Template-Directed Synthesis

DOI: 10.1002/anie.201000421

Polycatenation under Thermodynamic Control**

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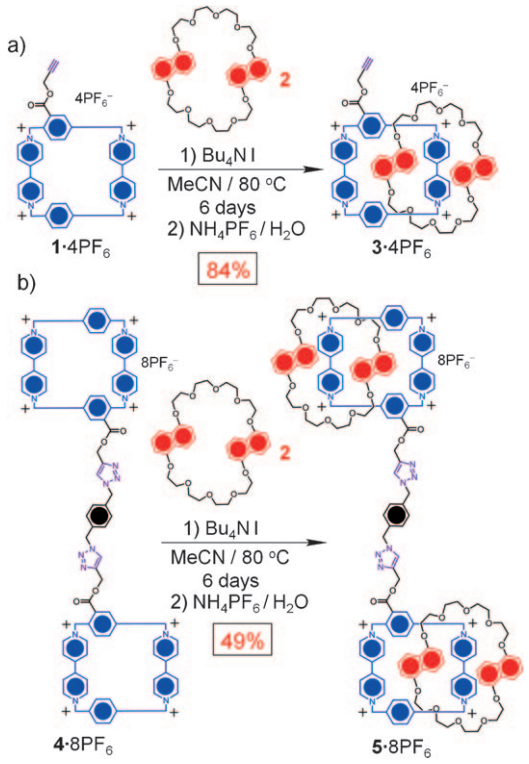
Molecular switches based on mechanically interlocked molecules[1,2] have been shown to operate just as effectively in condensed phases[3] as in solution. Thus, we have witnessed these bistable donor–acceptor catenanes and rotaxanes[2] serving as the switchable components[4] in molecular electronic devices,[4] nanoelectromechanical systems,[5] plasmonic devices,[6] and mechanized nanoparticles.[7,8] To date, fabrication has relied on the formation of self-assembled monolayers[9] of one sort or another. In an effort to improve upon the processibility of switchable bistable catenanes, they have been incorporated into polymeric scaffolds[10] in the form of side-chain poly[2]catenanes.[11,12] The weakness of this approach to the localizing of bistable catenanes on the sides of polymer chains is that their implantation relies upon kinetic control with its inherent absence of proof-reading and error-checking.[13] An attractive alternative, which is potentially much more modular and open to (complex) structural variation, is one in which multiple catenations are carried out under templation[14] on a reactive polymer itself under thermodynamic control.[15] Here, we describe the synthesis of a side-chain poly[2]catenane using a synthetic protocol—tested first of all on monomeric and dimeric analogues as models—in which nucleophilic substitutions, rendered dynamic under catalytic control,[16] are responsible for multiple catenations occurring all along the polymer chain, entirely driven in a synergistic fashion to completion by the intra- and intermolecular side-chain [π···π] stacking interactions of contiguous and interdigitated catenanes.

Donor–acceptor [2]catenanes comprised of the tetracationic cyclophane, cyclobis(paraquat-*p*-phenylene)[17] ($CBPQT^{4+}$), as the π-electron accepting ring interlocked mechanically with a π-electron-donating crown ether are typically formed by a clipping procedure[18] to make the mechanical bond with the simultaneous formation of the [2]catenane. This route, although much employed, suffers from the weakness of being irreversible, i.e., should reactive sites come together by mistake, the product is committed effectively, to becoming contaminated with constitutional defects. Circumventing kinetic control requires a process in which proof-reading and error-checking ultimately lead to the designed transformations—and avoid introducing constitutional anomalies in the case of chemically modified polymers—under equilibrium control. This process relies upon dynamic covalent chemistry,[13] wherein covalent bonds are formed and broken reversibly until the thermodynamically most stable outcome is obtained.

