Kinetics of the Self-Assembly of α-Cyclodextrin [2]Pseudorotaxanes with 1,12-Bis(4-(α-alkyl-α-methylmethanol)pyridinium)dodecane Dications in Aqueous Solution

A. Catherine Smith and Donal H. Macartney*

Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6, Canada

Received May 8, 1998

The kinetics and thermodynamics of the self-assembly of a series of [2]pseudorotaxanes comprised of α-cyclodextrin (α-CD) and racemic 1,12-bis(4-(α-alkyl-α-methylmethanol)pyridinium)dodecane dications ($L(CH_2)_{12}L^{2+}$) in aqueous solutions have been investigated using ^{1}H NMR spectroscopy. The mechanism of assembly involves inclusion of the α-methyl-α-alkylmethanol substituent groups ($-C(CH_3)(OH)R$, where R = Me, Et, Pr, Bu, allyl, and 4-butenyl) by α-CD, followed by a rate-determining passage of the cyclodextrin over the pyridinium group onto the dodecamethylene chain. Dicationic threads containing end groups with R = Ph or *i*-Pr or where L = 4-(α,α-diethylmethanol)-pyridinium did not form α-cyclodextrin pseudorotaxanes, even after prolonged heating. The trends in the rate and activation parameters may be related to the size, shape, and hydrophobicity of the alkyl substituents and are compared with several other systems from the literature. An increase in the length and hydrophobicity of the alkyl group increases the strength of end group inclusion and decreases the rate of threading. In addition, the presence of unsaturation in the alkyl substituent (allyl vs propyl and 4-butenyl vs butyl) results in an increase in the threading rate constant.

Introduction

The supramolecular complex[1] resulting from the threading of a cyclic molecular bead by a linear chain that is stoppered by bulky end units (preventing the supramolecular complex from dissociating into its cyclic and linear components) is termed a rotaxane.[2] If the end units are not sufficiently bulky to prevent dissociation from occurring, a pseudorotaxane is formed. A number of [2]-pseudorotaxanes and [2]rotaxanes (the [*n*] refers to the number of components) have been prepared using a variety of cyclic components,[3] including the cyclodextrins,[4] a family of cyclic oligosaccharides normally consisting of six (α-CD), seven (*β*-CD), or eight (*γ*-CD) α-(1→4)-linked D-(+)-glucopyranose units. These cyclic hosts possess hydrophobic interior cavities and hydrophilic rims bearing primary and secondary hydroxyl groups. Hydrophobic linear polymethylene chains, capped with charged end units ($L(CH_2)_nL^{m+}$), which have included aromatic *N*-heterocycles,[5,6] trialkylammonium and -phosphonium groups,[7] carboxylate groups,[8] and cobalt(III) amine,[9] pentacyanoferrate(II)[10] and cob(III)-alamin metal centers,[11] have frequently been employed as the threads for cyclodextrin pseudorotaxanes and rotaxanes.

The kinetics and mechanisms of the self-assembly of cyclodextrin [2]pseudorotaxanes and [2]rotaxanes have been investigated for a relatively limited, but growing, list of linear threads. There have been three mechanisms identified with the formations of pseudorotaxanes and rotaxanes of cyclodextrins in aqueous solution. The "threading" mechanism, in which a linear $L'(CH_2)_nL^{m+}$ species threads through the CD such that the polymethylene chain is included in the cavity, is the most straightforward for pseudorotaxane formation.[3] Threading rate constants and activation parameters have been reported for [2]pseudorotaxane formation where L = L′ = COO^- (*n* = 8−12),[8] L = L′ = pyridinium (*n* = 8−12),[5c,8]

(1) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995.

(2) Schill, G. *Catenanes, Rotaxanes, and Knots*; Academic Press: New York, 1971.

(3) For recent reviews, see: (a) Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 846. (b) Ogino, H. *New J. Chem.* **1993**, *17*, 683. (c) Gibson, H. W.; Bheda, M. C.; Engen, P. T. *Prog. Polym. Sci.* **1994**, *19*, 843. (d) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 843. (e) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725. (f) Harada, A. *Coord. Chem. Rev.* **1996**, *148*, 111. (g) Philp, D. Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1155. (h) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393. (i) Jäger, R.; Vöger, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 930. (j) Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1959. (k) Chambron, J.-C.; Sauvage, J.-P. *Chem. Eur. J.* **1998**, *4*, 1362.

(4) (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978. (b) Szejtli, J. *Cyclodextrins and their Inclusion Complexes*; Akadémiai Kiadó: Budapest, 1982. (c) Szejtli, J.; Osa, T. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 3. (d) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325. (e) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743.

(5) (a) Yonemura, H.; Saito, H.; Matsushima, S.; Nakamura, H.; Matsuo, T. *Tetrahedron Lett.* **1989**, *30*, 3143. (b) Yonemura, H.; Kasahara, M.; Saito, H.; Nakamura, H.; Matsuo, T. *J. Phys. Chem.* **1992**, *96*, 5765. (c) Saito, H.; Yonemura, H.; Nakamura, H.; Matsuo, T. *Chem. Lett.* **1990**, 535.

(6) Macartney, D. H. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2775.

(7) Lyon, A. P.; Banton, N. J.; Macartney, D. H. *Can. J. Chem.*, **1998**, *76*, 843.

(8) Watanabe, M.; Nakamura, H.; Matsuo, R. *Bull. Chem. Soc. Jpn.*, **1992**, *65*, 164.

(9) (a) Ogino, H. *J. Am. Chem. Soc.* **1981**, *103*, 1303. (b) Ogino, H.; Ohata, K. *Inorg. Chem.* **1984**, *23*, 3312.

(10) (a) Wylie, R. S.; Macartney, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 3136. (b) Wylie, R. S.; Macartney, D. H. *Supramolecular Chem.* **1993**, *3*, 29. (c) Waddling, C. A.; Macartney, D. H. *Inorg. Chem.* **1994**, *33*, 5912. (d) Lyon, A. P.; Macartney, D. H. *Inorg. Chem.* **1997**, *36*, 72. (e) Baer, A. J.; Macartney, D. H. *Inorg. Chem.*, submitted for publication.

(11) Hannak, R. B.; Farber, G.; Konrat, G.; Krauter, B. *J. Am. Chem. Soc.* **1997**, *119*, 2313.

10.1021/jo9808775 CCC: $15.00
Published on Web 11/18/1998

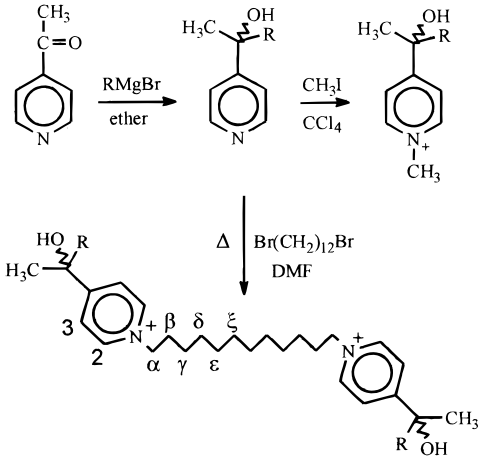
L = 1′-isopropyl-4,4′-bipyridinium (n = 10, L′ = bulky carbazole group),[5b] L = 1′-propyl-4,4′-bipyridinium (n = 8, L′ = 9-hydroxymethylanthracene),[12] L = L′ = 3-cyanopyridinium (n = 10),[10d] and $N(CH_3)_3^+$ (n = 9−12).[7] If the thread of the pseudorotaxane contains terminal groups with donor atoms, such as 4,4′-bipyridinium or pyrazinium, complexation to a metal center, such as the pentacyanoferrate(II) ion,[10] produces a rotaxane.

We have identified a second mechanism for forming metal complex-stoppered rotaxanes, which is a variation on the "threading" process for pseudorotaxanes.[10] With thread-bridged dimeric iron(II) complexes of the type $(NC)_5Fe(L(CH_2)_nL)Fe(CN)_5^{4-}$ (L = 4,4′-bipyridine, pyrazine, or 3- or 4-cyanopyridine, n = 8−12), a dissociation of one $Fe(CN)_5^{3-}$ end groups permits the threading of α-cyclodextrin to yield a semirotaxane $(NC)_5Fe\{L-(CH_2)_nL\cdot\alpha\text{-CD}\}^-$, which is rapidly recomplexed by the $Fe(CN)_5OH_2^{3-}$ ion to yield the rotaxane. These rotaxanes may therefore be formed irrespective of the order of adding the cyclic (α-CD), linear ($L(CH_2)_nL^{2+}$), and stopper ($Fe(CN)_5OH_2^{3-}$) components.

