in a translucent orange solution. This aqueous solution is then extracted four times (4 × 250 mL) with CH_2Cl_2 to remove the pyrene from **ExBox**·4Cl, causing the color of the solution to change from orange to colorless and the appearance of the aqueous layer to become turbid. It is important to point out that the bound state, pyrene⊂**ExBox** 4Cl, is more soluble[19] in H_2O than is the unbound state, **ExBox**·4Cl, presumably as a result of ion−dipole and dipole−dipole effects between the tetracationic cyclophane and the pyrene. The colorless turbid solution is then treated with 5% (w/v) NH_4PF_6 to precipitate **ExBox**·4PF$_6$ as a white solid in ∼85% purity by ^{1}H NMR spectroscopy (Figure 2a). Subsequent crystallization by slow vapor diffusion of i-Pr$_2$O into a concentrated solution of **ExBox**·4PF$_6$ in MeCN increases the purity to ∼94% by ^{1}H NMR spectroscopy (Figure 2b), and yet one more recrystallization using the same protocol affords the pure product: that is, >99% purity by ^{1}H NMR spectroscopy (Figure 2c) in 66% yield. In contrast to previously reported[9] procedures, this degree of purity was obtained without the use of SiO_2 flash chromatography.

A similar investigation targeted toward the optimization of the synthesis of **Ex^{0}Box**·4PF$_6$ (Figure 3a) and **Ex^{2}Box**·4PF$_6$ (Figure 3b) on an analytical scale at 2 mM in dry MeCN—with and without catalyst (TBAI)—was carried out over a 72 h period. Since the traditional templates employed previously in the reported[9,10,18] syntheses of the cyclophanes require additional synthetic and template-removal manipulations, the synthesis of each was carried out in the absence of template to ensure the ease of their implementation. The analytical RP-HPLC traces for the starting materials **Ex^{n}BIPY** and **Ex^{n}DB**·2PF$_6$ to prepare **Ex^{0}Box**·4PF$_6$ and **Ex^{2}Box**·4PF$_6$—in addition to traces relating to the reaction progress after 48 h at 25 °C versus the progress after the same time at 80 °C in the presence of catalytic amounts (0.2 equiv) of TBAI—are illustrated in Figure 3a,b, respectively. In the case of both reactions, the 25 °C conditions after 48 h yielded very small amounts of the cyclophanes, whereas the reactions carried out at 80 °C in the presence of TBAI catalyst led to the production of significantly more of the cyclophanes. It should be noted that TBAI is

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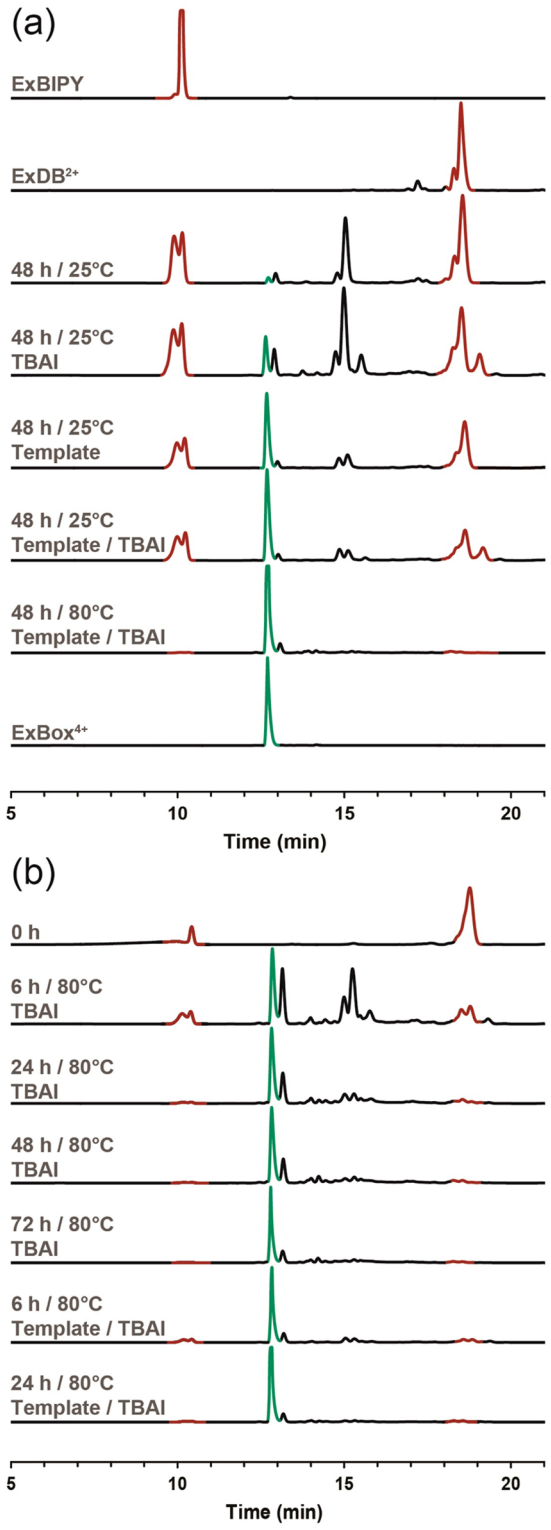

Figure 1. RP-HPLC traces (315 nm) for the optimization of the synthesis of **ExBox**·4PF$_6$ comparing different reaction parameters: (a) template, temperature, and TBAI catalyst; (b) time. RP-HPLC conditions: 0–100% MeCN (0.1% TFA) gradient in 30 min. Color code: **ExBox**$^{4+}$, green; **ExBIPY** (left) and **ExDB**$^{2+}$ (right), red.

