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Note

Diblock copolymers of ethylene oxide and 1,2-butylene oxide in aqueous solution Formation of unimolecular micelles

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ABSTRACT

The dependence of log(cmc) on hydrophobic block length n was examined for E_mB_n copolymers (E = oxyethylene, B = oxybutylene, subscripts denote number-average block lengths in repeat units) with n in the range 30–76. Combination with published data for E_mB_n diblock copolymers with shorter E-blocks shows two changes of slope in the log(cmc)–n plot corresponding to the onset of unimolecular micelle formation at $n \approx 12$ and completion of this process at $n \approx 30$. The results are discussed with reference to published data for E_mL_n and E_mCL_n (L from D,L-lactide; CL from ε-caprolactone) copolymers, which show similar behaviour.

1. Introduction

Aqueous micellar solutions of block copolymers based on poly(ethylene oxide) as the hydrophilic component combined with a number of hydrophobic polymers have potential as vehicles for drug solubilisation, see, for example, reviews by Attwood and Booth (2007), Chiappetta and Sosnik (2007), Savic et al. (2006), Gaucher et al. (2005) and Adams et al. (2003). A particular advantage of this family of copolymers is the so-called 'stealth' property of the poly(ethylene oxide) corona of their micelles which allows the drug-loaded micelles to evade scavenging by the mononuclear phagocyte system, so resulting in increased circulation times in the blood. In this note we focus attention on diblock copolymers prepared by sequential oxyanionic polymerisation of ethylene oxide followed by 1,2-butylene oxide. To describe the repeat units of the blocks we use the notation: $E = OCH_2CH_2$ (from ethylene oxide) and $B = OCH_2CH(C_2H_5)$ (from 1,2-butylene oxide), while subscripts m and n are used to denote number-average lengths in repeat units of the hydrophilic and hydrophobic blocks. For example, a diblock copolymer formed by sequential copolymerisation of ethylene oxide followed by 1,2-butylene oxide is denoted E_mB_n.

As discussed previously (see, e.g., Attwood et al., 2007; Booth et al., 2006), and for micelle association number $N \geq 50$ (Hall, 1987), the standard Gibbs energy of micellisation is obtained without significant error from the critical micelle concentration (cmc) through

$$\Delta_{mic}G^\circ = -RT \ln K_c = RT \ln(\text{cmc})$$

where the cmc is expressed in mol dm^{-3}, K_c is the unimer–micelle equilibrium constant, and the standard state is ideally dilute solution in which both unimers and micelles are of unit molarity. That is, log(cmc) is directly related to the standard Gibbs energy of micellisation at a given temperature, and can be used as a convenient indicator of the position of equilibrium in the system. If log(cmc/mol dm^{-3}) is known for series of copolymers with the same hydrophilic component, then the relative hydrophobicity per chain unit can be readily extracted: see, for example, Booth et al. (2006) and Attwood et al. (2007).

A change in the dependence of log(cmc) on hydrophobic block length indicates a change in the micellisation equilibrium. Such a change will occur if the dispersed copolymer molecules (unimers) start to form unimolecular micelles, i.e., when the longest coiled hydrophobic blocks in the distribution collapse to a globule, much as pictured by Brown et al. (1989), Tuzar and Kratochvil (1993), Chu (1995) and Cooke and Williams (2003). The consequence of collapse of the hydrophobic block is reduced contact of the chain units of the core-forming block with water and so

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a reduction in the hydrophobic effect which drives micellisation, as discussed in detail elsewhere (Kelarakis et al., 2001). Because of the block-length distribution, the conversion of unimer to unimolecular micelle changes gradually as the average value of n is increased, and another change in the dependence of log(cmc) on hydrophobic block length is expected at higher values of n when effectively all dispersed molecules are in the form of unimolecular micelles. As reviewed recently (Attwood et al., 2007), published values of the cmc for poly(ethylene oxide)/poly(D,L-lactide) and poly(ethylene oxide)/poly(ε-caprolactone) diblock copolymers (denoted E_mL_n and E_mCL_n respectively, where L = COOCH(CH_3) and CL = COO(CH_2)$_5$) cover a wide range of hydrophobic block length (n = 12–108 for E_mL_n copolymers and n = 2–74 for E_mCL_n copolymers), and plots of log(cmc) against n for these two copolymers do indeed show two changes in slope.

