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Parking and Restarting a Molecular Shuttle In Situ

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Abstract: Herein we report an easy-to-synthesize [2]rotaxane, which incorporates two ionic monopyridinium stations and one 2,2′-bipyridine station as the shaft of the dumbbell-shaped component and a bis-*p*-xylyl[26]crown-6 (BPX26C6) unit as the macrocyclic component. In this molecular shuttle, the BPX26C6 unit can be docked selectively on either the central 2,2′-bipyridine station or one of the two terminal pyridinium stations, and subsequently, returned to its shuttling molecular motion through the in situ addition of simple reagents (acid/base or metal ion/metal-ion-complexing ligand pairs).

Keywords: host–guest systems · molecular machines · molecular shuttles · molecular switches · rotaxanes

Introduction

Mechanically interlocked molecules attract a great deal of attention because of their potential for application in mesoscale devices and nanoscale molecular machinery.[1] Degenerate molecular shuttles,[2] in which macrocyclic units oscillate between symmetrical recognition sites, are commonly used as substrates for probing the dynamic behavior of these molecular machines in solution because rate data for these systems can be obtained readily through the use of dynamic ^{1}H NMR spectroscopy.[3] For molecular shuttles to exhibit behavior more suitable for use in molecular machines, it is necessary to prepare systems in which it is possible to precisely control the molecular motion (e.g., the ability to start and stop the shuttling process) and the location of the macrocyclic components in relation to the dumbbell-shaped component. Two methods have been reported previously for controlling the migration of interlocked macrocycles between degenerate binding sites:[4] 1) by covalently attaching a bulky group at the center of the thread component[5] and 2) by noncovalently dimerizing two molecular shuttles through the addition of Cu^I ions.[6] However, neither of these methods is suited to readily or reversibly controlling the shuttling motion in situ because covalently attaching a bulky group requires the formation and cleavage of a covalent bond and noncovalently dimerizing two molecular shuttles necessitates the use of an ion-exchange column to remove the complexed Cu^I ions and restart the shuttling process.[7] Thus, to the best of our knowledge, rotaxane-based systems that exhibit truly selective in situ parking and restarting of the motion of interlocked macrocycles at defined locations along dumbbell-shaped components have yet to be achieved. Herein, we report an easy-to-synthesize molecular shuttle, which incorporates two ionic monopyridinium stations and one 2,2′-bipyridine station on the shaft of the dumbbell-shaped component and a bis-*p*-xylyl[26]-crown-6 (BPX26C6)[8] unit as the macrocyclic component. With this system, the BPX26C6 unit can be docked selectively on either the central 2,2′-bipyridine or one of the two terminal pyridinium stations, and subsequently, returned to its shuttling molecular motion through the in situ addition of simple reagents (acid/base or metal ion/metal-ion-complexing ligand pairs).

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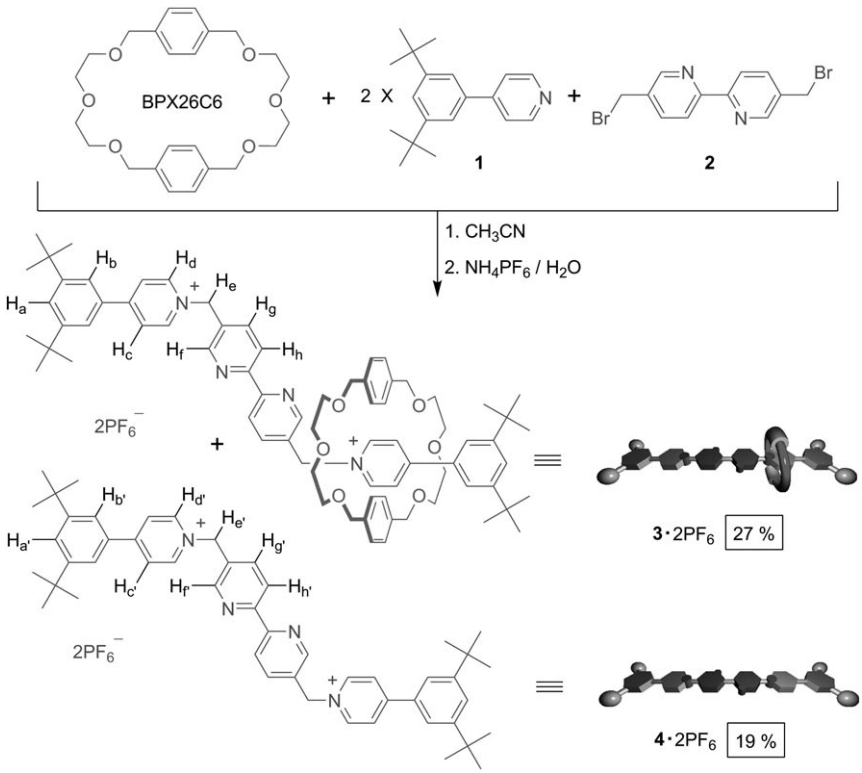
Results and Discussion

