Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 49 (2008) 1665–1669

Tetrahedron Letters

Bis-*p*-xylyl[26]crown-6/pyridinium ion recognition: one-pot synthesis of molecular shuttles

Yi-Lin Huang [a], Chi-Feng Lin [a], Pin-Nan Cheng [a], Chien-Chen Lai [b], Yi-Hung Liu [a], Shie-Ming Peng [a], Sheng-Hsien Chiu [a,*]

[a] *Department of Chemistry, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei 10617, Taiwan, ROC*
[b] *Institute of Molecular Biology, National Chung Hsing University and Department of Medical Genetics, China Medical University Hospital, Taichung, Taiwan, ROC*

Received 14 November 2007; revised 28 December 2007; accepted 2 January 2008
Available online 9 January 2008

Abstract

Simple one-pot syntheses allow the preparation of [2]rotaxane-based degenerate molecular shuttles featuring the recognition of pyridinium ions by BPX26C6 macrocycles. Because of the weak interactions between the BPX26C6 and pyridinium units in the [2]rotaxanes in CD_3COCD_3, the rates of shuttling of the BPX26C6 moieties between the pyridinium stations are rapid, relative to those of DB24C8-based shuttles, on the NMR spectroscopic time scale at ambient temperature.

Keywords: Crown ether; Molecular shuttle; Pyridinium ion; Rotaxane

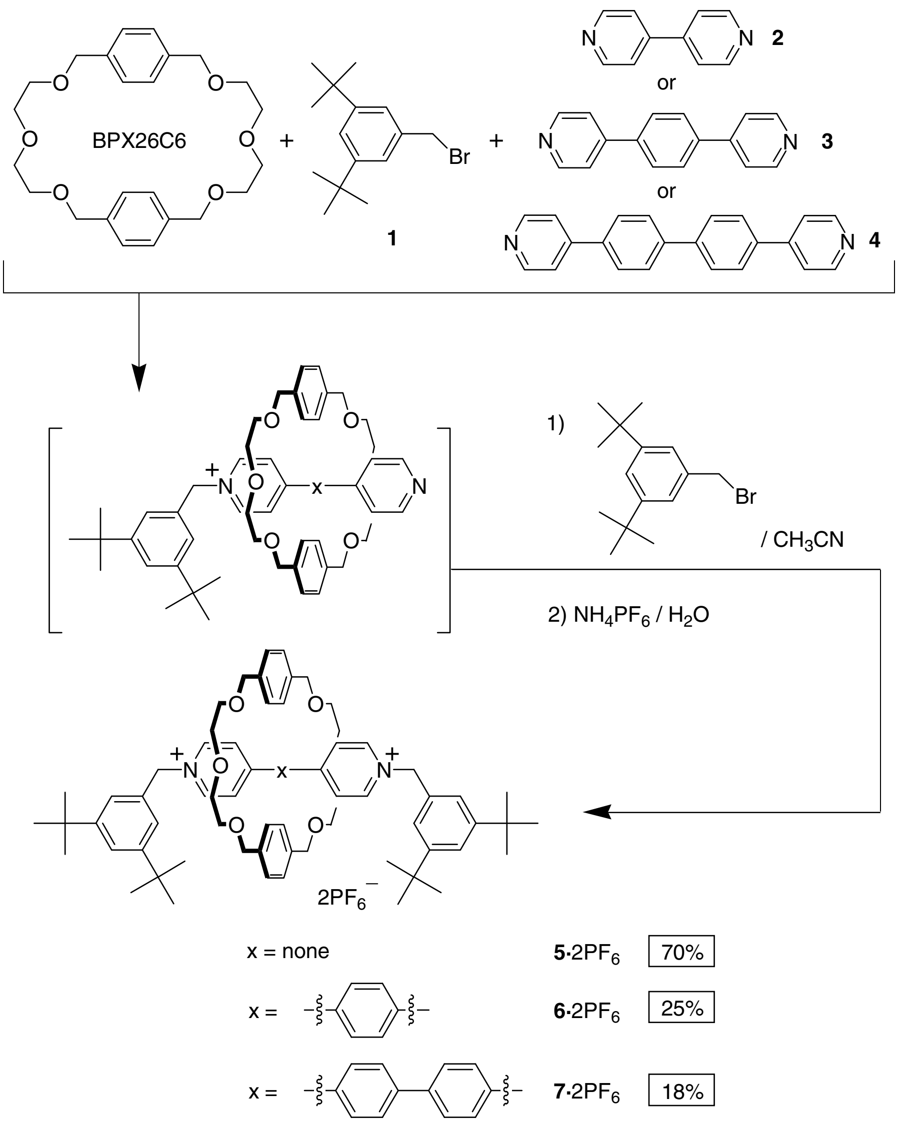
The synthesis of functional interlocked molecules is an attractive endeavor because these machine-like molecules[1] have applicability in mesoscale molecular electronic devices.[2] To understand the dynamic behavior of these molecular machines in solution, degenerate molecular shuttles,[3] in which a macrocyclic unit oscillates between identical recognition sites, are commonly used as probe substrates because rate data can be obtained readily using dynamic ^{1}H NMR spectroscopy.[4] In some instances, the placing of two identical recognition sites in the thread-like component involves a more lengthy synthetic process:[5] for example, if one of the recognition sites must be protected to prevent the formation of a fully occupied rotaxane.[6] Bipyridinium ions have served as recognition sites in many host molecules;[7] we suspected, however, that if a macrocycle were capable of recognizing monopyridinium ions,[8] then the reaction between a symmetrical bipyridine and two alkyl halides would result in the formation of a [2]rotaxane featuring two identical recognition sites for shuttling of the macrocycle. Previously, we reported that bis-*p*-xylyl[26]crown-6 (BPX26C6) is capable of forming complexes with pyridinium ions.[9] We took advantage of this property to perform unique one-pot syntheses of molecular rotaxanes from three neutral starting compounds (i.e., 4,4′-bipyridine, BPX26C6, and an aryl bromide). In this process, the initial alkylation of one of the pyridyl moieties in situ generated a cationic pyridinium recognition site, which then threaded through the crown ether; subsequent alkylation of the second pyridyl unit interlocked the two components (Scheme 1). Herein, we report that this one-pot synthetic approach is also an efficient method for preparing degenerate molecular shuttles, in which the BPX26C6 macrocyclic units shuttle rapidly between two distinct pyridinium ion moieties on the thread components at room temperature in CD_3COCD_3.

