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A Rotaxane-Like Complex with Controlled-Release Characteristics

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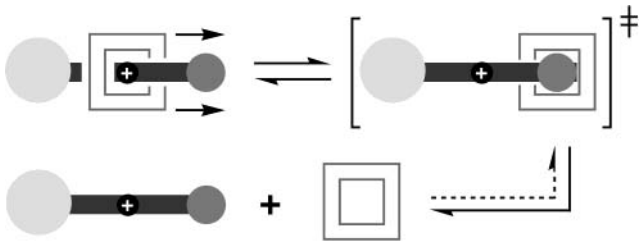
ABSTRACT



A rotaxane-like complex, based on a dumbbell-shaped component containing an NH_2^+ recognition site for a [25]crown-8 ring component and a slippage stopper in the form of a *p*-(*tert*-butyl)phenyl group, has been synthesized by a "threading-followed-by-stoppering" approach. The half-life for dissociation of this complex, which is very sensitive to its environment, can be varied from minutes to months by changing the temperature and the polarity of the solvent.

Much effort has been devoted during the past three decades to understanding and controlling noncovalent interactions utilized in the syntheses of interlocked compounds, such as rotaxanes and catenanes.[1] To demonstrate the potential applications of interlocked molecules in the field of drug delivery technologies,[2] it is essential to identify well-characterized supramolecular systems that have delicately balanced controlled-release properties that can be fine-tuned. Rotaxane-like complexes that can be isolated as discrete entities under certain conditions, but dissociate into their constituent parts under others—namely, rotaxane-like complexes capable of undergoing a slippage[3] process—may be a reasonable choice for such a system. In this Letter, we present a different synthetic approach to the construction of a new rotaxane-like "slippage complex" and report our attempts to elucidate the factors affecting the kinetic dissociation of the complex. This investigation may aid the design of supramolecular drug delivery systems[4] that take advantage of the controlled-release property.

The slippage method, which has been used sparingly[5] for preparing rotaxane-like complexes, involves slipping a macrocycle over bulky stopper groups located at the termini of a dumbbell-shaped molecule. Judicious choice[6] of the sizes and constitutions of the slippage stoppering group and the macrocycle's cavity is necessary in order to reach a fine balance between the system being capable of slippage or not. When such a balance is achieved, the macrocyclic component will possess enough thermal energy to permit slow passage

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(3) (a) Ashton, P. R.; Belohradsky, M.; Philp, D.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1993**, 1269−1274. (b) Raymo, F. M.; Stoddart J. F. *Pure Appl. Chem.* **1997**, *69*, 1987−1997. (c) Macartney, D. H. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2775−2778. (d) Händel, M.; Plevoets, M.; Gestermann, S.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1199−1201.

(4) For example, the so-called ionophorous antibiotics, (e.g., Nonactin, Monactin, and Dinactin), which bind to cations and are closely related to crown ethers, could, in theory, be incorporated into rotaxane-like complexes. See: (a) Kilbourn, B. T.; Dunitz, J. D.; Pioda, L. A.; Simon, W. *J. Mol. Biol*. **1967**, *30*, 559−563. (b) Eisenman, G.; Szabo, G.; McLaughlin, S. G. A.; Ciani, S. M. *Bioenergetics* **1973**, *4*, 93−148.

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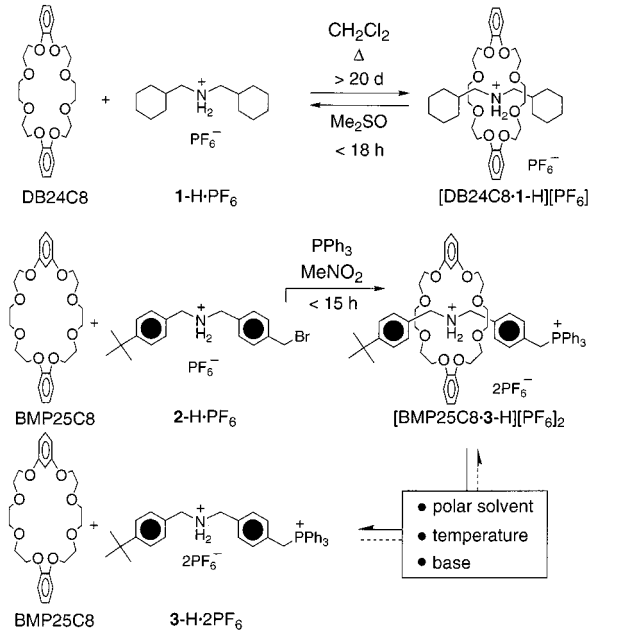
over the slippage stoppering group of the dumbbell. If the rodlike part of the dumbbell contains a recognition site for the macrocyclic component—i.e., if attractive noncovalent interactions are present—then a thermodynamic trap exists and a rotaxane-like complex can be isolated as a kinetically stable entity upon cooling to ambient temperature from a mixture that has been equilibrated at elevated temperatures. If the stoppers are too small, only pseudorotaxane formation—with fast rates of slipping on and off—will ensue and the complex will not be interlocked. If the stoppers are too large, slippage cannot occur and a rotaxane-like complex will not be formed.

