ORGANIC LETTERS

2002
Vol. 4, No. 21
3565−3568

Self-Assembly of Dendrimers by Slippage

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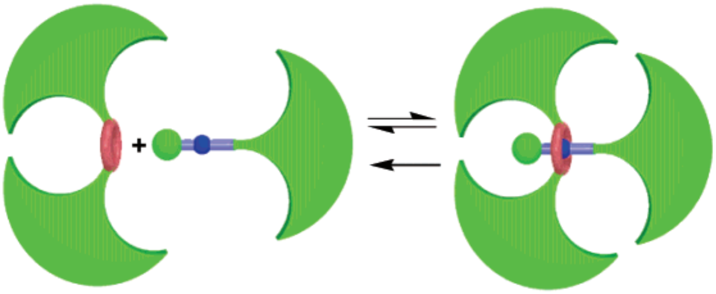
Received July 8, 2002

ABSTRACT



A dendrimer with rotaxane-like characteristics has been assembled under thermodynamic control from complementary wedge-shaped precursors by slippage in CH_2Cl_2. The driving force for the self-assembly process is the molecular recognition that exists as a result of [N^+–H···O] and [C–H···O] hydrogen bonds between an NH_2^+ center in one Fréchet-type benzyl ether wedge and a dibenzo[24]crown-8 unit that links the other two such wedges.

Although dendrimers containing mechanically interlocked components are known,[1] they are far from commonplace. Usually, they have been prepared by template-directed protocols wherein, at some point in the synthesis, a supramolecular species is formed that is then modified covalently[2] to introduce either the catenane or rotaxane architecture.[3] Recently, for example, we described[4] the construction of a dendrimer that contains two identical covalently linked bis-dendrons and a core unit fused to two rings that encircle the two bis-dendrons. In this work, the dendrons were introduced into an already interlocked molecular compound by Wittig chemistry[5] that allows no less than four surrogate stoppers to be replaced by dendrons. The resulting dendrimer with its mechanical branching points is kinetically stable in contrast with the so-called supramolecular dendrimers[6] and their assemblies[7] which are subject to thermodynamic control and are usually kinetically labile, in common with most noncovalently bonded superstructures. An intermediate situation between mechanically interlocked molecular dendrim-

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(1) (a) Amabilino, D. B.; Ashton, P. R.; Belohradsky, M.; Raymo, F. M.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1995**, 751−753. (b) Amabilino, D. B.; Ashton, P. R.; Balzani, V.; Brown, C. L.; Credi, A.; Fréchet, J. M. J.; Leon, J. W.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1996**, *118*, 12012−12020. (c) Hübner, G. M.; Nachtsheim, G.; Li, Q. Y.; Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 1269−1272. (d) Reuter, C.; Pawlitzki, G.; Wörsdörfer, U.; Plevoets, M.; Mohry, A.; Kubota, T.; Okamoto, Y.; Vögtle, F. *Eur. J. Org. Chem.* **2000**, 3059−3067. (e) Kim, K. *Chem. Soc. Rev.* **2002**, *31*, 96−107.

(2) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393−401.

(3) (a) Schill, G. *Catenanes, Rotaxanes and Knots*; Academic: New York, 1971. (b) *Molecular Catenanes, Rotaxanes and Knots*; Sauvage, J.-P., Dietrich-Buchecker, C., Eds.; VCH-Wiley: Weinheim, Germany, 1999.

(4) Elizarov, A. M.; Chiu, S.-H.; Glink, P. T.; Stoddart, J. F. *Org. Lett.* **2002**, *4*, 679−682.

(5) Rowan, S. J.; Stoddart, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 164−165.

(6) Supramolecular dendrimers are comprised of noncovalently bonded subunits: (a) Zimmerman, S. C.; Zeng, F.; Reichert, D. E. C.; Kolotuchin, S. V. *Science* **1996**, *271*, 1095−1098. (b) Emrick, T.; Fréchet, J. M. J. *Curr. Opin. Colloid Interface Sci.* **1999**, *4*, 15−23. (c) Percec, V.; Cho, W.-D.; Ungar, G. *J. Am. Chem. Soc.* **2000**, *122*, 10273−10281. (d) Lee, J. W.; Ko, Y. H.; Park, S.-H.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 746−749. (e) Zeng, F.; Zimmerman, S. C.; Kolotuchin, S. V.; Reichert, D. E. C.; Ma, Y. *Tetrahedron* **2002**, *58*, 825−843.

