JOC *Note*

Catalysis in the Self-Assembly of [2]Rotaxanes and [2]Pseudorotaxanes. Effect of the Length of Polyethereal Side Arms and Terminal Stoppers

Claudio D'Acerno,[†] Giancarlo Doddi,*[,†]
Gianfranco Ercolani,*[,‡] Silvia Franconeri,[†]
Paolo Mencarelli,*[,†] and Alessio Piermattei[†]

Dipartimento di Chimica e CNR-IMC, Università di Roma La Sapienza, P.le Aldo Moro 2, 00185 Roma, Italy, and Dipartimento di Scienze e Tecnologie Chimiche, Università di Roma Tor Vergata, Via della Ricerca Scientifica, 00133 Roma, Italy

giancarlo.doddi@uniroma1.it; ercolani@uniroma2.it; paolo.mencarelli@uniroma1.it

Received October 9, 2003

Abstract: The template effects exerted by compounds **3**, **5**, **6**, and **8** in the ring closure reaction of the trication **1**$^{3+}$ to yield the [2]pseudorotaxanes **15**$^{4+}$ and **17**$^{4+}$ and the [2]-rotaxanes **18**$^{4+}$ and **20**$^{4+}$ have been quantitatively evaluated in acetonitrile at 62 °C by UV/vis spectrophotometry. The rate of ring closure of the trication **1**$^{3+}$ largely increases in the presence of the templates up to a maximum of ca. 200 times in the case of **5** at a concentration of ca. 0.08 M. The results indicate that, in the self-assembly of a rotaxane, the template effect of the guest is lowered by the presence of two large stoppers (triisopropylsilyl) at the end of the linear chains; this effect is more important the shorter the chain and can be mainly ascribed to steric effects. Previously hypothesized entropic effects appear to be of lesser importance.

Introduction

The design and creation of machine-like molecular assemblies has attracted considerable attention in recent years because of potential applications in the field of information processing and technology.[1] Many such assemblies have as a distinctive structural feature one or more macrocycles threaded by a linear component whose unthreading is either fully reversible (pseudorotaxanes) or prevented by the presence of large stoppers at the ends of the chain (rotaxanes). The efficient preparation of these interesting supramolecular structures has enormously benefited from template-directed approaches.[2,3] However, despite the abundance of preparative reports and the general interest in the subject of templated synthesis, the kinetic study of template effects in the formation of rotaxanes lagged behind.

With the aim at evaluating the role played by large stoppers in the linear component, we recently investigated the template effect exerted by guests **4** and **7** in the ring closure reaction of the trication **1**$^{3+}$, which is the acyclic precursor of cyclobis(paraquat-*p*-phenylene) **2**$^{4+}$ (Scheme 1).[4] The results indicated that the two bulky triisopropylsilyl (TIPS) groups at the end of the polyethereal chains, which are of course a prerequisite for obtaining a stable rotaxane, do significantly lower the template ability of guest **7** with respect to guest **4,** which is devoid of terminal stoppers. This finding was rationalized taking into account both a destabilizing steric effect, which is enthalpic in nature, and a more subtle entropic effect due to the different moments of inertia of the side chains in **4** and **7**. However, we were unable to indicate which of the two effects is more important. To establish the relative importance of the two effects, we have changed the length of the side arms by taking into account guests **3** and **6**, and guests **5** and **8**, whose side arms are, respectively, shortened and lengthened by one oxyethylene unit. The study of the template effects of these guests in the cyclization of **1**$^{3+}$ is reported here.

Results and Discussion

The first-order rate constant ($k_0 = 8.3 \times 10^{-7}$ s^{-1}) for the cyclization of the trication **1**$^{3+}$, in the absence of any added template, to yield cyclobis(paraquat-*p*-phenylene) **2**$^{4+}$ was previously obtained by ^{1}H NMR in CD_3CN at 62 °C.[5] First-order rate constants (k_{obs}) in acetonitrile at 62 °C have been obtained in the presence of variable excess amounts of the polyether templates **3**−**8** (up to ~0.08 M) by following the kinetics of formation of either pseudorotaxanes or rotaxanes **15**$^{4+}$−**20**$^{4+}$. These compounds present a charge-transfer band at λ 520 nm,[6] which has been exploited to study the kinetics by UV/vis spectroscopy.