Previously, we reported the syntheses of [2]rotaxanes **5**·2PF_6 and **6**·2PF_6 through the one-pot reactions of BPX26C6, 3,5-di-*tert*-butylbenzyl bromide **1**, and bipyridine derivatives **2** and **3**, respectively, in CH_3CN (Scheme

---

[*] Corresponding author. Tel.: +886 2 33661675; fax: +886 2 33661677.
E-mail address: shchiu@ntu.edu.tw (S.-H. Chiu).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.020



Scheme 1. One-pot syntheses of three [2]rotaxanes.

1).[9] Because the recognition of BPX26C6 requires the presence of only one pyridinium ion, it seemed reasonable to us to expect that the interlocked BPX26C6 macrocycle might shuttle back and forth between the two pyridinium cationic stations on the thread component—thus, making [2]rotaxanes **5**·2PF$_6$ and **6**·2PF$_6$ possible degenerate molecular shuttles (Fig. 1). Because of the weak interactions between the BPX26C6 and pyridinium moieties and the short distance between the two stations, we found that the shuttling of the macrocycle in CD$_3$COCD$_3$ was fast on the time scale of ^{1}H NMR spectroscopy at 400 MHz at temperatures as low as 183 K; that is, we observed broadening of only one set of signals of the dumbbell-shaped component in the low-temperature ^{1}H NMR spectrum of rotaxane **6**·2PF$_6$ and sharp signals for rotaxane **5**·2PF$_6$, suggesting that the shuttling of the interlocked BPX26C6 units in these rotaxanes occurred with low energy barriers.

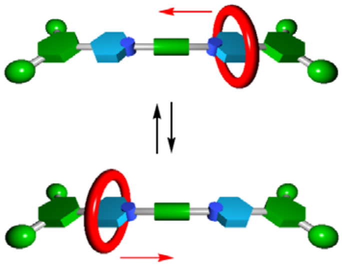


Fig. 1. Cartoon representation of transverse shuttling in a degenerate molecular shuttle.

