Soluble PEG-α-CD-Rotaxanes: Where on the PEG Chains Are the Permanently Threaded α-CDs Located and Are They Mobile?

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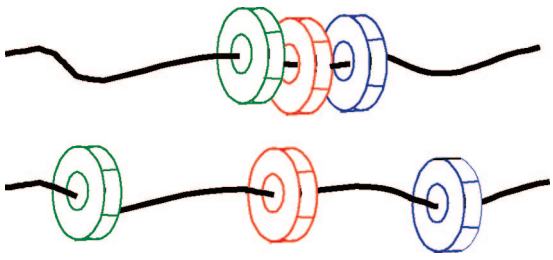
Introduction

Recently, Zhao and Beckham[1] directly synthesized a series of poly(ethylene glycol)- (PEG-) α-cyclodextrin- (CD-) rotaxanes, with PEGs of various molecular weights(1.5−20 kg/mol), which were permanently threaded by and 20−70% covered with α-CDs. They observed the free uncovered PEGs and the (PEG)-α-CD-rotaxanes in dilute dimethyl sulfoxide (DMSO-d_6) solutions with diffusion-ordered 2-D ^{1}H NMR (DOSY)[2] to both prove rotaxanation and to compare the self-diffusion coefficients, D, of uncovered and α-CD-rotaxanated PEGs. Because the diffusion coefficients observed for the ^{1}H resonances of $PEG_{3.4K}$ (molecular weight = 3400 g/mol) and α-CD were identical ($\sim 1.3 \times 10^{-11}$ m^2 s^{-1}) for the $PEG_{3.4K}$-α-CD-rotaxane, while unthreaded $PEG_{3.4k}$ and α-CD diffuse with $D = 3$ and 7×10^{-11} m^2 s^{-1}, respectively, rotaxanation was proved.

In addition, they observed that both the unthreaded and α-CD-rotaxanated PEGs showed Ds that similarly scaled[3] with their molecular weights (M), i.e., $D_{free} \sim M^{-0.55}$ and $D_{rotaxane} \sim M^{-0.60}$, and which are characteristic of solvated linear randomly coiling polymers. Making use of the Einstein−Stokes law,[4] which inversely relates the diffusion coefficient and hydrodynamic radius, R, they found for $PEG_{3.4K}$ that $R_{rotaxane}/R_{free} \sim 2$ over the temperature range 25−75 °C. This means that free, unthreaded and α-CD-rotaxanated $PEG_{3.4K}$ both behaved as randomly coiling chains in solution and expanded similarly with increasing temperature.

Here, we calculate the mean-square radii of gyration ($\langle s^2 \rangle_o$) and end-to-end distances ($\langle r^2 \rangle_o$) for uncovered and α-CD-rotaxanated $PEG_{3.4K}$ (M = 3400 g/mol) chains with a conformational model (RIS)[5,6] that properly accounts for the absence and presence of threaded α-CDs on the conformations of the PEG repeat units. Comparison to the observations of Zhao and Beckham lead to conclusions concerning both the distribution/positions and mobility of the 14 α-CDs that are threaded onto the $PEG_{3.4K}$-α-CD-rotaxane.



Calculations

The RIS conformational model derived by Mark and Flory[5] for PEG was modified to account for the conformational constraints placed on those repeat units threaded through α-CDs. Previously it was shown[6] that, when confined to occupy narrow cylindrical channels with a diameter in the range of the α-CD cavity (∼5 Å), PEG repeat units are essentially restricted to the fully extended, all trans planar zigzag conformation (see Figure 1). This means that only the (1,1) elements in the statistical weight matrices[7] ($\mathbf{U}_a$, $\mathbf{U}_b$, $\mathbf{U}_c$) are retained for the backbone bonds of PEG repeat units threaded through α-CDs. On the other hand, the first backbone bond in a PEG repeat unit that is threaded through and covered (C) by α-CD retains all three elements in the first column (1,1; 2,1; 3,1) of its statistical weight matrix when the previous repeat unit in the PEG chain is uncovered (U) and not threaded by α-CD. For uncovered PEG repeat units immediately following a covered repeat unit, the statistical weight matrix of its first backbone bond is reduced to the elements in the first row (1,1; 1,2; 1,3), reflecting the fact that the backbone bonds in the previous covered PEG repeat unit are restricted to the trans conformation.