A rotaxane-like complex [DB24C8·**1**-H][PF_6] has been synthesized[7] in 98% yield, after more than 20 days, in refluxing CH_2Cl_2 by the slippage of dibenzo[24]crown-8 (DB24C8) over the cyclohexyl termini of dumbbell **1**-H·PF_6. The need for long reaction times may make such synthetic approaches toward rotaxane-like complexes impractical, especially when trying to uncover other crown ether/slippage stopper pairs. To expedite the synthesis, we have made—and now report—a new rotaxane-like complex by a more traditional threading-followed-by-stoppering approach.[8] This protocol first allows a crown ether and a dialkylammonium ion thread containing a slippage stopper on one end and an electrophilic unit on the other to form the corresponding [2]pseudorotaxane and then attaches a bulky stopper via nucleophilic substitution to the reactive end of the thread at low temperature.

Although the *p*-(*tert*-butyl)phenyl group has been shown[8a] to be a sterically impassible stopper for DB24C8, it may not be so for crown ethers with larger cavities. We have found (Scheme 1) that it is not a true stopper, but rather a slippage stopper, for benzometaphenylene[25]crown-8 (BMP25C8).[9] When we mixed the bromo-functionalized

Scheme 1



thread **2**-H·PF_6 with BMP25C8 in $MeNO_2$ at ambient temperature and then added PPh_3,[10] the rotaxane-like complex [BMP25C8·**3**-H][PF_6]$_2$ was generated and isolated in 40% yield in less than 1 day. The lower yield, compared to the slippage synthesis of complex [DB24C8·**1**-H][PF_6], is a consequence of the weaker binding[11] between dialkylammonium ion-containing threads and this larger crown ether. An interesting phenomenon was observed relating to the polarity of the eluent used for column chromatography on silica gel: when using CH_2Cl_2/MeOH (19:1), no pure rotaxane-like complex was isolated. It always contained some decomplexation product. CH_2Cl_2/MeCN (9:1), however, gave the pure complex intact, even on a gram scale. This observation implies that the more polar mixture of CH_2Cl_2/MeOH/SiO_2 decreases the free energy of activation for the slipping off process relative to that in a less polar mixture of CH_2Cl_2/MeCN/SiO_2 and, in so doing, increases the rate of dissociation such that it occurs on the time-scale of flash chromatography. Other factors that can affect hydrogen bonding between the crown ether and the dialkylammonium ion-containing thread should affect the dissociation of complex [BMP25C8·**3**-H][PF_6]$_2$. Complex [DB24C8·**1**-H]-[PF_6] dissociates completely in less than 18 h at ambient temperature when dissolved in CD_3SOCD_3; dissociation was not studied in other solvents, at other temperatures, or in the presence of added bases. We have, however, now conducted investigations of the dissociation behavior of the

(5) The "slippage" methodology was first exploited for rotaxane syntheses that were conducted in a statistical manner. In the absence of mutual recognition interactions between the ring and thread, formation of a rotaxane-like complex relied simply upon chance encounters between the components. For examples, see: (a) Harrison, I. T. *J. Chem. Soc., Chem. Commun.* **1972**, 231−232. (b) Agam, G.; Gravier, D.; Zilkha, A. *J. Am. Chem. Soc.* **1976**, *98*, 5206−5214. (c) Schill, G.; Beckmann, W.; Schweikert, N.; Fritz, H. *Chem. Ber.* **1986**, *119*, 2647−2655. The successful marriage—first reported in 1993 (see ref 3a)—of template-directed approaches with slippage resulted in efficient noncovalent syntheses of rotaxane-like complexes. See also: ref 3b−d, and (d) Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, M.; Gandolfi, M. T.; Philp, D.; Prodi, L.; Raymo, F. M.; Reddington, M. V.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 4931−4951. (e) 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*, 302−310. (f) Ashton, P. R.; Fyfe, M. C. T.; Schiavo, C.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Tetrahedron Lett.* **1998**, *39*, 5455−5458. (g) Heim, C.; Affeld, A.; Nieger, M.; Vögtle, F. *Helv. Chim. Acta* **1999**, *82*, 746−759. (h) 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, 2000, pp 211−220.