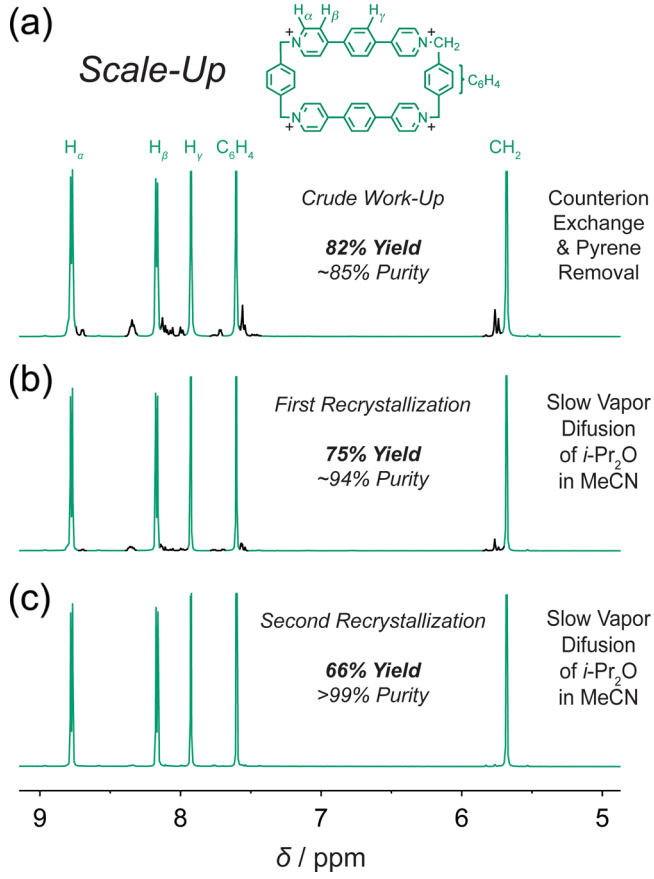

Figure 2. ^{1}H NMR spectra of **ExBox**·4PF$_6$ isolated over the course of the scale-up purification procedure: (a) crude product; (b) ~94% pure product; (c) >99% pure product obtained in 66% yield after a second recrystallization.

required in order to favor cyclophane production over oligomer formation in these cases, since no template was employed. The reactions that are carried out in the absence of TBAI tend to produce more oligomers. See the Supporting Information for additional RP-HPLC traces.

Using the optimized conditions—i.e., 2 mM in dry MeCN, TBAI (0.2 equiv), 80 °C, 72 h—established for **Ex^{0}Box**·4PF$_6$ and **Ex^{2}Box**·4PF$_6$, the preparations were carried out on a much larger scale with isolated yields (Table 1) of 20 and 37%, respectively. These isolated yields are higher by approximately a factor of 4 in comparison to the previously reported[10] yields (4–5 and 10–12%, respectively). Moreover, in the case of **Ex^{2}Box**·4PF$_6$, no SiO$_2$ flash chromatography was required; rather, only two crystallizations were necessary to isolate pure product. See the Supporting Information for synthetic details and the full characterization of both cyclophanes.

An attempt to synthesize **Ex^{3}Box**·4PF$_6$, following the strategy (Scheme 1, NEW) employed for **Ex$^{0-2}$Box**·4PF$_6$, revealed that the limited solubility of **Ex^{3}BIPY** in both MeCN and DMF impedes the preparation and isolation of **Ex^{3}DB**·2PF$_6$. In order to demonstrate the scope of the NEW synthetic methodology for the preparation of longer (n > 2), not previously reported, cyclophanes, **Ex^{3}BIPY-Me$_6$**—a soluble analogue of **Ex^{3}BIPY** substituted with six methyl groups—was optimized (Figure 3c) and employed in the synthesis (Figure 4a; the synthesis is outlined in the Supporting Information) of **Ex^{3}Box-Me$_{12}$**·4PF$_6$. The **Ex^{3}DB-Me$_6$**·2PF$_6$ precursor was prepared in 98% yield, starting from **Ex^{3}BIPY-Me$_6$**, and the cyclization was optimized employing the same reaction conditions as those used for synthesizing the smaller homologues. Optimized conditions (Figure 3c, no template, TBAI, 80 °C) were employed in the

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Table 1. Overview of the Isolated Yields for the Formation[a] of Ex^{n}Box·4PF$_6$ Using the OLD[b] and NEW[c] Protocols

		yield (%)	
entry	Ex^{n}Box·4PF$_6$	OLD	NEW
1	**Ex^{0}Box**	4–5[c,d]	20[h]
2	**ExBox**	42[b,e]	66[i]
3	**Ex^{2}Box**	10–12[b,f]	37[h]
4	**Ex^{3}Box-Me$_{12}$**	trace[c,g]	14[j]