We chose to consider 80-repeat-unit PEG chains, which correspond to the free and α-CD-rotaxanated $PEG_{3.4K}$ most thoroughly studied by Zhao and Beckham. The $PEG_{3.4K}$ chain was threaded through 14 α-CDs in its α-CD-rotaxane, and, because 2 PEG repeat units occupy a single α-CD cavity, this results in a 28/80 or 35% coverage of PEG repeat units. The dimensions [mean-square end-to-end distances ($\langle r^2 \rangle_o$) and their characteristic ratios, $C_n = \langle r^2 \rangle_o / nl^2$, and radii of gyration ($\langle s^2 \rangle_o$)] were calculated, respectively, for all and selected $PEG_{3.4K}$-α-CD-rotaxanes by matrix multiplication methods.[7] The distributions/positions of α-CDs threaded on the $PEG_{3.4K}$ chains in the rotaxanes were varied in the following manners: (i) covered, uncovered (C, U) repeat units were placed either completely randomly or "randomly", but with a bias favoring the threading by pairs of α-CDs covering four consecutive PEG repeat units (random); (ii) long consecutive blocks of C, U repeat units ($C_{28}U_{52}$ and $U_{26}C_{28}U_{26}$) (blocky/*fixed placement*); (iii) shorter randomly placed C, U blocks of repeat units (U_8, C_4; U_{12}, C_6; U_{16}, C_8 (blocky/*random placement*); (iv) all PEG repeat units treated with statistical weight matrices that are weighted as 65% U and 35% C, implying rapid movement of the 14 threaded α-CDs along the $PEG_{3.4K}$ chain.

Because each threaded α-CD must cover two consecutive PEG repeat units, the following procedure was used to construct the random and biased random ("random") $PEG_{3.4K}$-α-CD-rotaxanes mentioned above in point i: The first PEG unit was covered (C) with a probability of 28/80 (C/U). If C, then the second repeat was also covered, while if U then the second was covered with probability 28/79. Thus, the first pair of repeat units are either UU, UC, or CC, but not CU. If UC, then the third repeat unit was covered, and the fourth repeat is covered with probability 27/78. If either UU or CC, then the third is covered with probabilities 28/78 or 26/78, the latter probability either unbiased (random) or biased ("random"). Thus, the second (repeat units 3 and 4) and all subsequent pairs may be either UU, UC, CU, or CC. The fifth and sixth repeat units and all subsequent pairs are generated identically, except that now the previous pair of repeat units may also be CU. In the case for previous pairs UU and CU, the next unit is covered with probability $P = \{[28 - N_C]/[80 - (N_C + N_U)]\}$, where N_C, N_U are the current total number of C, U units in the rotaxanted chain being generated. When the previous pairs are UC and

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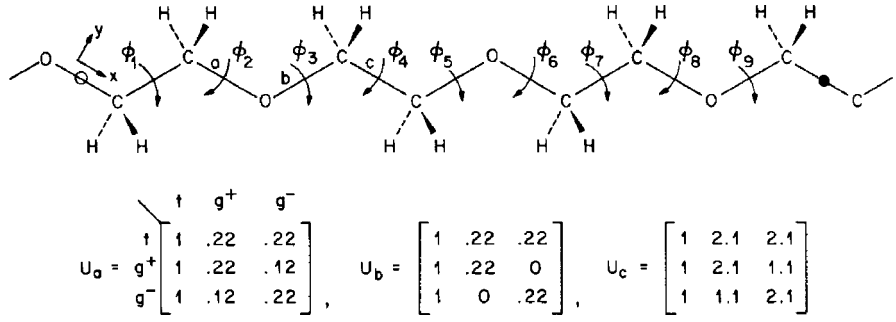

Figure 1. The PEG fragment considered[6] in the search of RIS[5] conformations that can be accommodated in narrow cylindrical channels. Also presented are the statistical weight matrices ($\mathbf{U}_a$,$\mathbf{U}_b$, $\mathbf{U}_c$) for each of the conformationally distinct bonds (a, b, c) in the PEG repeat unit with elements corresponding to $T = 25$ °C.

