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A Light-Gated STOP−GO Molecular Shuttle

Ali Coskun, Douglas C. Friedman, Hao Li, Kaushik Patel, Hussam A. Khatib, and J. Fraser Stoddart*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113

Received November 25, 2008; E-mail: stoddart@northwestern.edu

In the 18 years since the first molecular shuttle of a donor−acceptor nature was described in the literature,[1] degenerate [2]rotaxanes[2] with two identical binding sites and their bistable variants[3] have attracted a considerable amount of attention[4] as forerunners to molecular switches[5] and as prototypes of artificial molecular machines.[6] Degenerate [2]rotaxanes, with their two identical binding sites, generally exhibit equilibrium dynamics with free energies of activation ($\Delta G^{\ddagger}$) for the shuttling process starting[2c] as low as 10 kcal·mol^{-1}. This $\Delta G^{\ddagger}$ value can be raised quite dramatically by inserting "speed bumps" in the form of steric[7] and/or electrostatic[8] barriers into the linkers between the two identical binding sites. Herein, we show how light can be used, in conjunction with thermal energy, to raise and lower the free energy barrier at will and, in so doing, impart STOP and GO instructions upon the operation of a molecular shuttle.

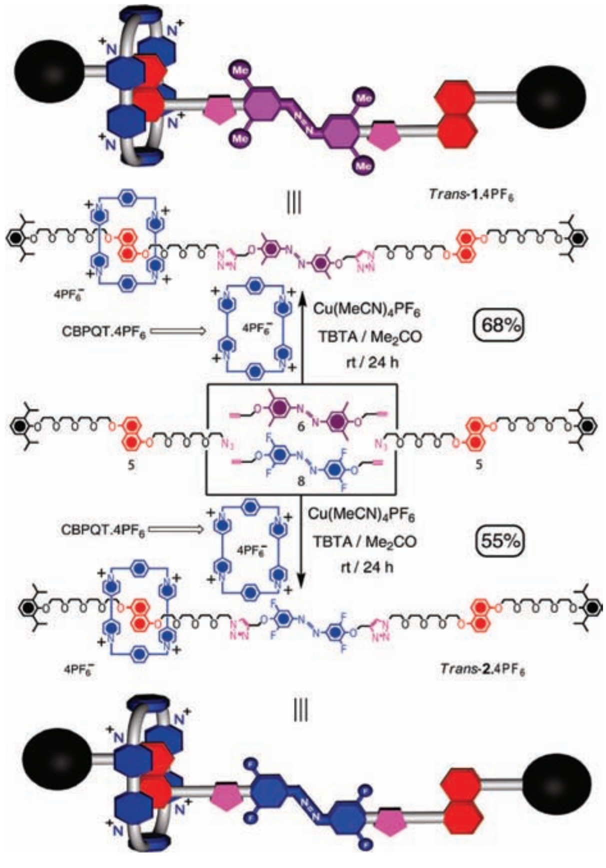
In approaching the design of a light-gated STOP−GO molecular shuttle, we recalled our introduction[9] of 4,4′-azobiphenyloxy (ABP) units into bistable catenanes and degenerate rotaxanes of the donor−acceptor kind more than a decade ago. In the late 90s, we were focusing our attention on the potential of the ABP unit to act as a binding site for a CBPQT^{4+} ring.[10] In our more recent research targeted toward the exploitation of the ABP unit as a light-operated gate,[11] we decided to introduce (i) four methyl groups on the one hand, and (ii) four fluorine atoms on the other, at the 3,5,3′,5′-positions of the ABP units to curtail binding by the CBPQT^{4+} ring if not sterically in the case of i, then electronically in the case of ii. The first approach led to a gate (ABP-Me$_4$) that remains closed all the time, whereas the second approach affords a gate (ABP-F$_4$) that we can close with UV light and open with visible light. The closed ABP-F$_4$ gate also opens slowly on picking up thermal energy from its surroundings.

