Enthalpy-driven micellization of oligocarbonate-fluorene end-functionalized Poly(ethylene glycol)☆

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ABSTRACT

A fluorescent pyrene probe method was applied to measure the critical micelle concentration (*CMC*) of oligocarbonate-fluorene end-functionalized poly(ethylene glycol) ($F_mE_{445}F_m$) triblock copolymers in water. The *CMC* decreases with lower temperature and higher values of the hydrophobic block length, *m*. When analyzed by a closed-assembly micelle model, the estimated energetic parameters find a negative $\Delta H°_{mic}$ and small positive $\Delta S°_{mic}$ suggestive of enthalpy-driven micellization, which differs from entropy-driven oxyethylene/oxybutylene triblock copolymers and octaethylene glycol-*n*-alkyl ethers. The enthalpy-driven micellization of $F_mE_{445}F_m$ may result from the limited hydration of individual hydrophobic F blocks that leads to few hydrogen-bonded waters released during F block association. The π-π stacking oligocarbonate-fluorene system also observed enthalpy-entropy compensation when compared to a series of published data on diblock and triblock copolymer systems. An anomalously low partition equilibrium constant for *m* = 15.3 implies a tightly-packed core that excludes pyrene intercalation into the fluorene core. This is discussed along with the possible limited applicability to estimate the *CMC* and potential model drug molecule insertions into the intercalated micelle core.

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1. Introduction

Polymeric micelles that self-assemble from amphiphilic block copolymers can serve as carriers in delivery applications [1–3]. The critical micelle concentration (*CMC*) determines how stable the micelles are against dilution under *in vivo* circulation. The *CMC* is important for nanoparticles to exploit the enhanced permeability and retention (EPR) effect in tumor tissues for anticancer drug delivery since long *in vivo* circulation times are required to achieve an effective targeting.

The *CMC* depends on the insoluble block length and temperature. Astafieva and Eisenberg *et al.* [4] showed that for polystyrene-*b*-poly(*tert*-butyl acrylate), log(*CMC*) decreases with an increase in the insoluble polystyrene block length. While in the study of Liu

and Chu *et al.* [5], log(*CMC*) has a linear dependence on the insoluble oxybutylene block length for oxyethylene/oxybutylene ($B_mE_nB_m$) triblock copolymers. A similar linear dependence of log(*CMC*) on insoluble block length was observed in Pluronics [6]. As for its temperature dependence, it is well known that the *CMC* decreases with increasing temperature for Pluronics [7,8]. A contrary dependence of *CMC* on temperature was observed for polystyrene-*b*-poly(ethylene/propylene) (PStPEp) and polystyrene-*b*-poly(ethylene/butylene)-*b*-polystyrene (SEBS) block copolymer in decane [9] and *n*-octane [10], respectively. Moreover, it is found that for *n*-dodecyl polyoxyethylene glycol monoether ($C_{12}H_{25}O(C_2H_4O)_nH$), *CMC* initially decreases to a minimum value and then increases as system temperature increases [11].

Based on the temperature dependence of the *CMC*, the standard enthalpy and entropy change of micellization, $\Delta H°_{mic}$ and $\Delta S°_{mic}$, respectively, may be estimated [9,12]. The standard free energy change $\Delta G°_{mic}$ of micellization can be derived from the *CMC* after applying a closed association model [9,12]. These energetic parameters are governed by molecular changes such as chain conformation and interfacial packing, aggregation number, and

water hydration extents as a function of temperature. Such changes are related to the thermodynamic stability of micelles in aqueous solution. Accordingly, many studies have focused on this topic. Meguro *et al.* [13] reported that the positive ΔH°_{mic} became smaller with higher hydrophobic group content, and the hydrophobic group is an important driving force for micelle formation of octa-ethylene glycol-*n*-alkyl ethers ($C_m E_8$) in aqueous solution. Similar work by Liu *et al.* [5] observed a positive ΔH°_{mic} for oxyethylene/oxybutylene ($B_m E_n B_m$) that decreased with increasing number of hydrophobic oxybutylene units. Bohorquez *et al.* [14] showed a discontinuity for micellization of Pluronic F127 (poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), $E_n P_m E_n$). They attributed this discontinuity to changes in the aggregation number and/or progressive entanglements between PEO chains. Tsui *et al.* [15] found a maximum in ΔH°_{mic} as a function of temperature in a series of Pluronics. Recently, Hoarfrost and Lodge [12] investigated the effect of solvent quality on the critical micelle temperature (CMT) of poly(ethylene oxide-*b-n*-butyl methacrylate) (PEO-*b*-P*n*BMA) in mixtures of ionic liquids. They concluded that ΔH°_{mic} and ΔS°_{mic} calculated from the CMT do not vary with solvent quality.

We notice that all the values of ΔH°_{mic} reported in the above-mentioned studies are positive. In this case, to accomplish the micellization process, ΔS°_{mic} must be positive to make the overall ΔG°_{mic} negative through $\Delta G^\circ_{mic} = \Delta H^\circ_{mic} - T\Delta S^\circ_{mic}$. A positive ΔH°_{mic} indicates the micellization process is entropy driven. The hydrophobic interaction is often viewed as entropic since the binding strength increases with increasing temperature where the effect is attributed to the dehydration of the molecules by water. This is true when the hydrophobic groups are individually hydrated because the hydrophobic hydration reduces the solvent configurational entropy and the release of hydrogen-bonded water during micellization becomes entropically favorable [16]. However, if individual hydrophobic groups are partially or completely dehydrated, Setny *et al.* suggest that ligand-receptor type associations can be driven by enthalpy [17]. Price and coworkers [9,18] reported that the micellization of polystyrene-*b*-poly(ethylene/propylene) (PStPEp) block copolymer in organic solvent of decane is enthalpy driven. Recently, Paul *et al.* [19] showed that the complex formation between bile salts and β-cyclodextrins is enthalpy dominant.

