Direct Synthesis of Cyclodextrin-Rotaxanated Poly(ethylene glycol)s and Their Self-Diffusion Behavior in Dilute Solution

Tiejun Zhao and Haskell W. Beckham*

School of Polymer, Textile and Fiber Engineering, Georgia Institute of Technology, Atlanta, Georgia 30332

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ABSTRACT: Poly[(ethylene glycol)-*rotaxa*-(α-cyclodextrin)]s, (PEG-*rotaxa*-αCD)s, were prepared by a direct route from commercially available poly(ethylene glycol)s (PEG) with molecular weights from 1.5 to 20 kg/mol. The rotaxanated structure was verified by diffusion-ordered 2D NMR spectroscopy (DOSY). The self-diffusion coefficients for PEG-*rotaxa*-αCD and PEG in dilute DMSO-d_6 scale with their respective molecular weights as $D_{\mathrm{PEG-}rotaxa\mathrm{-\alpha CD}} \sim M_n^{-0.60\pm0.05}$ and $D_{\mathrm{PEG}} \sim M_n^{-0.55\pm0.03}$. With increasing temperature, the hydrodynamic radius of the PEG-*rotaxa*-αCD increases by the same slope as the unthreaded PEG backbone. These polyrotaxanes, in which up to 70% of the backbone is covered with cyclodextrins, behave as random coils in good solvents.

Introduction

Rotaxanated polymers are topological copolymers composed of macrocycles threaded onto linear polymer backbones with no covalent bonds linking the two species. The degree of attraction between the two components strongly influences properties and governs the synthetic route. In the absence of attractive interactions, macrocycles can be trapped onto linear backbones if they are present during the polymerization;[1−4] this method is referred to as the statistical approach in which the threading yield scales directly with macrocycle size.[5] Macrocycles with sufficiently strong attractive interactions may be threaded directly onto linear polymers by a self-assembly method.[6−14] Once threaded, blocking the chain ends with bulky groups prevents dethreading and converts the polypseudorotaxane to a polyrotaxane.

The preparation of rotaxanated polymers via self-assembly is as easy as mixing solutions of the two components. The task is simplified further when both components are commercially available. This is the case for the polypseudorotaxanes based on cyclodextrins,[10−12] for which the prototypical structure is poly[(ethylene glycol)-*pseudorotaxa*-(α-cyclodextrin)].[11,12] Potential applications for these materials have been proposed in such areas as drug delivery[15,16] and molecular electronics.[17,18] Further development of these materials could be facilitated by reporting more structure/property relationships.[19]

Formation of polypseudorotaxanes with cyclodextrins proceeds by threading of a polymer backbone in solution, followed by aggregation of the threaded segments and precipitation of a solid inclusion complex. The resulting poly-*pseudorotaxa*-cyclodextrins will dissolve in water and dimethyl sulfoxide, but with rapid dethreading. Thus, to study the threaded-cyclodextrin architecture in solution, the polypseudorotaxanes must be end-capped to give the corresponding polyrotaxanes. The first reported poly-*rotaxa*-cyclodextrin resulted from the reaction of 2 equiv of 2,4-dinitrofluorobenzene with a threaded α,ω-diamino-terminated PEG suspended in DMF.[10−12] Other blocking groups have also been used with α,ω-diamino-terminated PEG.[20−23] In these end-capping reactions, the number of cyclodextrins permanently trapped onto the polymer is governed by a competition between the reaction and dethreading. Thus, a fully covered polypseudorotaxane does not necessarily yield a fully covered polyrotaxane. Limited coverage also occurs for backbones with molecular weights greater than about 1 kg/mol because threaded segments aggregate and precipitate before full coverage has been achieved, leading to gelation.[24] Turbidity has been used to measure the time required for gel formation, referred to as threading time, as a function of temperature and solvent quality.[25] The threading time can be prolonged by increasing temperature or the hydrogen-bonding strength of the solvent. More such systematic studies are needed to further define the conditions required to prepare a given rotaxanated structure.

The influence of molecular architecture on polymer dynamics has been examined for linear, branched, star, and rodlike polymers in solution and the melt[26−31] using pulsed-gradient echo NMR.[32] However, such studies have not been reported for the effect of threading on linear polymer dynamics. In this paper, we report the dilute-solution diffusion behavior of PEG and the corresponding PEG-*rotaxa*-αCD as a function of molecular weight. To date, most of the PEG-*rotaxa*-αCD's have been prepared from PEG by first converting the hydroxyl end groups to amino groups. To minimize the effort required to prepare a series of these polyrotaxanes, we have developed a more direct synthetic route from commercially available PEG that circumvents the bisamine. This direct synthetic route is also presented here.

Experimental Section

Materials. Poly(ethylene glycol) (PEG) was dried under vacuum overnight at room temperature prior to use (M_n = 1.5 and 3.4 kg/mol from Aldrich; M_n = 8, 10, 20, 35, and 100 kg/mol from Polymer Source; $M_w/M_n \leq 1.1$ for all PEGs). Unless stated otherwise, all other reagents and solvents were used

* Corresponding author: e-mail haskell.beckham@ptfe.gatech.edu.