[a]Starting from a 1:1 mixture of **Ex^{n}BIPY** and **Ex^{n}DB**·2PF$_6$ (2 mM; see Scheme 1). [b]Previously reported. [c]This work. [d]Conditions: MeCN, 25 °C, 14 days. [e]Conditions: pyrene (6 equiv), MeCN, 25 °C, 17 days. [f]Conditions: MeCN, 25 °C, 17 days. [g]Conditions: MeCN/DMF (1:1), 25 °C, 30 days. [h]TBAI (0.2 equiv), MeCN, 80 °C, 72 h. [i]Conditions: pyrene (6 equiv), TBAI (0.2 equiv), MeCN, 80 °C, 18 h. [j]Conditions: TBAI (0.2 equiv), DMF, 80 °C, 72 h.

scaled-up synthesis of **Ex^{3}Box-Me$_{12}$**·4PF$_6$. In this case, although the reaction proceeded less efficiently than in the case of the smaller cyclophanes, the pure **Ex^{3}Box-Me$_{12}$**·4PF$_6$ was isolated in 14% yield after two iterations of SiO_2 flash chromatography using 0.05–0.1% NH_4PF_6 in Me_2CO (w/v) and several crystallizations by slow vapor diffusion of *i*-Pr_2O into the MeCN solution. This modest yield is presumably caused, in part at least, by the steric interactions associated with the 12 methyl substituents attached to the two **Ex^{3}BIPY^{2+}** units present in the cyclophane. Considering these additional destabilizing steric interactions, the isolated yield[20] (14%) of **Ex^{3}Box-Me$_{12}$**·4PF$_6$ is not insignificant and demonstrates the potential of this synthetic methodology for the preparation of extended bipyridinium-based cyclophanes.

Ex^{3}Box-Me$_{12}$·4PF$_6$ was fully characterized by NMR spectroscopy and high-resolution mass spectrometry (HRMS) (see the Supporting Information). Single crystals suitable for diffraction were obtained by crystallization of the compound by slow vapor diffusion of *i*-Pr_2O into the MeCN solution. The solid-state structure is shown in Figure 4b–e. In common with the shorter **Ex^{n}Box^{4+}** cyclophanes, the width of the **Ex^{3}Box-Me$_{12}$$^{4+}$** cavity is 6.8 Å on average. At 23.3 Å, however, the length (Figure 4b) of **Ex^{3}Box-Me$_{12}$$^{4+}$** is almost double that of **Ex^{0}Box^{4+}**.

The average torsional angle (Figure 4d) between the neighboring 2,5-dimethylphen-1,4-ylene units is 75°, presumably so as to minimize the steric repulsions between the methyl groups which also confer increased solubility upon **Ex^{3}Box-Me$_{12}$**·4PF$_6$ and its precursors in comparison with that of **Ex^{3}Box**·4PF$_6$. The steric interactions between the methyl groups also give rise to the existence[21] of four elements of axial chirality[22] in **Ex^{3}Box-Me$_{12}$$^{4+}$**.

Having demonstrated the utility of this synthetic protocol in the preparation of four cyclophanes of different size and solubility, the role of the TBAI catalyst was investigated. Typically, TBAI is used as a catalyst to accelerate S_N2 substitution reactions under kinetic control. Previously, we have reported[14,15] the use of TBAI as a catalyst under thermodynamic control in the preparation of [2]catenanes comprised of **Ex^{0}Box^{4+}** and a π-electron-rich macrocycle. In these particular cases, it was demonstrated that the formation of the [2]catenane occurred as a result of the opening and closing of the cyclophane catalyzed by iodide at high temperatures. In order to understand the effect of TBAI during cyclophane formation in the case of the **Ex^{n}Box^{4+}** series reported herein, particularly in the case when no template is employed, four