A third method of forming rotaxanes is the so-called "slippage" process,[13−15] in which the threading of the cyclic component occurs efficiently only at elevated temperatures, as the diameters of the cavity of the cyclic host and end groups of the guest are closely matched in size. We have recently reported the kinetics of the formation of pseudorotaxanes with α-CD and dicationic threads, $L(CH_2)_{10}L^{2+}$, where L = $N(CH_3)_3^+$ or $P(CH_3)_3^+$.[7] In the system where L = $P(CH_3)_3^+$, rotaxane formation is not observed below about 45 °C, and the rate constant for the slippage process measured at 75 °C is about 10^6 faster than the extrapolated value for the dication with L = $N(CH_3)_3^+$, for which the end group diameter is smaller by about 0.54 Å.

In this laboratory, a kinetic study of the self-assembly of an α-CD pseudorotaxane with L = 4-*tert*-butylpyridinium (n = 10) indicated that the threading step was preceded by weak, reversible binding of α-CD to the *tert*-butyl end groups.[6] To more fully determine the roles of the end groups in the kinetics and mechanisms of the pseudorotaxane self-assembly processes, a series of racemic dicationic 1,12-bis(4-(α-methyl-α-alkyl-methanol)-pyridinium)dodecane threads, in which the size and hydrophobicity of the end groups may be varied, were synthesized (Scheme 1). The kinetics and mechanisms of the self-assembly of α-cyclodextrin [2]pseudorotaxanes in aqueous solution were investigated with these threads. The rate constants, activation parameters, and stability constants associated with the formation of the [2]pseudorotaxanes have been determined using ^{1}H NMR techniques. The stability constants for α-cyclodextrin inclusion complexes with the corresponding *N*-methyl-4-(α-methyl-α-alkylmethanol)pyridinium cations (Scheme 1), as end group models, have been also been determined by means of ^{1}H NMR chemical shift titrations and are compared with the values calculated from the analyses of the kinetics of the [2]pseudorotaxane assembly reactions. Analyses of the trends in the threading rate constants and activation parameters from this study and others from the literature have been made in terms of the size and shape of the thread end groups, as well as the changes in their solvation while passing through the α-cyclodextrin cavity.

Scheme 1. Syntheses of the Guest Compounds



Results and Discussion

Characterization of the [2]Pseudorotaxanes. When approximately equivalent concentrations of the α-CD host and a 1,12-bis(4-(α-alkyl-α-methylmethanol)-pyridinium)dodecane guest (designated $L(CH_2)_{12}L^{2+}$, where L = $pyrC(OH)(CH_3)R^+$) are mixed together in aqueous solution, the formation of the [2]pseudorotaxane, $L\{-(CH_2)_{12}\cdot\alpha\text{-CD}\}L^{2+}$, may demonstrated by ^{1}H and ^{13}C NMR spectroscopy. The resonances of the symmetry-related pyridine H_2 and H_3 protons, along with the resonances of the protons of the dodecamethylene chain (of which H_α and H_β are most easily distinguished (Figure 1a)) are split into pairs of peaks upon inclusion in the asymmetric cyclodextrin host. This splitting of the resonances is shown in the spectra in Figure 1b, in which 1.6 equiv of α-CD has been added to a $L(CH_2)_{12}L^{2+}$ thread bearing propyl substituents.

A 2D ROESY experiment (using NOE connections to the internal H3 (wider end) and H5 (narrower end) protons of the α-CD cavity) revealed that the upfield resonances of the split pairs of peaks are associated with the half of the thread at the narrower end of the α-CD. A proton-decoupled ^{13}C NMR spectrum of a $L(CH_2)_{12}L^{2+}$ thread (R = Et) mixed with 1.04 equiv of α-CD also

(12) Toki, A.; Yonemura, H.; Matsuo, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3382.
(13) (a) Harrison, I. T. *J. Chem. Soc., Chem. Commun.* **1972**, 231. (b) Harrison, I. T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 301.
(14) Schill, G.; Beckmann, W.; Schweickert, N.; Fritz, H. *Chem. Ber.* **1986**, *119*, 2647.
(15) (a) Ashton, P. R.; Belohradsky, M.; Philp, D.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1993**, 1269, 1274. (b) Amabilino, D. B.; Ashton, P. R.; Belohradsky, M.; Raymo, F. M.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1995**, 747, 751. (c) Ashton, P. R.; Ballardini, V.; Balzani, M.; Belohradsky, M.; Gandolfi, M. T.; Philp, D.; Raymo, F. M.; Reedington, M. V.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 4931. (d) 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. (e) Raymo, F. M.; Stoddart, J. F. *Pure Appl. Chem.* **1997**, *69*, 1987.

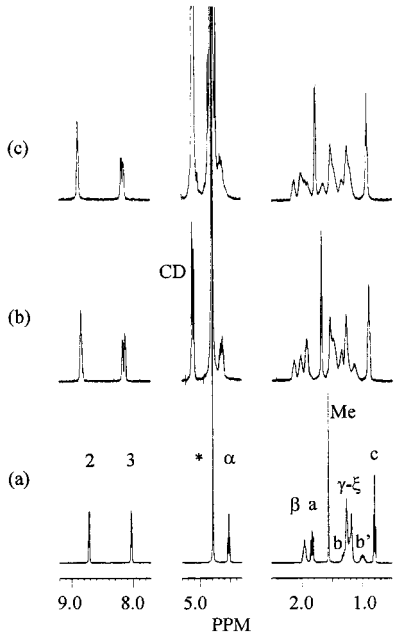


Figure 1. ^{1}H NMR spectra of (a) the dication $L(CH_2)_{12}L^{2+}$ (R = propyl) and the pseudorotaxanes formed with 5 mM $L(CH_2)_{12}L^{2+}$ and (b) 1.6 equiv of α-CD or (c) 8.2 equiv of α-CD, in D_2O at 25 °C. The thread protons are labeled as in Scheme 1, with * denoting the solvent HOD resonance and CD the H_1 proton of α-CD.

demonstrated qualitative evidence of pseudorotaxane formation, as many of the peaks for the symmetry-related guest carbons were split into pairs of resonances.

The formation of a pseudorotaxane is also indicated in the gas phase by positive-ion electrospray mass spectrometry. Using an aqueous solution of the α-CD (10 mM) and the $L(CH_2)_{12}L^{2+}$ thread (1 mM), where R = propyl, a peak at m/z = 735.4 (100%) consistent with the [2]pseudorotaxane $L\{(CH_2)_{12}\cdot\alpha\text{-CD}\}L^{2+}$ was observed. In addition, two smaller peaks were observed at m/z = 1221.7 (72%) and 1708.1 (8%), which may be attributed, respectively, to $L\{(CH_2)_{12}\cdot\alpha\text{-CD}\}\{L\cdot\alpha\text{-CD}\}^{2+}$, in which one 4-(α-propyl-α-methylmethanol)pyridinium end group on the [2]pseudorotaxane is included in the cavity of a second α-CD host molecule and $\{L\cdot\alpha\text{-CD}\}\{(CH_2)_{12}\cdot\alpha\text{-CD}\}\{L\cdot\alpha\text{-CD}\}^{2+}$, in which the second pyridinium end group is also included in a third α-CD host molecule. Further evidence of inclusion(s) of the pyridinium end groups when excess α-CD is present in solution is provided by ^{1}H NMR spectroscopy, as the resonances for the end-group methyl and alkyl functionalities shift substantially and often split into pairs upon binding by the cyclodextrin host(s). This is illustrated in Figure 1c, which depicts the ^{1}H NMR spectrum of the $L(CH_2)_{12}L^{2+}$ thread (R = propyl) with 8.2 equiv of α-CD added.

Three of the $L(CH_2)_{12}L^{2+}$ threads synthesized in this study were unable to form pseudorotaxanes when mixed with α-CD in solution. The end group on the 1,12-bis-(4-(α,α-diethylmethanol)pyridinium)dodecane dication was too large to permit threading through the α-CD, even with prolonged heating. Inclusion of the 1,12-bis(4-(α-alkyl-α-methylmethanol)pyridinium)dodecane dications with R = isopropyl and R = phenyl into the α-CD were similarly not observed.