We suspected that increasing the distance between the two pyridinium stations might increase the amount of time required for the interlocked BPX26C6 moiety to traverse between the two pyridinium stations and, thus, slow the shuttling process. To examine the shuttling of a BPX26C6 macrocycle along an elongated spacer unit containing two *p*-phenylene rings between the two pyridinium centers, we prepared [2]rotaxane **7**·2PF$_6$ in 18% yield, after ion exchange (NH$_4$PF$_6$/H$_2$O) and column chromatography,

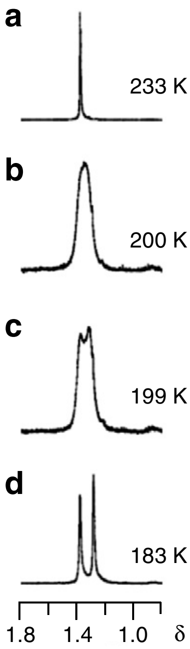
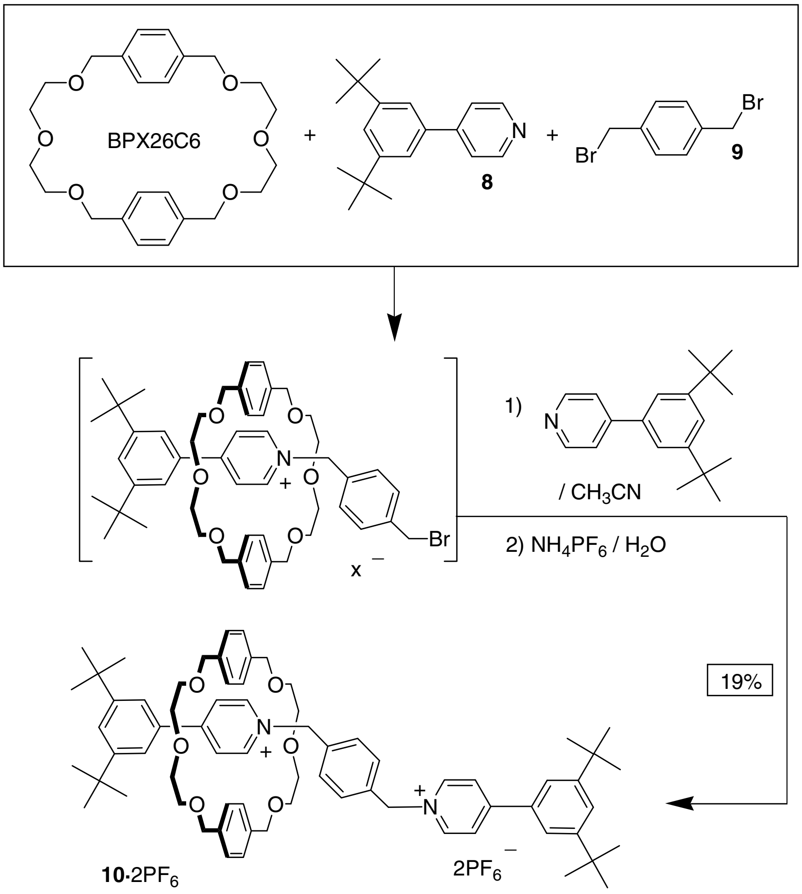


Fig. 2. Partial variable-temperature ^{1}H NMR spectra (400 MHz, CD_3COCD_3) of the molecular shuttle $\mathbf{7}\cdot 2PF_6$ at (a) 233, (b) 200, (c) 199, and (d) 183 K.