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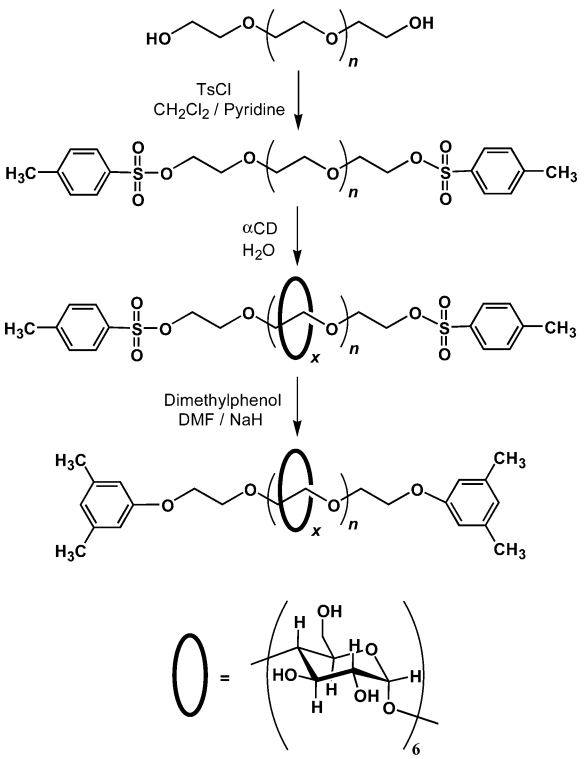
Scheme 1. Synthesis of Poly[(ethylene glycol)-*rotaxa*-(α-cyclodextrin)] from Poly(ethylene glycol)[a]



[a] The number of α-cyclodextrins (α-CD) per chain is shown in Tables 1 and 2 for PEG with number-average molecular weights of 1.5, 3.4, 8, and 20 kg/mol.

as received from Aldrich: methylene chloride (CH_2Cl_2) (anhydrous, 99.8%); dimethyl sulfoxide (DMSO) (anhydrous, 99.8%); dimethylformamide (DMF) (anhydrous, 99.9%); 3,5-dimethylphenol (99+%); pyridine (anhydrous, 99.8%); sodium hydride (95%); *p*-toluenesulfonyl chloride (*p*-TsCl) (99%); and *m*-toluenesulfonyl chloride (*m*-TsCl) (99%). The α-cyclodextrin (α-CD) was obtained from Wacker. The methanol and ethyl ether were A.C.S. grade from Fisher Scientific.

Preparation of Polyrotaxanes. The synthesis of α-cyclodextrin-rotaxanated poly(ethylene glycol) from PEG was accomplished by the route shown in Scheme 1. The PEG ditosylates (PEG-Ts_2) were prepared according to a published procedure.[33] A detailed description follows for the PEG with M_n = 3.4 kg/mol ($PEG_{3.4k}$) using *p*-toluenesulfonyl chloride.

Under a strong argon purge, $PEG_{3.4k}$ (5.0 g) was dissolved in CH_2Cl_2 (10 mL) in a round-bottomed flask immersed in an ice bath. The mixture was stirred for 10 min. *p*-TsCl (1.5 g, 7.8 mmol) and pyridine (1 mL, 12.4 mmol) were then introduced into the solution. The reaction was allowed to warm to room temperature after 3−4 h, stirred overnight, then concentrated to 5 mL and added dropwise to diethyl ether (60 mL). The white precipitate was collected by filtration, washed with 3 × 10 mL of diethyl ether (Et_2O), suspended in toluene (50 mL), and stirred for 1 h. The mixture was filtered, and the filtrate was rotary evaporated to collect a solid which was dissolved in 5 mL of CH_2Cl_2 and then precipitated into 60 mL of Et_2O. The white precipitate ($PEG_{3.4k}$-*p*Ts_2, 82% yield) was dried at room temperature under vacuum for 3 days.

$PEG_{1.5k}$-*p*Ts_2 (50% yield) and $PEG_{3.4k}$-*m*Ts_2 (80% yield) were prepared under the same conditions. PEG_{8k}-*p*Ts_2 and PEG_{20k}-*p*Ts_2 were prepared under similar conditions, however, without the step of suspending in toluene to eliminate the *p*-TsCl remnants. The tosyl chloride and pyridine quantities were adjusted to give the same number of equivalents per PEG chain end as that shown for the $PEG_{3.4k}$.

The α,ω-ditosyl-terminated PEG polypseudorotaxanes (PEG-Ts_2-*pseudorotaxa*-αCD) were prepared according to the published Harada method.[10−12] An α-CD aqueous solution (7.7 g, 7.9 mmol, in 60 mL of H_2O) was combined with 20 mL of an aqueous solution of PEG-Ts_2 at room temperature. The amount of PEG-Ts_2 dissolved in the 20 mL of water was determined to give the α-CD/PEG (mol/mol) ratios shown in Tables 1 and 2. The clear mixed solution became turbid within 30 min and was allowed to stand overnight. The water was then allowed to evaporate, and the solid was dried at room temperature under vacuum for at least 4 days. No attempt was made to remove unthreaded α-CD at this stage.