Recently, we have reported[16] the synthesis of donor–acceptor [2]- and [3]catenanes using an iodide-catalyzed thermodynamically reversible nucleophilic substitution to open and close one of the rings, namely the tetracationic cyclophane. In theory at least, the same approach (Scheme 1) should be applicable to the formation of polycatenanes[19] of the main-chain,[20] pendant,[21] bridged,[22] and side-chain[11,12]



Scheme 1. The synthesis of the degenerate [2]catenane **3**·4PF_6 and the degenerate bis[2]catenane **5**·8PF_6. a) The degenerate [2]catenane **3**·4PF_6 was obtained in one step by means of an iodide-catalyzed thermodynamically reversible nucleophilic substitution. A catalytic amount of Bu_4NI (30 mol%) in MeCN, together with **1**·4PF_6 and the crown ether **2**, were stirred for 6 d to yield **3**·4PF_6 in 84% yield as the PF_6^- salt, following counterion exchange with NH_4PF_6 in H_2O. b) Starting with **4**·8PF_6, the degenerate bis[2]catenane **5**·8PF_6 was isolated in 49% yield under thermodynamic control, following the same protocol as that employed in the synthesis of **3**·4PF_6.

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[**] This work was supported by the Non-equilibrium Energy Research Center (NERC) which is an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences under Award Number DE-SC0000989. L.F. gratefully acknowledges the support of Ryan and NERC Fellowships from Northwestern University.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201000421.

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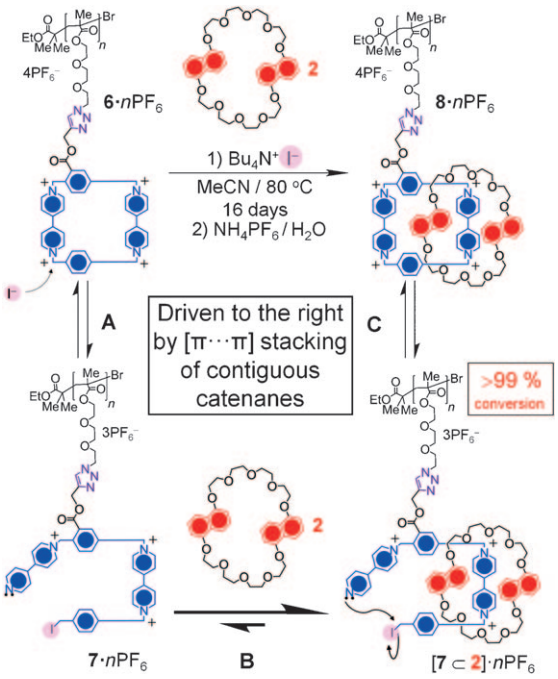
varieties. The side-chain poly[2]catenane requires that one of the two rings carries a tether to the main chain of the polymer—in the present case, a $CBPQT^{4+}$ ring, carrying a substituent arm on one of the *p*-phenylene rings. In order to establish if the iodide-catalyzed approach[16] to the catenation will work with a functionalized $CBPQT^{4+}$ ring, the derivative **1**·4PF_6 was treated (Scheme 1a) with a catalytic amount (30 mol%) of $Bu_4N^+I^-$ and 4.0 equivalents of the crown ether **2** (DNP38C10) in MeCN at 80°C for 6 days. The [2]catenane **3**·4PF_6 was isolated in 84% yield with no evidence[23] of "scrambling" of the $CBPQT^{4+}$ ring (see the Experimental Section). We extended this synthetic protocol to the production (Scheme 1b) of the bis[2]catenane **5**·8PF_6 in 49% yield from its precursors (see the Experimental Section), namely **4**·8PF_6, once again without any evidence of $CBPQT^{4+}$ ring "scrambling". These initial reactions indicate that this catalytic catenation, performed under thermodynamic control, can be executed with substituted $CBPQT^{4+}$ rings, despite their inherently lower binding of π-electron rich substances.[24]