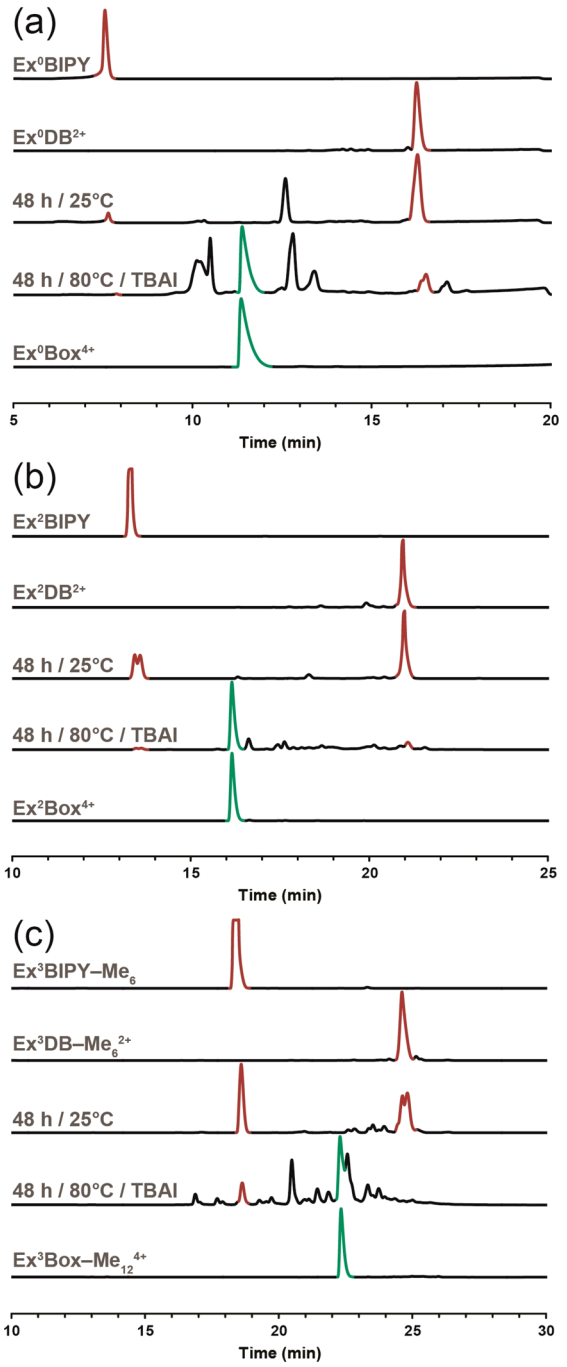

Figure 3. RP-HPLC traces (255 nm for n = 0, 295 nm for n = 2, 3) illustrating the optimization of the syntheses of (a) **Ex^{0}Box**·4PF$_6$, (b) **Ex^{2}Box**·4PF$_6$, and (c) **Ex^{3}Box-Me$_{12}$**·4PF$_6$ by comparing different reaction conditions. RP-HPLC conditions: 0–100% MeCN (0.1% TFA) gradient in 30 min. Color code: **Ex^{n}Box^{4+}**, green; **Ex^{n}BIPY** (left) and **Ex^{n}DB^{2+}** (right), red.

control experiments were carried out where 2 mM solutions of pure **Ex^{0}Box^{4+}** and **ExBox^{4+}** in dry MeCN were stirred vigorously and heated at 80 °C for 72 h either in the presence or absence of catalytic amounts (0.2 equiv) of TBAI. A comparison of the RP-HPLC data (Figure S6, Supporting Information) reveals that oligomers are produced when **Ex^{0}Box^{4+}** is subjected to catalytic amounts of TBAI and heat, whereas no such oligomer formation occurs in the case of **ExBox^{4+}**. We attribute this result to the higher degree of charge

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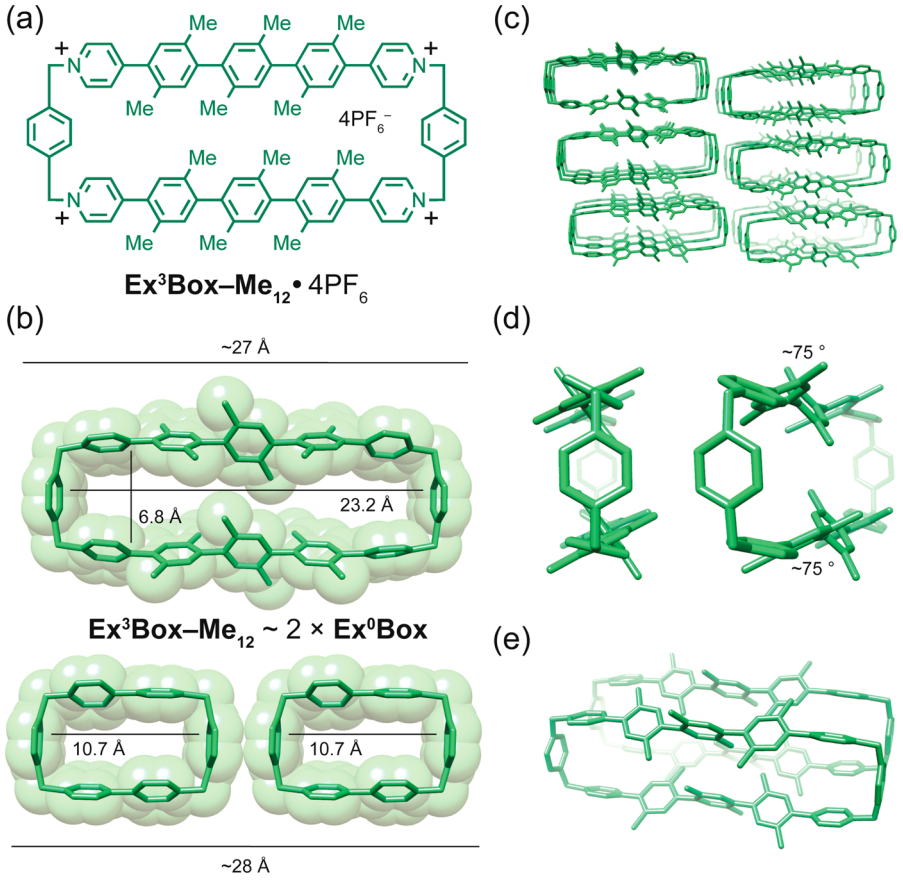