Table 1. PEG-*rotaxa*-αCD from PEG

M_n of PEG (kg/mol)	α-CD/PEG (mol/mol)[a]	PEG-*rotaxa*-αCD		
		yield (%)[b]	CD/chain	coverage (%)[c]
1.5	17	4	12	70
3.4	27	39	14	36
8	45	31	29	32
20	114	18	43	19

[a] Ratio in originating solution; the PEG is actually PEG-Ts_2. [b] Yield is based on the end-capping step (see Scheme 1). [c] Coverage = 2(CD per chain)/(PEG repeat units), assuming 2 PEG repeat units per CD.

Table 2. PEG-*rotaxa*-αCD from PEG with M_n of 3.4 kg/mol

α-CD/$PEG_{3.4k}$ (mol/mol)[a]	$PEG_{3.4k}$-*rotaxa*-αCD		
	yield (%)[b]	CD/chain	coverage (%)[c]
50	20	17	44
39	35	17	44
27	39	14	36
19	42	15	38
27[d]	*30*	*21*	*54*

[a] Ratio in originating solution; the $PEG_{3.4k}$ is actually $PEG_{3.4k}$-Ts_2. [b] Yield is based on the end-capping step (see Scheme 1). [c] Coverage = 2(CD per chain)/(PEG repeat units), assuming 2 PEG repeat units per CD. [d] PEG-*m*Ts_2 instead of PEG-*p*Ts_2 was used.

$PEG_{3.4k}$-Ts_2-*pseudorotaxa*-αCD. ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 7.90 (d, T_3, 8.5 Hz), 7.49 (d, T_2, 8.0 Hz), 5.52 (d, O_2H, 7.0 Hz), 5.44 (d, O_3H, 1.5 Hz), 4.81 (d, H_1, 3 Hz), 4.48 (t, O_6H, 5.8 Hz), 4.12 (t, T_4, 4.5 Hz), 3.78 (t, H_3, 9 Hz), 3.69−3.58 (m, $H_{6,5}$), 3.51 (s, PEG), 3.40 (t, H_2, 8.8 Hz), 3.33 (s, H_2O), 3.26−3.31 (m, H_4), 2.43 (s, T_1).

The dry PEG-Ts_2-*pseudorotaxa*-αCD was ground into a fine powder for 3 min (Micromill, Scienceware) and further vacuum-dried at 35 °C overnight before end-capping with 3,5-dimethylphenol to prepare the PEG polyrotaxanes (PEG-*rotaxa*-αCD). A solution of 3,5-dimethylphenol (0.86 g, 7.0 mmol) in DMF (12 mL) was slowly added to dry NaH (0.25 g) in a round-bottomed flask under a strong argon purge. The brown mixture was stirred for 10 min. The PEG-Ts_2-*pseudorotaxa*-αCD (1.0 g) was then added to the reaction flask and rinsed down with 4 mL of DMF. After stirring overnight, the reaction mixture was poured into 60 mL of methanol. The precipitate was collected by filtration, washed with 2 × 20 mL of methanol, dissolved in 6 mL of DMSO, and precipitated into 50 mL of methanol. The precipitate was again collected by filtration and washed with 2 × 20 mL of methanol. The procedure was repeated by dissolution in DMSO, precipitation into water, and washing with water. Finally, the white solid product (0.39 g, 39%) was dried at 110 °C overnight under vacuum.

$PEG_{3.4k}$-*rotaxa*-αCD. ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 6.57−6.45 (m, $P_{2,3}$), 5.64 (s, O_2H), 5.48 (s, O_3H), 4.80 (s, H_1), 4.43 (s, O_6H), 3.73 (m, H_3), 3.66 (m, H_6), 3.56 (broad, H_5), 3.51 (s, PEG), 3.44 (m, H_2), 3.31 (s, H_2O), 3.30 (m, H_4), 2.22 (s, P_1).

The amounts and concentrations of 3,5-dimethylphenol, NaH, and polypseudorotaxane were the same for all PEG's; thus, the already large excess of the end-capping reagent increased with increasing PEG molecular weight. Yields are shown in Tables 1 and 2. The number of α-CD's per PEG-*rotaxa*-αCD chain (N_{CD}) was estimated from the respective ^{1}H NMR spectra using $N_{CD} = 2I_1/I_m$, where I_1 = the integrated

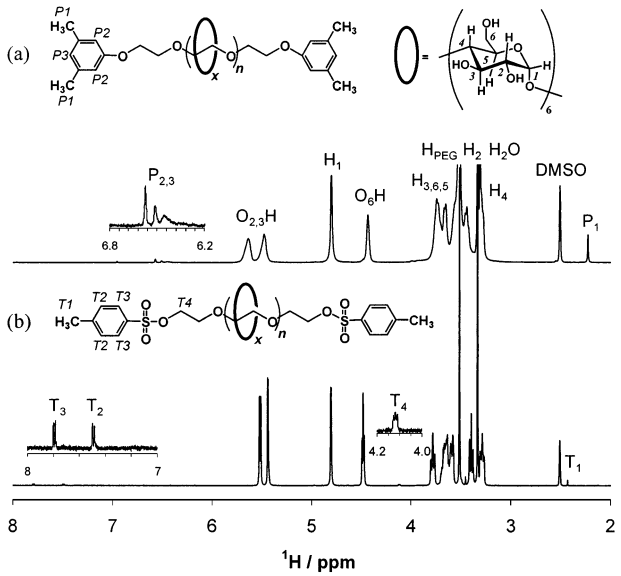


Figure 1. ^{1}H NMR spectra of (a) the polyrotaxane consisting of α-cyclodextrin threaded onto poly(ethylene glycol) (M_n = 3.4 kg/mol) end-capped with 3,5-dimethylphenyl groups ($PEG_{3.4k}$-*rotaxa*-αCD) and (b) the polypseudorotaxane prepared by threading α-cyclodextrin onto poly(ethylene glycol) (M_n = 3.4 kg/mol) end-capped with *p*-tosyl groups ($PEG_{3.4k}$-Ts_2-*pseudorotaxa*-αCD). Both solutions (0.7% w/v) were kept at room temperature for 16 h before the spectra were acquired at 25 °C.