Starting with **6**·*n*PF_6 [$M_w = 9.30(\pm0.19)\times10^5$ g mol^{-1}, $M_n = 6.10(\pm0.30)\times10^5$ g mol^{-1}, PDI = 1.50(±0.08) where $n \approx 160$, determined by size exclusion chromatography (SEC) in DMF],[11] we have employed (Scheme 2) very similar reaction conditions—namely 16 days in MeCN at 80°C with 4 equivalents of **2** per $CBPQT^{4+}$ repeating unit to obtain **8**·*n*PF_6. The resulting deep purple reaction mixture was added dropwise into a saturated aqueous solution of NH_4PF_6, leading to the precipitation of the side-chain poly[2]catenane **8**·*n*PF_6 as a purple solid (see the Experimental Section). Size exclusion chromatography, together with multi-angle light scattering (SEC-MALS)[25] experiments performed in DMF, afforded a M_w of $5.84(\pm0.09)\times10^6$ g mol^{-1}, a M_n of $4.24(\pm0.06)\times10^6$ g mol^{-1} and a PDI of 1.4(±0.2) where $n \approx 160$. The UV/Vis absorption spectrum (Figure 1a) of **8**·*n*PF_6, recorded in MeCN at 298 K, reveals the characteristic charge transfer (CT) band ($\lambda_{max} \approx 500$ nm) for dioxynaphthalene (DNP) units in a [π···π] stacking arrangement with bipyridinium ($BIPY^{2+}$) units.

The ^{1}H NMR spectrum (see the Supporting Information) of **8**·*n*PF_6 recorded in [D_7]DMF at 298 K reveals the presence of a resonance ($\delta = 2.55$ ppm) at high field which is diagnostic[26] of the $H_{4/8}$ protons on the DNP units residing inside $CBPQT^{4+}$ rings. We suspect that localized [2]catenanes along the polymer side-chains interact in a [π···π] stacking fashion both intra- and intermolecularly, influencing the reduction potentials of the bipyridinium units of the $CBPQT^{4+}$ rings. This interaction results in positive electrostatic cooperativity,[7,11] causing an anodic shift of the reduction potentials of the $BIPY^{2+}$ units with respect to those of the free $CBPQT^{4+}$ rings of **6**·*n*PF_6 as observed (Figure 1b) by cyclic voltammetry (CV). In other words, it is easier to reduce the $BIPY^{2+}$ units of the side-chain [2]catenanes in order to neutralize the accumulation of closely associated charge in the [π···π] stacked polymer aggregates. Additionally, the first bielectronic reduction process of **6**·*n*PF_6 characteristically separates[27] into two monoelectronic processes following the catenation of the $CBPQT^{4+}$ rings to give **8**·*n*PF_6. The alongside $BIPY^{2+}$ unit accepts an electron at −361 mV whereas the inside $BIPY^{2+}$ unit is not reduced until −440 mV. The CV (Figure 1b) of



Scheme 2. The synthesis and proposed mechanism for the formation of the degenerate side-chain poly[2]catenane **8**·*n*PF_6. The proposed mechanism accounts for the formation of the [2]catenanes along the polymer side-chains, starting from the side-chain poly$CBPQT^{4+}$ **6**·*n*PF_6, where $n \approx 160$, which then comes under (process **A**) reversible nucleophilic attack by iodide (I^-) ions at the benzylic methylenes of the $CBPQT^{4+}$ ring, which, in turn, opens the ring, generating the intermediate benzylic iodide **7**·*n*PF_6. There are four different C–N bonds present in the derivatized $CBPQT^{4+}$ ring which can, in principle, be attacked and cleaved by I^- ions. By employing a catalytic amount of the Bu_4NI, it is most unlikely that the reaction involving any one of these highly strained rings will proceed beyond its initial opening, thus accounting for the absence of "scrambled" products in the reaction mixture. The π-donating macrocycle **2** is now free (process **B**) to bind to the intermediate benzylic iodide $\mathbf{7}^{n+}$, generating the complex [**7**⊂**2**]·*n*PF_6. At this point, the pyridyl nitrogen lone pair in $\mathbf{7}^{n+}$ can undergo reverse nucleophilic attack (process **C**), regenerating the iodide catalyst while forming the mechanical bond, yielding **8**·*n*PF_6 quantitatively.

