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Polypseudorotaxanes between α-cyclodextrin and poly(propylene glycol)-b-poly(ethylene glycol)-b-poly(propylene glycol) copolymers studied by MALDI-TOF mass spectrometry

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ABSTRACT

MALDI-TOF mass spectrometry is used to show that formation of solid polypseudorotaxanes between α-cyclodextrin (α-CD) and poly(propylene glycol)–poly(ethylene glycol)–poly(propylene glycol) block copolymers (PPG–PEG–PPG, Reverse Pluronics) is a block length selective process. A comparison of copolymer composition matrices of neat Reverse Pluronics 10R5 and 17R4 and of the copolymers in their precipitated complexes with α-CD shows that the distribution with respect to an absolute PPG content is not affected by the complexation, which means that complexation occurs with Reverse Pluronics generally, not just with the fraction of copolymers with at least one outer block short or completely absent and that α-CD can slide even over block of 20 PG. Nevertheless, the complexation is a selective process with respect to PEG as copolymers with shorter PEG blocks are more abundant in the supernatant while the content of PPG remains almost unchanged for both Reverse Pluronics.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of α(1 → 4) linked glucopyranose units. Their availability and propensity to form inclusion complexes with various guests made them popular both for practical applications in food, toiletries & cosmetics, and pharmaceutical industries and for research on the self-assembling of well-planned nanostructures [1–7]. Inclusion complexation occurs when hydrophobic molecules or parts of a molecule fit into the CD cavity. For example, pseudorotaxane forms when a threadlike molecule penetrates CD. Similarly, polypseudorotaxane forms when a suitable chain-like molecule (i.e. oligomer or polymer), passes through cavities of several CD molecules [8,9]. Axial polypseudorotaxane can be transformed into polyrotaxane via the attachment of bulky end groups [10]. Various supramolecular applications were proposed for CD polyrotaxanes, from which for example slide-ring gels, in which CDs on various chains are crosslinked, draw significant attention because their mechanical properties are similar to those of various biomaterials [11,12].

The binding constant for threading of an isolated α-CD molecule onto a PEG chain is rather low – about 2 L/mol [13]. Given this value, one might expect less than one third of PEG to be included in CD in saturated α-CD solution. And yet, complexes with fully included polymer chains precipitate in high yields from aqueous solutions of α-CD/PEG or of other suitable polymer/CD pairs. Thus, the polypseudorotaxane formation in aqueous solutions has to be cooperative in nature. A possible mechanism for such cooperativity is suggested by spatial arrangement of CDs' molecules. Glucopyranose units are oriented

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in such a way that the remaining hydroxyls are situated at the rims of the torus – two secondary hydroxyls per glucopyranose unit at the wider rim and one primary hydroxyl at the narrower rim. Hydrogen bonds between hydroxyls on adjacent threaded CDs are thus possible and would promote formation of polypseudorotaxane. Nevertheless, the role of hydrogen bonding between CDs adjacent along the chain has been questioned. Although its cooperative effect was recognized the low solubility of polypseudorotaxane was proposed as a primary cause of solid-polypseudorotaxane high yields [14].

The formation of polypseudorotaxanes between CDs and hydrophilic homopolymers of various chain thicknesses complies with the requirement of guest/cavity fitting: α-CD forms solid complexes with PEG but not with poly(propylene glycol) (PPG), whereas β-CD, consisting of seven glucopyranose units, forms solid complexes with PPG but not with PEG [9]. The correlation between the size fit and polypseudorotaxane formation was, however, challenged by recent experiments. (i) Preparation of crystalline β-CD/PEG complexes was reported [15]. (ii) It was found that solid polypseudorotaxane are formed by α-CD and PPG–PEG–PPG triblock copolymers (Reverse Pluronics) [16,17]. Even though α-CD is supposed to be located on the PEG block in the solid polypseudorotaxane the outer PPG blocks had to thread through the α-CD cavity first. Thus the explanation why α-CD does not form solid polypseudorotaxane with PPG has to be more sophisticated than the plain incongruity between the PPG chain cross section and the α-CD cavity. This can have some ramification because polypseudorotaxane formed by CDs and PPG/PEG tribloc copolymers were suggested as components of a nanomachinery toolbox – molecular switches, molecular pistons and so on [9,18,19].