area of the α-CD H_1 signal at 4.80 ppm and I_m = the area of the methyl end groups of the end-capped PEG at 2.22 ppm (see Figure 1).

NMR Measurements. All NMR spectra were obtained on a Bruker DRX-500 spectrometer using 5 mm tubes. Sample concentrations were about 0.7% (w/v) in DMSO-d_6. All spectra were measured with 16 accumulations and a 10 s recycle delay. The DOSY experiments at room temperature employed the bipolar pulse pair and longitudinal eddy current delay (BPP-LED) sequence.[34] For measuring diffusion coefficients at temperatures other than room temperature, the double-stimulated-echo (DSTE) sequence was used.[35] Field gradient calibration was accomplished from 5 to 55 °C using the self-diffusion coefficient of pure water.[36,37] The calibration constant was found to be the same over the entire temperature range examined.

For the BPP-LED pulse sequence, the gradients were applied for 4 ms (δ), and the diffusion time (Δ) was varied from 180 to 800 ms depending on the molecular weight and concentration for a given sample. Even for the largest sample and the smallest diffusion window, the diffusion distance $(2\Delta D)^{1/2}$ is nearly 2 orders of magnitude larger than the estimated polymer coil size; thus, center-of-mass diffusion was measured for all samples. Gradient settling times were 1 ms, and the eddy current elimination duration was 20 ms. Homospoil gradients (1 ms) were applied during the diffusion and eddy current settling durations to destroy signals from unwanted coherence paths. The gradients (g) were incremented 16 times from 1.7 to 63.0 G/cm, resulting in attenuation of the PEG resonances to approximately 5% of their original intensities. A total of 16 free induction decays containing 8K complex data points were collected at each gradient setting.

For the DSTE sequence, gradient settling times were 2 ms and the eddy current elimination duration was 60 ms. The gradients were incremented 16 times from 9.7 to 63.0 G/cm. All other parameters were the same as those used with the BPP-LED sequence.

All DOSY spectra were constructed by assuming monoexponential diffusion decays for all chemical shifts.

Results and Discussion

Synthesis of Polyrotaxanes. Most of the published methods to prepare polyrotaxanes from PEG and cyclodextrins rely on the conversion of the PEG end groups from hydroxyl to amino groups. Using bisamines allows end-capping with reactants that do not effectively compete for the hydroxyl groups on the cyclodextrins. In our approach, we first convert commercially available PEG into ditosylated PEG,[33] thread the backbone, and then displace the tosyl end groups with bulky blocking groups to give the polyrotaxane. The reaction sequence is outlined in Scheme 1. The PEG ditosylate was threaded in aqueous solution following the standard Harada method of mixing separate solutions of α-CD and linear backbone at room temperature. The resulting white precipitate was a gel containing unthreaded α-CD along with the polypseudorotaxane product. Without removing the unthreaded CD, the tosyl end groups of the polypseudorotaxane were replaced by bulky 3,5-dimethylphenyl groups. The polyrotaxane products were precipitated in methanol and water to eliminate the unthreaded PEG and α-CD, respectively. A series of PEG-*rotaxa*-αCD's were prepared from PEG with number-average molecular weights of 1.5, 3.4, 8, and 20 kg/mol. Table 1 shows yield, number of α-CD's per chain, and percent α-CD coverage.

The yields in Table 1 represent the wt % of PEG-*rotaxa*-αCD produced from the respective PEG-*pseudorotaxa*-αCD. Based on PEG, the calculated yields are 6, 75, 48, and 48% for the 1.5, 3.4, 8, and 20 kg/mol PEG, respectively. These yields are comparable to or better than those reported for the preparation of PEG-*rotaxa*-αCD via α,ω-diamino-terminated PEG.[10−12,20,21] The real advantage of the method described here is the production of PEG-*rotaxa*-αCD from PEG in fewer steps.

The second column of Table 1 shows the ratio of CD's per PEG-Ts_2 chain in the originating or threading solution. For a 1.5 kg/mol PEG ($PEG_{1.5k}$), full coverage would be about 17 cyclodextrins, assuming one cyclodextrin includes two PEG repeat units. Thus, the CD/PEG ratio in the originating solution for the 1.5 kg/mol PEG (17/1) is the same as that required for 100% coverage. However, a gel is formed when using PEG backbones of this length and longer, which impedes complete threading. Unthreaded CD's are trapped in the gel. It is not clear whether the $PEG_{1.5k}$-*pseudorotaxa*-αCD is fully threaded; it certainly is not fully threaded after conversion to the polyrotaxane. After end-capping, the average number of CD's per chain is 12, which corresponds to 70% coverage. The threading level in the polyrotaxane is limited by the coverage of the polypseudorotaxane, and the competition between the end-blocking reaction and dethreading. When the end-blocking reactions were carried out in DMSO, a good solvent for the polypseudorotaxane complex, no polyrotaxanes were formed. This was attributed to the rapid dethreading that occurs upon dissolution in DMSO.