The syntheses of the degenerate [2]rotaxanes *trans*-**1**·4PF$_6$ and *trans*-**2**·4PF$_6$ are outlined in Scheme 1 and described in detail in the Supporting Information (SI). The azide **5**, incorporating a 1,5-dioxynaphthalene (DNP) unit in the middle of an oligoether chain, terminated at one end by a 2,6-diisopropylphenyl stopper, and at the other by an azide function, was obtained in high yield in three steps, starting from the known[12] monotosylate of BHEEEEN.[13] The tetramethylazobenzene derivative **6** was produced by reductive coupling of 3,5-dimethyl-4-propargyloxynitrobenzene[14] in 23% yield using LiAlH$_4$ as the reductant. The tetrafluoroazobenzene derivative **8** was prepared from 3,5-difluoro-4-methoxyaniline[15] and 2,6-difluorophenol in three steps. The degenerate [2]rotaxanes *trans*-**1**·4PF$_6$ and *trans*-**2**·4PF$_6$ were isolated in 68 and 55% yields, respectively, following the reaction of **5** with the corresponding azobenzene derivatives **6** and **8** in Me$_2$CO using copper(I)-catalyzed azide-alkyne cycloadditions[16,17] in the presence of CBPQT·4PF$_6$.

The absorption spectra (see Figure S1 in SI) of **6** ($\lambda_{\max} = 345$ and 437 nm) and **8** ($\lambda_{\max} = 340$ and 437 nm for $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ bands, respectively) were recorded[18] in MeCN at room temperature. Irradiation of these two ABP derivatives with UV light ($\lambda = 365$ nm, 7 mW·cm^{-2}) caused efficient photoisomerization[19] to occur, giving the corresponding *cis* isomers of **6** and **8** almost quantitatively. The trans configurations were restored upon irradiation of the cis isomers with visible light.

The photoisomerization of *trans*-**1**·4PF$_6$ and *trans*-**2**·4PF$_6$ followed the same behavioral pathway as **6** and **8**, respectively. For example, irradiation of *trans*-**2**·4PF$_6$ with UV light leads to efficient photoisomerization[19] (Figure S4 in SI) to its cis form; the cis isomer can be isomerized back to the trans form upon irradiation (Figure S5 in SI) with visible light (halogen lamp with a UV filter).

Scheme 1. Synthesis of the Degenerate [2]Rotaxanes *trans*-**1**·4PF$_6$ and *trans*-**2**·4PF$_6$ and Their Graphical Representations



^{1}H NMR spectroscopic investigations in CD$_3$CN reveal that, in both *trans*-**1**·4PF$_6$ and *trans*-**2**·4PF$_6$, the CBPQT^{4+} ring prefers to reside on the DNP units[20] rather than on the ABP-Me$_4$ or ABP-F$_4$ units. In the case of *trans*-**1**·4PF$_6$, the ^{1}H NMR spectra (see Figure S10 in SI) recorded in CD$_3$CN, within the temperature range 238−350 K, show that the CBPQT^{4+} ring prefers to reside exclusively on one of the two degenerate DNP units, that is, shuttling is not happening on the ^{1}H NMR time-scale even at 350 K. The implication is that the free energy of activation for shuttling

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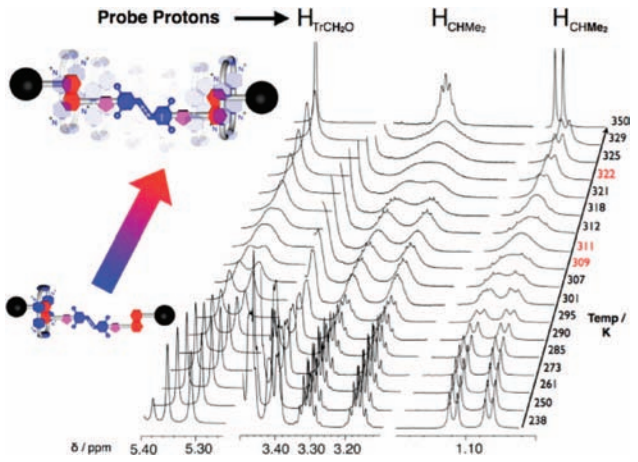

Figure 1. Partial 600 MHz ^1H NMR spectra recorded in CD_3CN at different temperatures displaying in red the coalescence of the signals for three sets of probe protons in *trans*-$\mathbf{2}\cdot4PF_6$.