(7) Noncovalently bonded aggregates wherein each component is considered to be a dendrimer: (a) Percec, V.; Cho, W.-D.; Mosier, P. E.; Ungar, G.; Yeardley, J. P. *J. Am. Chem. Soc.* **1998**, *120*, 11061−11070. (b) Uppuluri, S.; Swanson, D. R.; Piehler, L. T.; Li, J.; Hagnauer, G. L.; Tomalia, D. A. *Adv. Mater.* **2000**, *12*, 796−800. (c) Percec, V.; Cho, W.-D.; Ungar, G.; Yeardley, D. J. P. *Chem. Eur. J.* **2002**, *8*, 2011−2025.

10.1021/ol026479c CCC: $22.00

ers and supramolecular dendrimers is provided by dendritic pseudorotaxanes[8] where the components of the superstructure are not only noncovalently bonded with one another, but also interpenetrate each other.

The slippage methodology[9] provides a bridge between kinetically stable, mechanically interlocked compounds and kinetically labile, supramolecular assemblies. Some time ago, we established[10] that the secondary dialkylammonium ion $(RCH_2)_2NH_2^+$, where R is a cyclohexyl group and the counterion is PF_6^-, will form a kinetically stable [2]rotaxane when the salt and dibenzo[24]crown-8 (DB24C8) are heated (Figure 1) under reflux (at 40 °C) in CH_2Cl_2 (50 mM in salt and 150 mM in DB24C8) for 32 days.[11] An almost 98% conversion to the rotaxane in this experiment is reflected in a 90% yield of a crystalline product which showed no tendency to dissociate in $CDCl_3/CD_3CN$ (3:1) solution upon standing for several weeks at 20 °C. However, when this crystalline product was dissolved in CD_3SOCD_3, it was found to have dissociated completely into its components inside 18 h on standing at 25 °C.

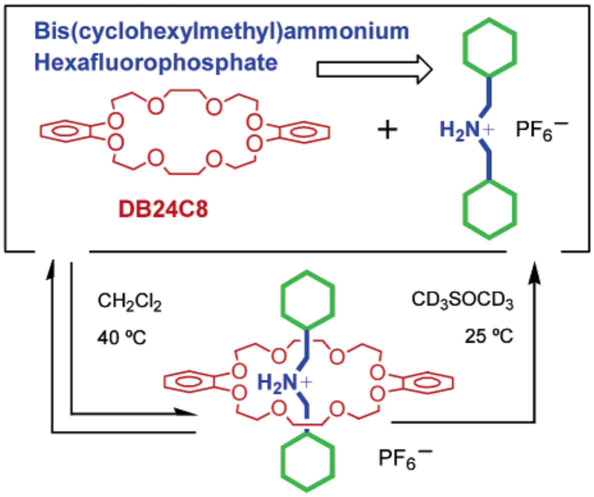
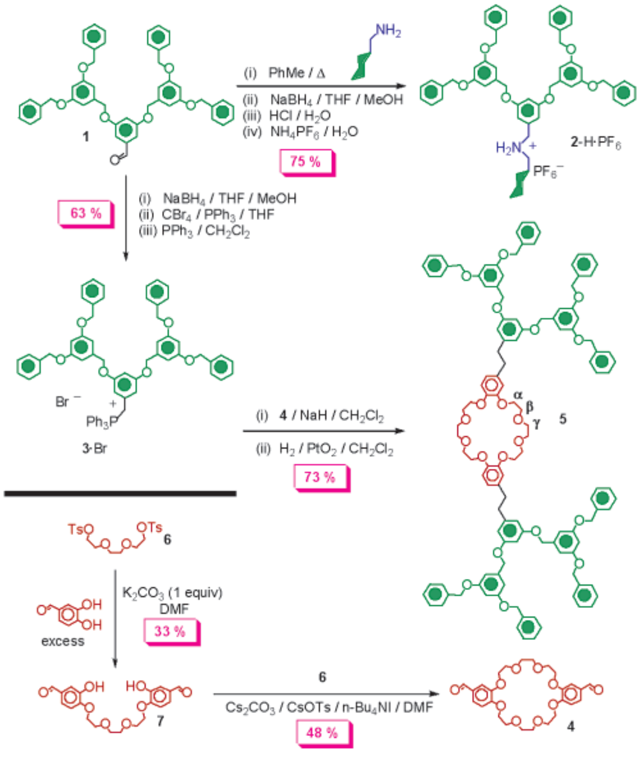


Figure 1. A slippage system par excellence!