A PPG block, however, would not have to pass through the α-CD cavity for α-CD to access the PEG block if solid polypseudorotaxanes were formed with the fraction of copolymers with at least one outer block very short or completely absent (the diblock selection mechanism). The high yields of precipitate around 80% observed with α-CD and Reverse Pluronics [16] indicates that this is not the case; nevertheless a direct proof has not been given. Moreover, even such high yields would be compatible with a weaker restriction, i.e., with the exclusion of Reverse Pluronics with long PPG blocks from precipitation. The methods giving average composition (e.g., NMR) cannot identify the decrease in the length of PPG blocks in polypseudorotaxanes because the lower content of PPG in the precipitated Reverse Pluronics can also be due to a longer PEG block. In fact, preferential precipitation of Reverse Pluronics with a longer middle blocks might be expected as the yield of solid complex PEG homopolymer/α-CD is low for low molecular weight PEG [20]. Therefore, bivariate (composition, molecular weight) distributions should be compared to obtain adequate information on the block-length selectivity of polypseudorotaxane formation.

In the present study, MALDI-TOF mass spectrometry (MS) is used for this purpose because it can provide a bivariate distribution in the form of copolymer composition matrix [21]. The resolution of MALDI-TOF MS is so high that the molecular weight of the individual components of an investigated mixture can be determined. For copolymers, the molecular weight is given by the content of each of the monomeric units in the molecule and thus conveys the information on the composition. The transformation of MALDI-TOF mass spectra to compositional distributions is complicated by the fact that even though the relation between molecular weight and composition is unique in principle, the relation is one-to-several rather than one-to-one because of finite MALDI-TOF MS resolution. Frequently, more than one composition can be assigned to the molecular weight observed in the spectrum. As a result, several copies of virtually the same pattern, called fingerprints, can be found in the copolymer composition matrix obtained from a MALDI-TOF mass spectrum of binary-copolymer but only one of them corresponds to the composition of the measured sample [22].

The process of transformation of the MALDI-TOF mass spectrum of a binary copolymer into the copolymer composition matrix was recently reviewed and analyzed in the scope of the number theory, the rules of the "copolymer fingerprints" multiplicity were derived and methods for true fingerprint identification suggested [23]. Such procedure also eliminates the effect of the present homopolymers, which are included in the results of methods giving the average values as NMR or SEC. We apply the developed methodology to the analysis of Reverse Pluronics 10R5 and 17R4, both directly and after complexation with α-CD. We then compare the obtained compositional distributions in order to establish whether any preferential complexation with respect to PPG and PEG blocks length occurs. We are especially interested in detection of the possible presence of the diblock selection mechanism.

2. Experimental section

2.1. Materials

Poly(propylene glycol)–poly(ethylene glycol)–poly(propylene glycol) copolymers (Reverse Pluronics) 10R5 and 17R4, dimethylformamide, α-cyclodextrin (α-CD), sodium trifluoroacetate ($NaAcF_3$), and anthracene-1,8,9-triol (dithranol) were obtained from Aldrich and were used as received. Number average molecular weights and the contents of PEG provided by the vendor are given in Table 1; contents of PEG was verified by ^{1}H-NMR [24].

2.2. Preparation of solid polypseudorotaxane

One mL of 13% aqueous α-CD solution was added to 15 mg of Reverse Pluronic in a 1.5 mL vial. The vial was vortexed for 20 min, sonicated for 10 min, and then vortexed again for 90 min. The suspension that formed was centrifuged and left to stand overnight. Next day, the supernatant, which remained clear, was transferred as completely as possible to a new vial