in *trans*-$\mathbf{1}^{4+}$ is in excess of 30 kcal·mol^{-1}. By contrast, the ^1H NMR spectra of *trans*-$\mathbf{2}\cdot4PF_6$ recorded in CD_3CN and observed in the range 238−350 K display temperature dependences for the resonances associated with the $CH\mathbf{Me}_2$, $\mathbf{CH}Me_2$, and $TrCH_2O$ (Tr = triazole) protons (Figure 1) which undergo, in turn, coalescences at temperatures (T_c) of 309, 322, and 311 K, respectively. The rate constants (k_c) and the corresponding $\Delta G^{\ddagger}_c$ values calculated[21] at these temperatures are listed in Table 1. At 15.6 kcal·mol^{-1}, the free energy of activation ($\Delta G^{\ddagger}_c$) for the shuttling process is in the same league as those $\Delta G^{\ddagger}_c$ values observed previously[22] for other degenerate molecular shuttles where the links between the two identical recognition units are, for example, polyether chains or terphenyl linkers. When the ^1H NMR spectrum of *trans*-$\mathbf{2}\cdot4PF_6$ was recorded (Figure 2a) at 309 K—the T_c of the $H_{CH\mathbf{Me}2}$ probe protons—we observed dramatic changes across the whole spectrum upon irradiation with UV light for 14 min. New signals appeared for *cis*-$\mathbf{2}^{4+}$ that were well resolved sets of resonances, indicating that the ABP-F_4 gate in its cis configuration stops the shuttling of the $CBPQT^{4+}$ ring.

Table 1. Kinetic and Thermodynamic Parameters Obtained from Temperature-Dependent ^1H NMR Spectra Recorded on the Degenerate [2]rotaxane $\mathbf{2}\cdot4PF_6$ in CD_3CN

proton	δ (ppm)	Δυ (Hz)	k_c (s^{-1})	T_c (K)	$\Delta G^{\ddagger}$ (kcal·mol^{-1})^c
$H_{\mathbf{CH}Me2}$	3.35	86	191	322^a	15.6
$H_{CH\mathbf{Me2}}$	1.18	31	69	309^b	15.5
$H_{Tr\mathbf{CH2}O}$	5.36	25	56	311^b	15.7

^{a} Calibrated using neat ethylene glycol. ^{b} Calibrated using neat MeOH. ^{c} Value ±0.1.

Separate singlets at $\delta = 5.16$ and 5.22 for the $Tr\mathbf{CH}_2O$ protons and separate doublets at $\delta = 1.13$ and 1.17 for the $CH\mathbf{Me}_2$ protons indicate (Figure 2b) in *cis*-$\mathbf{2}^{4+}$ that the $CBPQT^{4+}$ ring resides on only one of the two DNP units along the dumbbell component. Irradiation of *cis*-$\mathbf{2}^{4+}$ with a halogen lamp for 20 min effected an 80% reversion to *trans*-$\mathbf{2}^{4+}$ with its characteristically broad resonances commensurate with slow shuttling of the $CBPQT^{4+}$ ring on the ^1H NMR time-scale at 309 K. By alternating UV and visible light (Figure 2b−e) to gate $\mathbf{2}^{4+}$ between its trans and cis isomers, shuttling of the $CBPQT^{4+}$ ring experiences a STOP−GO−STOP−GO sequence. Complete isomerization of *cis*-$\mathbf{2}^{4+}$ back to its trans isomer was also achieved by heating the sample of *cis*-$\mathbf{2}\cdot4PF_6$ at 350 K for 60 min. An alternating process of UV light and heat can also be repeated as shown in Figure 3. Starting (Figure 3a) with *trans*-$\mathbf{2}^{4+}$, the sequence Δ−UV−Δ−UV−Δ is revealed in the ^1H NMR spectra recorded in the sequence a/b/c/d/e.

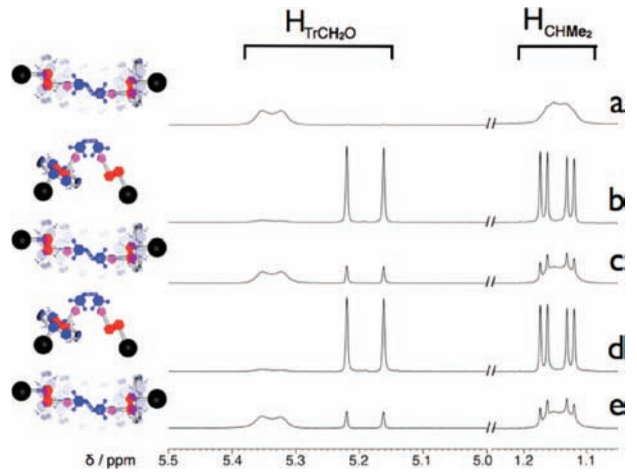

Figure 2. Partial 600 MHz ^1H NMR spectra recorded in CD_3CN of (a) *trans*-$\mathbf{2}\cdot4PF_6$ at 309 K, (b) after 14 min irradiation with UV light to yield mainly *cis*-$\mathbf{2}\cdot4PF_6$, (c) after 20 min irradiation with visible light to restore *trans*-$\mathbf{2}\cdot4PF_6$, (d) after 14 min irradiation with UV light and to yield mainly the *cis*-$\mathbf{2}\cdot4PF_6$, (e) after 20 min irradiation with visible light to restore *trans*-$\mathbf{2}\cdot4PF_6$.