Table 1. $\langle s^2\rangle_o$, $\langle r^2\rangle_o$, $C_n = 240$ Calculated for 80 Repeat Unit $PEG_{3.4K}$ Chains That Are Either Uncovered (U) or Covered (C) and Threaded through 14 α-CDs

PEG chain	$\langle s^2\rangle_o$, Å^2	$\langle r^2\rangle_o$, Å^2	$C_n = \langle r^2\rangle_o/nl^2$
free, 80U	342 (345)[a]	2007[b]	3.9
all repeat units rapidly U(65%) and C(35%)		2419	4.7
random			
52U, 28C (randomly placed)		3860	7.5
52U, 28C (CC 2× random)		4994	8.6
52U, 28C (CC 4× random)		**7939**	**13.7**[e]
52U, 28C (CC 5× random)		**9501**[d]	**16.4**[e]
blocky			
fixed placement			
$C_{28}U_{52}$		12093	23.5
$U_{26}C_{28}U_{26}$		12762	24.8
random placement			
U_{16}, C_8		10466	20.3
U_{12}, C_6	**1198 (1346)**[a]	**8079**[c]	**15.7**[e]
U_8, C_4		6432	12.5

[a] $\langle s^2\rangle_o = \langle r^2\rangle_o/6$. [b] $d[\ln(\langle r^2\rangle_o)]/dT = +0.0003$ °C^{-1}. [c] $d[\ln(\langle r^2\rangle_o)]/dT = +0.0001$ °C^{-1}. [d] $d[\ln(\langle r^2\rangle_o)]/dT = \sim 0$ °C^{-1}. [e] PEG-α-CD-rotaxanes with correct calculated dimensions ($\langle r^2\rangle_o$), i.e., ~4× those of the unthreaded PEG.

CC, the next repeat unit added is always C and C with P biased, respectively.

Except for the free, uncovered $PEG_{3.4K}$ and its rapidly moving U(65%) and C(35%) and regular fixed $C_{28}U_{52}$ and $U_{26}C_{28}U_{26}$ rotaxanes, a Monte Carlo population of 40 chains were generated for each $PEG_{3.4K}$-α-CD-rotaxane. The mean-square dimensions were calculated for each generated $PEG_{3.4K}$-α-CD-rotaxane chain and these were averaged over each complete 40 chain population. The dimensions of free and all $PEG_{3.4K}$-α-CD-rotaxanes were calculated at 25 °C, while in a few cases dimensions were also evaluated at 60 °C.

Results and Discussion

Of the dimensions calculated for the $PEG_{3.4K}$-α-CD-rotaxanes and presented in Table 1, only the underlined entries yield calculated average dimensions ($\langle s^2\rangle_o$ or $\langle r^2\rangle_o$ and C_n) that are ~4× those calculated for the uncovered, free PEG chain. [Remember Zhao and Beckham observed $R_{rotaxane}/R_{free} \sim 2$, so presumably $(\langle s^2\rangle_o$ or $\langle r^2\rangle_o$ or $C_n)_{rotaxane}$ /$(\langle s^2\rangle_o$ or $\langle r^2\rangle_o$ or $C_n)_{free} \sim 4$.[8]] In one case the 52 uncovered (U) were randomly positioned, while the 28 covered (C) repeat units were placed with either (4 or 5) times the random probability for the consecutive threading of α-CDs, ie., (4 or 5) × {[28 − (no. of PEG repeat units already covered)]/[80 − (current no. of PEG repeat units in the Monte Carlo generated chain)]} = (4 or 5) × P. In the other PEG-α-CD-rotaxane, U_{12},C_6, repeat unit blocks with12 uncovered and 6 covered (threaded by 3 α-CDs) PEG repeat units were randomly inserted.