[†] Università di Roma La Sapienza.

[‡] Università di Roma Tor Vergata.

(1) (a) *Acc. Chem. Res.* **2001**, *34*, 409−522 (Molecular Machines Special Issue**)**. (b) *Molecular Machines and Motors*; Sauvage, J.-P., Ed.; Structure And Bonding, Vol. 99; Springer: Berlin, 2001. (c) *Molecular Switches*; Feringa, B. L., Ed.; Wiley-VCH: Weinheim, Germany, 2001. (d) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines—A Journey into the Nano World*; Wiley-VCH: Weinheim, Germany, 2003.

(2) For general reviews on template effects, see: (a) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469−475. (b) Hoss, R.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 375−384. (c) Busch, D. H.; Vance, A. L.; Kolchinski, A. G. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Sauvage, J.-P., Hosseini, M. W., Eds.; Pergamon: Oxford, 1996; Vol. 9, Chapter 1. (d) Gerbeleu, N. V.; Arion, V. B.; Burgess, J. *Template Synthesis of Macrocyclic Compounds*; Wiley-VCH: Weinheim, Germany, 1999. (e) *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2000.

(3) For reviews on template-directed syntheses of rotaxanes, see: (a) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725−2828. (b) Belohradsky, M.; Raymo, F. M.; Stoddart, J. F. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1−43. (c) Amabilino, D. B.; Raymo, F. M.; Stoddart, J. F. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D., MacNicol, D. D., Vögtle, F., Sauvage, J.-P., Hosseini, M. W., Eds.; Pergamon: Oxford, 1996; Vol. 9, Chapter 3. (d) Gibson, H. W. In *Large Ring Molecules*; Semlyen, J. A., Ed.; Wiley: New York, 1996; pp 191−262. (e) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154−1196. (f) *Molecular Catenanes, Rotaxanes and Knots*; Sauvage, J.-P., Dietrich-Buchecker, C. O., Eds.; Wiley-VCH: Weinheim, Germany, 1999. (g) Bruce, J. I.; Sauvage, J.-P. *Adv. Mol. Struct. Res.* **1999**, *5*, 153−187. (h) Blanco, M. J.; Jimenez, M. C.; Chambron, J. C.; Heitz, V.; Linke, M.; Sauvage, J.-P. *Chem. Soc. Rev.* **1999**, *28*, 293−305. (i) Gibson, H. W.; Mahan, E. J. In *Cyclic Polymers*, 2nd ed.; Semlyen, J. A., Ed.; Kluwer: Dordrecht, The Netherlands, 2000; pp 415−560.

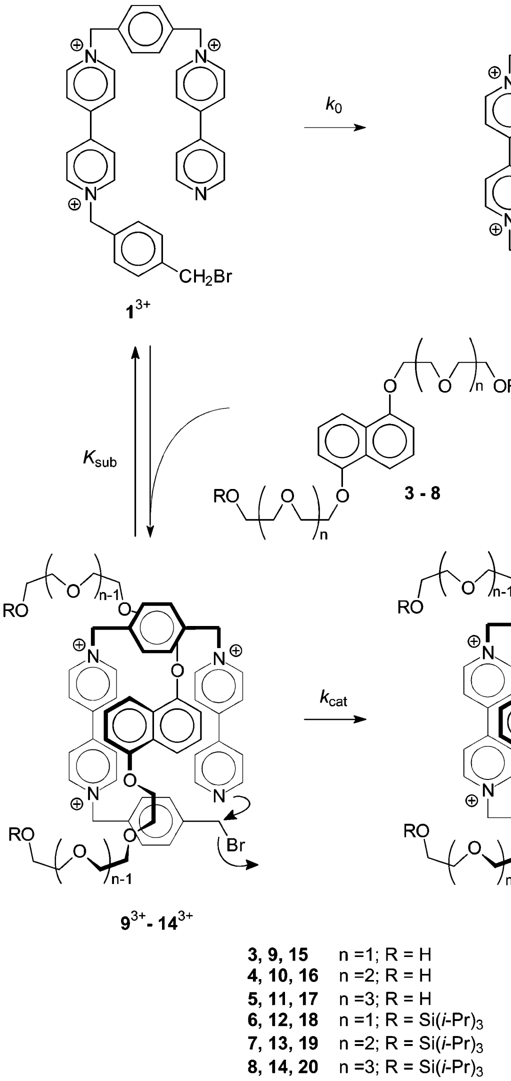
(4) Doddi, G.; Ercolani, G.; Franconeri, S.; Mencarelli, P. *J. Org. Chem.* **2001**, *66*, 4950−4953.