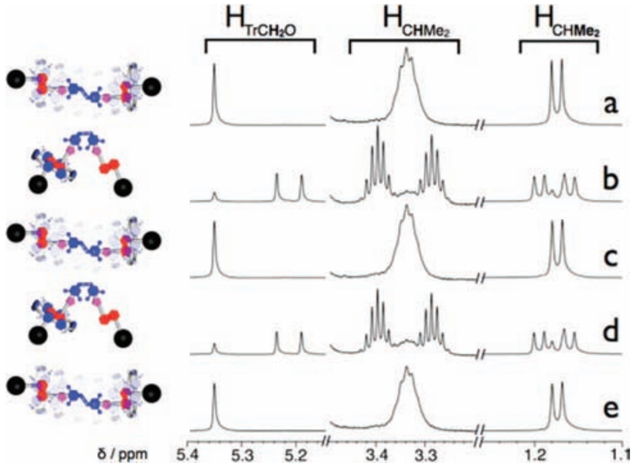

Figure 3. Partial 600 MHz ^1H NMR spectra recorded in CD_3CN of (a) *trans*-$\mathbf{2}\cdot4PF_6$ at 350 K, (b) after 14 min irradiation with UV light producing *cis*-$\mathbf{2}\cdot4PF_6$, (c) after 60 min at 350 K restoring *trans*-$\mathbf{2}\cdot4PF_6$, (d) after 14 min irradiation with UV light producing *cis*-$\mathbf{2}\cdot4PF_6$ and, (e) after 60 min at 350 K restoring *trans*-$\mathbf{2}\cdot4PF_6$.

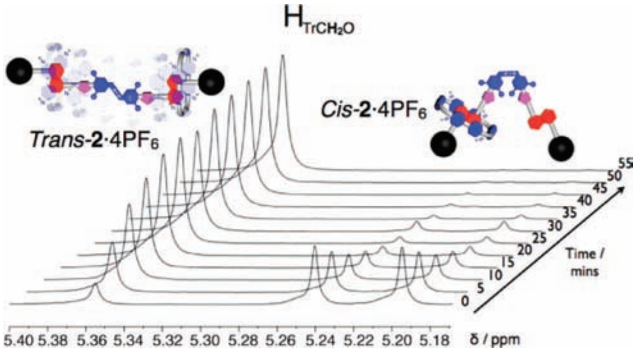

Figure 4. Partial 600 MHz ^1H NMR spectra recorded in CD_3CN of $\mathbf{2}\cdot4PF_6$ showing the thermal relaxation of *cis*-$\mathbf{2}\cdot4PF_6$ to *trans*-$\mathbf{2}\cdot4PF_6$.

The rate of the thermal gate-opening process was determined at 350 K by ^1H NMR spectroscopy. Irradiation of *trans*-$\mathbf{2}\cdot4PF_6$ with

UV light for 14 min resulted in a >90% conversion of trans isomer to *cis*-**2**·4PF$_6$. The cis isomer was then allowed to relax thermally at 350 K while spectra were recorded (Figure 4) at 5 min intervals for 55 min. The rate of relaxation process was deduced from integration of the singlets for the TrC**H**$_2$O protons in the cis and trans isomers. The first order rate constant $k_{c\rightarrow t}$ was found to be 0.124 s^{-1} at 350 K, giving rise to a $\Delta G^{\ddagger}$ value of ca. 22 kcal·mol^{-1}—a free energy barrier which is consistent with the cis-to-trans thermal relaxation of electron-deficient azobenzene derivatives,[19] including the corresponding dumbbell where $k_{c\rightarrow t}$ was found to be 0.098 s^{-1} at 350 K, giving rise to a $\Delta G^{\ddagger}$ value of ca. 20 kcal·mol^{-1}.

Now that we have established how to gate degenerate donor−acceptor molecular shuttles, we are poised to be able to isolate and identify the metastable and ground-state co-conformations[3,5] of bistable donor−acceptor [2]rotaxanes—the matching of ON/OFF switching with STOP−GO gating is finally on the cards.