The addition of the larger β- and γ-cyclodextrins to solutions of the dication threads in Scheme 1 do not, with one exception, result in splittings of the thread proton resonances, as observed with the α-CD pseudorotaxane formations. Instead, the proton resonances of the thread and the cyclodextrins exhibit small chemical shifts changes upon mixing. These may be the result of CD inclusions of the substituted pyridinium headgroups and/or the formation of pseudorotaxanes, whose rates of formation and dissociation are rapid on the NMR time scale. The exception to this is the reaction between β-CD and the thread where R = phenyl, which upon mixing produces small but distinct splittings in the pyridine proton resonances ($\Delta\delta$ = 0.013 ppm for H2 and 0.005 ppm for H3) into pairs of doublets. Upon warming the solution, coalescence of the peaks occurs at about 40 °C for H3 and about 60 °C for H2. For the pseudorotaxanes described above with α-CD, no coalescence of the split peaks is observed up to 90 °C.

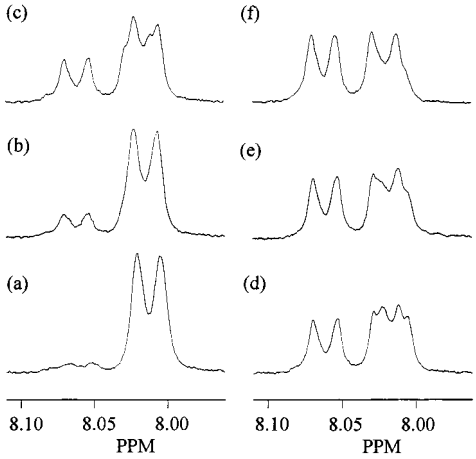


Figure 2. Time dependence of the pyridine H_3 resonance of the $L(CH_2)_{12}L^{2+}$ (R = butyl) upon inclusion into α-CD to form a pseudorotaxane at 25 °C in D_2O (I = 0.10 M (NaCl)); $[L(CH_2)_{12}L^{2+}]$ = 3 mM, [α-CD] = 15 mM: (a) 1, (b) 17, (c) 48, (d) 79, (e) 110, (f) 125 min.

Kinetics and Mechanism of [2]Pseudorotaxane Formation. The reactions between α-cyclodextrin and the 1,12-bis(4-(α-alkyl-α-methyl-methanol)pyridinium)-dodecane dications ($L(CH_2)_2L^{2+}$) to yield [2]pseudorotaxanes were slow enough (with the exception of R = methyl) to be conveniently monitored by using ^{1}H NMR spectroscopy. Upon formation of the pseudorotaxane, the symmetry-related protons on each half of the dicationic threads become inequivalent due to the asymmetry of the α-CD cavity, with proximity of the protons to either the narrow or wide rim of the host molecule resulting in a different induced chemical shift. In this study, the pyridine H_3 resonances of the dicationic thread were monitored, since the doublet that represents the H_3 protons of the free thread split into a well-separated pair of doublets upon α-CD inclusion of the dodecamethylene chain and is not obscured by resonances from other protons. With the exceptions of the dication with R = isopropyl and phenyl, which did not form pseudorotaxanes even with prolonged heating at 80 °C, pseudorotaxane formation was observed at room temperature, as illustrated in Figure 2 for the complex where R = butyl.

The kinetics of the pseudorotaxane formations, containing threads with R = Et, allyl, Pr, Bu, and 4-butenyl, were investigated in D_2O (I = 0.10 M (NaCl)) as a function of the concentration of α-cyclodextrin, present in excess over the thread. The concentrations of the free and threaded dications were determined by integrating

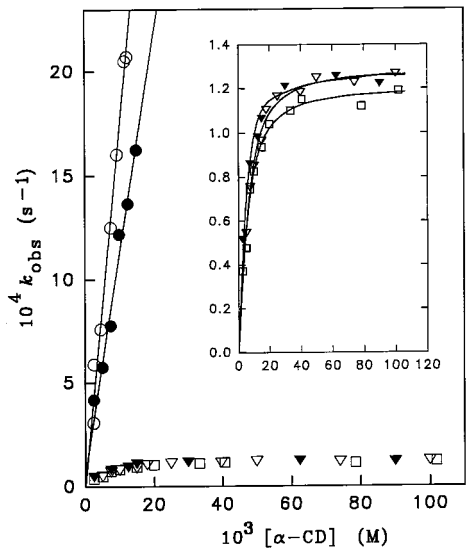


Figure 3. Plots of k_{obs} against [α-CD] for the formation of the [2]pseudorotaxanes of α-cyclodextrin and $[L(CH_2)_{12}L]^{2+}$ (L = 4-(α-alkyl-α-methylmethanol)pyridinium) threads with the alkyl substituents R = (○) ethyl, (●) allyl, (▽) propyl, (▼) butyl, and (□) 4-butenyl, in D_2O (I = 0.10 M (NaCl)) at 25 °C. Inset: expanded plots for R = (▽) propyl, (▼) butyl, and (□) 4-butenyl (axes labels are the same as the main plot).

Scheme 2. Mechanism of [2]Pseudorotaxane Self-Assembly

$$L(CH_2)_{12}L^{2+} + \alpha\text{-CD} \overset{K_{CD1}}{\rightleftharpoons} L(CH_2)_{12}\{L\bullet\alpha\text{-CD}\}^{2+}$$

$$L(CH_2)_{12}\{L\bullet\alpha\text{-CD}\}^{2+} + \alpha\text{-CD} \overset{K_{CD2}}{\rightleftharpoons} \{L\bullet\alpha\text{-CD}\}(CH_2)_{12}\{L\bullet\alpha\text{-CD}\}^{2+}$$

$$L(CH_2)_{12}\{L\bullet\alpha\text{-CD}\}^{2+} \xrightarrow{k_1} L\{(CH_2)_{12}\bullet\alpha\text{-CD}\}L^{2+}$$

$$\{L\bullet\alpha\text{-CD}\}(CH_2)_{12}\{L\bullet\alpha\text{-CD}\}^{2+} \xrightarrow{k_2} L\{(CH_2)_{12}\bullet\alpha\text{-CD}\}\{L\bullet\alpha\text{-CD}\}^{2+}$$

$$L\{(CH_2)_{12}\bullet\alpha\text{-CD}\}\{L\bullet\alpha\text{-CD}\}^{2+} + \alpha\text{-CD} \overset{K_{CD3}}{\rightleftharpoons} \{L\bullet\alpha\text{-CD}\}\{(CH_2)_{12}\bullet\alpha\text{-CD}\}\{L\bullet\alpha\text{-CD}\}^{2+}$$

the pyridinium H_3 protons, and formation reactions were found to be first-order processes. The dependences of the observed rate constants on the concentration of α-CD are depicted in Figure 3. For the dications with R = ethyl and allyl, the observed rate constants displayed a first-order dependence on the concentration of α-CD up to 15 mM, beyond which the reactions were too rapid to monitor. The formation of the pseudorotaxane with R = methyl was too rapid to be accurately monitored by ^{1}H NMR spectroscopy. With the dicationic threads with R = propyl, butyl, and 4-butenyl, the observed rate constants approached limiting values above 25 mM α-cyclodextrin (Figure 3).

The observed kinetic behavior is consistent with a mechanism involving α-cyclodextrin inclusion(s) of the terminal pyridinium end unit(s) of the dication, followed by threading to place the dodecamethylene chain within the cyclodextrin cavity, as depicted in Scheme 2.

The observed rate constant may be expressed in terms of the threading rate constants k_1 and k_2 and the end group inclusion stability constants K_{CD1} and K_{CD2} (eq 1).

$$k_{obs} = \frac{k_1 K_{CD1}[CD] + k_2 K_{CD1} K_{CD2}[CD]^2}{1 + K_{CD1}[CD] + K_{CD1} K_{CD2}[CD]^2} \qquad (1)$$

Since the values of k_{obs} for the threads where R = ethyl and allyl were measured at very low α-CD concentrations (2.5 mM to 15 mM), it can be assumed that the $[CD]^2$ terms in the rate expression are negligible and eq 1 can thus be simplified to eq 2. At these low concentrations

$$k_{obs} = \frac{k_1 K_{CD1}[CD]}{1 + K_{CD1}[CD]} \qquad (2)$$

of α-CD, such that $K_{CD1}[CD] \ll 1$, the rate expression simplifies further to eq 3, and a linear dependence of k_{obs} on [α-CD] would result (Figure 3). The slopes of the plots

$$k_{obs} = k_1 K_{CD1}[CD] \qquad (3)$$

of k_{obs} vs α-CD for these dicationic threads are equal to $k_1 K_{CD1}$, which are presented in Table 1.