(5) Capobianchi, S.; Doddi, G.; Ercolani, G.; Keyes, J. W.; Mencarelli, P. *J. Org. Chem.* **1997**, *62*, 7015−7017.

(6) Ballardini, R.; Balzani, V.; Gandolfi, M. T.; Prodi, L.; Venturi, M.; Philp, D.; Ricketts, H. G.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1301.

10.1021/jo035483e CCC: $27.50

SCHEME 1



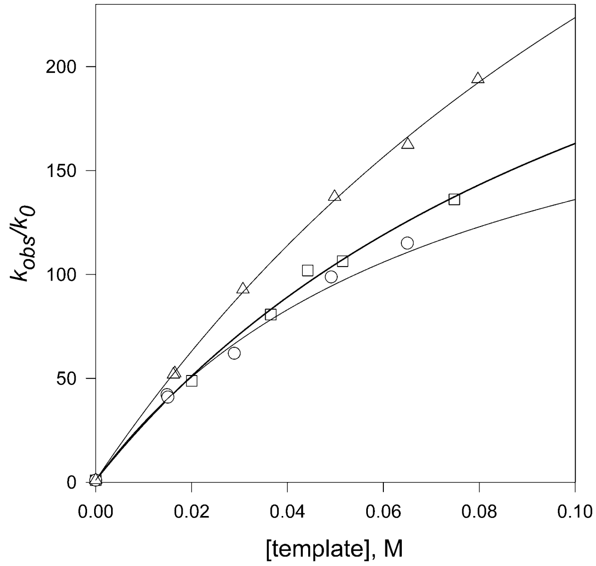


FIGURE 1. Rate enhancement produced by templates **3** (□), **4** (○), and **5** (△) on the ring closure reaction of the trication $\mathbf{1}^{3+}$. The points are experimental, and the curves are calculated (see the text).

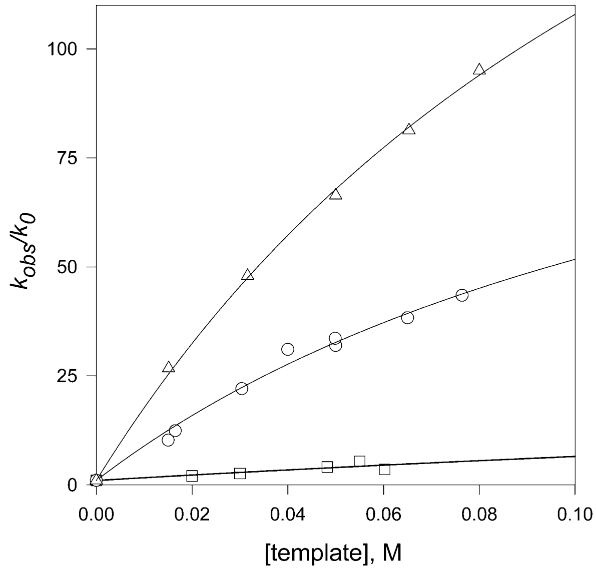


FIGURE 2. Rate enhancement produced by templates **6** (□), **7** (○), and **8** (△) on the ring closure reaction of the trication $\mathbf{1}^{3+}$. The points are experimental, and the curves are calculated (see the text).

To avoid polymerization reactions, the concentration of the substrate $\mathbf{1}^{3+}$ has been kept as low as possible ($\sim 3-5 \times 10^{-4}$ M). The ratios k_{obs}/k_0 for templates **3** and **5** and **6** and **8** are plotted in Figures 1 and 2, respectively, against their concentrations. Such ratios provide a measure of the rate enhancements produced by the presence of the templates. For the sake of comparison, the previously published data relative to templates **4** and **7**[4] are also reported in the corresponding figure.