Previously, we reported that BPX26C6 is capable of forming pseudorotaxane complexes with monopyridinium ions in solution, which allows the one-pot synthesis of molecular rotaxanes.[8b] Thus, we proposed that a one-pot reaction of BPX26C6, bulky pyridine derivative **1**,[9] and dibromide **2**[10] would yield a [2]rotaxane in which the BPX26C6 unit could shuttle between the two terminal monopyridinium stations and pass over the 2,2′-bipyridine moiety with each transition. Indeed, we isolated [2]rotaxane **3**·2 PF_6 (27% yield after ion exchange and column chromatography) from the reaction of **1** (120 mM), **2** (60 mM), and BPX26C6 (90 mM) in CH_3CN (Scheme 1).

The sharp and simple signals observed in the ^{1}H NMR spectrum (Figure 1a) recorded in CD_3NO_2 at 298 K for **3**·2 PF_6, in addition to the significant broadening of the pyridinium (H_c and H_d) and adjacent methylene (H_e) signals, suggested that the BPX26C6 unit shuttles rapidly between the two monopyridinium stations under these conditions. After cooling the solution to 223 K, the corresponding partial ^{1}H NMR spectrum (Figure 1f) displays signals for all of the protons and indicates asymmetry in the dumbbell-shaped component (e.g., two signals appear at $\delta = 1.32$ and 1.43 ppm for the two pairs of *tert*-butyl groups), which suggests that under these conditions the BPX26C6 unit shuttles between the two monopyridinium stations sufficiently slowly on the ^{1}H NMR spectroscopy timescale, such that one of the monopyridinium stations is encircled by the macrocycle and the other is not. At 260 K, the signal at $\delta = 7.72$ ppm in Figure 1a began to split into two signals (Figure 1c) with a limiting frequency difference ($\Delta\nu$) of 47.2 Hz (Figure 1f). Therefore, the rate of shuttling (k_c) of the macrocycle between the two monopyridinium stations, was 105 s^{-1}, which corresponds to a free energy of activation for the shuttling process ($\Delta G_c^{\pm}$) of 12.8 kcal mol^{-1} at a coalescence temperature (T_c) of 260 K, as derived by using the Eyring equation.[11]

We obtained single crystals that were suitable for X-ray crystallographic analysis by vapor diffusion of isopropyl ether into a solution of **3**·2 PF_6 in CH_3CN. The solid-state structure of $\mathbf{3}^{2+}$ (Figure 2) shows the interlocked nature of the ion, with the BPX26C6 macrocycle encircling one of the pyridinium stations.[12]