The rates of pseudorotaxane formation for the dicationic threads where R = propyl, 4-butenyl, and butyl were slow enough to measure by ^{1}H NMR spectroscopy, even at high concentrations of α-CD. At the very lowest concentrations of α-CD, the assumptions leading to eq 3 hold, and the initial linear portion of the curves in the inset to Figure 2 would have a slope equal to $k_1 K_{CD1}$. However, as the concentration of α-CD increases, the curves approach limiting values of k_{obs}, and the $[CD]^2$ terms in the rate law begin to dominate until the conditions $K_{CD1}K_{CD2}[CD]^2 \gg K_{CD1}[CD] \gg 1$ and $k_2 K_{CD1}K_{CD2}[CD]^2 \gg k_1 K_{CD1}[CD]$ may be assumed. This reduces the expression in eq 1 to $k_{obs} = k_2$. Thus, the values of k_{obs} at high concentrations of α-CD provide initial estimates of k_2 for each of the three dications (R = propyl, 4-butenyl, and butyl) in the nonlinear least-squares fits (Experimental Section), from which values of k_1, k_2, K_{CD1}, and K_{CD2} for pseudorotaxane formation can be generated. These rate and equilibrium parameters are listed in Table 2.

Since the dicationic threads possess two end groups and thus two initial binding sites for the cyclodextrin host (Scheme 2), statistical binding ratios might be expected. The value of K_{CD1} represents the binding of one host molecule to one of the two available end groups. After binding, only one included end group exists from which the cyclodextrin can dissociate. The K_{CD2} value repre-

Table 1. Rate and Activation Parameters for Pseudorotaxane Formation from $L(CH_2)_{12}L^{2+}$ (L = pyrC(OH)(CH$_3$)R$^+$) and α-CD, where R = Ethyl and Allyl[a]

	R group	
$L(CH_2)_{12}L^{2+}$	ethyl	allyl
$10k_1K_{CD1}$ (M^{-1} s^{-1})	1.71 ± 0.09	1.00 ± 0.05
$\Delta H^{\ddagger}$ (kJ mol^{-1})	138 ± 8	109 ± 8
$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})	165 ± 24	64 ± 24
K_{MeL} (M^{-1})[b]	60 ± 3[c]	79 ± 7[d]
10^3k_1 (s^{-1})	2.9 ± 0.3	1.3 ± 0.2
$\Delta H^{\ddagger}_1$ (kJ mol^{-1})	178 ± 13	130 ± 9
$\Delta S^{\ddagger}_1$ (J K^{-1} mol^{-1})	266 ± 39	99 ± 27

[a] At 25 °C, I = 0.10 M (NaCl) in D_2O. [b] Inclusion stability constant for N-CH_3L^+ cation. [c] $\Delta H°$ = −40 ± 5 kJ mol^{-1}, $\Delta S°$ = −101 ± 15 J K^{-1} mol^{-1}. [d] $\Delta H°$ = −21 ± 1 kJ mol^{-1}, $\Delta S°$ = −35 ± 3 J K^{-1} mol^{-1}.

Table 2. Rate and Activation Parameters for Pseudorotaxane Formation from $L(CH_2)_{12}L^{2+}$ (L = pyrC(OH)(CH_3)R^+) and α-CD, where R = Propyl, 4-Butenyl, and Butyl[a]

	R group		
$L(CH_2)_{12}L^{2+}$	propyl	4-butenyl	butyl
$10^4 k_1$ (s^{-1})	0.65 ± 0.12	0.90 ± 0.14	0.69 ± 0.13
$10^4 k_2$ (s^{-1})	1.30 ± 0.09	1.25 ± 0.13	1.21 ± 0.10
$\Delta H^{\ddagger}_2$ (kJ mol^{-1})	148 ± 9	103 ± 13	131 ± 7
$\Delta S^{\ddagger}_2$ (J K^{-1} mol^{-1})	176 ± 28	27 ± 38	120 ± 21
K_{CD1} (M^{-1})	580 ± 120	990 ± 200	550 ± 110
K_{CD2} (M^{-1})	180 ± 20	290 ± 30	160 ± 20
K_{MeL} (M^{-1})[b]	581 ± 24	805 ± 84	389 ± 80

[a] At 25 °C, I = 0.10 M (NaCl) in D_2O. [b] Inclusion stability constant for N-CH_3L^+ cation.

sents the binding of a second host molecule to the other available end group. Now, however, there are two included end groups from which a cyclodextrin can dissociate, leading to a theoretical statistical ratio of 4:1 for K_{CD1}:K_{CD2}. The theoretical statistical ratio of the threading rate constants, k_1:k_2, is 1:2, as the value of k_1 represents the rate constant when only one end group is included into the cyclodextrin host, whereas k_2 represents the rate constant for threading when both end groups are included. The rate and equilibrium constants presented in Table 2 indicate the experimental K_{CD1}:K_{CD2} and k_1:k_2 ratios are fairly close to the statistical ratios, and therefore, the threadings of the two end groups onto the dodecamethylene chain proceed virtually independently of one another.

The activation parameters associated with the rate constants for the pseudorotaxane formation with $L(CH_2)_{12}L^{2+}$ guests and α-CD hosts were determined by studying the effect of temperature on the observed rate constants at low (R = ethyl and allyl) or high (R = propyl, butyl, and 4-butenyl) α-CD concentrations. In the case of the threads where R = ethyl and allyl, lower concentrations of α-CD (10 mM) were used such that $k = k_{obs}/[CD] = k_1K_{CD1}$ (k_2 is too large to be measured by ^{1}H NMR spectroscopy). The parameters listed in Table 1 are therefore a sum of the activation parameter associated with k_1 and the thermodynamic parameter associated with K_{CD1}. For R = propyl, butyl, and 4-butenyl, the rate constants were measured at high concentrations of α-CD (100 mM), such that $k_{obs} \approx k_2$.

The inclusion complexes formed between N-methyl-(4-(α-alkyl-α-methylmethanol)pyridinium cationic guests (designated as N-CH_3L^+) and α-CD hosts are good models of the end group binding of $L(CH_2)_{12}L^{2+}$ guests by α-CD prior to the threading step of pseudorotaxane formation. The values of K_{CD} for the N-CH_3L^+ guests where R = ethyl, allyl, propyl, 4-butenyl, butyl, and isopropyl were determined using ^{1}H NMR chemical shift titrations[10] and are presented in Tables 1 and 2. The thermodynamic parameters associated with K_{CD}, for N-CH_3L^+ inclusion in α-CD, were calculated to be $\Delta H° = -40 \pm 5$ kJ mol^{-1} and $\Delta S° = -101 \pm 15$ J K^{-1} mol^{-1} for R = ethyl and $\Delta H° = -21 \pm 1$ kJ mol^{-1} and $\Delta S° = -35 \pm 3$ J K^{-1} mol^{-1} for R = allyl. Using these equilibrium constants and the associated thermodynamic parameters as estimates for the binding the dicationic thread end groups by α-CD, values of k_1, $\Delta H^{\ddagger}_1$, and $\Delta S^{\ddagger}_1$ may be calculated (Table 1).

Determining a stability constant for the pseudorotaxanes, K_{pr}, from a ^{1}H NMR titration is complicated by the slow approach to equilibrium at the low thread and α-CD concentrations normally employed (<3 mM) and by the additional equilibria involving the inclusions of the end groups (such as K_{CD3} in Scheme 2). For this reason, a detailed stability constant measurement was only attempted for the dication with R = methyl, as it threads quickly and exhibits weak binding of the end groups by α-CD. The NMR titration at 25 °C in D_2O (I = 0.10 M (NaCl)) yielded a value of $(8.9 \pm 2.4) \times 10^3$ M^{-1}. This value is in the range of pseudorotaxane stability constants determined for other $L(CH_2)_{12}L^{2+}$ threads ($(3-10) \times 10^3$ M^{-1}).[5,7,8,10]

Trends in Pseudorotaxane Formation Parameters. The stability constants K_{CD} generally increase with the length of the alkyl substituent R. Similar trends are observed for the neutral 4-(α-alkyl-α-methylmethanol)pyridines,[16] alkylbenzenes,[17] and alkylmethanols,[18] the data for which are presented in Table 3. With the neutral pyridines and the N-methylpyridinium cations, it is observed that K_{CD} for R = butyl is lower than the value for R = propyl. This may be due to a protrusion of the hydrophobic group out the other end of the CD cavity, such that propyl represents the optimal length for the R substituent. This is supported by the trend in the value for the unsaturated R groups, allyl and 4-butenyl. The value for 4-butenyl is greater than that for butyl, while the value for allyl is lower than for propyl. This opposite trend may be related to the less hydrophobic nature of the −CH=CH− group. The very low value for R = isopropyl is likely due to the branched nature of the alkane that is too large to be accommodated in the α-CD cavity.

