Can Multivalency Be Expressed Kinetically? The Answer Is Yes

Jovica D. Badjić, Stuart J. Cantrill, and J. Fraser Stoddart*

California NanoSystems Institute and Department of Chemistry and Biochemistry, University of California, Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095-1569

Received November 10, 2003; E-mail: stoddart@chem.ucla.edu

The preparation of supermolecules by way of strict self-assembly has attracted considerable interest, particularly in the bottom-up construction[1] of molecular machines and devices. Paraquat derivatives have been used[2] in the preparation of interpenetrating complexes (pseudorotaxanes) and the derived mechanically interlocked compounds, catenanes, and rotaxanes. Multivalent interactions,[3] incorporating both statistical and chelate contributions, are very important in nature and have been explored in the noncovalent synthesis[4] of various elaborate supermolecules by us[5] and others.[6] Inspired by the multivalency concept,[3] we report here the strict self-assembly of a triply threaded two-component superbundle 3in-[1⊃2]-[PF$_6$]$_6$, which can be used[7] in building (Figure 1) photo- and redox-active molecular devices. It transpires that a trifurcated trisbipyridinium salt [1][PF$_6$]$_6$ and a tritopic triscrown ether 2 form the thermodynamically stable 3in-[1⊃2][PF$_6$]$_6$ by way of a metastable doubly threaded complex 2in-[1⊃2][PF$_6$]$_6$ obtained fleetingly from a singly threaded intermediate species 1in-[1⊃2][PF$_6$]$_6$.

The trifurcated trisbipyridinium salt [1][PF$_6$]$_6$ was synthesized (Supporting Information) in four steps from 1,3,5-tris(*p*-formylphenyl)benzene,[8] while the synthesis of the tritopic crown ether 2 has been described[9] previously. On the basis of molecular modeling and our previous studies on and knowledge of related systems,[10] 3in-[1⊃2][PF$_6$]$_6$ should be stabilized by (i) $\pi-\pi$ stacking interactions[11] between the triphenylene core of the tritopic crown ether 2 and the benzenoid core of [1][PF$_6$]$_6$, (ii) $\pi-\pi$ stacking interactions[11] between the catechol rings in 2 and the bipyridinium units in [1][PF$_6$]$_6$, and (iii) [C–H⋯O] interactions[12] between the α-bipyridinium protons in [1][PF$_6$]$_6$ and some of the oxygen atoms in the polyether loops of 2.

When equimolar amounts (5 mM) of [1][PF$_6$]$_6$ and 2 were mixed in CD$_3$COCD$_3$, the ^{1}H NMR spectrum (253 K), recorded immediately (Figure 2b) after mixing, displayed a complex array of well-defined resonances. The absence of any resonances corresponding to either free [1][PF$_6$]$_6$ (Figure 2a) or 2 (Figure 2d) is suggestive of a strong interaction between the two components. Closer inspection of the ^{1}H NMR spectrum (Figure 2b) of the mixture reveals that all of the signals can be divided rather easily into two sets with approximately 2:1 ratios in their intensities, suggesting the formation of either a doubly or singly threaded supermolecule with averaged C_s symmetry. The significant downfield shift of the doublet observed at δ 10.0, corresponding to *four* α-bipyridinium protons in [1][PF$_6$]$_6$ is presumably a result of the formation of [C$_\alpha$–H⋯O] interactions[12] with the crown ether oxygen atoms in 2 and in accordance with the threading of *two* bipyridinium arms through *two* crown ethers as represented by 2in-[1⊃2][PF$_6$]$_6$ in Figure 1. With the aid of ^{1}H–^{1}H COSY and TROESY 2D NMR spectroscopic experiments (Supporting Information), it was possible to assign most of the resonances in Figure 2b to a 1:1 complex with averaged C_s symmetry, i.e., a doubly threaded superbundle, which is kinetically stable[13] on the NMR timescale. Furthermore, the upfield shifts of the aromatic core proton signals, H$_a$ in [1]-
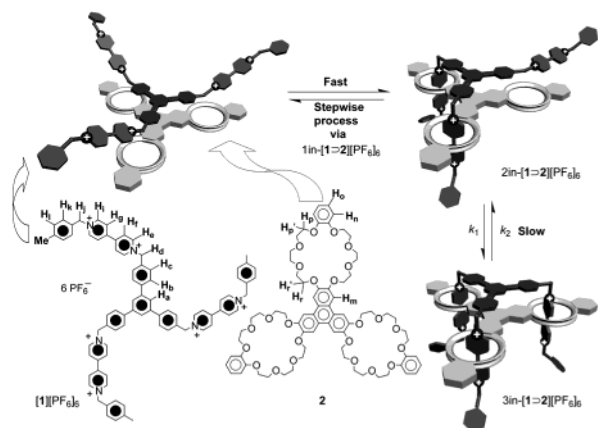