(6) Raymo, F. M.; Houk, K. N.; Stoddart, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 9318−9322.

(7) 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.

(8) For recent examples, see: (a) Rowan, S. J.; Stoddart, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 164−165. (b) Loeb, S. J.; Wisner, J. A. *Chem. Commun.* **2000**, 845−846. (c) Seel, C.; Vögtle, F. *Chem. Eur. J.* **2000**, *6*, 21−24. (d) Buston, J. E. H.; Young, J. R.; Anderson, H. L. *Chem. Commun.* **2000**, 905−906.

(9) Cantrill, S. J.; Fulton, D. A.; Heiss, A. M.; Pease, A. R.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. Eur. J.* **2000**, *6*, 2274−2287.

(10) See for example: (a) Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 129−132. (b) Rowan, S. J.; Cantrill, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Org. Lett.* **2000**, *2*, 759−762.

(11) Ashton, P. R.; Bartsch, R. A.; Cantrill, S. J.; Hanes, R. E., Jr.; Hickingbottom, S. K.; Lowe, J. N.; Preece, J. A.; Stoddart, J. F.; Talanov, V. S.; Wang, Z.-H. *Tetrahedron Lett.* **1999**, *40*, 3661−3664.

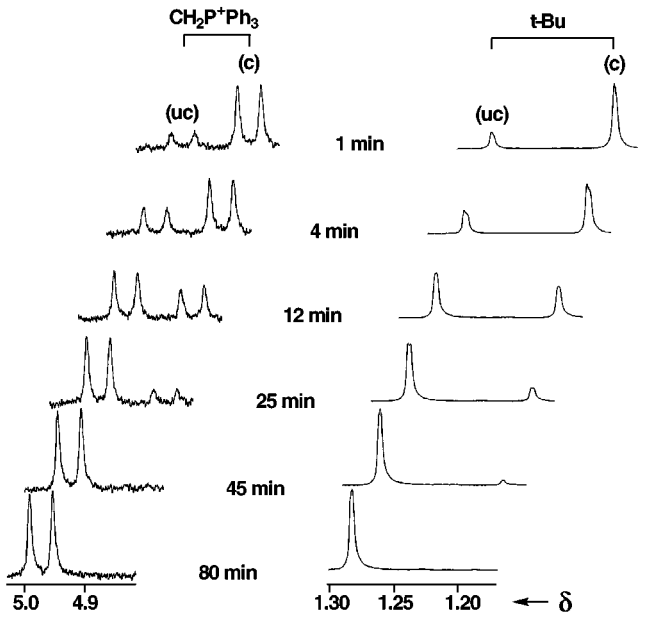


Figure 1. Partial ^{1}H NMR (400 MHz, 298 K) spectra displaying the dissociation of the components of complex [BMP25C8•**3**-H][PF_6]$_2$ in CD_2Cl_2/CD_3SOCD_3 (1:1). The regions displayed correspond to the signals for the methylene protons adjacent to the phosphonium stopper (left) and for the *tert*-butyl protons of the slippage stopper (right). The descriptors (c) and (uc) refer to complexed and uncomplexed states of the dumbbell-like component.

[BMP25C8•**3**-H][PF_6]$_2$ complex under these different conditions, using ^{1}H NMR spectroscopy as probe.

The ^{1}H NMR spectra illustrated in Figure 1 show dissociation of the complex [BMP25C8•**3**-H][PF_6]$_2$ in a 1:1 CD_2Cl_2/CD_3SOCD_3 mixture over time. The singlets at δ 1.18 and 1.28 are for the *tert*-butyl protons in the complex [BMP25C8•**3**-H][PF_6]$_2$ and the free thread **3**-H•2PF_6, respectively. As time progressed, the signal at δ 1.18 decreased and the signal at δ 1.28 increased proportionally. The relative intensities of the signals at δ 4.84 for the $CH_2{-}^{+}PPh_3$ methylene protons of the complex [BMP25C8•**3**-H][PF_6]$_2$ decreased with time as the signals at δ 4.97 for the corresponding protons of the uncomplexed thread **3**-H•2PF_6 increased. Similar effects were observed (not shown) for the protons of the complexed and uncomplexed crown ethers. From integration of pertinent signals in these spectra, we have been able to determine the rate constant (k_d),[12] the half-life ($t_{1/2}$),[13] and the free energy of activation ($\Delta G^{\ddagger}$) for this dissociation process. Additionally, we have monitored this dissociation in other solvents and at other temperatures in order to calculate the enthalpic ($\Delta H^{\ddagger}$) and entropic ($\Delta S^{\ddagger}$) contributions to the dissociation process (Figure 2 and Table 1).