Both α-CD-rotaxanes (boldface entries in Table 1) having calculated dimensions 4× that of the free $PEG_{3.4K}$ have blocky distributions/coverage of threaded α-CDs, with α-CD block lengths of 2.9 or 3.7 (average of 6 or 7 covered PEG repeat units) and 3.0 (exactly 6 covered PEG repeat units), respectively, implying a preference for the adjacent threading of α-CDs. However, as can be seen in Table 1, increasing the block lengths of consecutively covered PEG repeat units beyond 6−8 (3−4 consecutively threaded α-CDs) yields dimensions well in excess of 4× that of the free $PEG_{3.4K}$ chain.

By comparison, random insertion of the 52 U and 28 C repeat units results in dimensions that are less than double those of the uncovered free $PEG_{3.4K}$ chain, and not 4× greater, as observed by Zhao and Beckham.

To determine whether or not the somewhat blocky coverage of threaded α-CDs needed to produce the 4-fold increase in PEG-α-CD-rotaxane chain dimensions results in a significant diminishing of the ability of the partially included PEG to randomly coil, the mean-square radii of gyration, $\langle s^2\rangle_o$, were explicitly calculated for both the free and U_{12},C_6 rotaxanated PEG chains (see Table 1). The same matrix methods[7] used to obtain $\langle r^2\rangle_o$ were used to calculate $\langle s^2\rangle_o$ and these were compared to the values expected for a completely randomly coiling chain, i.e., $\langle s^2\rangle_o = (\langle r^2\rangle_o)/6$. The directly calculated (matrix method) and expected ($\langle r^2\rangle_o/6$) values are nearly coincident for the free PEG chain, and the directly calculated radius of gyration, $(\langle s^2\rangle_o)^{1/2}$ of the blocky U_{12},C_6 rotaxanated PEG chain (1198 Å$^2)^{1/2}$ is only ~ 5−6% shorter than the expected value (1346 Å$^2)^{1/2}$. This result strongly suggests that the 4-fold expansion of end-to-end dimensions, $\langle r^2\rangle_o$, calculated for PEG-rotaxanes with a somewhat blocky coverage of α-CDs is achieved without seriously altering their ability to random-coil, because their explicitly calculated $\langle s^2\rangle_o$s remain very close to the expected randomly coiling values [($\langle r^2\rangle_o/6$)s]. The $PEG_{3.4K}$-α-CD-rotaxane, at least, does not appear to be behaving like a wormlike chain, even though 35% of its repeat units are threaded through and covered by α-CDs and restricted to all-trans conformations.

It should be noted that subsequent to the study by Zhao and Beckham,[1] Karino et al.,[9] and Fleury et al.[10] reported DLS and SANS observations of PEG-α-CD rotaxanes in DMSO-d_6. From DLS, Karino et al. estimated a diffusion coefficient for α-CD close to that obtained by Zhao and Beckham from DOSY NMR, and the scattering functions they observed with SANS for free PEG and the PEG-α-CD rotaxane were similar. (It should be noted that, unfortunately, they did not specify the molecular weight or the α-CD coverage for their PEG-α-CD-rotaxane.) Fleury et al. synthesized PEG-α-CD rotaxanes with different α-CD coverages (~1, 15, and 33%) and observed them with SANS in DMSO-d_6 to which 1.4% v/v *N*-methylpyrrolidone