While the percent coverage decreases with increasing PEG chain length, the number of α-CD's per chain increases. Full coverage of the chain is precluded by gel formation when chain lengths exceed about 30 oxyethylene units.[24] The time until gelation, or threading time, is not simply governed by the number of threaded CD's, but the number of threaded CD's that are sufficiently adjacent to hydrogen bond, form stacks, and aggregate with stacks on other chain segments. Kinetic studies have revealed that threading time is increased by the

presence of additives or solvents that compete for hydrogen bonds[25] and delay the formation of threaded-CD stacks and also as backbone molecular weight increases.[12] For the higher-molecular-weight backbones, the decreased concentration of end groups means more CD's can thread per chain before the stacks reach a critical concentration for aggregation.

In an attempt to change the number of threaded CD's per chain, we varied the α-CD/PEG ratio in the threading solution during preparation of polypseudorotaxanes with the 3.4 kg/mol PEG. Table 2 shows the results for varying the α-CD/PEG ratio from 50 to 19, which is 130 to 50% of full coverage, respectively, if all CD's were threaded. The top four rows of Table 2 show that subtle to insignificant differences in the numbers of CD's per chain (14 to 17) can be caused by changing the α-CD/PEG ratio in the originating solution. Thus, α-CD/PEG ratios corresponding to less than 100% coverage may be used for the backbones on which threading is limited by gelation. Note the yield increases from 20 to 42% as the α-CD/PEG ratio decreases from 50 to 19. This is attributed to a decrease in the fraction of unthreaded CD trapped in the polypseudorotaxane gel when lower α-CD/PEG ratios are used.

The last row of Table 2 (data are italicized) reveals a more promising approach for controlling the number of CD's per polyrotaxane backbone; the polyrotaxane represented by these data was prepared with an α-CD/PEG ratio of 27 (70% of full coverage), but using a $PEG_{3.4k}$ with *m*-tosylate end groups as opposed to *p*-tosylate end groups. The resulting polyrotaxane contains 21 threaded CD's, while the polyrotaxane prepared under the same conditions but from $PEG_{3.4k}$-*p*Ts_2 contains 14 threaded CD's. The difference is attributed to the apparent bulkiness of the *m*-tosylate end groups, which leads to slower dethreading rates during the end-capping reaction and thus trapping of a greater number of CD's. End-capping a $PEG_{3.35k}$ bisamine with 2,4-dinitrofluorobenzene in DMF, Harada reported the trapping of 20 CD's onto the backbone,[10] which is similar to the value we report here.

Proof of Threaded Architecture. Supporting evidence for threaded polymer architectures is often provided in the form of NMR, X-ray, and GPC data.[3,4,10−12] Perhaps the strongest evidence that the precipitated complex consists of chains threaded by cyclodextrins is the simple fact that chains with bulky end groups do not form complexes and precipitate.[12] Standard ^{1}H NMR spectra of the polypseudorotaxane prepared from PEG with $M_n = 3.4$ kg/mol and the polyrotaxane prepared from it are shown in Figure 1. The spectrum of the $PEG_{3.4k}$-Ts_2-*pseudorotaxa*-αCD appears identical to the spectrum of a physical blend of the two components, clearly indicating that these polypseudorotaxanes exist as unthreaded mixtures in DMSO. In contrast, the spectrum of the $PEG_{3.4k}$-*rotaxa*-αCD contains broadened peaks, attributed to the decrease in conformational flexibility caused by rotaxanation. Note also the slight changes in the chemical shifts of the cyclodextrin peaks, most notably the downfield shift for the peaks of the secondary hydroxyl groups ($O_{2,3}H$) and the upfield shift for the primary hydroxyl peak (O_6H). The H_2 peak located between the water and PEG peaks also shifts noticeably downfield. Peaks representative of the tosyl end groups in the polypseudorotaxane are replaced with those for the 3,5-dimethylphenyl end groups in the polyrotaxane. No peaks due to unthreaded cyclodextrins appear in the spectrum of the polyrotaxane.

Definitive proof of threading can be provided with two-dimensional diffusion-ordered NMR spectroscopy (DOSY).[38] We expect a measurable decrease in the diffusion coefficients of the cyclodextrin-rotaxanated polymers compared to their unthreaded components. Figure 2 shows the 2D DOSY spectrum of the $PEG_{3.4k}$-Ts_2-*pseudorotaxa*-αCD (0.7% w/v) in DMSO-d_6. All α-CD peaks are correlated with a diffusion coefficient (D) around 7.07×10^{-11} m^2 s^{-1}, while the PEG peaks (backbone and end groups) are associated with a slightly smaller diffusion coefficient of 3.02×10^{-11} m^2 s^{-1}; these D values are very close to those of pure α-CD and PEG, respectively, in DMSO-d_6 under similar conditions. These data indicate the $PEG_{3.4k}$-Ts_2-*pseudorotaxa*-αCD dethreads in DMSO and exists as two separate components. Diffusion coefficients of the polypseudorotaxane were measured within minutes of dissolution in DMSO and were equivalent to those measured after 16 h in solution. Thus, dethreading is relatively rapid upon dissolution in DMSO, a conclusion also supported by the failure of the end-capping reaction to trap cyclodextrins onto the backbone if DMSO is used as a solvent for this reaction.