Figure 4. (a) Structural formula of $Ex^3Box\text{-}Me_{12}\cdot 4PF_6$. (b) Plan views of the $Ex^3Box\text{-}Me_{12}\cdot 4PF_6$ and $Ex^0Box\cdot 4PF_6$ solid-state structures (stick and space-filling representations). (c) Plan view of the $Ex^3Box\text{-}Me_{12}\cdot 4PF_6$ superstructure. (d) End view of the $Ex^3Box\text{-}Me_{12}\cdot 4PF_6$ superstructure illustrating the torsional angle (~75°) between adjacent 2,5-dimethylphen-1,4-ylene rings. (e) Plan view of the $Ex^3Box\text{-}Me_{12}\cdot 4PF_6$ superstructure demonstrating the packing of two cyclophanes which possess the same axial chirality (*RRSS*). The hydrogen atoms, counterions, and solvent molecules are omitted for the sake of clarity.

strain present in Ex^0Box^{4+} versus that in $ExBox^{4+}$—namely, the electronic coupling between the pyridinium rings of each bipyridinium unit when $n = 1$ is diminished[10]—and therefore the benzylic positions of the cyclophane are less electrophilic. Thus, the improved rate of product formation in each cyclophane can be attributed to the kinetic effect of the TBAI catalyst, while in the case of Ex^0Box^{4+} there exists some thermodynamic ring-opening/-closing equilibrium, which may account for the lower synthetic yields.

A new synthetic protocol has been established that aids and abets the synthesis of bipyridinium-based cyclophanes—namely, Ex^nBox^{4+}—in a practical and efficient manner. A series of four Ex^nBox^{4+} cyclophanes (n = 0–3) have been prepared on a large scale in modest to high yields without the need for SiO_2 flash chromatography in two cases (n = 1, 2). With this NEW protocol, it is possible to reduce the total time required for isolation (synthesis and purification) of pure cyclophanes by a factor of ~5 for Ex^0Box^{4+}, ~23 for $ExBox^{4+}$, and ~6 for Ex^2Box^{4+}. The isolated yields obtained by this method are increased by a factor of ~4 for Ex^0Box^{4+}, 1.6 for $ExBox^{4+}$, and ~4 for Ex^2Box^{4+} in comparison to the previously reported protocols, which were carried out at room temperature. Furthermore, we have demonstrated that this synthetic methodology can be employed successfully without the use of a template. As a proof of concept, we synthesized, in 14% yield, a nearly 2.5 nm long cyclophane consisting of 12 aromatic rings, which could only be isolated in trace amounts using the OLD protocol. We envision this practical methodology can, in principle, be broadly applied to any bipyridinium-based cyclophanes—regardless of whether or not a suitable template is available—in order to obtain the desired compound in higher yield and in a more efficient manner.

EXPERIMENTAL SECTION

General Considerations. All reagents were purchased from commercial suppliers and used without further purification unless stated otherwise. $Ex^0DB\cdot 2PF_6$,[17] **ExBIPY**,[9] $ExDB\cdot 2PF_6$,[9] Ex^2BIPY,[10] $Ex^2DB\cdot 2PF_6$,[10] and 4,4″-dibromo-2,2′,2″,5,5′,5″-hexamethyl-1,1′:4′,1″-terphenyl[23] were synthesized as reported previously. Analytical high-performance liquid chromatography (HPLC) was performed on reverse-phase HPLC (RP-HPLC) instruments, using a C_{18} column and a binary solvent system (MeCN and H_2O with 0.1% TFA). Nuclear magnetic resonance (NMR) spectra were recorded on NMR spectrometers, with working frequencies of 600.168 (^1H) and 499.373/125.579 ($^1H/^{13}C$) MHz, respectively. Chemical shifts are reported in ppm relative to the signals corresponding to the residual nondeuterated solvents (CD_3CN, δ_H 1.94 ppm and δ_C = 1.32 and 118.26 ppm; $CDCl_3$, δ_H 7.26 ppm and δ_C 77.16 ppm). High-resolution mass spectra (HRMS) were measured using an ESI source.

Cyclobis(paraquat-1,4-phenylene) Tetrakis(hexafluorophosphate) ($CBPQT\cdot 4PF_6$, $Ex^0Box\cdot 4PF_6$). A mixture of 4,4′-bipyridine (0.095 g, 0.61 mmol), $Ex^0DB\cdot 2PF_6$ (0.50 g, 0.61 mmol), and TBAI (0.045 g, 0.12 mmol) in dry MeCN (307 mL) was stirred at 80 °C for 72 h. Concentrated HCl (~3 mL) was added to stop the reaction and to precipitate the crude product from the MeCN solution. The precipitate was collected by filtration and washed

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(Me_2CO and CH_2Cl_2) to remove the residual tetrabutylammonium salt. The precipitate was then dissolved in a 1:1 mixture of MeOH and H_2O, reprecipitated as the PF_6^- salt (white) by adding solid NH_4PF_6 (~5% (w/v)), and collected by filtration. This crude material was subjected to column chromatography using silica gel and Me_2CO and 0.25−1.0% NH_4PF_6 in Me_2CO (w/v) as the eluents, followed by crystallization by slow vapor diffusion of *i*-Pr_2O into a concentrated MeCN solution, yielding pure **Ex^{0}Box·4PF$_6$** (134 mg, 20%) as a white solid. The ^{1}H NMR spectrum of the pure product matched the previously reported[5] spectrum (see the Supporting Information).