from the reaction between BPX26C6, 3,5-di-*tert*-butylbenzyl bromide, and bipyridine **4** in CH_3CN.[10] The partial ^{1}H NMR spectrum of $\mathbf{7}\cdot 2PF_6$ in CD_3COCD_3 at ambient temperature exhibited only one set of signals for the dumbbell, suggesting that the interlocked BPX26C6 macrocycle shuttled rapidly between the two pyridinium centers on the ^{1}H NMR spectroscopic time scale under these conditions. When we cooled the solution to 183 K, however, we observed (Fig. 2) the two distinct halves of the dumbbell-shaped component of $\mathbf{7}^{2+}$, as indicated by the presence of two peaks at δ 1.27 and 1.37 for the two sets of terminal *tert*-butyl groups, suggesting that the migration of the BPX26C6 moiety between the two pyridinium centers was slow on the ^{1}H NMR time scale. The two *tert*-butyl signals coalesced (Fig. 2b) at 200 K with a limiting frequency difference ($\Delta\nu$) of 40 Hz, corresponding to a rate constant (k_c) of 89 s^{-1} for the process of the macrocycle shuttling between the pyridinium centers. From the Eyring equation, we calculated a free energy of activation of 9.8 kcal mol^{-1} for the shuttling process at the coalescence temperature ($T_c = 200$ K).[11]

To increase the synthetic flexibility of this one-pot synthesis of molecular shuttles, we reversed the position of the reacting units of the dumbbell-shaped component, that



Scheme 2. One-pot synthesis of rotaxane $\mathbf{10}\cdot 2PF_6$.

is, rather than reacting one central bipyridine unit with two bulky aryl bromide stoppers, we investigated the reaction of two bulky pyridine stoppers with one central aryl dibromide. Because pyridinium recognition sites would be generated in situ using this approach, we expected the corresponding semirotaxane and [2]rotaxane to be produced in this one-pot reaction. Gratifyingly, the reaction of BPX26C6, 4-(3,5-di-*tert*-butylphenyl)pyridine (**8**), and dibromo-*p*-xylene (**9**) in CH_3CN provided the corresponding [2]rotaxane **10**$\cdot$2PF$_6$ in 19% yield after anion exchange (NH_4PF_6/H_2O) and column chromatography (Scheme 2).[12]

Following vapor diffusion of isopropyl ether into a CH_3CN solution of **10**$\cdot$2PF$_6$, we obtained single crystals that were suitable for X-ray crystallographic analysis. The solid-state structure of **10**$\cdot$2PF$_6$[13] (Fig. 3) reveals the interlocked nature of the [2]rotaxane, with the BPX26C6 macrocyclic unit encircling only one of the pyridinium stations, suggesting that this [2]rotaxane would behave as a degenerate molecular shuttle in solution. Similar to the behavior of the molecular shuttle **7**$\cdot$2PF$_6$, the partial ^{1}H NMR spectrum (Fig. 4) of **10**$\cdot$2PF$_6$ in CD_3COCD_3 at ambient temperature displays only one set of signals for the dumbbell component, suggesting that the BPX26C6 moiety also shuttles rapidly between the two pyridinium centers under these conditions. The signal of the two sets of *tert*-butyl groups splits into two singlets (Fig. 4b) at 183 K; the limiting frequency difference (Δv) of 51.6 Hz suggests a value of k_c of 115 s^{-1} and a free energy of activation of 9.8 kcal mol^{-1} for the process of the macrocycle shuttling between the pyridinium centers at the coalescence temperature ($T_c = 203$ K). The similar dynamic data for shuttling despite the shorter distance between the two pyridinium N atoms in the molecular shuttle **10**$\cdot$2PF$_6$, relative to those in **7**$\cdot$2PF$_6$, suggest that the degree of flexibility of the *p*-xylene spacer plays a role in increasing the energy barrier for the shuttling process.

We have demonstrated that simple one-pot syntheses allow the preparation of [2]rotaxane-based degenerate molecular shuttles featuring the recognition of pyridinium ions by BPX26C6 macrocycles. Because of the weak interactions between the BPX26C6 and pyridinium units in [2]rotaxanes in CD_3COCD_3, the rates of shuttling of the BPX26C6 moieties between the pyridinium stations are rapid, relative to those of DB24C8-based shuttles,[14] on the NMR spectroscopic time scale at ambient temperature. Increasing the distance between the two pyridinium N atoms and modifying the flexibility of their spacer units are the two feasible methods for increasing the energy barrier for the shuttling process.