The 2D DOSY spectrum for the $PEG_{3.4k}$-*rotaxa*-αCD is shown in Figure 3. The α-CD and PEG diffusion coefficients are equivalent, demonstrating that these two components are moving together in solution, as required by a rotaxanated structure. The diffusion coefficient of the PEG-*rotaxa*-αCD (14 CD's per chain from the ^{1}H NMR spectrum) is around 1.29×10^{-11} m^2 s^{-1}, which is smaller than the D for the $PEG_{3.4k}$ of the corresponding polypseudorotaxane. This D reduction is consistent with an increase in the hydrodynamic volume of the polymer due to the presence of threaded cyclodextrins. The end groups exhibit the same diffusion coefficients as the PEG backbone, signifying that uncoupled reactant residues have been completely removed from the samples. (This is also true for the polypseudorotaxane backbone represented by the data in Figure 2.) This is especially important for the polyrotaxanes since the NMR resonance of the end-group methyl protons was used for estimating the number of threaded α-CD's.

DOSY data were processed by assuming a monoexponential diffusion decay and thus a single diffusion coefficient for every chemical shift channel in the 2D data representations of Figures 2 and 3. This assumption is not valid in regions of the spectrum where resonances overlap, such as adjacent to the strong water peak around 3.3 ppm. In these regions, the calculated diffusion coefficients are weighted averages of the components whose signals overlap. Thus, it appears as if the diffusion coefficients vary continuously from one component to the next, giving smeared line shapes along the diffusion axis on both sides of the water peak in Figures 2 and 3. More complex analyses[39,40] can be used to resolve diffusion coefficients of multiple components at a given chemical shift. We recently reported the use of such methods to quantitatively determine the threaded macrocycle fraction in polyrotaxanes also containing unthreaded macrocycles; for example, direct evidence of threading and threaded fraction can be provided prior to purification.[38] However, these multicomponent analysis schemes typically require high signal-to-noise-ratios which can be time-consuming to collect. For purified

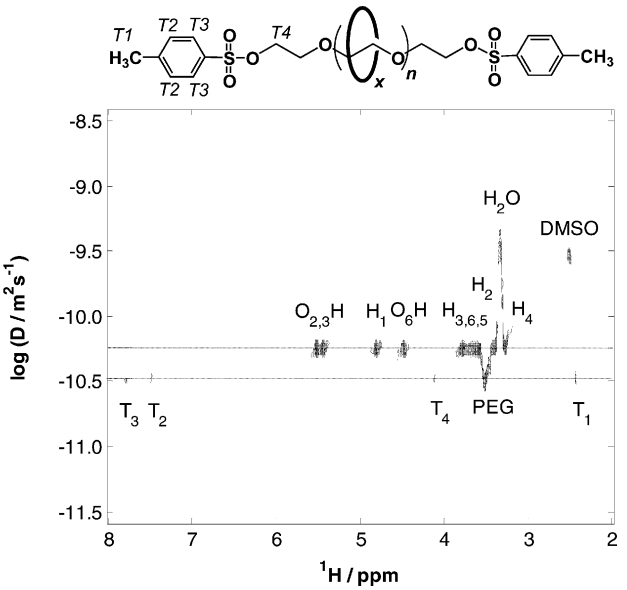


Figure 2. 2D DOSY spectrum of the $PEG_{3.4k}$-Ts_2-*pseudorotaxa*-αCD in DMSO-d_6 at 25 °C. The two horizontal lines mark the diffusion coefficients for the α-cyclodextrin and the α,ω-ditosyl-terminated PEG, indicating the material exists as two separate components when dissolved in DMSO and not as the threaded structure shown above this spectrum. See Figure 1 for α-CD peak designations.

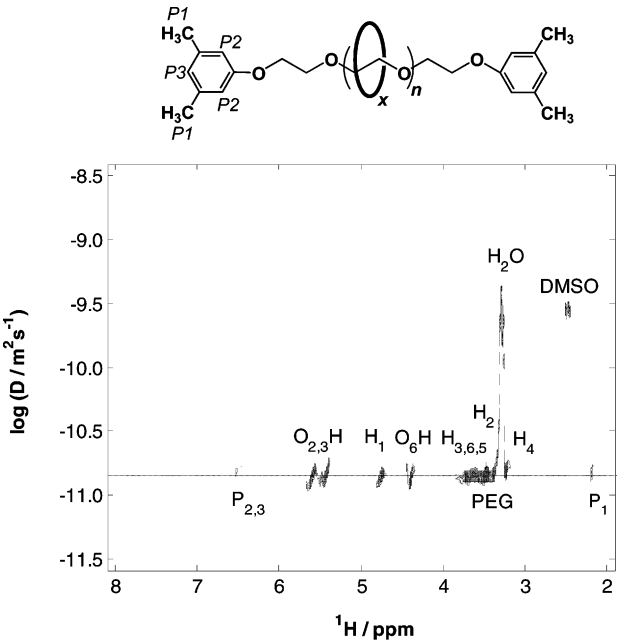


Figure 3. 2D DOSY spectrum of $PEG_{3.4k}$-*rotaxa*-αCD in DMSO-d_6 at 25 °C. The polyrotaxane is end-capped with 3,5-dimethylphenyl groups. The horizontal line marks the single diffusion coefficient for the backbone and cyclodextrin, indicating the material translates as a single entity when dissolved in DMSO, thus proving the threaded architecture. The average number of CD's per chain is 14. See Figure 1 for α-CD peak designations.