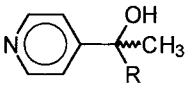
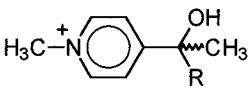
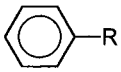
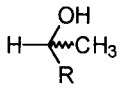
The rate constants for [2]pseudorotaxane formation from α-cyclodextrin and $L(CH_2)_nL^{m+}$ threads span about 7 orders of magnitude (Table 4). Rapid pseudorotaxane formation ($10^3 - 10^4$ M^{-1} s^{-1}) has been observed for dicationic threads with planar carboxylate or pyridinium end groups, with the α-CD cavity flattening to accommodate the aromatic rings. The presence of in-plane ring substituents such as with L = 3-cyanopyridinium (2.4 M^{-1} s^{-1}) slows down the threading process somewhat. The presence of tetrahedral end groups, such as in the $L(CH_2)_{10}L^{2+}$ threads with 4-*tert*-butylpyridinium and trialkylammonium (Table 4), present greater steric barriers to threading.

An examination of the values of k_1 presented in Tables 1 and 2 reveals that the first-order rate constant for the threading process for the systems in the present study decreases as the length of the R substituent increases. This observation could be a result of the α-CD binding more strongly to the end groups as they become longer and more hydrophobic, combined with the possibility that the α-CD molecule requires more energy to distort and thread over sterically larger groups. While both the entropy and the enthalpy of activation for the threading process of pseudorotaxane formation are effected by a large number of contributions and are thus difficult to appreciate conceptually, it is possible to describe some factors that may influence the values of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ presented in Tables 1 and 2.

All of the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values measured are large and positive. The unfavorable enthalpy of pseudorotaxane formation is thought to be caused by the large amount

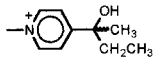
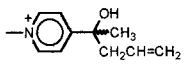
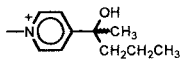
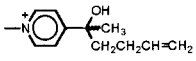
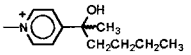
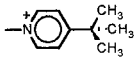
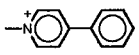
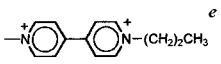
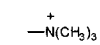
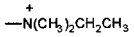
(16) Smith, A. C.; Lyon, A. P.; Tobin, L.; Macartney, D. H. Manuscript in preparation.
(17) Sanemasa, I.; Akamine, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2059.
(18) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808.

Table 3. Stability Constants (K_{CD}, M^{-1}) for Inclusion Complexes Formed between α-CD and Compounds Bearing α-Alkyl-α-methylmethanol Groups

R				
CH_3	24 ± 3 [a]		33 ± 3 [c]	4.9 ± 0.4 [d]
CH_2CH_3	45 ± 4 [a]	60 ± 3 [b]	110 ± 10 [c]	26 ± 2 [d]
$CH_2CH_2CH_3$	410 ± 67 [a]	581 ± 24 [b]	590 ± 10 [c]	135 ± 13 [d]
$CH(CH_3)_2$		17 ± 1 [b]	72 ± 1 [c]	19 ± 2 [d]
$CH_2CH_2CH_2CH_3$	282 ± 27 [a]	389 ± 80 [b]		355 ± 35 [d]

[a] Reference 16. [b] This work. [c] Reference 17. [d] Reference 18.

Table 4. The Rate Constants (25 °C) and Activation Parameters for the Self-Assembly of α-Cyclodextrin Pseudorotaxanes with $[L(CH_2)_nL]^{2+}$ Threads (unless Otherwise Indicated)

L	n	$10^2 k_{in}$ (M^{-1} s^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})
	12	17.1 ± 0.9	138 ± 8	165 ± 24
	12	10.0 ± 0.5	109 ± 8	64 ± 24
	12	3.74 ± 0.24		
	12	7.09 ± 0.34		
	12	3.82 ± 0.24		
	10	0.76 ± 0.14 [a]	102 ± 10	58 ± 32
	12	400 000 [b]	47.4	-17.0
	12	1 300 000 [b,c]		
	10	4 600 000 [d]		
 [e]	10	83 ± 13 [f]	49.8 ± 0.4	-79.5 ± 8.0
	10	16.4 ± 2.2 [g]	117 ± 2	134 ± 6
	10	0.58 ± 0.04 [g]	120 ± 6	114 ± 16
	10	240 ± 90 [d]		

[a] Reference 6. [b] Reference 5c. [c] Reference 8. [d] Wylie, R. S.; Lyon, A. P.; Macartney, D. H. Unpublished results. [e] Asymmetric $[L(CH_2)_{10}L']^{n+}$ thread used, where L is the viologen shown in the chart and L′ is a bulky carbazole group that cannot thread through α-CD. [f] Reference 5b.

of distortion the α-CD host undergoes while threading past the branched portion of the end group, followed by the planar pyridinium group. The favorable entropy is probably due to the desolvation of the ordered water

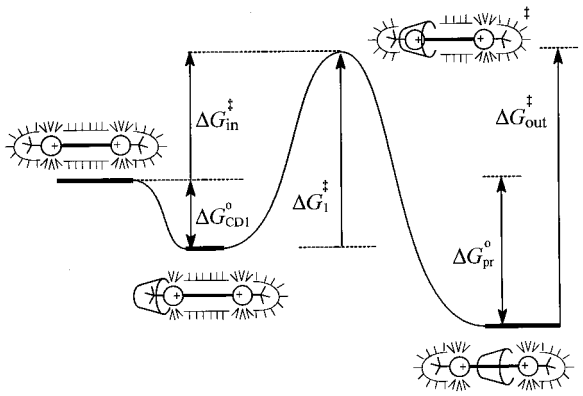


Figure 4. Free energy profile for the formation of a pseudorotaxane between α-CD and a dicationic thread composed of a hydrophobic polymethylene chain and pyridinium end groups with hydrophobic substituents. The symbol ⊥⊥⊥ represents water clusters about the hydrophobic groups,[19] while the tilted V symbol represents solvation of the hydrophilic groups.

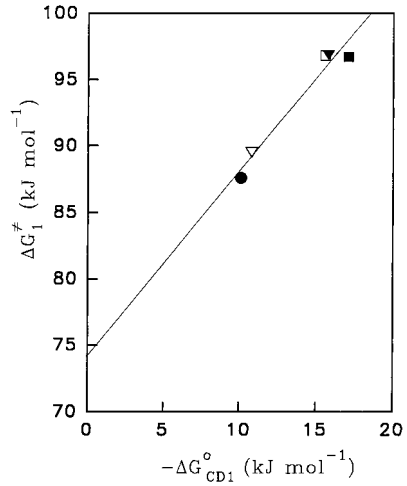


Figure 5. Plot of the free energy of activation for the threading step of pseudorotaxane formation, using 1,12-bis-(4-(α-alkyl-α-methylmethanol)pyridinium)dodecane threads and α-CD hosts, against the standard free energy for the inclusion of the pyridinium end group at 25 °C. R = ethyl (●), allyl (▽), propyl (▼), butyl (□), and 4-butenyl (■).

molecules surrounding the positive pyridinium functionality and the regaining of motional freedom of the hydrophobic R substituent upon formation of the pseudorotaxane. Two distinct trends in the activation parameters listed in Tables 1 and 2 can be observed. First, the dicationic threads with saturated R substituents on their end groups tend to have larger values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the threading step of pseudorotaxane formation than the dicationic threads with the analogous unsaturated R substituents (i.e., R = propyl vs allyl and R = butyl vs 4-butenyl). The larger $\Delta H^{\ddagger}$ values can be attributed to the need to overcome larger hydrophobic interactions between the saturated end groups and the α-CD cavity when the host threads over the end group and rests on the polymethylene chain. Smaller values of $\Delta S^{\ddagger}$ for the dicationic threads with unsaturated R substituents are probably caused by the fact that they do not gain back as much freedom of motion as their corresponding saturated R groups upon resolvation, due to the rigidity of the double bond. A second trend, of substantially decreasing values of $\Delta S^{\ddagger}$ for the threading process of α-CD pseudorotaxane formation as the length of the R substituent of the dicationic threads increases ($\Delta S^{\ddagger}_{R\,=\,butyl} < \Delta S^{\ddagger}_{R=propyl} < \Delta S^{\ddagger}_{R=ethyl}$), is also evident. This trend can be explained by the fact that end groups with longer R substituents require resolvation of a larger surface area upon the threading of the α-CD host, thus ordering a larger number of water molecules into "water clusters"[19] and decreasing the value of $\Delta S^{\ddagger}$. These desolvation and resolvation processes that occur during the self-assembly of the pseudorotaxanes are shown schematically in Figure 4, which depicts a free-energy profile for the formation of an α-CD pseudorotaxane using a dicationic thread with hydrophobic end group substituents.