As BPX26C6 has a much stronger binding affinity towards doubly protonated 2,2′-bipyridinium ions than towards monopyridinium ions in CD_3NO_2,[13] we believed that the addition of a suitable amount of acid would enable us to park the macrocyclic unit on the 2,2′-bipyridinium station in the center of the dumbbell-shaped component (Figure 3). Thus, when we added trifluoroacetic acid (TFA; 2 equiv) to a solution of **3**·2 PF_6 in CD_3NO_2, analysis of the ^{1}H NMR spectrum revealed sharp signals for the pyridinium moieties and their adjacent methylene groups (Figure 4b). In comparison with the spectrum of the protonated free dumbbell-shaped component ($\mathbf{4}H_2^{4+}$; Figure 4d), the signals of the 2,2′-bipyridinium aromatic protons (H_f and H_g) of the doubly protonated molecular shuttle ($\mathbf{3}H_2^{4+}$) were significantly shifted upfield, but the signals of the monopyridinium protons were relatively unchanged, which suggested that the macrocyclic unit BPX26C6 did indeed preferentially encircle the protonated 2,2′-bipyridinium station in the center of the [2]rotaxane. Subsequent addition of Et_3N (2 equiv) to this mixture gave a ^{1}H NMR spectrum (Figure 4c) that was similar to that of the original solution of **3**·2 PF_6 (Figure 4a), which implied that dynamic movement of the BPX26C6 unit between the two terminal monopyridinium stations had been restored. Thus, [2]rotaxane **3**·2 PF_6 behaves as an acid/base-controlled molecular shuttle in solution;[14] the interlocked BPX26C6 macrocycle can be parked selectively at the central 2,2′-bipyridinium station on the dumbbell-shaped component (in $\mathbf{3}H_2^{4+}$ obtained by the addition of TFA) or it can



Scheme 1. The synthesis of **3**·2 PF_6.

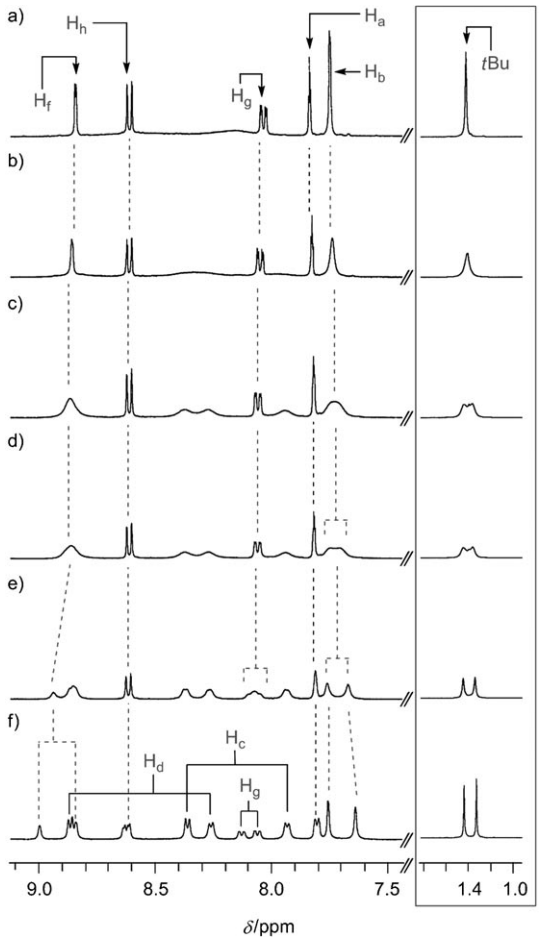


Figure 1. Partial ^{1}H NMR spectra (400 MHz, CD_3NO_2) of **3**·2 PF_6 recorded at a) 298, b) 273, c) 260, d) 258, e) 243, and f) 223 K.

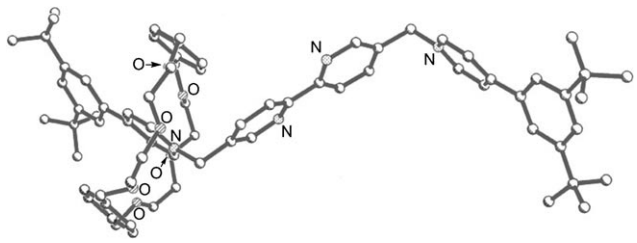


Figure 2. Ball-and-stick representation of the solid-state structure of $[\mathbf{3}]^{2+}$.

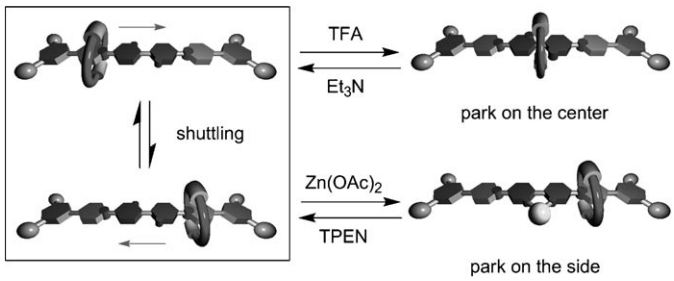


Figure 3. Cartoon representation of the selective docking of the macrocyclic component at different stations along the dumbbell-shaped component of **3**·2 PF_6.