Cyclobis(4,4′-(1,4-phenylene)bipyridin-1-ium-1,4-phenylenebis(methylene)) Tetrakis(hexafluorophosphate) (ExBox·4PF$_6$). A mixture of **ExBIPY** (0.035 g, 0.15 mmol), **ExDB·2PF$_6$** (0.13 g, 0.15 mmol), pyrene (0.19 g, 0.94 mmol), and TBAI (0.011 g, 0.030 mmol) in dry MeCN (75 mL) was stirred at 80 °C for 18 h. Concentrated HCl (~3 mL) was added to stop the reaction and to precipitate the crude product from the MeCN solution as an orange solid. The precipitate was collected by filtration and washed (Me_2CO and CH_2Cl_2) to remove the residual tetrabutylammonium salt and any (uncomplexed) pyrene. The orange precipitate was then dissolved in H_2O, and the complexed pyrene was removed by way of extraction using CH_2Cl_2 (4 × ~250 mL). The removal of the pyrene from within the cyclophane caused the H_2O layer to change from orange to white and the appearance of the aqueous layer to become turbid and opaque. The turbid white H_2O layer was diluted in half with MeOH (and turned into transparent solution), and the product was reprecipitated as the PF_6^- salt (white) by adding solid NH_4PF_6 (~5% (w/v)) and collected by filtration. This crude material required no column chromatography. Two crystallizations by slow vapor diffusion of *i*-Pr_2O into a concentrated MeCN solution yielded pure **ExBox·4PF$_6$** (124 mg, 66%) as a white solid. The ^{1}H NMR spectrum of the pure product matched the previously reported[9] spectrum (see Figure 2 and the Supporting Information). The yield obtained after allowing the reaction to proceed for 72 h was the same as for the 18 h experiment.

Cyclobis(4,4′-(4,4′-biphenylene)bipyridin-1-ium-1,4-phenylenebis(methylene)) Tetrakis(hexafluorophosphate) (Ex^{2}Box·4PF$_6$). A mixture of **Ex^{2}BIPY** (0.11 g, 0.36 mmol), **Ex^{2}DB·2PF$_6$** (0.35 g, 0.36 mmol), and TBAI (0.027 g, 0.072 mmol) in dry MeCN (180 mL) was stirred at 80 °C for 72 h. Concentrated HCl (~3 mL) was added to stop the reaction and to precipitate the crude product from the MeCN solution as a yellow solid. The precipitate was collected by filtration and washed (Me_2CO and CH_2Cl_2) to remove the residual tetrabutylammonium salt. The precipitate was then dissolved in hot MeOH and reprecipitated as the PF_6^- salt (yellow) by adding solid NH_4PF_6 (~5% (w/v)) and collected by filtration. This crude material required no column chromatography. Two to three crystallizations by slow vapor diffusion of *i*-Pr_2O into a concentrated MeCN solution yielded pure **Ex^{2}Box·4PF$_6$** (186 mg, 37%) as a yellow solid. The ^{1}H NMR spectrum of the pure product matched the previously reported[10] spectrum (see the Supporting Information).

4,4′-(2,2′,2″,5,5′,5″-Hexamethyl-[1,1′:4′,1″-terphenyl]-4,4″-diyl)dipyridine (Ex^{3}BIPY-Me$_6$). A mixture of pyridin-4-ylboronic acid pinacol ester (1.16 g, 5.66 mmol), 4,4″-dibromo-2,2′,2″,5,5′,5″-hexamethyl-1,1′:4′,1″-terphenyl (1.07 g, 2.26 mmol), $PdCl_2$(dppf) (0.19 g, 0.23 mmol), CsF (2.07 g, 13.6 mmol), and a 2:1 mixture of *p*-dioxane and H_2O (12 mL) was stirred under reflux for 2 days. After the reaction mixture was cooled to room temperature, DMF (50 mL) was added. The precipitate that formed was filtered and washed with DMF (3 × 25 mL), CH_2Cl_2 (100 mL), and Me_2CO (50 mL) to afford the major portion (0.66 g) of the pure product. The second portion was obtained on adding concentrated HCl (5 mL) to the filtrate, forming the diprotonated salt, which was filtered and dissolved in hot MeOH (200 mL). Upon the addition of solid KOH, white precipitate formed and was collected to afford the second portion (0.16 g) of the pure product. The desired product was obtained in the total amount of 820 mg (78%) as a white solid and as a ~1:1 mixture of two diastereoisomers—a pair of enantiomers (*RR* and *SS*), and one *meso* isomer (*RS*)—undergoing fast isomerization at room temperature. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.70−8.64 (m, two overlapped AA′ of AA′XX′ systems, J = 6.0, 2.7 Hz, 4H), 7.36−7.33 (m, two overlapped XX′ of AA′XX′ systems, J = 6.0, 2.8 Hz, 4H), 7.15−7.13 (m, two overlapped singlets, 2H), 7.13−7.11 (m, two partially overlapped singlets, 2H), 7.06−7.03 (m, two almost resolved singlets (~1:1 ratio), 2H), 2.32−2.29 (m, two overlapped singlets, 6H), 2.16−2.12 (m, two almost resolved singlets (~1:1 ratio), 6H), 2.12−2.09 (m, two partially overlapped singlets, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ (six signals could not be detected because of the signal overlap) 149.9, 149.8, 141.92, 141.86, 140.1, 140.0, 137.88, 137.85, 133.92, 133.87, 133.0, 132.9, 132.09, 132.07, 131.94, 131.87, 130.9, 130.79, 130.77, 124.5, 20.0, 19.9, 19.6, 19.4. HRMS (ESI): m/z calcd for $C_{34}H_{32}N_2$ 469.2638 $[M + H]^+$, found 469.2649 $[M + H]^+$ ($|\Delta|$ = 2.31 ppm).