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Supporting Information Available: Experimental details and spectral characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Anelli, P.-L.; Spencer, N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 5131–5133.

(2) (a) Murakami, H.; Kawabuchi, A.; Kotoo, K.; Kunitake, M.; Nakashima, N. *J. Am. Chem. Soc.* **1997**, *119*, 7605–7606. (b) Cao, J. G.; Fyfe, M. C. T.; Stoddart, J. F.; Cousins, G. R. L.; Glink, P. T. *J. Org. Chem.* **2000**, *65*, 1937–1946. (c) Kawaguchi, Y.; Harada, A. *Org. Lett.* **2000**, *2*, 1353–1356. (d) Leigh, D. A.; Troisi, A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 350–353. (e) Collin, J. P.; Dietrich-Buchecker, C.; Gavina, P.; Jimenez-Molero, M. C.; Sauvage, J. P. *Acc. Chem. Res.* **2001**, *34*, 477–487. (f) Kawai, H.; Umehara, T.; Fujiwara, K.; Tsuji, T.; Suzuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4281–4286. (g) Yoon, I.; Miljanić, O. Š.; Benitez, D.; Khan, S. I.; Stoddart, J. F. *Chem. Commun.* **2008**, 4561–4563.

(3) (a) Ashton, P. R.; Bissell, R. A.; Spencer, N.; Stoddart, J. F.; Tolley, M. S. *Synlett* **1992**, 923–926. (b) Bissell, R. A.; Córdova, E.; Kaifer, A. E.; Stoddart, J. F. *Nature* **1994**, *369*, 133–137. (c) Jeppesen, J. O.; Nielsen, K. A.; Perkins, J.; Vignon, S. A.; Di Fabio, A.; Ballardini, R.; Gandolfi, M. T.; Venturi, M.; Balzani, V.; Becher, J.; Stoddart, J. F. *Chem.—Eur. J.* **2003**, *9*, 2982–3007. (d) Bottari, G.; Leigh, D. A.; Perez, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 13360–13361. (e) Aprahamian, I.; Dichtel, W. R.; Ikeda, T.; Heath, J. R.; Stoddart, J. F. *Org. Lett.* **2007**, *9*, 1287–1290.

(4) Stoddart, J. F.; Colquhoun, H. M. *Tetrahedron* **2008**, *64*, 8231–8263.

(5) 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. R. *Nature* **2007**, *445*, 414–417.

(6) (a) Berna, J.; Leigh, D. A.; Lubomska, M.; Mendoza, S. M.; Perez, E. M.; Rudolf, P.; Teobaldi, G.; Zerbetto, F. *Nat. Mater.* **2005**, *4*, 704–710. (b) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72–191. (c) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines—Concepts and Perspectives for the Nanoworld*; Wiley-VCH: Weinheim, Germany, 2008.

(7) Bělohradský, M.; Elizarov, A. M.; Stoddart, J. F. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1719–1728.

(8) Brough, B.; Northrop, B. H.; Schmidt, J. J.; Tseng, H.-R.; Houk, K. N.; Stoddart, J. F.; Ho, C.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8583–8588.

(9) (a) Asakawa, M.; Ashton, P. R.; Balzani, V.; Brown, C. L.; Credi, A.; Matthews, O. A.; Newton, S. P.; Raymo, F. M.; Shipway, A. N.; Spencer, N.; Quick, A.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem.—Eur. J.* **1999**, *5*, 860–875. (b) Around the same time, ABP units—both para−para and meta−meta disubstituted—were introduced into degenerate donor−acceptor [2]rotaxanes. Attempts to control shuttling by photoisomerization of the ABP units were, however, inconclusive; see: Kauffman, C.; Müller, W. M.; Vögtle, F.; Weinman, S.; Abramson, S.; Fuchs, B. *Synthesis* **1999**, *84*, 9–853. (c) For a much more recent demonstration of the control of the shuttling rate in a degenerate, two-station, hydrogen-bonded [2]rotaxane by reversible photoisomerization of the ring size, see: Hirose, K.; Shiba, Y.; Ishibashi, K.; Doi, Y.; Tobe, Y. *Chem.—Eur. J.* **2008**, *14*, 3427–3433.