The data in Figures 1 and 2 show that the ring closure of the trication $\mathbf{1}^{3+}$ is significantly accelerated by the presence of templates **3**−**8** up to a maximum of ca. 200 times in the case of **5** at a concentration of ca. 0.08 M. However, before commenting upon these rate increases, it is useful to go deep into the analysis of the kinetic data.

Consider the kinetic scheme illustrated in Scheme 1. Assuming that the equilibrium of formation of complexes $\mathbf{9}^{3+}$−$\mathbf{14}^{3+}$ is fast with respect to the ring closure reaction, the rate increase produced by the template, k_{obs}/k_0, is given by eq 1.[7]

$$\frac{k_{obs}}{k_0} = \frac{1 + K_{T\#}[\text{template}]}{1 + K_{sub}[\text{template}]} \qquad (1)$$

Since the concentration of template is in large excess with respect to that of the substrate, in fact its analytical concentration can be substituted for its actual concentration in eq 1. The constants $K_{T\#}$ ($=k_{cat}K_{sub}/k_0$) and K_{sub} are the association constants of the template with the cyclic transition state and with the open chain precursor $\mathbf{1}^{3+}$, respectively. Catalysis will be observed when the template binds the transition state more strongly than the reactants.[8,9] On increasing the template concentration, the ratio k_{obs}/k_0 tends to a plateau value

---

[7] D'Acerno, C.; Doddi, G.; Ercolani, G.; Mencarelli, P. *Chem.*−*Eur. J.* **2000**, *6*, 3540−3546.

[8] Cacciapaglia, R.; Mandolini, L. *Chem. Soc. Rev.* **1993**, *22*, 221−231.

[9] Kraut, J. *Science* **1988**, *242*, 533−540.

TABLE 1. Association Constants in CH_3CN at 62 °C

template	K_{sub}, M^{-1}	$K_{\mathrm{T\#}}$, M^{-1}	$K_{\mathrm{T\#}}/K_{\mathrm{sub}}$
3	8 ± 2	2900 ± 200	360 ± 70
4[a]	11 ± 2	3000 ± 210	273 ± 30
5	6 ± 1	3450 ± 100	627 ± 50
6		59 ± 15	
7[a]	7 ± 2	850 ± 80	121 ± 23
8	7 ± 1	1790 ± 70	256 ± 19

[a] Reference 4.

given by the ratio $K_{\mathrm{T\#}}/K_{\mathrm{sub}}$. If however the product K_{sub} [template] is ≪1 even at the maximum template concentration, eq 1 reduces to the linear form of eq 2 in which the tendency to saturation disappears.

$$\frac{k_{\mathrm{obs}}}{k_0} = 1 + K_{\mathrm{T\#}}[\mathrm{template}] \qquad (2)$$

All the curves in Figures 1 and 2 with the exception of that relative to guest **6** show a clear tendency to saturation; thus, the values of k_{obs}/k_0 have been fitted to eq 1, except in the case of **6**, where they have been fitted to eq 2. The association constants obtained from the fitting procedure are reported in Table 1; they have been used to calculate the curves in Figures 1 and 2 by eq 1 or, in the case of **6**, by eq 2.

The saturation value, $K_{\mathrm{T\#}}/K_{\mathrm{sub}}$, is the maximum theoretical rate enhancement which would be attained when the substrate is completely bound to the template. The corresponding values, reported in Table 1, indicate that the complexed forms of $\mathbf{1}^{3+}$ are more reactive than the free one. The enhancements range from ~30 times for guest **6** (this very approximate value has been estimated by assuming $K_{\mathrm{sub}}[\mathrm{template}] \approx 0.1$, from which $K_{\mathrm{sub}} \approx 2$ M^{-1}) to ~600 times for guest **5**. Such rate enhancements are due to the fact that the associations of the acyclic trication $\mathbf{1}^{3+}$ with all the templates are rather weak whereas the cyclic transition state shows a much greater ligand affinity toward them. This is mainly due to the preorganization of the cyclic transition state and, secondarily, to the development of a further positive charge on the initially neutral nitrogen atom.