Bis(4-bromomethylbenzyl)(4,4′-(2,2′,2″,5,5′,5″-hexamethyl-[1,1′:4′,1″-terphenyl]-4,4″-diyl)bipyridin-1-ium) Bis(hexafluorophosphate) (Ex^{3}DB-Me$_6$·2PF$_6$). A mixture of α,α'-dibromo-*p*-xylene (2.42 g, 9.18 mmol) and a 1:1 mixture of CH_2Cl_2 and MeCN (60 mL) was heated at 50 °C with stirring until all of the solid material dissolved. Next, the temperature of the oil bath was raised to 90 °C, and a suspension of **Ex^{3}BIPY-Me$_6$** (430 mg, 0.918 mmol) in MeCN (30 mL) was added in four aliquots slowly over the course of 75 min. After it was heated under reflux for 19 h, the reaction mixture was cooled to room temperature and the yellow precipitate was collected by filtration and washed (CH_2Cl_2). The yellow solid was dissolved in a 6:1 mixture of DMF and MeOH (300 mL) followed by the addition of NH_4PF_6 (~4 g) and H_2O (~700 mL), resulting in the precipitation of pure **Ex^{3}DB-Me$_6$·2PF$_6$** (1.01 g, 98%), which was collected by filtration as a yellowish solid and as a ~1:1 mixture of two diastereoisomers—a pair of enantiomers (*RR* and *SS*), and one *meso* isomer (*RS*)—undergoing fast isomerization at room temperature. ^{1}H NMR (500 MHz, CD_3CN, ppm): δ 8.78−8.74 (m, two overlapped AA′ of AA′XX′ systems, J = 6.8, 3.3 Hz, 4H), 8.09−8.05 (m, two overlapped XX′ of AA′XX′ systems, J = 6.8, 3.5 Hz, 4H), 7.58−7.54 (m, two overlapped AA′ of AA′BB′ systems, J = 8.2, 4.4 Hz, 4H), 7.51−7.47 (m, two overlapped BB′ of AA′BB′ systems, J = 8.2, 4.4 Hz, 4H), 7.37−7.34 (m, two overlapped singlets, 2H), 7.21−7.18 (m, two almost resolved singlets (~1:1 ratio), 2H), 7.08−7.05 (m, two partially overlapped singlets, 2H), 5.75−5.71 (m, two overlapped singlets, 4H), 4.64−4.59 (m, two overlapped singlets, 4H), 2.39−2.36 (m, two overlapped singlets, 6H), 2.14−2.12 (m, two almost resolved singlets (~1:1 ratio), 6H), 2.08−2.06 (m, two partially overlapped singlets, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ (13 signals could not be detected because of the signal overlap) 159.9, 145.0, 144.8, 141.1, 140.61, 140.59, 135.64, 135.63, 135.2, 134.2, 134.11, 134.08, 133.81, 133.79, 133.5, 133.4, 132.24, 132.21, 131.40, 131.37, 131.1, 130.5, 129.6, 64.3, 33.6, 19.9, 19.5, 19.44, 19.35. HRMS (ESI): m/z calcd for $C_{50}H_{48}Br_2F_{12}N_2P_2$ 979.1821 $[M - PF_6]^+$, found 979.1792 $[M - PF_6]^+$ ($|\Delta|$ = 2.96 ppm).

Cyclobis(4,4′-(2,2′,2″,5,5′,5″-hexamethyl-[1,1′:4′,1″-terphenyl]-4,4″-diyl)bipyridin-1-ium-1,4-phenylenebis(methylene)) Tetrakis(hexafluorophosphate) (Ex^{3}Box-Me$_{12}$·4PF$_6$). A mixture of **Ex^{3}BIPY** (176 mg, 0.375 mmol), **Ex^{3}DB-Me$_{12}$·2PF$_6$** (422 mg, 0.375 mmol), and TBAI (28 mg, 0.076 mmol) in dry DMF (186 mL) was stirred at 80 °C for 72 h. The reaction mixture was cooled to room temperature, and NH_4PF_6 (5 g) and H_2O (0.6 L) were added to precipitate the crude product, which was collected by filtration and washed (H_2O and CH_2Cl_2). Purification by column chromatography (2×) using silica gel and 0.05% NH_4PF_6 in Me_2CO (w/v) as an eluent and two crystallizations by slow vapor diffusion of *i*-Pr_2O into a concentrated MeCN solution yielded pure **Ex^{3}Box-Me$_{12}$·4PF$_6$** (90 mg, 14%) as a white solid and as a mixture of five diastereoisomers—two pairs of enantiomers (*RRRR*/*SSSS* and *RRRS*/*SSSR*) and three *meso* isomers (*RRSS*, *RSRS*, and *RSSR*)—undergoing fast isomerization at room temperature. ^{1}H NMR (500 MHz, CD_3CN, ppm): δ 8.78−8.71 (m, five overlapped AA′ of AA′XX′ systems, 8H), 8.00−7.92 (m, five overlapped XX′ of AA′XX′ systems, 8H), 7.68−7.63 (m, five overlapped singlets, 8H), 7.24−7.05 (m, 10 partially overlapped singlets, 8H), 6.98−6.92 (m, five partially overlapped singlets, 4H), 5.79−5.68 (m, five overlapped singlets, 8H), 2.34−1.89 (m, 15 partially overlapped singlets, 36H). ^{13}C NMR (125 MHz,