8·*n*PF_6 also suggests that the catenation of **6**·*n*PF_6 goes entirely to completion. We interpreted this unexpected result as suggestive of a remarkable level of positive cooperativity, i.e., the iodide-catalyzed catenations appear to be driven to completion in the side-chain poly[2]catenane. Why should this be the case? We hypothesize that it is the formation within **8**·*n*PF_6 of intra- and interchain donor–acceptor stacks which encourages each and every $CBPQT^{4+}$ ring to become catenated in a synergistic fashion with a DNP38C10 ring under the equilibrium conditions of the catalytic reaction, a hypothesis that is supported by both calorimetry and light-scattering measurements. When subjected to isothermal titration microcalorimetry (ITC) in order to measure the strength of complexation with a diethyleneglycol-disubstituted dioxynaphthalene guest in MeCN at 298 K prior to its catenation, **6**·*n*PF_6 affords a strong exothermic binding isotherm (Figure 1c) corresponding to a change in enthalpy ($\Delta H°$) of −14.2(±1.5) kcal mol^{-1}. By contrast, **8**·*n*PF_6 exhibits

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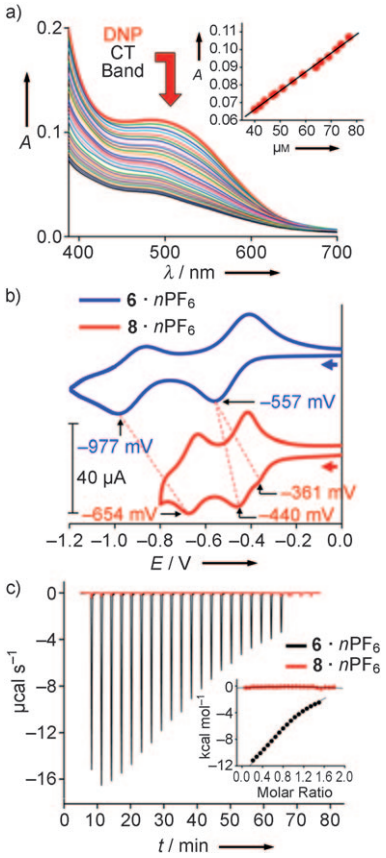

Figure 1. The characterization of the mechanical bond along the side-chains of the polycatenane. a) Absorption spectra showing the charge transfer (CT) band of **8**·nPF$_6$ measured over a range of concentrations in MeCN at 298 K. Inset: The CT band varies linearly with concentration, thus confirming that the [2]catenanes are distributed along the polymer side-chains since the two rings do not dissociate upon dilution as would be the case for a pseudorotaxane. b) Stacked cyclic voltammograms recorded in MeCN at 298 K, illustrating the characteristic anodic shifts as a result of positive electrostatic cooperativity and the splitting of the first bielectronic reduction process (−557 mV) into two monoelectronic processes (−361 and −440 mV) which results from the catenation of the CBPQT^{4+} rings along the polymer chain, causing the otherwise identical BIPY^{2+} units to lose their electrochemical equivalence, such that the alongside BIPY^{2+} unit reduction potential occurs at −361 mV, whereas the inside BIPY^{2+} unit is reduced at −440 mV. c) Stacked binding isotherms obtained by isothermal titration microcalorimetry at 298 K in MeCN, allowing us to assess the complexation of the diethyleneglycol-disubstituted-dioxynaphthalene derivative with **6**·nPF$_6$ prior to catenation, and **8**·nPF$_6$ subsequently, demonstrating that the CBPQT^{4+} rings are no longer vacant and so cannot accommodate guest molecules on account of catenation.

(Figure 1c) a flat binding isotherm, suggesting that there are no longer any vacant CBPQT^{4+} rings on the side-chains of **8**·nPF$_6$ for the binding of π-electron rich substances.