Upon inspection of Table 1 and Figure 1, it is apparent that guests **3**−**5**, which are devoid of terminal stoppers and which give rise to the formation of pseudorotaxanes, have similar catalytic effects. Indeed the increase of the length of the side arms beyond the two oxyethylene units of **3** involves only modest variations, with a non clearly recognizable trend, of both the values of K_{sub} and $K_{\mathrm{T\#}}$. The behaviors of guests **6**−**8** giving rise to the formation of rotaxanes and illustrated in Figure 2 are, in contrast, much more differentiated. In this case there is a clear trend showing that catalysis increases on increasing the length of the side arms. Comparing the results for the pairs **3**/**6**, **4**/**7**, and **5**/**8**, having the same number of oxygens along the polyethereal chains but differing for the nature of the end groups, it appears that substitution of the TIPS groups for the terminal hydrogens involves a significant lowering of catalysis that can be mainly ascribed to the lower values of the $K_{\mathrm{T\#}}$ constants. This effect is clearly dependent on the side chain length: it is dramatic for the shortest one (**3**/**6** pair) where the $K_{\mathrm{T\#}}$ value is reduced from 2900 to 59 M^{-1}, whereas it is much smaller for the longest one (**5**/**8** pair) where the $K_{\mathrm{T\#}}$ value is only halved. These results confirm our previous finding that the two bulky TIPS groups reduce the template ability of the guest,[4] but underscore the fact that this effect is greater the shorter the chain. It is known that two structural features are required for optimum complexation of a guest molecule by cyclobis(paraquat-*p*-phenylene), namely, an aromatic core, which is essential in placing the guest in the host cavity mainly by $\pi-\pi$ stacking interactions,[10] and two side arms with suitably placed oxygen atoms that interact with the acidic α-hydrogens of the pyridinium rings of the host by [C−H···O] hydrogen bonding.[11] The latter interactions should be the most affected by the steric hindrance of the two TIPS stoppers. In our previous paper we suggested that also entropic effects could play a significant role.[4] Indeed the interaction between the oxygen atoms of the side arms and the pyridinium α-protons restricts the conformational motion of the polyethereal chains with a consequent entropy loss. The entropy associated with internal rotations depends not only on potential energy barriers but also on the reduced moments of inertia of the rotating groups.[12] An increase of the reduced moments of inertia has the effect of decreasing the spacing between the energy levels of internal rotations, and thus of increasing the conformational entropy at temperatures above absolute zero. The two heavy TIPS groups placed at the end of the side arms increase the conformational entropy of the chain, and thus, restriction of conformational motion of the side arms upon binding occurs with a greater entropy loss. Now we are in a position to say which of the two effects is more important. Indeed increasing the length of the side arms and placing the heavy TIPS groups at the end of them has the effect of increasing the moment of inertia associated with internal rotations involving an increase of conformational entropy. On the contrary, steric effects exerted by the bulky TIPS groups are more important the shorter the chain. In other words if entropic effects were dominant, we should expect that the ratio $K_{\mathrm{T\#}}(\mathrm{H})/K_{\mathrm{T\#}}(\mathrm{TIPS})$ increases on increasing the chain length, whereas if steric effects were dominant, we should expect the contrary. The results point out that steric effects are more important than entropic effects. Assuming that steric effects are negligible in the reaction in the presence of guest **8**, we can estimate that the entropic effects due to the different masses of end groups should not account for more than a factor of 2.

In conclusion the results here presented indicate that, in the self-assembly of a rotaxane, the template effect of the guest is lowered by the presence of two large stoppers at the end of the linear chains; this effect is more important the shorter the chain and can be mainly ascribed to steric effects.

Experimental Section

Materials and Methods. 1,1″-[1,4-Phenylenebis(methylene)]-1′-(4-(bromomethyl)benzyl)-bis(4,4′-bipyridinium) tris(hexafluorophosphate) ($\mathbf{1}^{3+}\cdot 3PF_6^-$) was from our previous work.[4]

---

[10] Ercolani, G.; Mencarelli, P. *J. Org. Chem.* **2003**, *68*, 6472−6473.