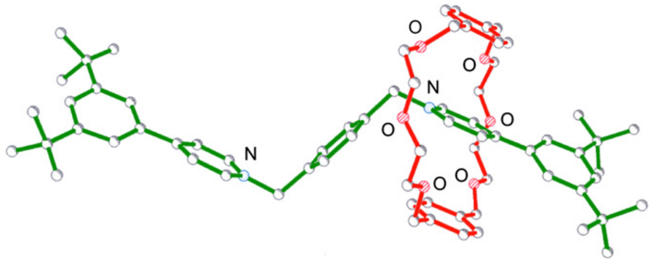


Fig. 3. Ball-and-stick representation of the solid-state structure of [2]rotaxane **10**$^{2+}$.

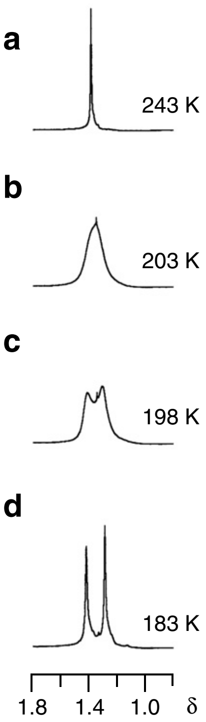


Fig. 4. Partial variable-temperature ^{1}H NMR spectra (400 MHz, CD_3COCD_3) of the molecular shuttle **10**$\cdot$2PF$_6$ at (a) 243, (b) 203, (c) 198, and (d) 183 K.

Acknowledgment

We thank the National Science Council of Taiwan for financial support (NSC-95-2113-M-002-016-MY3).

References and notes

1. (a) Collin, J.-P.; Dietrich-Buchecker, C.; Gaviña, P.; Jiménez-Molero, M. C.; Sauvage, J.-P. *Acc. Chem. Res.* **2001**, *34*, 477; (b) Leigh, D. A.; Wong, J. K. Y.; Dehez, F.; Zerbetto, F. *Nature* **2003**, *424*, 174; (c) Badjić, J. D.; Balzani, V.; Credi, A.; Silvi, S.; Stoddart, J. F. *Science* **2004**, *303*, 1845; (d) Champin, B.; Mobian, P.; Sauvage, J.-P. *Chem. Soc. Rev.* **2007**, *36*, 358; (e) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72; (f) Bunker, B. C.; Huber, D. L.; Kushmerick, J. G.; Dunbar, T.; Kelly, M.; Matzke, C.; Cao, J.; Jeppesen, J. O.; Perkins, J.; Flood, A. H.; Stoddart, J. F. *Langmuir* **2007**, *23*, 31.
2. (a) *Molecular Electronics: Science and Technology*; Aviram, A., Ratner, M., Eds.; New York Academy of Sciences: New York, 1998; (b) Collier, C. P.; Mattersteig, G.; Wong, E. W.; Luo, Y.; Beverly, K.; Sampaio, J.; Raymo, F. M.; Stoddart, J. F.; Heath, J. R. *Science* **2000**, *289*, 1172; (c) Yu, H.; Luo, Y.; Beverly, K.; Stoddart, J. F.; Tseng, H.-R.; Heath, J. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 5706; (d) Saha, S.; Leung, K. C.-F.; Nguyen, T. D.; Stoddart, J. F.; Zink, J. I. *Adv. Funct. Mater.* **2007**, *17*, 685; (e) Green, J. E.; Choi, J. W.;

Boukai, A.; Bunimovich, Y.; Johnston-Halperin, E.; DeIonno, E.; Luo, Y.; Sheriff, B. A.; Xu, K.; Shin, Y. S.; Tseng, H.-R.; Stoddart, J. F.; Heath, J. Ru. *Nature* **2007**, *445*, 414.