It is known that polyelectrolytes, for example **6**·nPF$_6$ and **8**·nPF$_6$, exhibit aggregation[28] behavior, forming three-dimensional architectures in solution. The ability to mitigate repulsive intra- and interchain Coulombic interactions in both **6**·nPF$_6$ and **8**·nPF$_6$ stems from the screening effects[29] of the loosely coordinated hexaflurophosphate (PF_6^-) counterions[30] which are retained around the polyelectrolyte aggregate to maintain electric neutrality. In solutions of high ionic strength, the aggregation behavior can be suppressed such that individual polymer chains are free in solution in what some polymer chemists call a Θ state.[28] During its synthesis, we believe that positive cooperativity arising from [π···π] stacking which drives the catenations along the polymer chain—leading to the formation of **8**·nPF$_6$ in a near quantitative manner—originates from both intra- and interchain interactions. Merck Molecular Force Field (MMFF94) calculations on poly(methylacrylic acid) of five repeat units forecasts an average distance of ca. 3.4 Å between the carbonyl carbon atoms of adjacent repeating units, suggesting that perhaps intermolecular and non-contiguous intramolecular [π···π] interactions accompany contiguous intramolecular ones. Since the thermodynamic reaction was run in a salt-free solution (zero ionic strength, $C_s = 0$), aggregation during the synthesis of the polycatenane is not suppressed.

Mass analysis (see the Supporting Information) of **6**·nPF$_6$, as determined by SEC-MALS, reveals that the r.m.s. radius of gyration (R_g) of the polymer aggregates experiences a contraction upon catenation, despite having a larger molar mass [**6**·nPF$_6$ $R_g = 100.1(\pm0.4)$ nm; **8**·nPF$_6$ $R_g = 74.2(\pm0.1)$ nm] of the CBPQT^{4+} side-chains, suggesting that intra- and interchain [π···π] stacking interactions are occurring in solution. A SEC-MALS conformation plot of $\log r_g$ as a function of $\log M_w$ for **8**·nPF$_6$ yields (Figure 2) a slope of

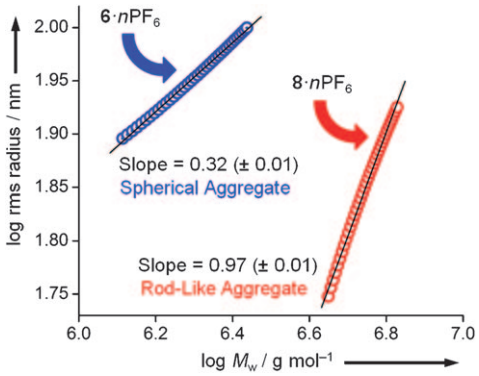

Figure 2. A log–log conformation plot (log of rms radius versus log of molecular weight) for **6**·nPF$_6$ (blue, slope of 0.34(±0.01)) and **8**·nPF$_6$ (red, slope of 0.34(±0.01)) obtained from SEC-MALS, illustrating the contraction of the polymer aggregate, resulting in a conformational change from spherical to rodlike aggregates upon localizing [2]catenanes on the polymer side-chains that are capable of both intra- and interchain [π···π] stacking.

0.97(±0.01), a value which is consistent[25] with rodlike polymer aggregates being present in solution, whereas **6**·nPF$_6$ yields a slope of 0.32(±0.01), suggesting the existence[11,25] of spherically shaped polymer aggregates. The contraction of the R_g is paralleled by a contraction of hydrodynamic radius (R_h) and an increase in the diffusion coefficient (D_o), as determined (Figure 3) by dynamic light scattering, where, for polymer **6**·nPF$_6$ (Figure 3a), the aggregate R_h is 133.7(±24.2) nm, $D_o = 4.5(\pm0.4) \times 10^{-12}$ m^{2}s^{-1} while the R_h for the side-chain polycatenane aggregate (Figure 3b) is 53.6(±12.1) nm, $D_o = 11.1(\pm1.3) \times 10^{-12}$ m^{2}s^{-1}. The ratio of