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$CDCl_3$, ppm): δ (42 signals could not be detected because of the signal overlap) 159.904, 159.893, 159.886, 159.8, 144.99, 144.96, 144.44, 144.41, 140.52, 140.514, 140.507, 140.46, 140.45, 140.44, 136.89, 136.88, 135.6, 135.1, 134.98, 134.97, 134.03, 134.01, 133.73, 133.70, 133.4, 133.14, 133.13, 132.403, 132.397, 132.35, 132.3, 132.2, 131.37, 131.36, 131.33, 131.25, 129.6, 64.62, 64.61, 64.60, 19.84, 19.77, 19.43, 19.36, 19.34, 19.32, 19.31, 19.27. HRMS (ESI): m/z calcd for $C_{84}H_{80}F_{24}N_4P_4$ 717.2828 $[M - 2PF_6]^{2+}$, found 717.2847 $[M - 2PF_6]^{2+}$ ($|\Delta|$ = 1.38 ppm).

X-ray Crystallography. *(a) Method.* **Ex^{3}Box-Me$_{12}$·4PF$_6$** (3.0 mg, 1.7 μmol) was dissolved in MeCN (0.8 mL), and the mixture was passed through a 0.45 μm filter equally into three 1 mL tubes. The tubes were placed together in one 20 mL vial containing *i*-Pr_2O (~3 mL), and the vial was capped. Slow vapor diffusion of *i*-Pr_2O into the solution of **Ex^{3}Box-Me$_{12}$**·4PF$_6$ in MeCN (2 mM) over the course of 1 week yielded colorless single crystals of MeCN⊂**Ex^{3}Box-Me$_{12}$**·4PF$_6$ (0.167 × 0.044 × 0.027 mm). Single crystals of MeCN⊂**Ex^{3}Box-Me$_{12}$**·4PF$_6$ were mounted in inert oil and transferred to the cold gas stream of a Bruker Kappa APEX CCD area detector equipped with a Cu Kα microsource with MX optics. TWINABS-2012/1 (Bruker, 2012) was used for absorption correction. For component 1, wR_2(int) was 0.0952 before and 0.0421 after correction. For component 2, wR_2(int) was 0.1296 before and 0.0402 after correction. The ratio of minimum to maximum transmission is 0.69. The final HKLF 4 output contains 9365 reflections, R(int) = 0.0727 (3767 reflections with $I > 3\sigma(I)$, R(int) = 0.0628).

(b) Crystal Parameters for C_2H_3N⊂$C_{84}H_{80}N_4(PF_6)_4$. Colorless block (0.167 × 0.044 × 0.027 mm), triclinic, $P\bar{1}$ (No. 2), a = 7.0565(9) Å, b = 11.3492(17) Å, c = 26.647(3) Å, α = 78.589(9)°, β = 89.279(9)°, γ = 84.548(11)°, V = 2082.4(5) Å^3, T = 99.99 K, Z = 1, ρ_{calcd} = 1.409 g cm^{-3}, M = 1766.45 g mol^{-1}, μ(Cu Kα) = 1.735 mm^{-1}. Of a total of 3991 reflections that were collected, 3991 were unique. Final R_1 = 0.1188, and wR_2 = 0.2358 (all data). Site occupancy factors for the partially occupied MeCN solvent molecule were freely refined to approximately 50%. They were held constant at 50% for the final refinement cycles. The crystal under investigation was found to be nonmerohedrally twinned. The orientation matrices for the two components were identified using the program Cell_Now (Sheldrick, 2005), and the data were processed using both orientation matrices with SAINT. The exact twin matrix identified by the integration program was found to be (0.99829,0.00050,0.01214/−0.01797,0.99290,0.01597/−0.16174,−0.07915,1.00561). The absorption correction was carried out using TWINABS V2008/4 (Sheldrick, 2008) to create an HKLF 5 file, which was used in all refinements; the structure was solved using direct methods with only the non-overlapping reflections of component 1. The twin fraction refined to a value of 0.465(5). CCDC Number: 959014.

■ ASSOCIATED CONTENT

Supporting Information

Figures and a CIF file giving NMR, RP-HPLC, XRD, and HRMS data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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