Figure 1. Schematic representation of the stepwise self-assembly of the two-component triply threaded supramolecular bundle 3in-[1⊃2][PF$_6$]$_6$ by way of a doubly threaded 2in-[1⊃2][PF$_6$]$_6$ intermediate, starting from the trifurcated trisbipyridinium salt [1][PF$_6$]$_6$ and the triscrown ether 2.
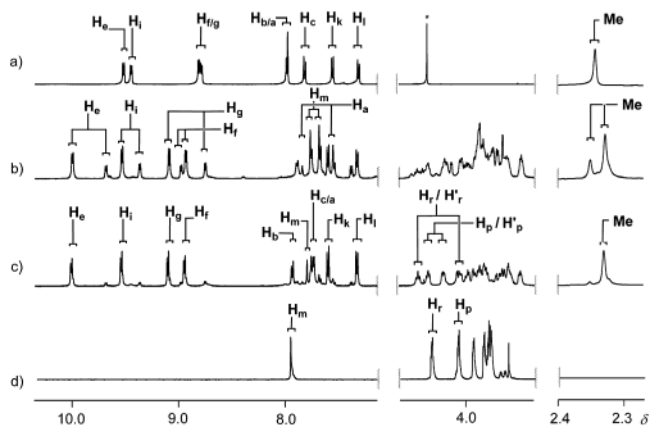

Figure 2. Partial ^{1}H NMR spectra (500 MHz, CD$_3$COCD$_3$, 5.0 mM each, 253 K) of (a) [1][PF$_6$]$_6$, (b) an equimolar mixture of [1][PF$_6$]$_6$ and 2 immediately after the mixing, (c) an equimolar mixture of [1][PF$_6$]$_6$ and 2 235 h after the mixing, and (d) triscrown ether 2.

[PF$_6$]$_6$ and H$_m$ in 2, suggest that the two central aromatic cores reside in this 1:1 complex within $\pi-\pi$ stacking distance of each other, thus stabilizing the superbundle. The singlet for the methyl protons (Me) in the ^{1}H NMR spectrum of [1][PF$_6$]$_6$ separates (Figure 2b) into two broad singlets with relative intensities of 2:1 which correspond, respectively, to *two* complexed and *one* uncomplexed arms of 2in-[1⊃2][PF$_6$]$_6$.

Interestingly, the ^{1}H NMR spectrum of the equimolar mixture of [1][PF$_6$]$_6$ and 2 changed very gradually with time, until after 235 h, the initial set of resonances with relative intensity ratios of 2:1 were replaced (Figure 2c) with a new set of resonances. On the basis of ^{1}H–^{1}H COSY and TROESY 2D NMR spectroscopic evidence (Supporting Information), we have assigned the new set

Table 1. Kinetic and Thermodynamic Parameters for the Conversion of 2in-[**1**⊃**2**][PF$_6$]$_6$ to 3in-[**1**⊃**2**][PF$_6$]$_6$

$k_1{}^a$	$k_2{}^a$	K	$\Delta G_1{}^{\ddagger \text{ThinSpace}b}$	$\Delta G_2{}^{\ddagger\, b}$	ΔG^b
4.7 ± 0.1	1.4 ± 0.1	3.4 ± 0.1	20.9 ± 0.3	21.5 ± 0.3	-0.60 ± 0.01

^{a} In s^{-1} × 10^6. ^{b} In kcal mol^{-1}.

of resonances to a single 1:1 complex with averaged C_{3v} symmetry, i.e., 3in-[**1**⊃**2**][PF$_6$]$_6$. The resonances of the central aromatic core protons, namely H$_a$ in [**1**][PF$_6$]$_6$ and H$_m$ in **2**, showed significant upfield shifts, compared to the corresponding resonances of the free components (Figure 2a,d), indicating intimate π−π stacking[9,11] of the central aromatic cores. The previously enantiotopic OCH$_2$ protons in **2** (Figure 2a) become diastereotopic in 3in-[**1**⊃**2**][PF$_6$]$_6$ (Figure 2c) when all three bipyridinium units became threaded through the crown ether moieties. Furthermore, the resonances for the *six equivalent* α-bipyridinium H$_e$ protons in 3in-[**1**⊃**2**][PF$_6$]$_6$ (Figure 2c) are dramatically shifted, as compared to the signals for these same protons in [**1**][PF$_6$]$_6$ (Figure 2a) as a result of [C$_\alpha$−H···O] interactions.[12] The single resonance for the Me protons in 3in-[**1**⊃**2**][PF$_6$]$_6$ (Figure 2c) also confirms the binding of all three bipyridinium units.