3. (a) Anelli, P.-L.; Spencer, N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 5131; (b) Anelli, P.-L.; Asakawa, M.; Ashton, P. R.; Bissell, R. A.; Clavier, G.; Gorski, R.; Kaifer, A. E.; Langford, S. J.; Mattersteig, G.; Menzer, S.; Philp, D.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Tolley, M. S.; Williams, D. J. *Chem. Eur. J.* **1997**, *3*, 1113; (c) Bermudez, V.; Capron, N.; Gase, T.; Gatti, F. G.; Kajzar, F.; Leigh, D. A.; Zerbetto, F.; Zhang, S. *Nature* **2000**, *406*, 608; (d) Loeb, S. J.; Wisner, J. A. *Chem. Commun.* **2000**, 1939; (e) Leigh, D. A.; Troisi, A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 350; (f) Chiu, S.-H.; Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **2002**, *22*, 5170; (g) Aprahamian, I.; Miljanic, O. S.; Dichtel, W. R.; Isoda, K.; Yasuda, T.; Kato, T.; Stoddart, J. F. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1856.
4. The dynamic data were generally estimated using the coalescence method described in Sutherland, I. O. *Annu. Rep. NMR Spectrosc.* **1971**, *4*, 71.
5. (a) Ashton, P. R.; Philp, D.; Spencer, N.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1124; (b) Asakawa, M.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, M.; Gandolfi, M. T.; Kocian, O.; Prodi, L.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1997**, *119*, 302; (c) Belohradsky, M.; Elizarov, A. M.; Stoddart, J. F. *Coll. Czech. Chem. Commun.* **2002**, *67*, 1719; (d) Vignon, S. A.; Jarrosson, T.; Iijima, T.; Tseng, H.-R.; Sanders, J. K. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 9884.
6. Cao, J.; Fyfe, M. C. T.; Stoddart, J. F.; Cousins, G. R. L.; Glink, P. T. *J. Org. Chem.* **2000**, *65*, 1937.
7. (a) Allwood, B. L.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1058; (b) Schalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568; (c) Kim, H.-J.; Jeon, W. S.; Ko, Y. H.; Kim, K. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 10; (d) Huang, F.; Fronczek, F. R.; Gibson, H. W. *J. Am. Chem. Soc.* **2003**, *125*, 9272; (e) Lukyanenk, N. G.; Kirichenko, T. I.; Lyapunov, A. Y.; Mazepa, A. V.; Simonov, Y. A.; Fonari, M. S.; Botoshansky, M. M. *Chem. Eur. J.* **2005**, *11*, 262; (f) Huang, F.; Switek, K. A.; Zakharov, L. N.; Fronczek, F. R.; Slebodnick, C.; Lam, M.; Golen, J. A.; Bryant, W. S.; Mason, P. E.; Rheingold, A. L.; Ashraf-Khorassani, M.; Gibson, H. W. *J. Org. Chem.* **2005**, *70*, 3231; (g) Huang, F.; Zakharov, L. N.; Rheingold, A. L.; Ashraf-Khorassani, M.; Gibson, H. W. *J. Org. Chem.* **2005**, *70*, 809; (h) Wang, W.; Kaifer, A. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 7042; (i) Cheng, P.-N.; Huang, P.-Y.; Li, W.-S.; Ueng, S.-H.; Hung, W.-C.; Liu, Y.-H.; Lai, C.-C.; Peng, S.-M.; Chao, I.; Chiu, S.-H. *J. Org. Chem.* **2006**, *71*, 2373.
8. For the recognition of (mono)pyridinium ions using anionic templates, see: (a) Curiel, D.; Beer, P. D.; Paul, R. L.; Cowley, A.; Sambrook, M. R.; Szemes, F. *Chem. Commun.* **2004**, 1162; (b) Sambrook, M. R.; Beer, P. D.; Wisner, J. A.; Paul, R. L.; Cowley, A. R. *J. Am. Chem. Soc.* **2004**, *126*, 15364; For the recognition of (mono)pyridinium ions by crown ether or cryptand hosts, see: (c) Huang, F.; Slebodnick, C.; Ratliff, A.; Gibson, H. W. *Tetrahedron Lett.* **2005**, *46*, 6019; (d) Huang, F.; Slebodnick, C.; Rheingold, A. L.; Switek, K. A.; Gibson, H. W. *Tetrahedron* **2005**, *61*, 10242; (e) Huang, F.; Slebodnick, C.; Mahanb, E. J.; Gibson, H. W. *Tetrahedron* **2007**, *63*, 2875.