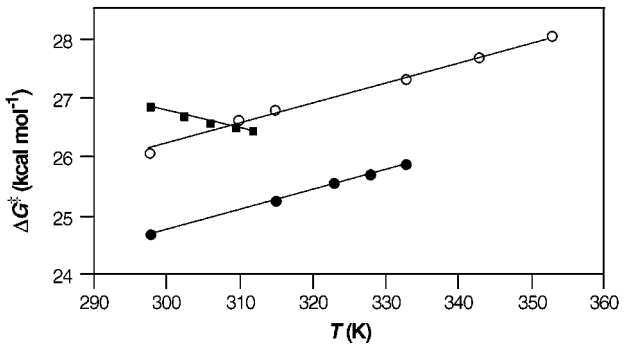


Figure 2. Plot of $\Delta G^{\ddagger}$ vs T (K) for dissociation of complex [BMP25C8•**3**-H][PF_6]$_2$ in CD_3OD (●), CD_3CN (○), and CD_2Cl_2 (■) as a function of temperature. The slope and intercept of each line give $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ (see Table 1), respectively.

At ambient temperature, complete dissociation of complex [BMP25C8•**3**-H][PF_6]$_2$ into its components in CD_3SOCD_3 requires less than 6 min, which is at least 50 times faster than dissociation of the slippage complex [DB24C8•**1**-H][PF_6] under the same conditions.[7] This result could imply that there is a less tight fit between the *p*-(*tert*-butyl)phenyl group and the cavity of BMP25C8 than between the cyclohexyl unit and DB24C8. In contrast to the dissociation in CD_3SOCD_3, complex [BMP25C8•**3**-H][PF_6]$_2$ dissociates very slowly in CD_2Cl_2 and has a half-life of approximately two months. In CD_2Cl_2/CD_3SOCD_3 mixtures, the half-life of the complex can vary from 10 min (CD_2Cl_2/CD_3SOCD_3 = 1:1) to 2 h (CD_2Cl_2/CD_3SOCD_3 = 3:1). Thus, one is able to control the half-life of the dissociation of the complex from minutes to hours to months simply by changing the ratio between the CD_2Cl_2 and CD_3SOCD_3 in solvent mixtures. The dissociation of complex [BMP25C8•**3**-H][PF_6]$_2$ in CD_2Cl_2 has a half-life of months at 298 K, but days at 312 K. The reaction is accelerated more than 15 times by only a 14 K increase in temperature. Over the same temperature range, the dissociative rate increased only 2- to 3-fold in CD_3CN and CD_3OD. These observations are a result of positive entropy of activation ($\Delta S^{\ddagger}$) for the dissociation process in CD_2Cl_2 and a negative $\Delta S^{\ddagger}$ for dissociation in CD_3CN and CD_3OD. Enthalpies of activation ($\Delta H^{\ddagger}$) are positive in all three solvents. The value of $\Delta S^{\ddagger}$ may be related to two major factors. (1) A loss of translational, rotational, and vibrational degrees of freedom of the macrocyclic polyether upon "stretching out" to pass over the slippage stopper would contribute negative entropy to the total entropy of activation in all solvents. (2) A change in the solvation of the dumbbell-like component when the macrocycle migrates from the ammonium center to the stopper would also affect the entropy of activation. The hydrophilic dialkylammonium ion center becomes exposed to the solvent, and the hydrophobic stopper becomes shielded by the

(12) In all of the solvents investigated, first-order dissociation kinetics are observed to be in operation, i.e., good straight lines are observed (see Supporting Information) when ln[A_0]/[A_t] is plotted against t, where [A_t] is the concentration of rotaxane-like complex at time t and [A_0] is its initial concentration. This outcome is a consequence of the fact that the reverse "slipping-on" process does not occur appreciably in the more polar solvents (CD_3SOCD_3 and CD_3OD), and the data for the less polar solvents (CD_2Cl_2 and CD_3CN) were collected in the early stages of the experiment where the "slipping-on" process is not yet occurring to any significant extent.

(13) See Table 1, footnote d.