(10) (a) CBPQT^{4+} = Cyclobis(paraquat-*p*-phenylene); see: Asakawa, M.; Dehaen, W.; L'abbé, G.; Menzer, S.; Nouwen, J.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 9591–9595. (b) 4,4′-Azobiphenyloxy derivative (ABP) can bind to the CBPQT^{4+} ring in its trans configuration in MeCN (K_a = 469 ± 37 M^{-1}). The [ABP⊂CBPQT]·4PF$_6$ complex dissociates upon irradiation with UV light, showing that CBPQT^{4+} has either low or no affinity towards the *cis*-azobenzene moiety.

(11) For a recent discussion of photoactivated moving parts in both molecules and integrated hybrid systems based on the photoisomerization of azobenzene derivatives, see: (a) Lu, J.; Choi, E.; Tamanoi, F.; Zink, J. I. *Small* **2008**, *4*, 421–428. (b) A fine example of the use of a light-activated α-methyl stilbene "gate" in the functioning of a molecular information ratchet has been described recently; see: Serreli, V.; Lee, C. F.; Kay, E. R.; Leigh, D. A. *Nature* **2007**, *445*, 523–527.

(12) Liu, Y.; Saha, S.; Vignon, S. A.; Flood, A. H.; Stoddart, J. F. *Synthesis* **2005**, 3437–3445.

(13) BHEEEEN = 1,5-bis[2-(2-(2-(2-hydroxy-ethoxy)ethoxy)ethoxy)ethoxy]-naphthalene; see: Ashton, P. R.; Huff, J.; Menzer, S.; Parsons, I. W.; Preece, J. A.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. *Chem.—Eur. J.* **1996**, *2*, 31–44.

(14) Sawada, T.; Yamada, M.; Thiemann, T.; Mataka, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, *16*, 2623–2627.

(15) Niemann, C.; Benson, A. A.; Mead, J. F. *J. Am. Chem. Soc.* **1941**, *63*, 2204–2208.

(16) (a) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613–628. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (c) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

(17) (a) Dichtel, W. R.; Miljanić, O. Š.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10388–10390. (b) Miljanić, O. Š.; Dichtel, W. R.; Aprahamian, I.; Rohde, R. D.; Agnew, H. D.; Heath, J. R.; Stoddart, J. F. *QSAR 2 Comb. Sci.* **2007**, *26*, 1165–1174.

(18) The absorption spectra recorded in MeCN for 4,4′-dimethoxydiazo-benzene, BHEEEEN and CBPQT·4PF$_6$ have λ_{max} values of 355, 295, and 260 nm, respectively. Note that the fluorine substituents on the azobenzene ring system in **8** causes a 15 nm hypsochromic shift, and similar behavior was observed for the methyl substituted derivative **6**.

(19) The addition of substituents to the ABP unit have been shown not only to influence the wavelength at which both the trans→cis and cis→trans isomerizations occur, but also the pathway by which the cis isomer isomerizes back to the trans-isomer. The activation barrier for cis→trans isomerization is usually around 22 kcal·mol^{-1}; see: (a) Talaty, E. R.; Fargo, J. C. *Chem. Commun. (London)* **1967**, 65–66. (b) Lunak, S., Jr.; Nepras, M.; Hrdina, R.; Mustroph, H. *Chem. Phys.* **1994**, *184*, 255–260.

(20) The ^{1}H NMR resonances for the H-2/6, H-3/7, and H-4/8 protons of the encircled DNP units in *trans*-**1**·4PF$_6$ and *trans*-**2**·4PF$_6$ experienced characteristic upfield shifts of -0.7, -1.4, and -5.3 ppm, respectively. For comparison see: Amabilino, D. B.; Anelli, P.-L.; Ashton, P. R.; Brown, G. R.; Córdova, E.; Godínez, L. A.; Hayes, W.; Kaifer, A. E.; Philp, D.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Tolley, M. S.; Williams, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 11142–11170.

(21) The rate constants, k_c, at the coalescence temperatures, T_c, were determined using the approximate expression, $k_c = \pi(\Delta\nu)/(2)^{1/2}$, where $\Delta\nu$ is the limiting chemical shift (in Hz) between the exchanging proton resonances. The Eyring equation, $\Delta G^{\ddagger}_c = -RT \ln(k_c h/k_B T_c)$ was used to calculate $\Delta G^{\ddagger}_c$ values at T_c; see: Sutherland, I. O. *Annu. Rep. NMR Spectrosc.* **1971**, *4*, 71.

(22) Kang, S. S.; Vignon, S. A.; Tseng, H.-R.; Stoddart, J. F. *Chem.—Eur. J.* **2004**, *10*, 2555–2564.

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