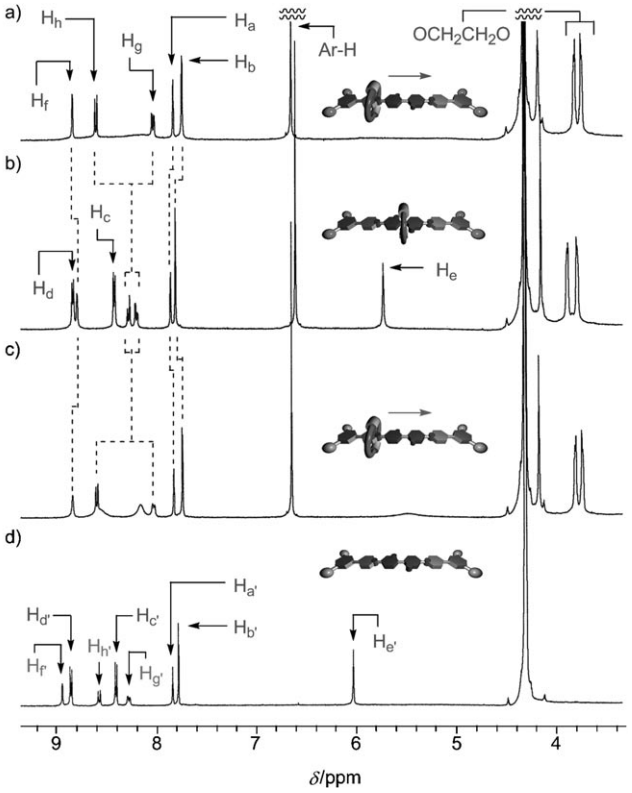


Figure 4. Partial ^{1}H NMR spectra (400 MHz, CD_3NO_2, 298 K) of a) **3**·2 PF_6, b) **3**·2 PF_6 + TFA (2 equiv), c) solution b) after addition of Et_3N (2 equiv), and d) free dumbbell-shaped component **4**·2 PF_6 + TFA (1:2).

move freely and reversibly between the two terminal monopyridinium stations (in the deprotonated form ($\mathbf{3}^{2+}$) obtained by the addition of Et_3N).

As a result of the small size of BPX26C6, we believed that the coordination of a suitable metal ion (and, more importantly, its associated ligands) to the central 2,2′-bipyridine station would stop the shuttling of the macrocycle by forcing it to reside at one of the terminal monopyridinium stations (Figure 3). The addition of $Zn(OAc)_2$ to a solution of **3**·2 PF_6 in CD_3NO_2 caused dramatic changes to the ^{1}H NMR spectrum, which now displays sets of signals for each of the two monopyridinium moieties and their adjacent methylene protons (Figure 5b).[15] The signals at $\delta = 5.15$ and 6.08 ppm for the respective pairs of H_e protons suggest that the dumbbell-shaped component exhibits the asymmetry associated with the BPX26C6 unit selectively encircling just one of the monopyridinium stations, that is, the shuttling process slows considerably after the addition of $Zn(OAc)_2$. To remove the coordinated metal ion from the 2,2′-bipyridine unit, we added tetrapyridineethylenediamine (TPEN),[16] which strongly binds Zn^{2+} ions, to the solution. The resulting ^{1}H NMR spectrum (Figure 5c) is similar to that of **3**·2 PF_6 (Figure 5a), which suggests that the Zn^{2+} ion is no longer chelated to the dumbbell-shaped component