rotaxane products, assuming single-component diffusion is normally adequate for identifying whether the macrocycle is threaded or not; for this, long acquisition times are not required (<1 h for the DOSY spectra reported here).

The presence of water in the sample can affect the apparent *D* value for nonadjacent resonances if these peaks are due to exchangeable groups, such as hydroxyls on cyclodextrin. In general, a higher water content leads to a larger apparent *D* for the hydroxyl groups.[41] For the spectra shown here, care was taken to use dry DMSO-d_6.

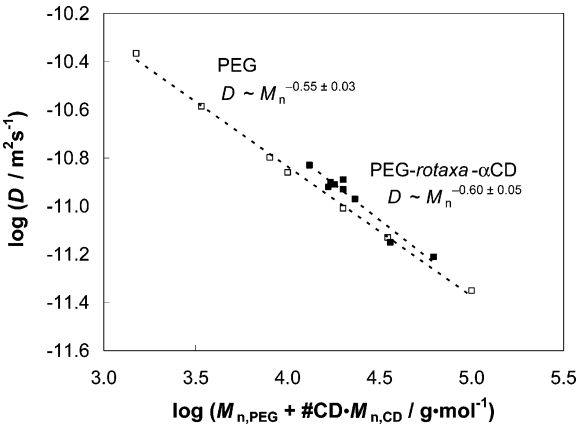


Figure 4. Self-diffusion coefficients vs molecular weight for PEG (□) and PEG-*rotaxa*-αCD (■) in DMSO-d_6 at 25 °C. Solution concentrations are 0.7% (w/v). Dashed lines are least-squares fits to the data.

The end groups in these PEG-*rotaxa*-αCD's represent 0.4−1.9% (w/w) of the sample and appear in the 2D DOSY spectra at the same *D* as the backbone resonances. Thus, DOSY is a nice technique for determining whether a minor component is attached to a polymer or not. For polyrotaxanes prepared by statistical threading, the fraction of threaded macrocycles can be quite low and difficult to distinguish from unthreaded macrocycles using methods such as gel permeation chromatography.[3] Provided that peaks due to the macrocycles and polymer backbone are sufficiently resolved in the chemical shift dimension, DOSY is a very sensitive method for discriminating threaded from unthreaded macrocycles in rotaxanated polymers.

Polyrotaxane Self-Diffusion in Dilute Solution. DOSY spectra were measured for all the polyrotaxanes listed in Tables 1 and 2, the corresponding unthreaded PEG backbones from which these polyrotaxanes were prepared, and PEG with molecular weights of 10, 35, and 100 kg/mol. The DOSY spectra for all PEG-*rotaxa*-αCD's were similar to the one shown in Figure 3; in each case, the self-diffusion coefficient of the polyrotaxane was smaller than the *D* for the corresponding unthreaded PEG backbone. These self-diffusion coefficients are plotted vs molecular weight in Figure 4. In general, the diffusion coefficients for the polyrotaxanes appear on nearly the same line as those for PEG, extrapolated to the corresponding higher molecular weight. The lack of perfect coincidence can be attributed to changes in the statistical segment length, excluded volume, or expansion factor due to polymer−solvent interactions[42] caused by threading cyclodextrins onto the PEG backbone. The chain lengths for a given PEG and its rotaxanated analogue are the same.

The diffusion coefficients shown in Figure 4 were not determined at infinite dilution but well within the dilute regime.[27] The data were fit with a power-law expression, $\log(D) = A + \alpha \log(M_n)$, where α is the slope of the dashed lines shown in Figure 4. Using a $D \sim M_n^{\alpha}$ scaling law for polymers in dilute solution,[42] the scaling constants (α) are -0.55 ± 0.03 for PEG and -0.60 ± 0.05 for PEG-*rotaxa*-αCD. Since scaling constants between −0.6 and −0.5 are characteristic for solvated linear random coils,[27,31,43] the PEG and PEG-*rotaxa*-αCD apparently behave as random coils in good solvents.