In the knowledge of these remarkable experimental findings, it occurred to us that a possible approach to the preparation of mechanically bonded dendrimers might be provided by using the slippage protocol involving one dendron carrying a DB24C8 ring and another dendron that is attached to one side of an NH_2^+ center, leaving the other side free to support a cyclohexylmethyl group, i.e., a slippage stopper for the DB24C8 ring. For the dendrons, we chose Fréchet-type benzyl ether wedges because (i) they are readily available and soluble in solvents such as CH_2Cl_2 and (ii) we surmised that the phenolic ether functions would not interfere with the $[N^+{-}H\cdots O]$ hydrogen bonds and $[C{-}H\cdots O]$ interactions that constitute most of the noncovalent bonding in the recognition motif involving a $CH_2NH_2^+CH_2$ center and a DB24C8 ring.

Scheme 1. Preparation of Dendritic Wedges for Assembly by Slippage



The preparations of (i) a dialkylammonium salt **2**-H·PF_6, carrying a dendritic wedge and bearing a cyclohexylmethyl group, respectively, on either side of its NH_2^+ center, and (ii) a bis-dendron **5** containing a DB24C8 recognition site are summarized in Scheme 1. The synthesis of the benzyl ether-based dendritic aldehyde **1**, which serves as a common intermediate in the preparation of both **2**-H·PF_6 and **5**, was carried out according to a literature procedure.[12] Reductive amination of **1** with aminomethylcyclohexane, followed by

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[8] (a) Yamaguchi, N.; Hamilton, L. M.; Gibson, H. W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3275−3279. (b) Gibson, H. W.; Yamaguchi, N.; Hamilton, L.; Jones, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 4653−4665.

[9] The slippage methodology was exploited early on when rotaxanes were prepared in a statistical manner. For examples see: (a) Harrison, I. T. *J. Chem. Soc., Chem. Commun.* **1972**, 231−232. (b) Schill, G.; Beckmann, W.; Schweikert, N.; Fritz, H. *Chem. Ber.* **1986**, *119*, 2647−2655. The first successful template-directed synthesis of rotaxanes by slippage was reported in 1993. See: (c) Ashton, P. R.; Belohradsky, M.; Philp, D.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1993**, 1269−1274. For a discussion of the phenomenon see: (d) Fyfe, M. C. T.; Raymo, F. M.; Stoddart, J. F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; VCH-Wiley: Weinheim, Germany, 2000; pp 211−220. For recent examples see: (e) Sohgawa, Y. H.; Fujimori, H.; Shoji, J.; Furusho, Y.; Kihara, N.; Takata, T. *Chem. Lett.* **2001**, *8*, 774−775. (f) Jeppesen, J. O.; Becher, J.; Stoddart, J. F. *Org. Lett.* **2002**, *4*, 557−560.

[10] Ashton, P. R.; Baxter, I.; Fyfe, M. C. T.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 2297−2307.

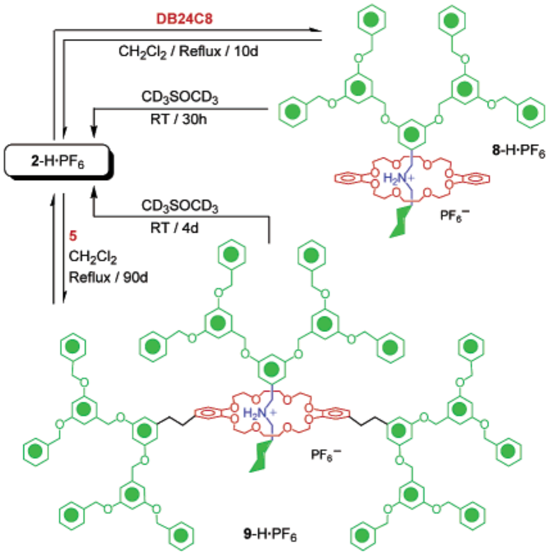
[11] An initial slippage experiment, which was performed (ref 10) with the concentrations of both components at 10 mM, afforded the [2]rotaxane in appreciable quantities after 16 weeks! As expected, increasing the concentrations and using an excess of DB24C8 resulted in a higher yield of the [2]rotaxane in a shorter time.