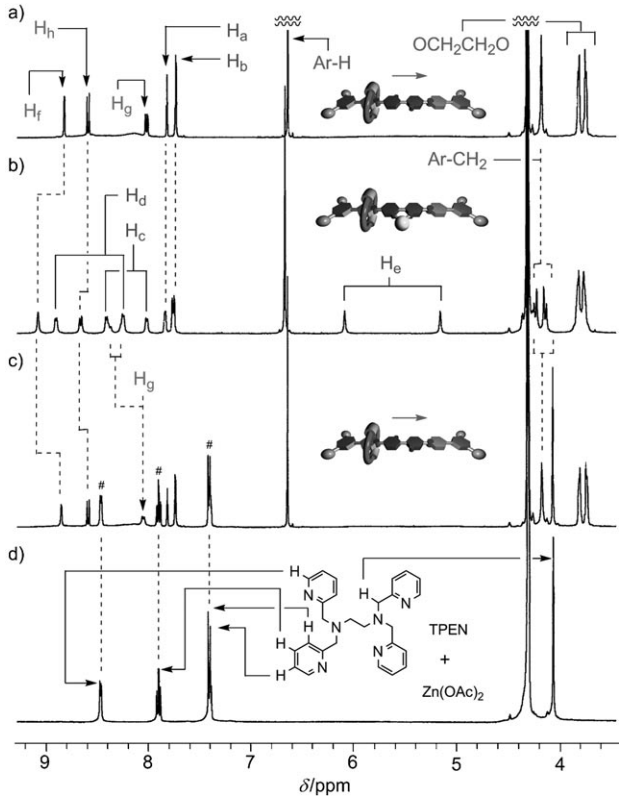


Figure 5. Partial ^{1}H NMR spectra (400 MHz, CD_3NO_2, 298 K) of a) **3**·2 PF_6, b) **3**·2 PF_6 + $Zn(OAc)_2$ (1 equiv), c) solution b) after addition of TPEN (1 equiv), and d) TPEN + $Zn(OAc)_2$ (1:1). #: Signals from $[Zn]^{2+}$-complexed TPEN.

and that the initial molecular shuttling motion is restored. Thus, the sequential addition of $Zn(OAc)_2$ and TPEN to a solution of **3**·2 PF_6 in CD_3NO_2 leads to a reversible process of initial selective docking of the macrocyclic unit onto one of the terminal monopyridinium stations of the dumbbell-shaped component and subsequent regeneration of the original shuttling motion between the two monopyridinium stations.[17]

Conclusion

We have demonstrated that the macrocyclic component of **3**·2 PF_6 can be parked selectively at either the central 2,2′-bipyridinium station or one of the two terminal monopyridinium stations by the addition of TFA or $Zn(OAc)_2$, respectively. The original shuttling state was then recovered by the addition of a complementary reagent (Et_3N or TPEN, respectively), thus **3**·2 PF_6 mimics the behavior of a molecular machine in which the reversible molecular motion can be stopped and restarted at will. These three discrete and identifiable states of **3**·2 PF_6 suggest that it has the potential for applications as a molecular switch, a molecular logic gate, or a molecular sensor, each of which is currently under investigation in our laboratory.

Experimental Section

General: All glassware, stirrer bars, syringes, and needles were either oven- or flame-dried prior to use. All reagents, unless otherwise indicated, were obtained from commercial sources. Anhydrous CH_2Cl_2 and MeCN were prepared by distillation over CaH_2 under N_2. Reactions were conducted under either N_2 or Ar. Thin-layer chromatography (TLC) was performed by using Merck 0.25 mm silica gel (Merck Art. 5715). Column chromatography was performed by using Kieselgel 60 (Merck, 70–230 mesh). Melting points were determined by using a Fargo MP-2D melting point apparatus. For the ^{1}H NMR spectroscopic analyses, the deuterated solvent was used as the lock and an internal standard was provided by either the solvent's residual protons or TMS. Chemical shifts are reported in parts per million (ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiple).