The values of $\Delta G^{\ddagger}_{1}$ and ΔG°_{CD1} shown on the free-energy profile in Figure 4 can be calculated for the five dicationic guests studied in this study. The first-order rate constants (k_1) for the threading step of α-CD pseudorotaxane formation (Tables 1 and 2) can be used to calculate the values of $\Delta G^{\ddagger}_{1}$ associated with this step of the mechanism. Similarly, the α-CD inclusion stability constants (K_{CD1}) for the end group binding of these dicationic threads allow the calculation of ΔG°_{CD1}, using the equation $-\Delta G^{\circ}_{CD1} = RT\ln K_{CD1}$. A plot of $\Delta G^{\ddagger}_{1}$ vs $-\Delta G^{\circ}_{CD1}$, shown in Figure 5, displays a linear relationship between these two parameters, with $\Delta G^{\ddagger}_{1}$ increasing as $\Delta G c^{\circ}_{CD1}$ decreases. The intercept of this plot represents the value of $\Delta G^{\ddagger}_{1}$ for a 4-(α-alkyl-α-methylmethanol)pyridinium dicationic thread whose end groups do not bind significantly to α-CD (i.e., a dicationic thread with $K_{CD1} \approx 1\ M^{-1}$ and thus $\Delta G^{\circ}_{CD1} \approx 0$ kJ mol^{-1}). At this point, $\Delta G^{\ddagger}_{1}$ is effectively equal to $\Delta G^{\ddagger}_{in}$, and there is no stabilization due to end group binding prior to the threading step of pseudorotaxane formation. The value of $\Delta G^{\ddagger}_{in}$ from the plot in Figure 5 is approximately 74 kJ mol^{-1}, which corresponds to a second-order rate constant of approximately 0.67 M^{-1} s^{-1} (assuming that $K_{CD1} = 1\ M^{-1}$). This rate is about four times larger than the fastest rate of threading measured in this study for a $[L(CH_2)_{12}L]^{2+}$ guest (see Table 4) and would represent the value of k_{in} for the formation of a pseudorotaxane using a dicationic thread similar to those synthesized for this thesis, with small R substituents (such as R = H or CH_3) that provide no steric or thermodynamic barriers to threading. With the larger cavities of the β- and γ-cyclodextrins, pseudorotaxane formation with the $L(CH_2)_{10}L^{2+}$ threads in the present study occurs rapidly. With the exception of the β-CD pseudorotaxane with the thread where R = phenyl, dissociation of these complexes is also rapid on the NMR time scale. We are presently exploring techniques for determining the rate constants for the rapid formation and dissociation of these and other α- and β-CD pseudorotaxanes.

While the end groups of the dicationic ligands possess chiral centers, we are unable to detect any preferential binding of one optical isomer over the other in the chiral α-cyclodextrin host. We have, however, observed that the neutral 4-(α-alkyl-α-methylmethanol)pyridine compounds exhibit differential binding in the larger β-cyclodextrin cavity, when coordinated to the pentacyanoferrate(II) center.[16] With neutral 4-(α-phenyl-α-methylmethanol)-pyridine (L), for example, the pyridine H_3 resonance of

(19) Yoshida, N.; Seiyama, A.; Fujimoto, M. *J. Phys. Chem.* **1990**, *94*, 4246.

the $Fe(CN)_5L^{3-}$ complex splits into two resonances, one shifting downfield (yielding $K_{CD} = 1000 \pm 200\ M^{-1}$) and the other upfield ($K_{CD} = 400 \pm 100\ M^{-1}$). The preferential β-CD binding of one guest enantiomer over the other has been observed for a number of guests, such as (*R*)- and (*S*)-2-phenylpropanoic acids, for which K_{CD} values of 1090 ± 30 and $1010 \pm 40\ M^{-1}$, respectively, have been measured.[28] Further kinetic and binding studies on the effects of guest chirality are ongoing in this laboratory.

Experimental Section

Materials. The α-, β-, and γ-cyclodextrins (Aldrich) were dried at 80 °C under reduced pressure for at least 8 h prior to use.

General Procedure for the Synthesis of the 4-(α-Alkyl/aryl-α-methylmethanol)pyridines. The racemic 4-(α-alkyl-α-methylmethanol)pyridine compounds were prepared according to the method of Weber and Seebach.[20] To a stirred solution of 4-acetylpyridine (40 mmol, Aldrich) in diethyl ether (100 mL) under N_2 at −20 °C was added the appropriate alkylmagnesium bromide (48 mmol, Aldrich). Isopropylmagnesium bromide was prepared from Mg turnings and isopropyl bromide in ether.[21] The reaction mixture was allowed to warm to room temperature. After 1 h, saturated NH_4Cl solution was added, and the organic layer was separated, washed with brine, dried over Na_2SO_4, and freed from the solvent under reduced pressure. The product was further purified by flash chromatography (90% ether, 10% methanol, silica gel 60 with particle size 0.040−0.063 mm (230−400 mesh ASTM, EM Separations Technology)), recrystallization from H_2O, and/or distillation, with yields ranging from 10% to 80%.

R = Me: mp 136−138 °C (lit.[22] mp 139−140 °C); ^{1}H NMR (D_2O) δ 8.49 (d, 2H, J = 6.1 Hz), 7.52 (d, 2H, J = 6.1 Hz), 1.56 (s, 6H) ppm.

R = Et: mp 101−103 °C (lit.[22] mp 102−104 °C); ^{1}H NMR (D_2O) δ 8.49 (d, 2H, H_2, J = 5.3 Hz), 7.48 (d, 2H, J = 5.3 Hz), 1.85 (q, 2H, J = 7.4 Hz), 1.53 (s, 3H), 0.76 (t, 3H, J = 7.4 Hz) ppm. Anal. Calcd for $C_9H_{13}NO\cdot{}^1/_8H_2O$: C, 70.44; H, 8.70; N, 9.13. Found: C, 70.53; H, 8.57; N, 9.21.

R = Pr: mp 68−69 °C; ^{1}H NMR (D_2O) δ 8.45 (d, 2H, J = 5.0 Hz), 7.45 (d, 2H, J = 5.0 Hz), 1.78 (t, 2H, J = 8.4 Hz), 1.51 (s, 3H), 1.24 (m, 1H), 1.04 (m, 1H), 0.80 (t, 3H, J = 7.3 Hz) ppm. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.67; H, 9.17; N, 8.48. Found: C, 72.45; H, 9.22; N, 8.39.

R = Bu: mp 69−71 °C; ^{1}H NMR (D_2O) δ 8.48 (d, 2H, J = 4.7 Hz), 7.48 (d, 2H, J = 4.7 Hz), 1.83 (m, 2H), 1.54 (s, 3H), 1.23 (m, 2H), 1.22 (m, 1H), 1.02 (m, 2H), 0.80 (t, 3H, J = 7.4 Hz) ppm. Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.43; H, 9.25; N, 7.72.

R = allyl: ^{1}H NMR (D_2O) δ 8.49 (d, 2H, J = 4.8 Hz), 7.48 (d, 2H, J = 4.8 Hz), 5.65 (m, 1H), 5.08 (m, 2H), 2.61 (m, 2H), 1.56 (s, 3H) ppm. Anal. Calcd for $C_{10}H_{13}NO\cdot{}^1/_2H_2O$: C, 69.74; H, 8.19; N, 9.13. Found: C, 70.53; H, 7.58; N, 8.22.

R = 4-butenyl: ^{1}H NMR (D_2O) δ 8.47 (d, 2H, J = 4.7 Hz), 7.47 (d, 2H), 5.80 (m, 1H), 4.97 (m, 2H), 2.02 (m, 1H), 1.84 (m, 1H), 1.91 (m, 2H), 1.54 (s, 3H) ppm. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.30; H, 8.42; N, 7.73.

R = *i*-Pr: ^{1}H NMR (D_2O) δ 8.46 (d, 2H, J = 6.2 Hz), 7.46 (d, 2H, J = 6.2 Hz), 2.03 (m, 1H, J = 6.8 Hz), 1.51 (s, 3H), 0.86, (d, 3H, J = 6.8 Hz), 0.76 (d, 3H, J = 6.8 Hz) ppm. Anal. Calcd for $C_{10}H_{15}NO\cdot{}^1/_8H_2O$: C, 72.69; H, 9.15; N, 8.48. Found: C, 71.59; H, 9.08; N, 8.30.