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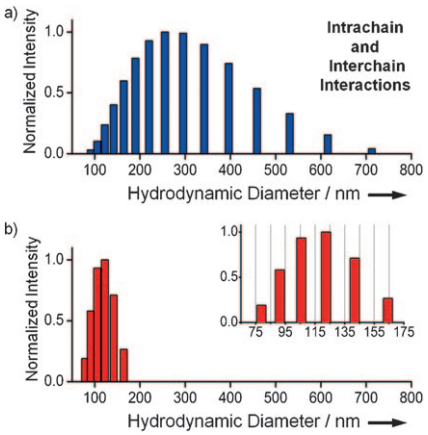

Figure 3. Dynamic light scattering size distribution histograms monitoring the conformational transition of the hydrodynamic diameter (D_h) upon catenation of the polymer side-chains. a) The size distribution histogram of a 0.39 mM solution of **6**·nPF$_6$ (blue), illustrating the expanded hydrodynamic diameter in DMF at 298 K. b) The size distribution histogram of a 0.39 mM solution of **8**·nPF$_6$ (red), illustrating the contracted hydrodynamic diameter in DMF at 298 K.

R_g/R_h (ρ) is a parameter[31] that describes qualitatively how the polymer chains are interacting in real space. Prior to catenation, this parameter ρ is calculated to be 0.74 approaching 0.77, a range which is consistent[32] with spherical aggregates of uniform density—i.e., the polyCBPQT^{4+} **6**·nPF$_6$ behaves[11] almost like a large micelle in which the tetracationic cyclophanes most likely protrude (Figure 4a) outwards on account of Coulombic repulsions, leaving the relatively hydrophobic backbone to reside in the interior. Following catenation to give **8**·nPF$_6$, ρ becomes equal to 1.4 approaching 1.5, a range which is consistent[32] with random coils and linear chains, which are semi-flexible and much smaller in size. This observation is in agreement with the SEC-MALS data and the hypothesis that the side-chain [2]catenanes of **8**·nPF$_6$ are [π···π] stacked (Figure 4b) both intra- and intermolecularly leading to changes in aggregate conformations in order to accommodate the [π···π] stacking, after having provided the synergy to drive their own formation.

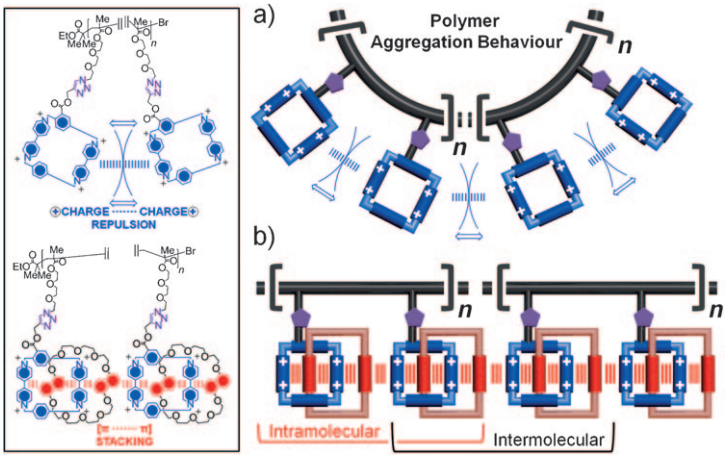

Figure 4. A graphical representation alongside the structural formulas (left) illustrating the effects of inter- and intramolecular a) Coulombic repulsion among the tetracationic side-chains of **6**·nPF$_6$ which could be responsible for the expanded hydrodynamic radius and r.m.s. radius of gyration, leading to spherical aggregates (assuming little or no ion-pairing between the CBPQT^{4+} rings and the PF$_6^-$ counterions) in DMF at 298 K and the inter- and intramolecular b) [π···π] stacking interactions which could be responsible for the contraction of **8**·nPF$_6$ aggregates following catenation.