[11] Houk, K. N.; Menzer, S.; Newton, S. P.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1479−1487.

[12] Ercolani, G. *J. Org. Chem.* **1999**, *64*, 3350−3353 and references therein.

The compounds **3**,[13] **5**,[14] and **6**[15] were prepared according to literature procedures.

1,5-Bis[2-[2-[2-[2-(triisopropylsilyloxy)ethoxy]ethoxy]ethoxy]-ethoxy]naphthalene (**8**) was prepared by following the procedure reported for the simpler homologue **7**:[15] Triisopropylsilyl triflate (1.53 g, 4.9 mmol) in dry CH_2Cl_2 (20 mL) was added to a solution of **5** (1.0 g, 1.96 mmol) and 2,6-dimethylpyridine (0.52 g, 4.9 mmol) in dry CH_2Cl_2 (30 mL) under N_2. After the mixture was stirred at room temperature overnight, the organic layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH, 95/5) to afford **8** as a pale oil (1.24 g, 77%). ES-MS: $m/z = 843.0$ $(M + NH_4)^+$, 848.0 $(M + Na)^+$. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 1.05−1.08 (42 H, m), 3.57−3.86 (24 H, m), 4.00 (4 H, m), 4.29 (4 H, m), 6.84 (2 H, d, $J = 8$ Hz), 7.35 (2 H, t, $J = 8$ Hz), 7.87 (2 H, d, $J = 8$ Hz). Anal. Calcd for $C_{44}H_{80}O_{10}Si_2$: C, 64.04; H, 9.77. Found: C, 63.65; H, 9.42.

HPLC grade acetonitrile was used in the kinetic experiments without further purification. Kinetic measurements were carried out on a UV−vis spectrophotometer.

Kinetic Measurements. Kinetic measurements were carried out, at 62 °C, in acetonitrile, in a 3 mL cuvette (optical path 1 cm) kept in the thermostated cell compartment of the spectrophotometer. In a typical run, 100 μL of a 0.010 M solution of $\mathbf{1}^{3+}\cdot 3PF_6^-$ was added to a 2.5 mL solution of the template **3**, **5**, **6**, or **8** at the appropriate concentration (see below). The appearance of the charge-transfer band of $\mathbf{15}^{4+}$, $\mathbf{17}^{4+}$, $\mathbf{18}^{4+}$, or $\mathbf{20}^{4+}$ was followed at λ 520 nm. In all of the cases a clean first-order behavior was observed. Relative kinetic constants (k_{obs}/k_0, where $k_0 = 8.3 \times 10^{-7}$ s^{-1}) at the various template concentrations (corrected for the volume increase at 62 °C and given in parentheses in M) were as follows: (template **3**) 1 (0), 48.8 (2.00×10^{-2}), 80.7 (3.65×10^{-2}), 101.9 (4.42×10^{-2}), 106.4 (5.15×10^{-2}), 136.1 (7.48×10^{-2}); (template **5**) 1 (0), 51.8 (1.62×10^{-2}), 52.4 (1.65×10^{-2}), 92.8 (3.07×10^{-2}), 137.4 (4.98×10^{-2}), 162.4 (6.51×10^{-2}), 194.0 (7.97×10^{-2}); data plotted in Figure 1; (template **6**) 1 (0), 2.2 (2.00×10^{-2}), 2.62 (3.00×10^{-2}), 4.08 (4.83×10^{-2}), 5.40 (5.50×10^{-2}), 3.53 (6.02×10^{-2}); (template **8**) 1 (0), 26.8 (1.51×10^{-2}), 48.0 (3.16×10^{-2}), 66.4 (5.00×10^{-2}), 81.3 (6.53×10^{-2}), 95.1 (8.00×10^{-2}); data plotted in Figure 2.

JO035483E

---

(13) Brown, C. L.; Philp, D.; Spencer, N.; Stoddart, J. F. *Isr. J. Chem.* **1992**, *32*, 61−67.

(14) 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.

(15) Bravo, J. A.; Raymo, F. M.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Eur. J. Org. Chem.* **1998**, 2565−2571.