was added to disrupt hydrogen-bonding and prevent aggregation of the PEG_{20K}-α-CD rotaxanes. They interpreted the SANS data [I (cm^{-1}) vs q ($Å^{-1}$)] observed for free and the 1 and 15% covered rotaxanes using the Debye form factor appropriate to random coils. For reasons not apparent from their scattering curve nor discussed, but in agreement with Karino et al., who treated both free and rotaxanated PEGs similarly, Fleury et al. employed the rodlike form factor for the PEG_{20K}-rotaxane with the heaviest (33%) α-CD coverage. They estimated a rod length of $L \sim 500$ Å, with a resulting radius of gyration $R_g = 145$ Å ($R_g^2 = L^2/12$). By comparison, the free unthreaded and randomly coiling PEG_{20K} had an $R_g = 66$ Å. Even though they treated the 33% covered rotaxane as a rod, Fleury et al. obtained R_g(rotaxane)/R_g(free) ~ 2.2, similar to the ~2 reported by Zhao and Beckham. If the PEG_{20K}-rotaxane with 33% α-CD coverage were behaving like a rod, then this ratio would be expected to be much higher.

The PEG-α-CD-rotaxanes synthesized and studied by the latter group, including those with up to 54% α-CD coverage of free PEGs with molecular weights from 1.5K to 20K, showed hydrodynamic radii R that scaled with their total molecular weights (M), ie., $R \propto M^{0.60}$, while their free PEGs showed $R \propto M^{0.55}$. This is clearly the behavior of randomly coiling chains, albeit with some modest excluded volume expansion similar for both the rotaxanated and free PEG chains, and certainly not the behavior of worm- or rodlike chains. This is confirmed by the nearly identical expansions of the free and 35%-rotaxanated $PEG_{3.4K}$s observed with increasing temperature.

Syntheses and observation of a set of PEG-α-CD-rotaxanes, each with the same high α-CD coverage, e.g., 70%, but threaded with PEGs of different molecular weights, would permit a more definite conclusion concerning whether or not, or at what coverage, PEG-α-CD-rotaxanes might evidence rodlike behavior in solution.

The dimensions calculated for the $PEG_{3.4K}$-α-CD-rotaxanes are generally found to increase with increasing temperature, as do those of the unthreaded $PEG_{3.4K}$ chain, also in agreement with the observations of Zhao and Beckham. Thus, it appears likely that hydrogen-bonding between the −OHs on the rims of adjacent threaded α-CDs leads to a somewhat blocky distribution/coverage, resulting in the larger sizes ($\langle r^2 \rangle_o$), yet still randomly coiling, guest PEG chains.

If the 14 α-CDs threaded on the $PEG_{3.4K}$ chain in the α-CD-rotaxane are presumed to translate rapidly, so that each PEG repeat unit is covered or uncovered 35 and 65% of the time, respectively, the dimensions calculated are very similar to those of the completely unthreaded free $PEG_{3.4K}$ chain. Thus, the segregation, or association, of threaded α-CDs into blocks of average length 3−4 covering 6−8 consecutive PEG repeat units are relatively stable and long-lived, at least with respect to the time necessary for a PEG chain to sample its various backbone bond conformations in solution.

Before closing, it may be worth mentioning the more recent report by Zhao, Beckham et al. describing the formation and characterization of solid inclusion compounds (ICs) between α-CDs and PEGs, both perdeuterated and protonated, and mostly α-hydroxy-ω-ethyl terminated.[11] They observed that for $M >$ 3200 the PEG backbones were only partially covered with α-CDs that aggregated to form crystalline hydrogen-bonded stacks or columns of α-CD-threaded PEGs separated by amorphous layers of unthreaded PEG. Analyses of SAXS and SANS observations of the partially included perdeuterated PEG-α-CD-ICs led them to suggest that the crystalline stacks contained ~2−7 α-CDs, depending on the PEG chain length (M), consistent with the 3−4 α-CD block lengths we have suggested for the $PEG_{3.4K}$-α-CD-rotaxane in solution. As a consequence, the resultant solid-state morphologies of the PEG-α-CD-IC crystals with partially included PEG chains may have their bases in the equilibrium distributions of α-CDs threaded on the PEG chains in solution prior to crystallization, rather than upon threading/dethreading or sliding of the α-CDs to maximize the sizes of the resulting α-CD crystalline stacks.

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