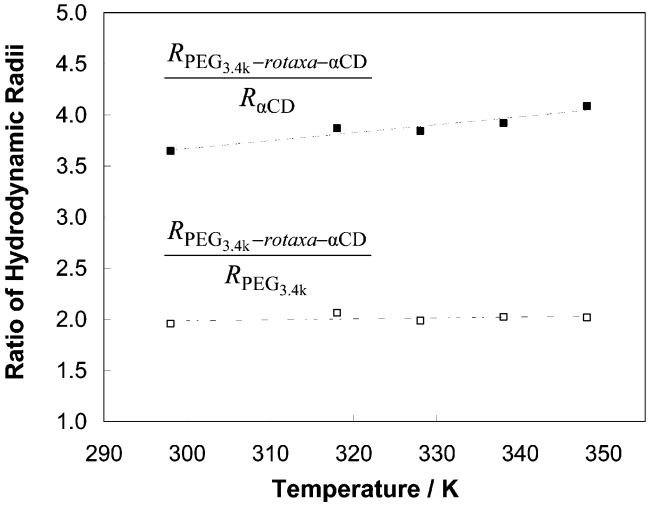


Figure 5. Hydrodynamic radii of $PEG_{3.4k}$-*rotaxa*-αCD ($R_{PEG_{3.4k}\text{-}rotaxa\text{-}\alpha CD}$) and its unthreaded components ($R_{PEG_{3.4k}}$ and $R_{\alpha CD}$) vs temperature. These radii are plotted as ratios determined using the self-diffusion coefficients of the respective species measured in DMSO-d_6 (0.7% w/v). The number of CD's per chain for this polyrotaxane is 14, which cover about 36% of the PEG backbone. Dashed lines are least-squares fits to the data.

Scaling constants around −0.33 are indicative of highly branched or collapsed linear polymers,[44,45] while constants < −0.6 (asymptotically approaching −1) are indicative of semiflexible wormlike behavior or rigid rods.[29] For example, the rodlike poly(γ-benzyl-α,L-glutamate) is characterized by α values around −0.70[46] or −0.78.[47,48] Using the same DOSY methodology described here, we recently determined an α value of −0.71 for a soluble poly(*p*-phenylene ethynylene) derivative.[49] Thus, PEG-*rotaxa*-αCD in dilute DMSO does not exhibit rodlike behavior, at least when α-CD covers from 20 to 70% of the backbone. PEG-*rotaxa*-αCD self-diffusion exhibits a similar molecular weight dependence as the unthreaded PEG.

The self-diffusion coefficients for $PEG_{3.4k}$-*rotaxa*-αCD (with 14 threaded CD's) and its unthreaded components were measured from 25 to 75 °C using the double-stimulated-echo sequence to compensate for convection at temperatures above ambient. Invoking the Einstein−Stokes law,[50] the self-diffusion coefficients were inversely related to hydrodynamic radii (R) at a given temperature:

$$\frac{R_{PEG_{3.4k}\text{-}rotaxa\text{-}\alpha CD}}{R_{\alpha CD}} = \frac{D_{\alpha CD}}{D_{PEG_{3.4k}\text{-}rotaxa\text{-}\alpha CD}} \quad (1)$$

$$\frac{R_{PEG_{3.4k}\text{-}rotaxa\text{-}\alpha CD}}{R_{PEG_{3.4k}}} = \frac{D_{PEG_{3.4k}}}{D_{PEG_{3.4k}\text{-}rotaxa\text{-}\alpha CD}} \quad (2)$$

where R and D are the hydrodynamic radii and diffusion coefficients, respectively, of the species signified with the attending subscripts. These ratios are plotted in Figure 5 as a function of temperature. With increasing temperature, the hydrodynamic radius of the PEG-*rotaxa*-αCD increases with respect to the R of α-CD but is constant with respect to the R for the unthreaded $PEG_{3.4k}$ backbone. The hydrodynamic radius of the cyclodextrin is expected to remain fairly constant over the temperature range examined. Thus, the hydrodynamic radius of the PEG-*rotaxa*-αCD is characterized by a similar temperature dependence as the unthreaded PEG. For polyoxyethylene, the temperature coefficient of the mean-square unperturbed length, $d \ln \langle r^2 \rangle_0 / dT$, is positive.[51] Thus, in the absence of polymer−solvent interactions, polyoxyethylene random coils are expected to expand with increasing temperature. Even in the presence of polymer−solvent interactions that are different for the PEG and PEG-*rotaxa*-αCD, these coils expand with increasing temperature and with nearly identical temperature coefficients from 298 to 348 K.

Summary

A series of polyrotaxanes were synthesized from α-cyclodextrin and commercially available poly(ethylene glycol) with molecular weights of 1.5, 3.4, 8, and 20 kg/mol using a more concise method than those reported previously. The rotaxanated structure (i.e., threaded architecture) was verified by diffusion-ordered NMR spectroscopy in DMSO-d_6; the self-diffusion coefficients of the cyclodextrins and PEG backbone in PEG-*rotaxa*-αCD were equivalent. On the other hand, the self-diffusion coefficients of the cyclodextrins and PEG backbones were not equivalent for the polypseudorotaxanes, indicating rapid dethreading in DMSO. The molecular weight dependence of the self-diffusion coefficients were found to obey the following scaling laws: $D_{PEG\text{-}rotaxa\text{-}\alpha CD} \sim M_n^{-0.60\pm0.05}$ and $D_{PEG} \sim M_n^{-0.55\pm0.03}$, characteristic of random coils in good solvents for both PEG-*rotaxa*-αCD and PEG. In addition, the temperature dependence of the self-diffusion coefficient for PEG-*rotaxa*-αCD (with 14 threaded CD's) is similar to that for the unthreaded backbone; the hydrodynamic radii for both polymers expand in DMSO with increasing temperature from 298 to 348 K.

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