9. Cheng, P.-N.; Lin, C.-F.; Liu, Y.-H.; Lai, C.-C.; Peng, S.-M.; Chiu, S.-H. *Org. Lett.* **2006**, *8*, 435.
10. *Characterization data*: **7**·2PF$_6$. Mp 280–281 °C; ^{1}H NMR (400 MHz, CD$_3$CN): $\delta = 1.38$ (s, 36H), 3.67–3.87 (m, 16H), 4.12 (s, 8H), 5.40 (s, 4H), 6.45 (s, 8H), 7.45 (d, $J = 1$ Hz, 4H), 7.62 (t, $J = 1$ Hz, 2H), 7.88–8.06 (m, 12H), 8.48 (d, $J = 7$ Hz, 4H); ^{13}C NMR (100 MHz, CD$_3$CN): $\delta = 31.5$, 35.6, 64.7, 70.7, 71.2, 73.4, 124.1, 124.5, 125.7, 128.0, 128.2, 129.1, 132.6, 133.7, 136.8, 142.2, 143.5, 152.3, 153.5 ppm; HR-MS (FAB): m/z calcd for $C_{76}H_{94}F_6N_2O_6P$: 1275.6753 [**7**·PF$_6$]$^+$, found m/z 1275.6588.
11. The shuttling rate constant (k_c) at the coalescence temperature (T_c) was estimated by employing the expression $k_c = \pi(\Delta v)/(2)^{1/2}$, where Δv is the chemical shift difference between the two coalescing signals in the absence of exchange. The relationship $\Delta G^{\ddagger}_c = -RT_c \ln(k_c h/k_B T_c)$, where R, h, and k_B correspond, respectively, to the gas, Planck, and Boltzmann constants, was used to obtain values for the free energy of activation for shuttling ($\Delta G^{\ddagger}_c$) at T_c.
12. *Characterization data*: **10**·2PF$_6$. Mp 217–218 °C; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 1.40$ (s, 36H), 3.65–3.79 (m, 16H), 4.13 (s, 8H), 5.18 (br, 4H), 6.50 (s, 8H), 7.47 (s, 4H), 7.59–7.70 (m, 6H), 7.84 (d, $J = 7$ Hz, 4H), 8.48 (br, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 31.7$, 35.5, 63.0, 70.3, 71.2, 73.4, 121.9, 125.1, 126.0, 128.0, 130.6, 132.8, 133.9, 136.2, 143.3, 151.9 ppm (one carbon is missing, possibly because of signal overlap); HR-MS (FAB): m/z calcd for $C_{70}H_{90}F_6N_2O_6P$: 1199.6440 [**10**·PF$_6$]$^+$, found m/z 1199.6420.
13. *Crystal data for* **10**·2PF$_6$: [$C_{70}H_{90}N_2O_6$·MeCN][PF$_6$]$_2$, $M_r = 1386.43$, triclinic, space group $p\bar{1}$, $a = 11.8586$ (2), $b = 25.5735$ (4), $c = 25.6752$ (4) Å, $V = 7651.0$ (2) Å^3, $\rho_{\text{calcd}} = 1.204\ \text{g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 0.135\ \text{mm}^{-1}$, $T = 295(2)$ K, colorless needle, 11,483 independent measured reflections, F^2 refinement, $R_1 = 0.1266$, $wR_2 = 0.3147$.
14. In comparison, the migration of interlocked dibenzo[24]crown-8 (DB24C8) macrocyclic units between two xylene-spacer-linked NH$_2^+$ centers is a much slower process (Ref. 6), even in polar solvents such as CD$_3$SOCD$_3$ ($\Delta G^{\ddagger} = 21.3\ \text{kcal mol}^{-1}$; $T_c = 424$ K), that is, with similar spacer units and at ambient temperature, the rate of shuttling of interlocked DB24C8 units between two NH$_2^+$ centers in CD$_3$SOCD$_3$ is slower than that of BPX26C6 units between two pyridinium stations in CD$_3$COCD$_3$, presumably because of the smaller size of the cavity of the DB24C8 moiety and also possibly because of the stronger interactions between the interlocked DB24C8 and NH$_2^+$ moieties (even in a solvent that is unfavorable for hydrogen bonding, CD$_3$SOCD$_3$) than those between the pyridinium stations and BPX26C6 units (in CD$_3$COCD$_3$).