The self-assembly of oligocarbonate-fluorene end-functionalized poly(ethylene glycol) triblock copolymers $F_m E_n F_m$ (Scheme 1) in aqueous solution are analyzed within the thermodynamic framework of micellization. Previous work [20–22] showed the structural aspects of the $F_m E_n F_m$ self-assembly into micelles, but not the temperature effect on the *CMC*. Here, the pyrene I_{338}/I_{333} ratio method was applied to determine the *CMC* dependence on temperature and hydrophobic block length, *m*. The energetic parameters are estimated and compared to related polymer systems to provide insights into the driving force of copolymer self-assembly. The equilibrium partition coefficient of pyrene was also estimated. This mimics method used to characterize drug molecules, since $F_m E_n F_m$ could serve as a drug carrier through the electroactive nature of fluorene groups and the biodegradable polycarbonate platform [23]. The results are discussed in relation to
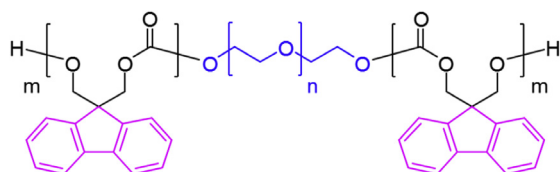
Table 1
Energetic parameters of $F_m E_{445} F_m$ calculated[⊥] by Eq. (1).

Polymer	M_n^a [kg/mol]	$Đ_M^b$	ΔH°_{mic} [kJ mol^{-1}]	ΔS°_{mic} [kJ mol^{-1} K^{-1}]	ΔG°_{mic} at 25 °C [kJ mol^{-1}]
$F_{34.8}E_{445}F_{34.8}$	37.2	1.55	–	–	–
$F_{15.3}E_{445}F_{15.3}$	27.3	1.37	-21.3 ± 0.7	0.078 ± 0.004	-44.4 ± 1.2
$F_{5.6}E_{445}F_{5.6}$	22.4	1.28	-30.3 ± 0.3	0.052 ± 0.002	-45.9 ± 0.5
$F_2E_{445}F_2$	20.6	1.23	-22.6 ± 2.0	0.066 ± 0.012	-42.3 ± 3.5
$F_{1.2}E_{445}F_{1.2}$	20.2	1.22	-21.0 ± 0.5	0.062 ± 0.003	-39.5 ± 1.0

[⊥]Uncertainties (error bars) were estimated by one standard deviation of the linear regression fit coefficients. [a] Based on ^{1}H NMR spectroscopy in CDCl$_3$ [b] Uncorrected polystyrene equivalent molar-mass dispersity ($Đ_M$) as determined by size exclusion chromatography in tetrahydrofuran.

the potential application of $F_m E_n F_m$ micelles as nano-carriers.

2. Materials and methods[2]

$F_m E_n F_m$ triblock copolymer was synthesized as reported in previous studies [21,23]. By varying the feed ratio of spiro[fluorene-9,5'- [1,3]-dioxan]-2'-one (monomer) to that of PEG diol macro-initiator (Sigma-Aldrich, product number 95172 LOT BCBF2828V), a series of polymers were obtained *via* ring opening polymerization in the presence of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as the catalyst. As shown in Scheme 1, E represents the middle poly(-ethylene glycol), and F is the symmetric substituted oligocarbonate-fluorene group with degree of polymerizations *n* and *m*, respectively. These polymers, with the hydrophilic block length *n* = 445 (based on certificate of analysis), and the hydrophobic block length *m* = 34.8, 15.3, 5.6, 2, and 1.2 (determined from ^{1}H NMR spectroscopy in CDCl$_3$ by comparing the integral values of protons corresponding to PEG to that of oligocarbonate-fluorene segments), are named as $F_{34.8}E_{445}F_{34.8}$, $F_{15.3}E_{445}F_{15.3}$, $F_{5.6}E_{445}F_{5.6}$, $F_2E_{445}F_2$, and $F_{1.2}E_{445}F_{1.2}$, respectively, with number-average relative molar mass (M_n) [22] in Table 1. The selected solvent used in this study is 18 MΩ cm resistivity water. Pyrene (puriss. p.a., for fluorescence, $\geq$ 99.0% (GC), Sigma-Aldrich), inhibitor-free tetrahydrofuran (THF, Sigma-Aldrich), and acetone (Fisher Chemical) were used as received.

2.1. Sample preparation

$F_2E_{445}F_2$ and $F_{1.2}E_{445}F_{1.2}$: $F_2E_{445}F_2$ and $F_{1.2}E_{445}F_{1.2}$ block copolymers were dissolved directly in water as clear solutions of 1 mg/mL with stirring. After approximately 24 h, the solutions were diluted to the required concentrations ranging from (5×10^{-4} to 1.0) mg/mL. 50 μL of 0.01 mg/mL pyrene in acetone was added to a clean glass vial. After acetone was evaporated, 5 mL of polymer solution was added to the vial. The final pyrene concentration in solution is 5×10^{-7} M (M has been used to represent the SI unit mol/L to conform to the requirement of the Journal). The solution was stirred overnight at room temperature prior to further experiments.

$F_{34.8}E_{445}F_{34.8}$, $F_{15.3}E_{445}F_{15.3}$ and $F_{5.6}E_{445}F_{5.6}$: An alternate sample preparation method was used in this case, since no fluorescence signal changes was measured as a function of polymer concentration. This reproducible behavior suggests that after the micelles are formed pyrene is excluded from the core. Thus, for $F_{34.8}E_{445}F_{34.8}$,

Scheme 1. Chemical structure of $F_m E_n F_m$ triblock copolymer.