R = Ph: mp 137−138 °C (lit.[23] 142−143 °C); ^{1}H NMR (D_2O) δ 8.48 (d, 2H, J = 6.0 Hz), 7.60 (d, 2H, J = 6.2 Hz), 7.57−7.46 (m, 5H), 1.97 (s, 3H) ppm. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.94; N, 7.02. Found: C, 77.75; H, 6.54; N, 7.15.

General Procedure for the Synthesis of the *N*-Methyl-4-(α-alkyl-α-methylmethanol)pyridinium Iodides. The *N*-methyl-4-(α-alkyl-α-methylmethanol)pyridinium iodides were prepared according to the method of Toma et al.[24] by adding methyl iodide (12.1 mmol, Aldrich) to a solution of the appropriate 4-(α-alkyl-α-methylmethanol)pyridine compound in carbon tetrachloride (when using 4-(α,α-dimethylmethanol)-pyridine, methanol was used as the solvent[25]). After the reaction was maintained in the dark for several days, it was combined with approximately 100 mL of diethyl ether to precipitate the product as an orange oil. The crude product was dissolved in warm ethanol and precipitated again with diethyl ether. Several iterations of this step afforded the pure hygroscopic solid in 60−95% yields.

R = Me: mp 133−135 °C (lit.[25] mp 135−136 °C); ^{1}H NMR (D_2O) δ 8.71 (d, 2H, J = 6.6 Hz), 8.09 (d, 2H, J = 6.6 Hz), 4.35 (s, 3H), 1.62 (s, 6H) ppm.

R = Et: mp 126−127 °C; ^{1}H NMR (D_2O) δ 8.70 (d, 2H, J = 6.7 Hz), 8.05 (d, 2H, J = 6.7 Hz), 4.35 (s, 3H), 1.91 (q, 2H, J = 7.5 Hz), 1.60 (s, 3H), 0.79 (t, 3H, J = 7.5 Hz) ppm; ^{13}C{^{1}H} NMR (D_2O) δ 167.26, 144.72, 124.54, 75.09, 47.63, 35.19, 27.58, 7.33 ppm. Anal. Calcd for $C_{10}H_{16}NOI$: C, 40.97; H, 5.51; N, 4.78. Found: C, 40.88; H, 5.49; N, 4.77.

R = Pr: ^{1}H NMR (D_2O) δ 8.70 (d, 2H, J = 6.8 Hz), 8.06 (d, 2H, J = 6.8 Hz), 4.35 (s, 3H), 1.88 (t, 2H, J = 8.3 Hz), 1.61 (s, 3H), 1.36 (m, 1H), 1.06 (m, 1H), 0.85 (t, 3H, J = 7.3 Hz) ppm. Anal. Calcd for $C_{11}H_{18}NOI$: C, 43.01; H, 5.91; N, 4.56. Found: C, 42.65; H, 5.97; N, 4.61.

R = Bu: ^{1}H NMR (D_2O) δ 8.75 (d, 2H, J = 6.9 Hz), 8.11 (d, 2H, J = 6.9 Hz), 4.40 (s, 3H), 1.95 (t, 2H, J = 6.9 Hz), 1.66 (s, 3H), 1.31 (m, 2H), 1.35 (m, 1H), 1.04 (m, 1H), 0.87 (t, 3H, J = 7.2 Hz) ppm. Anal. Calcd for $C_{12}H_{20}NOI\cdot{}^1/_2H_2O$: C, 43.65; H, 6.41; N, 4.24. Found: C, 44.04; H, 6.12; N, 4.16.

R = allyl: ^{1}H NMR (D_2O) δ 8.72 (d, 2H, J = 6.0 Hz), 8.06 (d, 2H, J = 6.0 Hz), 5.70 (m, 1H), 5.11 (m, 2H), 4.36 (s, 3H), 2.68 (d, 2H, $J_{a,b}$ = 7.1 Hz), 1.64 (s, 3H) ppm. Anal. Calcd for $C_{11}H_{16}NOI\cdot{}^1/_2H_2O$: C, 42.05; H, 5.45; N, 4.46. Found: C, 42.35; H, 5.24; N, 4.37.

R = 4-butenyl: ^{1}H NMR (D_2O) δ 8.73 (d, 2H, J = 6.1 Hz), 8.09 (d, 2H, J = 6.1 Hz), 5.82 (m, 1H), 5.04 (m, 2H), 4.37 (s, 3H), 2.02 (t, 2H, J = 5.8 Hz), 2.15 (m, 1H), 1.87 (m, 1H), 1.65 (s, 3H) ppm. Anal. Calcd for $C_{12}H_{18}NOI$: C, 45.16; H, 5.68; N, 4.39. Found: C, 45.08; H, 5.66; N, 4.31.

R = *i*-Pr: ^{1}H NMR (D_2O) δ 8.69 (d, 2H, J = 6.7 Hz), 8.05 (d, 2H, J = 6.7 Hz), 4.35 (s, 3H), 2.12 (m, 1H, J = 6.8 Hz), 1.60 (s, 3H), 0.95 (d, 3H, J = 6.8 Hz), 0.75 (d, 3H, J = 6.8 Hz) ppm. Anal. Calcd for $C_{11}H_{18}NOI\cdot{}^1/_2H_2O$: C, 41.79; H, 6.06; N, 4.43. Found: C, 42.09; H, 5.89; N, 4.27.

General Procedure for the Synthesis of the 1,12-Bis-(4-(α-alkyl-α-methylmethanol)pyridinium)dodecane Dibromides. The 1,12-bis(4-(α-alkyl-α-methylmethanol)pyridinium)dodecane dibromides were prepared by a modification of the method of Attalla et al.[26] The appropriate 4-(α-alkyl-α-methylmethanol)pyridine compound (2.5 mmol) was dissolved in DMF (5 mL), and 1,12-dibromododecane (0.5 mmol, Aldrich) was then added to the solution. After being stirred at 50 °C for 8 h, the reaction was cooled and combined with approximately 100 mL of diethyl ether to precipitate the product as an orange oil. The crude product was dissolved in warm ethanol and precipitated again with diethyl ether. Several iterations of this step afforded the pure hygroscopic solid in 60−80% yields.

R = Me: ^{1}H NMR (D_2O) δ 8.74 (d, 4H, J = 6.5 Hz), 8.09 (d, 4H, J = 6.5 Hz), 4.55 (t, 4H, J = 7.1 Hz), 1.97 (m, 4H), 1.60 (s, 12H), 1.29−1.21 (m, 16H) ppm. Anal. Calcd for $C_{28}H_{46}N_2O_2$-

(20) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117.
(21) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol. 1, p 415.
(22) Zymalkowski, F.; Reimann, E. *Liebigs Ann. Chem.* **1968**, *715*, 98.
(23) Zeng, X.; Jiaqiang, C.; Gu, Y. *Tetrahedron Lett.* **1995**, *36*, 7275.
(24) Toma, H. E. *Can. J. Chem.* **1973**, *57*, 2079.
(25) Ferles, M.; Stern, P.; Vysata, F. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1979.
(26) Attalla, M. I.; McAlpine, N. S.; Summers, L. A. *Z. Naturforsch.* **1984**, *39B*, 74.
(27) Chu, C.; Teague, P. C. *J. Org. Chem.* **1958**, *23*, 1578.
(28) Brown, S. E.; Coates, J. H.; Duckworth, P. A.; Lincoln, S. F.; Easton, C. F.; May, B. L. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1035.

$Br_2 \cdot {}^1/_2H_2O$: C, 55.00; H, 7.75; N, 4.58. Found: C, 55.17; H, 7.77; N, 4.66.

R = Et: ^{1}H NMR (D_2O) δ 8.75 (d, 4H, J = 6.6 Hz), 8.06 (d, 4H, J = 6.6 Hz), 4.56 (t, 4H, J = 7.0 Hz), 1.99 (m, 4H), 1.91 (q, 8H, J = 7.4 Hz), 1.59 (s, 6H), 1.30−1.22 (m, 16H), 0.78 (t, 6H) ppm. Anal. Calcd for $C_{30}H_{50}N_2O_2Br_2 \cdot 3H_2O$: C, 52.63; H, 8.24; N, 4.09. Found: C, 52.63; H, 8.24; N, 3.92.