At the outset of this research, our aim was to test the viability of the iodide-catalyzed dynamic nucleophilic substitution for [2]catenane formation in the synthesis of the side-chain donor–acceptor polycatenanes under thermodynamic control, being aware that only two examples are recorded[11,12] in the literature for the preparation of these polymer architectures and both of them are formed under kinetic control. To our surprise, the localization of [2]catenanes under thermodynamic control along the polymer side-chains proceeded quantitatively, aided and abetted by the positive cooperativity of both intra- and interside-chain [π···π] stacking interactions, effectively driving the conversion to the polycatenane iteratively to completion. The process, after all is said and done, results in an overall contraction and a change in the self-organization of the polycatenane aggregates in solution. We would like to think that further investigations of these types of artificial polymers will assist in the elucidation of the mechanisms which are responsible for the intracellular pathological aggregation of biomacromolecules—e.g., neurofilaments whose side-chains are in fact biopolymer brushes[33]—and are the root cause of neurodegenerative diseases like amyotrophic lateral sclerosis and Parkinson's disease.[34]

Experimental Section

3·4PF$_6$: **1**·4PF$_6$[35] (30 mg, 0.025 mmol) was added to a solution of **2** (31.8 mg, 0.05 mmol) in dry MeCN (1 mL). A catalytic amount of Bu$_4$NI (2.8 mg, 0.0075 mmol) was added to the solution, and the reaction mixture was stirred at 80 °C for 6 d before being cooled to room temperature. The resulting deep purple solution was added dropwise to a saturated aqueous solution of NH$_4$PF$_6$ to precipitate out the crude product as the PF$_6^-$ salt. The crude product was then redissolved in MeCN and subjected to column chromatography (MeOH/MeNO$_2$/H$_2$O/NH$_4$Cl 7:1:2:2 M). The eluent was removed under vaccum and the solid was dissolved in hot H$_2$O. A saturated aqueous solution of NH$_4$PF$_6$ was added dropwise and the precipitate which was formed was recovered by filtration to afford **3**·4PF$_6$ (38 mg, 84%) as a purple solid. ^{1}H NMR (CD$_3$CN, 600 MHz, 233 K): δ = 2.13 (d, J = 7.8 Hz, 1H), 2.20 (d, J = 7.8 Hz, 1H), 3.14 (s, 0.5H), 3.20 (s, 0.5H), 3.57–4.28 (m, 36H), 5.06–5.21 (m, 2H), 5.44 (q, 1H), 5.55 (m, 2H), 5.63 (s, 2H), 5.70 (m, 1H), 5.93 (t, J = 7.2 Hz, 1H), 6.00 (t, J = 7.9 Hz, 1H), 6.27–6.64 (m, 8H), 7.09 (t, J = 5.2 Hz, 6H), 7.20 (s, 1H), 7.26 (m, 1H), 7.92 (d, J = 4.2 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 8.06–8.20 (m, 3H), 8.32 (m, 1H), 8.40 (s, 0.5H), 8.46 (s, 0.5H), 8.54–8.67 (m, 4H), 8.73 (t, J = 6.5 Hz, 1H), 8.83–8.95 ppm (m, 3H); ^{13}C NMR (CD$_3$CN, 600 MHz, 233 K): δ = 53.8, 60.9, 63.9, 64.7, 67.4, 67.5, 67.8, 69.3, 69.5, 69.7, 70.3, 70.5, 70.8, 70.9, 76.3, 103.5, 103.6, 105.2, 107.4, 107.8, 113.4, 123.9, 125.1, 125.5, 126.9, 127.8, 130.7, 150.7, 153.0 ppm; HRMS (ESI): m/z calcd for $C_{76}H_{78}O_{12}N_4P_4F_{24}$: 1818.42; found: 1673.4520 $[M-PF_6]^+$, 764.2450 $[M-2PF_6]^{2+}$.