Table 1. Kinetic Data for the Dissociation of [BMP25C8·**3**-H][PF_6]$_2$ into Its Components in Various Solvents[a]

solvent	k_d (s^{-1})[b,c]	$t_{1/2}$ (h)[c]	$\Delta G^{\ddagger}$ (kcal mol^{-1})[e]	$\Delta H^{\ddagger}$ (kcal mol^{-1})[f]	$\Delta S^{\ddagger}$ (cal $mol^{-1}K^{-1}$)[f]
CD_2Cl_2	$1.3 \pm 0.1 \times 10^{-7}$	1500[d]	26.9 ± 0.1	35.5 ± 0.8	29.2 ± 8
CD_3CN	$5.3 \pm 0.1 \times 10^{-7}$	360[d]	26.0 ± 0.1	15.7 ± 0.4	-34.8 ± 4
CD_3OD	$5.4 \pm 0.1 \times 10^{-6}$	36	24.7 ± 0.1	14.4 ± 0.3	-34.5 ± 3
CD_2Cl_2:CD_3SOCD_3 (3:1)	$9.2 \pm 0.3 \times 10^{-5}$	2.0	23.0 ± 0.1	–	–
CD_2Cl_2:CD_3SOCD_3 (1:1)	$1.0 \pm 0.1 \times 10^{-3}$	0.18	21.5 ± 0.1	–	–

[a] Experiments were performed with an initial concentration of [BMP25C8·**3**-H][PF_6]$_2$ of 2.6 mM. [b] The k_d values were obtained from the slope of the straight line in the plot of $\ln([A_0]/[A_t])$ against t using the relationship of $\ln([A_0]/[A_t]) = k_d t$. The values $[A_0]$ and $[A_t]$ correspond to the initial concentration of the complex and the concentration of the complex at time t, respectively, and were obtained from integration of the signals associated with the probe protons in the complexed and uncomplexed *tert*-butyl groups. [c] Calculated at 298 K. [d] The values of "half-life" quoted are the theoretical values that would be observed in a nonequilibrating system, i.e., if the reverse "slipping-on" process was prevented by constant removal of the separated components from the system. [e] The $\Delta G^{\ddagger}$ values were calculated using the relationship $\Delta G^{\ddagger} = -RT \ln(k_d h/kT)$ where R, h, and k correspond to the gas, Planck and Boltzmann constants. [f] The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were obtained from the intercept and slope of the straight line in the plot of $\Delta G^{\ddagger}$ against T using the relationship $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

macrocycle during the process of dethreading, i.e., the rotaxane-like complex is more polar in the transition state involving unthreading than it is when the macrocycle encircles the NH_2^+ center. In polar solvents, the solvent molecules are more ordered around the polar ammonium center than when around the nonpolar stoppers. On the other hand, the same phenomenon makes the CD_2Cl_2 solvent molecules less ordered in the transition state than in the ground state and, thus, a positive value of the entropy of solvation probably contributes to the total entropy of activation. In CD_2Cl_2, it would appear that the positive effect on the solvation entropy dominates over the negative effect of loss of freedom of motion of the macrocyclic polyether and thus a positive entropy of activation is observed. This situation implies that the rate of dissociation of complex [BMP25C8·**3**-H][PF_6]$_2$ is very sensitive to small changes in temperature and that the thermally controlled release of the macrocyclic component is capable of being finely tuned.

Although addition of *i*-Pr_2NH to MeCN and MeOH solutions of the complex [BMP25C8·**3**-H][PF_6]$_2$ accelerates the initial dissociation reaction rates, these rates decrease after a certain time. This behavior, which no doubt relates to the acid−base and crown ether complexation equilibria between the secondary dialkylammonium salts of the dumbbell-shaped compound and of the added secondary dialkylamine base, is currently under investigation.

In conclusion, we have assembled a rotaxane-like complex [BMP25C8·**3**-H][PF_6]$_2$ by a "threading-followed-by-stopping" method. The half-life for dissociation of this complex is extremely sensitive to changes in its environment and can be varied from minutes to hours to months by changing the temperature and the polarity of the solvent. A fundamental understanding of such simple controlled-release complexes will aid the design of more complicated supramolecular assemblies that may find applications in novel drug delivery systems.

Acknowledgment. We thank UCLA and the Petroleum Research Fund, administered by the American Chemical Society, for generous financial support.

Supporting Information Available: The synthesis and ^1H and ^{13}C NMR spectra of the complex [BMP25C8·**3**-H][PF_6]$_2$ and graphical representation of the kinetic data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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