X-Ray crystallographic analysis: CCDC 665821 (**3**·2 PF_6) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[2]Rotaxane 3·2 PF_6: A mixture of 3,5-di-*tert*-butylbenzyl bromide (169 mg, 0.6 mmol), 5,5′-bis(bromomethyl)-2,2′-bipyridine (101 mg, 0.3 mmol), and BPX26C6 (186 mg, 0.45 mmol) in CH_3CN (0.5 mL) was stirred for 3 d at ambient temperature. After the solvent had been removed under reduced pressure, the residue was washed with diethyl ether(5 mL), suspended in MeCN (2 mL), and then filtered. The solid was collected for further isolation of dumbbell **4**·2 PF_6 (see below). Saturated aqueous NH_4PF_6 (10 mL) was added to the filtrate and the organic solvent was evaporated under reduced pressure. The precipitate was collected, washed with H_2O (20 mL), and purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2) to afford **3**·2 PF_6 as a white solid (113 mg, 27%). As a result of shuttling of the macrocycle, the signals of the pyridinium and adjacent methylene protons were broadened severly. M.p. >235 °C decomp; ^{1}H NMR (400 MHz, CD_3CN, 298 K): δ = 1.43 (s, 36H), 3.66–3.80 (m, 16H), 4.10 (s, 8H), 6.52 (s, 8H), 7.65 (s, 4H), 7.75 (t, J = 1.2 Hz, 2H), 8.00 (d, J = 8 Hz, 2H), 8.58 (d, J = 8 Hz, 2H), 8.80 ppm (s, 2H); ^{13}C NMR (100 MHz, CD_3CN, 298 K): δ = 31.4, 35.7, 60.8, 70.5, 71.3, 73.3, 121.6, 122.7, 125.9, 126.7, 127.7, 128.2, 130.1, 133.4, 136.9, 138.8, 143.9, 150.0, 152.3, 155.3 ppm; HRMS (ESI): *m*/*z*: calcd for $[\mathbf{3}\cdot PF_6]^+$: 1277.6653; found: 1277.6767; *m*/*z*: calcd for $[\mathbf{3}]^{2+}$: 566.3503; found: 566.3518.

4·2 PF_6: The precipitate that was collected from the filtration process described above was dissolved in MeOH (2 mL) and then saturated aqueous NH_4PF_6 (10 mL) was added. After the organic solvent had been removed under reduced pressure, the precipitate was collected and washed with H_2O (20 mL) to yield **4**·2 PF_6 as a pink solid (56 mg, 19%). M.p. >175 °C decomp; ^{1}H NMR (400 MHz, CD_3CN): δ = 1.38 (s, 36H), 5.78 (s, 4H), 7.70 (d, J = 2 Hz, 4H), 7.76 (t, J = 2 Hz, 2H), 7.96 (dd, J = 8, 2 Hz, 2H), 8.32 (d, J = 7 Hz, 4H), 8.50 (d, J = 8 Hz, 2H), 8.75 (d, J = 8 Hz, 4H), 8.77 ppm (d, J = 2 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ = 31.3, 35.7, 61.4, 121.5, 122.8, 125.9, 127.1, 130.0, 133.5, 138.0, 144.2, 149.7, 152.7, 156.0, 157.9 ppm; HRMS (ESI): *m*/*z*: calcd for $[\mathbf{4}\cdot PF_6]^+$: 861.4454; found: 861.4384; *m*/*z*: calcd for $[\mathbf{4}]^{2+}$: 358.2404; found: 358.2335.

Acknowledgement

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[12] Crystal data for **3**•H_2O•2PF_6: $[C_{74}H_{94}O_7N_4][PF_6]_2$; $M_r = 1441.47$; triclinic; space group $P\bar{1}$; $a = 12.1307(2)$, $b = 12.8642(1)$, $c = 27.3374(4)$ Å; $V = 3867.49(9)$ Å^3; $\rho_{calcd} = 1.238$ g cm^{-3}; $\mu(Mo_{K\alpha}) = 0.137$ mm^{-1}; $T = 295(2)$ K; colorless prisms; 13556 independent measured reflections; F^2 refinement; $R_1 = 0.0988$, $wR_2 = 0.2862$.

[13] The association constant, K_a, for the complexation of BPX26C6 to 4-methylpyridinium hexafluorophosphate in CD_3NO_2 was determined to be (17 ± 5) M^{-1} from the results of an NMR spectroscopy dilution experiment. Previously, we reported a K_a value of (130 ± 15) M^{-1} for the complexation between BPX26C6 and 2,2′-bipyridinium bis(hexafluorophosphate) in the same solvent; see: N.-C. Chen, P.-Y. Huang, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Chem. Commun.* **2007**, 4122–4124.

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