The change in the ^{1}H NMR spectrum of an equimolar mixture of [**1**][PF$_6$]$_6$ and **2**, each 5.5 mM, at 253 K with time (235 h) was monitored (Supporting Information) by ^{1}H NMR spectroscopy. The concentration of the initially formed 2in-[**1**⊃**2**][PF$_6$]$_6$ decreases, while the concentration of 3in-[**1**⊃**2**][PF$_6$]$_6$ increases. When the concentration of the initially formed 2in-[**1**⊃**2**][PF$_6$]$_6$ was plotted versus time and the data points were fitted (Supporting Information) to the model for a reversible first-order rate reaction, good agreement was found.[14] This finding supports the evidence for the presence of two species, i.e., 2in-[**1**⊃**2**][PF$_6$]$_6$ and 3in-[**1**⊃**2**][PF$_6$]$_6$, in admixture and slowly equilibrating. The calculated rate constants for the forward (k_1) and backward (k_2) reactions and the corresponding free energies ($\Delta G_1{}^\ddagger$ and $\Delta G_2{}^\ddagger$) are presented in Table 1. The high energy barrier (20.9 kcal mol^{-1}) for the formation of 3in-[**1**⊃**2**][PF$_6$]$_6$ suggests that the initial rapid formation of 2in-[**1**⊃**2**]-[PF$_6$]$_6$ is followed by a much slower binding step, during which time the third and uncomplexed bipyridinium arm is appropriately positioned such that the final threading process can take place. The singly threaded complex 1in-[**1**⊃**2**][PF$_6$]$_6$ is most certainly being formed along the way. Presumably, however, the relatively short lifetime of this 1:1 complex does not allow us to detect it by conventional NMR spectroscopy.

In conclusion, we have discovered that the strict self-assembly[4,15] of a two-component triply threaded superbundle 3in-[**1**⊃**2**][PF$_6$]$_6$ from its components in solution is very much a two-step process,[16] with the first one being kinetically and the second one thermodynamically controlled. This observation begs the important question: are there instances[17] in nature where multivalency is expressed as a kinetically controlled process, prior to an equilibrium state being reached and, if so, what are the biological consequences, if any?

Supporting Information Available: Experimental details for the synthesis of [**1**][PF$_6$]$_6$, ^{1}H−^{1}H COSY, TROESY 2D NMR spectra of 2in-[**1**⊃**2**][PF$_6$]$_6$ and 3in-[**1**⊃**2**][PF$_6$], and rate constant measurements (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3343−3391. (b) Leigh, D. A.; Wong, J. K. Y.; Dehez, F.; Zerbetto, F. *Nature* **2003**, *424*, 174−179. (c) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines: A Journey into the Nano World*; Wiley-VCH: Weinheim, Germany, 2003.

(2) (a) Wisner, J. A.; Loeb, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2838−2840. (b) Huang, F.; Gibson, H. W.; Bryant, W. S.; Negvekar, D. S.; Fronczek, F. R. *J. Am. Chem. Soc.* **2003**, *125*, 9367−9371. (c) Davidson, G. J. E.; Loeb, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 74−77.

(3) (a) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754−2794. (b) Gestwicki, J. E.; Cairo, C. W.; Strong, L. E.; Oetjen, K. A.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 14922−14933. (c) Kitov, P. I.; Bundle, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 16271−16284. (d) Ercolani, G. *J. Am. Chem. Soc.* **2003**, *125*, 16097−16103.

(4) (a) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *254*, 1312−1319. (b) Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *Acc. Chem. Res.* **1994**, *27*, 198−203. (c) Crego-Calama, M.; Reinhoudt, D. N. *Science* **2002**, *295*, 2403−2407.

(5) Fulton, D. A.; Cantrill, S. J.; Stoddart, J. F. *J. Org. Chem.* **2002**, *67*, 7968−7981 and references therein.