[12] Pollak, K. W.; Sanford, E. M.; Fréchet, J. M. J. *J. Mater. Chem.* **1998**, *8*, 519−527.

protonation of the resulting amine and counterion exchange, produced **2**-H•PF_6 in 75% yield overall. The bis-dendron **5** incorporating the crown ether was prepared by reducing the aldehyde **1**, brominating the benzyl alcohol, and reacting the benzyl bromide with Ph_3P to generate the triphenylphosphonium salt **3**•Br in 63% yield overall. Wittig olefination of **3**•Br with the *syn*-diformyl-DB24C8 derivative **4**[13] afforded a mixture of cis and trans olefins which were then subjected to catalytic hydrogenation, yielding **5** in 73% yield overall.

On account of the fact that the dialkylammonium ion 2^+ carries a large π-electron-rich dendritic wedge, it was decided to perform a model slippage experiment (Scheme 2) first of all with DB24C8. Consequently, a CH_2Cl_2 solution (10 mM) of **2**-H•PF_6 was heated under reflux with DB24C8 (100 mM), resulting in the appearance in the ^1H NMR spectrum, recorded in CD_2Cl_2, of a new set of signals which increased in their intensities with time and have chemical shifts (see below) commensurate with the formation of a [2]rotaxane. When the slippage kinetics had slowed significantly (after 10 days), the mixture was separated into its components by preparative TLC (SiO_2: CH_2Cl_2/THF, 95:5). The [2]rotaxane **8**-H•PF_6 was isolated in 39% yield in its pure form, along with unreacted **2**-H•PF_6 and DB24C8. Comparison (Figure 2) of the ^1H NMR spectrum of **8**-H•PF_6 with the spectra of its free components, namely **2**-H•PF_6 and DB24C8, supports the fact that it has a [2]rotaxane architecture. In particular (i) the downfield shifts of the signals for the methylene group protons adjacent to the NH_2^+ center and (ii) the separating out of the signals for both the α-OCH_2 and γ-OCH_2 protons into two pairs of well-resolved multiplets, reflecting their diastereotopicities in the [2]rotaxane, should be noted. The FAB mass spectrum afforded further strong evidence for the interlocked nature of the components of **8**-H•PF_6 with the presence in it of a base peak at *m*/*z* 1288.6, corresponding to the **8**-H^+ ion alongside a much less intense peak for the **2**-H^+ ion at *m*/*z* 840.4. These experiments prove convincingly that, not only is the dendritic dumbbell **2**-H•PF_6 able to undergo slippage through the DB24C8 ring, but also the product formed in the process is stable enough to be isolated by chromatography without undergoing dissociation. Thus, it may be safely concluded that, under relatively nonpolar conditions, **8**-H•PF_6 behaves as a molecular species, i.e., it is a [2]rotaxane.