R = Pr: ^{1}H NMR (D_2O) δ 8.78 (d, 4H, J = 6.7 Hz), 8.10 (d, 4H, J = 6.7 Hz), 4.59 (t, 4H, J = 7.1 Hz), 2.02 (m, 4H), 1.89 (t, 4H, J = 8.4 Hz), 1.63 (s, 6H), 1.32−1.24 (m, 16H), 1.24 (m, 2H), 0.94 (m, 2H), 0.86 (t, 6H, J = 7.2 Hz) ppm. Anal. Calcd for $C_{32}H_{54}N_2O_2Br_2 \cdot H_2O$: C, 56.81; H, 8.34; N, 4.14. Found: C, 56.68; H, 8.14; N, 4.13.

R = Bu: ^{1}H NMR (D_2O) δ 8.79 (d, 4H, J = 6.3 Hz), 8.10 (d, 4H, J = 6.3 Hz), 4.60 (t, 4H, J = 6.8 Hz), 2.02 (m, 4H) 1.92 (t, 4H, J = 7.9 Hz), 1.63 (s, 6H), 1.31−1.01 (m, 24H, H_b), 0.83 (t, 6H, J = 7.2 Hz) ppm. Anal. Calcd for $C_{34}H_{58}N_2O_2Br_2 \cdot H_2O$: C, 57.95; H, 8.58; N, 3.98. Found: C, 58.00; H, 8.49; N, 4.00.

R = allyl: ^{1}H NMR (D_2O) δ 8.76 (d, 4H, J = 6.7 Hz), 8.06 (d, 4H, J = 6.7 Hz), 5.68 (m, 2H), 5.07 (m, 4H) 4.46 (t, 4H, J = 7.0 Hz) 2.66 (d, 4H, J = 7.3 Hz) 1.98 (m, 4H), 1.63 (s, 6H), 1.28−1.21 (m, 16H, H) ppm. Anal. Calcd for $C_{32}H_{50}N_2O_2Br_2 \cdot {}^1/_2H_2O$: C, 57.92; H, 7.75; N, 4.22. Found: C, 58.04; H, 7.74; N, 4.32.

R = 4-butenyl: ^{1}H NMR (D_2O) δ 8.64 (d, 4H, J = 6.8 Hz), 7.96 (d, 4H, J = 6.8 Hz), 5.66 (m, 2H), 4.85 (m, 4H), 4.45 (t, 4H, J = 7.1 Hz), 1.88 (m, 8H), 1.99 (m, 2H), 1.71 (m, 2H), 1.50 (s, 6H), 1.17−1.04 (m, 16H) ppm. Anal. Calcd for $C_{34}H_{54}N_2O_2Br_2 \cdot H_2O$: C, 58.29; H, 8.06; N, 4.00. Found: C, 58.38; H, 8.02; N, 4.00.

R = *i*-Pr: ^{1}H NMR (D_2O) δ 8.76 (d, 4H, J = 6.5 Hz), 8.08 (d, 4H, J = 6.5 Hz), 4.54 (t, 4H, J = 7.1 Hz), 2.13 (m, 2H), 2.01 (m, 4H), 1.61 (s, 6H), 1.31−1.23 (m, 16H), 0.82 (d, 6H, J = 6.8 Hz), 0.62 (d, 6H, J = 6.8 Hz) ppm. Anal. Calcd for $C_{32}H_{54}N_2O_2Br_2 \cdot {}^1/_2H_2O$: C, 57.57; H, 8.30; N, 4.20. Found: C, 57.43; H, 8.09; N, 4.20.

R = Ph: ^{1}H NMR (D_2O) δ 8.73 (d, 4H, J = 6.6 Hz), 8.06 (d, 4H, J = 6.6 Hz), 7.48−7.37 (m, 10H), 4.54 (t, 4H, J = 7.2 Hz), 2.03 (s, 6H), 1.95 (m, 4H), 1.25−1.16 (m, 16H) ppm. Anal. Calcd for $C_{38}H_{50}N_2O_2Br_2 \cdot H_2O$: C, 61.29; H, 7.04; N, 3.76. Found: C, 60.31; H, 6.82; N, 4.10.

Synthesis of 1,12-Bis(4-(α,α-diethylmethanol)pyridinium)dodecane Dibromide. The 4-(α,α-diethylmethanol)-pyridine used in this synthesis was prepared in 23% yield (mp 142−145 °C lit.[22] mp 146−148 °C) as described above, using ethyl 4-pyridyl ketone (prepared according to the method of Chu et al.[27]) in place of 4-acetylpyridine. The 1,12-bis(4-(α,α-diethylmethanol)pyridinium)dodecane dibromide was prepared in 75% yield, as described above, from 4-(α,α-diethylmethanol)-pyridine and 1,12-dibromododecane: ^{1}H NMR (D_2O): δ 8.76 (d, 4H, J = 6.4 Hz), 8.05 (d, 4H, J = 6.4 Hz), 4.57 (t, 4H, J = 7.1 Hz), 1.98 (m, 4H), 1.95 (q, 8H, J = 7.5 Hz), 1.30−1.22 (m, 16H), 0.75 (t, 12H, J = 7.5 Hz) ppm. Anal. Calcd for $C_{32}H_{54}N_2O_2Br_2 \cdot 2{}^1/_2H_2O$: C, 54.62; H, 8.45; N, 3.98. Found: C, 54.62; H, 7.96; N, 4.35.

Physical Measurements. The ^{1}H and ^{13}C NMR spectra, along with the kinetic measurements and chemical shift titrations, were recorded on a Bruker AM-400 instrument, with the temperature of the probe maintained within ±1 °C. For the kinetics experiments, a solution of the appropriate 1,12-bis(4-(α-alkyl-α-methylmethanol)pyridinium)dodecane dication ($[L(CH_2)_{12}L]^{2+}$, 3.0 mM after mixing) was measured into an NMR tube, followed by the addition of a known concentration of α-CD solution varied (2.5−100 mM after mixing) to give a total volume of 600 μL. All solutions were maintained at a constant ionic strength (I = 0.10 M) using NaCl.

The cyclodextrin inclusion stability constants for the *N*-methyl-4-(α-alkyl-α-methylmethanol)pyridinium cations were determined by ^{1}H NMR chemical shift titrations, as described previously.[29] Solutions of the appropriate guest compound were prepared in D_2O and maintained at a constant ionic strength of 0.10 M with NaCl. The solution (500 μL) was titrated with 10−100 μL aliquots (using graduated gastight Hamilton syringes) of a cyclodextrin solution that contained the same concentration of the guest. The solutions were mixed thoroughly in the NMR tube and allowed to equilibrate in the probe (298 ± 1 K) prior to obtaining a spectrum. In these experiments, the concentration of the included species was found by analyzing the areas of the pyridine H_3 resonances. Upon α-CD inclusion of the $[L(CH_2)_{12}L]^{2+}$ thread, the H_3 doublet resonance becomes two separate doublets due to the asymmetry of the α-CD cavity. The upfield doublet of the included species appears at a chemical shift similar to that of the nonincluded species and is of the same area as the downfield peak of the included species. Thus, the fraction of the ligand that is included, I, is given by $(2 \times A_i)/A_{tot}$, where A_i is the area of the downfield peak for the included ligand and A_{tot} is the total area of both the included and free ligand peaks. The plots of $\ln(I_\infty - I_t)$ vs time yielded straight lines with slope $= -k_{obs}$ (I_∞ was determined after the samples were maintained at 25 °C for at least 24 h). The subsequent plots of k_{obs} vs [α-CD] were then analyzed with nonlinear regression analysis (eq 1) using Simplex minimization to determine K_{CD} values and limiting rate constants.[29−32] The chemical shift titrations provided plots of $\Delta\delta$ vs [α-CD] that were analyzed in the same manner.

The electrospray ionization mass spectrometry experiments were performed on a Fisons VG QUATTRO triple quadrupole mass spectrometer, with an atmospheric pressure electrospray source and a mass range for singly charged ions of 4000. The samples were prepared in distilled water containing 0.10 M α-CD and were introduced into the source at a flow rate of 5 mL min^{-1}. Elemental analyses were performed by Canadian Microanalytical Services Ltd (Delta, BC).

Acknowledgment. The financial support of this research by the Natural Sciences and Engineering Research Council of Canada, in the form of research and equipment grants (D.H.M.), is gratefully acknowledged. One of us (A.C.S.) thanks Queen's University and the Government of Ontario, Ministry of Education and Training, for scholarship and conference travel support.

JO9808775

(29) Wylie, R. S.; Macartney, D. H. *Inorg. Chem.* **1993**, *32*, 1830.
(30) Connors, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; Wiley-Interscience: New York, 1987.
(31) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Durr, H., Eds.; VCH: Weinheim, 1991; p 123.
(32) Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375.