(6) (a) Rao, J.; Lahiri, J.; Isaacs, L.; Weis, R. M.; Whitesides, G. M. *Science* **1998**, *280*, 708−711. (b) Kitov, P. I.; Sadawska, J. M.; Mulvey, J. P.; Armstrong, G. D.; Ling, H.; Pannu, N. S.; Read, R. J.; Bundle, D. R. *Nature* **2000**, *403*, 669−672. (c) Gibson, H. W.; Yamaguchi, N.; Hamilton, L.; Jones, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 4653−4665.

(7) Ashton, P. R.; Ballardini, R.; Balzani, V.; Credi, A.; Dress, K. R.; Ishow, E.; Kleverlaan, C. J.; Kocian, O.; Preece, J. A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Wenger, S. *Chem. Eur. J.* **2000**, *6*, 3558−3574.

(8) 1,3,5-Tris(*p*-formylphenyl)benzene was reduced initially with NaBH$_4$ to 1,3,5-tris(*p*-hydroxybenzyl)benzene, followed by chlorination with *N*-chlorosuccinimide to yield 1,3,5-tris(*p*-chlorobenzyl)benzene. Further reaction with 4,4′-bipyridine, followed by anion exchange, produced [**6**]-[PF$_6$]$_3$, which was then reacted with *p*-methylbenzyl bromide to yield [**1**]-[PF$_6$]$_6$ after anion exchange. For further details, see Supporting Information.

(9) Fyfe, M. C. T.; Lowe, J. N.; Stoddart, J. F.; Williams, D. J. *Org. Lett.* **2000**, *9*, 1221−1224. (b) Balzani, V.; Clemente-Leon, M.; Credi, A.; Lowe, J. N.; Badjić, J. D.; Stoddart, J. F.; Williams, D. J. *Chem. Eur. J.* **2003**, *9*, 5348−5360.

(10) (a) Ashton, P. R.; Langford, S. J.; Spencer, N.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1996**, 1387−1388. (b) Ashton, P. R.; Glink, P. T.; Martínez-Díaz, M. V.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1930−1933.

(11) (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534. (b) Adams, H.; Hunter, C. A.; Lawson, K. R.; Perkins, J.; Spey, S. E.; Urch, C. J.; Sanderson, J. M. *Chem. Eur. J.* **2001**, *7*, 4863−4877.

(12) (a) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290−296. (b) Raymo, F. M.; Bartberger, M. D.; Houk, K. N.; Stoddart, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 9264−9267. (c) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76.

(13) At temperatures below 253 K, an equimolar mixture (8.5 mM) of 4,4′-dibenzylbipyridinium bis(hexafluorophosphate) and DB24C8 in CD$_3$-COCD$_3$ reveals peaks in the ^{1}H NMR spectra for the 1:1 complex as well as for the free species, i.e., complexation−decomplexation is slow on the NMR timescale. Thus, it is not surprising that 2in-[**1**⊃**2**][PF$_6$]$_6$ is kinetically stable at 253 K.

(14) The experimental data points were fitted to a model for the reversible first-order reaction by nonlinear square fitting using SigmaPlot 8.0 software. For further details, see: Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 1995; Chapter 3.

(15) For further examples of strict self-assembly, see: (a) Zimmerman, S. C. *Science* **1997**, *276*, 543−544. (b) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (c) Fujita, M. *Acc. Chem. Res.* **1999**, *32*, 53−61. (d) Lehn, J.-M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4763−4768. (e) Felix, O.; Crego-Calama, M.; Luyten, I.; Timmerman, P.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **2003**, *8*, 1463−1474.

(16) By comparison (ref 9), a trifurcated trisammonium salt, wherein the three bipyridinium units in [**1**][PF$_6$]$_6$ are replaced by three CH$_2$NH$_2$$^+CH_2$ units, forms a triply threaded superbundle with **2** instantaneously. No intermediates are observed on the laboratory timescale. We suspect that the difference in the rates of formation of the two superbundles can be traced back to the relative rigidity of [**1**]$^{6+}$ compared with its trisammonium-based analogue.

(17) Indeed, there are instances in nature, e.g., a recent study carried out on the high-avidity, reversible low-affinity multivalent interactions of the lectin XL35 with the jelly coat proteins surrounding oocytes in *Xenopus laevis* shows that they require a very long time to reach equilibrium, so long in fact that the partners do not attain true equilibrium on the timescale of the biological event, namely polyspermy, yet are such that their metastable mode of interaction is probably more than enough to guarantee an insurmountable physical block to polyspermy. See: Arranz-Plaza, E.; Tracy, A. S.; Siriwardena, A.; Pierce, J. M.; Boons, G.-J. *J. Am. Chem. Soc.* **2002**, *124*, 13035−13046.

JA0395285