Scheme 2. Slippage and Deslippage



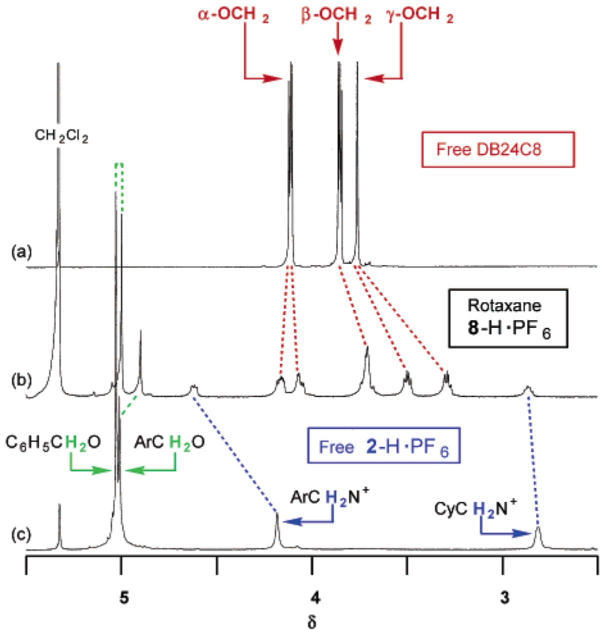


Figure 2. Partial ^1H NMR spectra (500 MHz, CD_2Cl_2) of the dendritic wedge-shaped [2]rotaxane **8**-H•PF_6 formed by slippage between **2**-H•PF_6 and DB24C8: (a) free DB24C8, (b) the [2]-rotaxane **8**-H•PF_6, and (c) free **2**-H•PF_6.

With both the wedge-shaped components in hand, and in the knowledge that slippage can be performed between **2**-H•PF_6 and DB24C8, we decided to investigate the self-assembly of the triply branched dendritic [2]rotaxane **9**-H•PF_6 from **2**-H•PF_6 and **5**. We used conditions similar to those employed in the preparation of **8**-H•PF_6 with the exception that **2**-H•PF_6 and **5** were present in the reaction mixture in a 3:1 molar ratio. The reaction proceeded very slowly. After 90 days, the reaction mixture was subjected to silica gel column chromatography and the most apolar component, which turned out to be the [2]rotaxane **9**-H•PF_6, was isolated pure in 19% yield. The interlocked nature of

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(13) The synthesis of **4** is also outlined in Scheme 1. In the reaction of triethyleneglycol bistosylate (**6**) with 3,4-dihydroxybenzaldehyde in the presence of a base, only one pure isomer, namely **7**, is isolated. The regioselectivity, expressed doubly in this nucleophilic substitution, is believed to be dictated by the stabilization of the phenoxide ion in the position para to the formyl group. See: (a) Reitz, A.; Avery, M. A.; Verlander, M. S.; Goodman, M. *J. Org. Chem.* **1981**, *46*, 4889−4863. (b) Allwood, B.; Kohnke, F. H.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 311−314. (c) Bourgeois, J.-P.; Echegoyen, L.; Fibbioli, M.; Pretsch, E.; Diederich, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2118−2121. The ^1H NMR spectrum recorded in CD_3SOCD_3 (see Supporting Information) is consistent with the presence of only one isomer, i.e., compound **7**, as already reported in the literature.

the two components of **9**-H^+ was confirmed by FAB mass spectrometry and by ^1H NMR spectroscopy. The mass spectrum revealed a base peak at *m*/*z* 2770 corresponding to the **9**-H^+ ion. The ^1H NMR spectrum (Figure 3) of **9**-H•PF_6 displays signals reminiscent of those observed in the spectrum of **8**-H•PF_6, especially those for the methylene protons in the $CH_2NH_2^+CH_2$ and α-, *β*-, and *γ*-OCH_2 units, that are consistent with a "rotaxane-like complex". Thus, under certain conditions, this "complex" may be considered to be a rotaxane. Yet, under different conditions, this "complex" behaves like a pseudorotaxane. When **9**-H•PF_6 was dissolved in CD_3SOCD_3, a solvent which acts as a very good hydrogen bond acceptor, the dissociation of the "rotaxane-like complex" into its components, **2**-H•PF_6 and **5**, took place slowly and could be followed by ^1H NMR spectroscopy. The half-life for the first-order decay[14] of this "complex" was 17.7 h, a $t_{1/2}$ that is considerably longer than that observed[10] for the "complex" shown in Figure 1. When this same experiment was carried out on **8**-H•PF_6, we found that it dissociated into its two components, **2**-H•PF_6 and DB24C8, with a $t_{1/2}$ of 7.8 h.