5·8PF$_6$: **4**·8PF$_6$[36] (17.2 mg, 0.007 mmol) was added to a solution of **2** (10.9 mg, 0.017 mmol) in dry MeCN (1 mL). A catalytic amount of Bu$_4$NI (1.33 mg, 0.004 mmol) was added

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to the solution, and the reaction mixture was stirred at 80 °C for 6 d before being cooled to room temperature. The resulting deep purple solution was added dropwise to a saturated aqueous solution of NH_4PF_6 to precipitate out the crude product as the PF_6^- salt. The crude product was then redissolved in Me_2SO—containing 0.1% CF_3CO_2H acid by volume—and purified by RP-HPLC (H_2O/MeCN, 0–100% in 40 min, $\lambda = 254$ nm). The purple fractions were collected and the eluent was removed under vacuum. The purple solid was dissolved in hot H_2O and a saturated aqueous solution of NH_4PF_6 was added dropwise until no further precipitate was observed. It was recovered by filtration to afford **5**·8PF_6 (12.5 mg, 49%) as a purple solid. ^{1}H NMR (CD_3CN, 600 MHz, 233 K): $\delta = 2.13$ (br s, 2H), 2.24 (br s, 2H), 3.55–4.27 (m, 69H), 4.97–5.29 (m, 4H), 5.36–5.50 (m, 2H), 5.52–5.86 (m, 13H), 5.87–6.12 (m, 8H), 6.16–6.75 (m, 15H), 7.01–7.16 (m, 11H), 7.18–7.22 (m, 2H), 7.23–7.27 (m, 2H), 7.28–7.31 (m, 1H), 7.75–7.88 (br s, 4H), 7.89–8.01 (m, 3H), 8.02–8.29 (m, 8H), 8.29–8.39 (m, 2H), 8.39–8.44 (s, 1H), 8.45–8.52 (s, 1H), 8.52–8.71 (m, 6H), 8.72–8.80 (m, 2H), 8.80–8.99 ppm (m, 6H); ^{13}C NMR (CD_3CN, 600 MHz, 233 K): $\delta = 52.8$, 59.4, 61.0, 64.7, 67.4, 69.5, 69.6, 70.3, 70.5, 70.9, 103.6, 105.1, 107.4, 107.8, 113.4, 117.0, 123.8, 123.9, 125.1, 125.5, 127.1, 128.3, 130.6, 135.8, 136.3, 142.0, 143.5, 150.7, 153.0 ppm; HRMS (ESI): m/z calcd for $C_{160}H_{164}O_{24}N_{14}P_8F_{48}$: 3824.91; found: 1130.0049 $[M-3PF_6]^{3+}$, 811.2672 $[M-4PF_6]^{4+}$.

8·*n*PF_6: **6**·*n*PF_6[24] (24.7 mg, 0.017 mmol, starting $M_w = 9.30(\pm0.19)\times10^5$ g mol^{-1}, $M_n = 6.10(\pm0.30)\times10^5$ g mol^{-1}, PDI = 1.50(±0.08) and with an elution time of 20.1 min in DMF) was added to a solution of **2** (44.2 mg, 0.069 mmol) in dry MeCN (1 mL). A catalytic amount of Bu_4NI (3.2 mg, 0.005 mmol) was then added to the solution, and the reaction mixture was stirred at 80 °C for 16 d, before being cooled to room temperature. The resulting deep purple solution was added dropwise to a saturated aqueous solution of NH_4PF_6 to precipitate out the crude product as the PF_6^- salt. The precipitate was recovered by filtration and washed with CH_2Cl_2 and $CHCl_3$ (3 × 25 mL) and subjected immediately to size exclusion chromatography-multiangle light scattering (SEC-MALS) in order to characterize **8**·*n*PF_6 (12.5 mg, 49%) as a purple solid with a $M_w = 4.32(\pm0.09)\times10^6$ g mol^{-1}, $M_n = 3.13(\pm0.06)\times10^5$ g mol^{-1}, PDI = 1.50(±0.01) and an elution time of 16.8 min in DMF.

Received: January 24, 2010
Published online: March 29, 2010

Keywords: catenanes · polymers · self-assembly · template-directed synthesis · thermodynamics

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