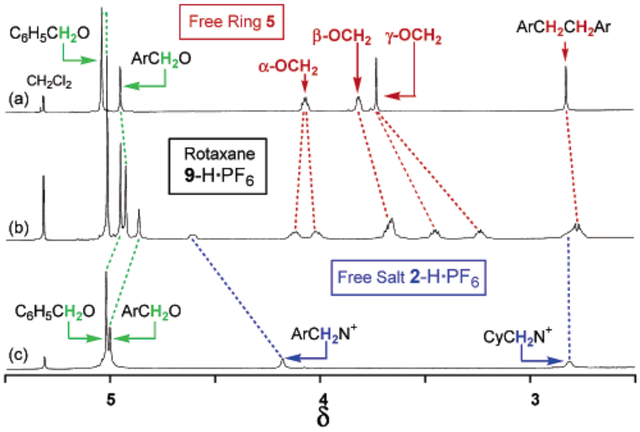

Figure 3. Partial ^1H NMR spectra (500 MHz, CD_2Cl_2) of the dendritic [2]rotaxane **9**-H•PF_6 self-assembled by slippage between **2**-H•PF_6 and the crown ether-based bis-dendron **5**: (a) free ring **5**, (b) the [2]rotaxane **9**-H•PF_6, and (c) free **2**-H•PF_6.

To date, this investigation has established the principle that mechanically interlocked dendrimers can be self-assembled under thermodynamic control by using the slippage protocol.[9] The major driving force for the rotaxane formation in refluxing dichloromethane is believed to arise from [N^+−H•••O] hydrogen bonding and [C−H•••O] interactions. The fact that the equilibrium for the formation (Scheme 2) of the dendritic [2]rotaxane **9**-H•PF_6 from its components is not as favorable as that observed (Figure 1) in the model system[10] could find its explanation in a number of different factors present (Scheme 2) in both the dumbbell-shaped component **2**-H•PF_6 and the ring component **5** that are absent in the bis(cyclohexylmethylammonium) ion and DB24C8. The dendritic wedges present in **2**-H•PF_6 and **5** contain six phenolic oxygen atoms and seven benzenoid rings, all of which are going to enter into a competition with the DB24C8 core oxygen atoms to accept hydrogen bonds from the single, all-important $CH_2NH_2^+CH_2$ center, i.e., the immediate molecular and supramolecular environments around this hydrogen bond donating center impair the strengths of the [N^+−H•••O] hydrogen bonding and [C−H•••O] interactions at the recognition site. Presumably, if we were to employ wedges containing only saturated hydrocarbon building blocks, we could anticipate a much more highly efficient slippage "reaction". Given this scenario, which we are testing currently, there is good reason to suppose that dendrimers containing mechanical bonds can be assembled and disassembled with close to 100% efficiencies, depending upon their immediate environments, where solvent, temperature, and pH are all parameters that can be manipulated at will.[14] The prospect of being able to trap guest molecules within a closed dendritic host system, which can subsequently be broken apart in a controlled manner, is one that has very obvious implications for the slow release[15] of drugs in patients.

Acknowledgment. We thank the National Science Foundation (CHE-9910199) and the Petroleum Research Fund, administered by the American Chemical Society (PRF-35071-AC4), for generous financial support. This material is based upon work supported by the National Science Foundation under equipment grant number CHE-9974928.

Supporting Information Available: ^1H and ^{13}C NMR and mass spectra of compounds **2**-H•PF_6, **4**, **5**, **7**, **8**-H•PF_6, and **9**-H•PF_6, experimental procedures for their preparation, and the calculations of $t_{1/2}$ for both **8**-H•PF_6 and **9**-H•PF_6 in CD_3SOCD_3 at 25 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] The ability to assemble and disassemble dendrimers where hydrogen bonding between the components is complemented by a mechanical bond renders the rotaxane-like dendrimer much more stable than a conventional supramolecular dendrimer where multiple hydrogen bonds, even when they act cooperatively, lead to dynamic superstructures for the most part, i.e., the mechanical bond can be employed to bring added stability to supramolecular dendrimers based on hydrogen-bonding interactions.

[15] (a) Park, K. *Controlled Drug Delivery. Challenges and Strategies*; American Chemical Society: Washington, DC, 1997. (b) Ooya, T.; Yui, N. *J. Controlled Release* **1999**, *58*, 251−269. (c) Chiu, S.-H.; Rowan, S. J.; Cantrill, S. J.; Glink, P. T.; Garrell, R. L.; Stoddart, J. F. *Org. Lett.* **2000**, *2*, 3631−3634.