Our interest in the formation of unimolecular micelles is not primarily in their solubilisation potential, although their hydrophobic interior may provide a site for the limited incorporation of water-insoluble drugs, but in their effect on the dependence of the value of the cmc on hydrophobic-block length for all types of micellisable block copolymers. The first change in slope has been reported for certain poly(ethylene oxide)/polyether diblock copolymers (Booth et al., 2006) but, because the ranges of block lengths available were narrow, the second transition was not seen. For example, apart from a recently published result for $E_{45}B_{26}$ (Elsabahy et al., 2007), values of the cmc for E_mB_n copolymers have been restricted to relatively short block lengths, n = 7–18. In this note we report new determinations for E_mB_n copolymers with n in the range 30–76.

2. Experimental

Five E_mB_n copolymers with narrow chain-length distributions ($M_w/M_n \approx 1.05$) and long B-block lengths ($E_{110}B_{30}$, $E_{209}B_{45}$, $E_{100}B_{51}$, $E_{114}B_{56}$, and $E_{155}B_{76}$) were available from a previous study: see Ryan et al. (2001) for details. 1,6-Diphenyl-1,3,5-hexatriene (DPH) was obtained from BioChemika (Fluka) and used as received. Stock copolymer solutions were prepared by dissolving the copolymers in Milli-Q water, allowing 24 h for complete dissolution before diluting to required concentrations within the range 0.01–14 mg dm^{-3}. Solubilisation of DPH was used to determine the onset of micellisation, as in an investigation of triblock copolyethers by Alexandridis et al. (1994), and before that an investigation of ionic surfactants by Chattopadhyay and London (1984). DPH was dissolved in methanol and added to the copolymer solution, so that the final copolymer solution contained 1% (v/v) methanol and 0.004 mM DPH, a mixture shown to provide the same values of the cmc as those obtained by other methods for copolymers in water alone. An F-4500 Hitachi fluorescence spectrophotometer was used in the experiments, with solution temperatures maintained at 25 or 30 ± 0.2 °C.

3. Results

Preliminary investigations indicated advantage in using the intensity of fluorescence of DPH at 430 nm rather than the intensity of absorption at 356 nm. Examples of the dependence of fluorescence intensity on copolymer concentration (logarithmic scale) are illustrated in Fig. 1. The value of the cmc was obtained from the intersection of the straight line through the data points with the baseline. Values of the cmc at 25 °C obtained for the five copolymers are listed in Table 1, together with the molar masses of the copolymers taken from Ryan et al. (2001). Solutions of two of the copolymers, $E_{110}B_{30}$ and $E_{209}B_{45}$, were also studied at 30 °C: values of the cmc were unchanged.

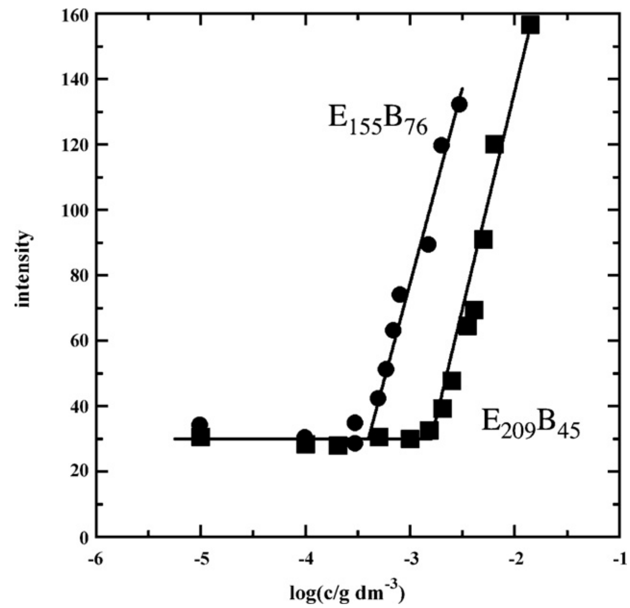

Fig. 1. Dependence of the intensity of fluorescence on the logarithm of copolymer concentration in aqueous solutions of copolymers $E_{209}B_{45}$ and $E_{155}B_{76}$, as indicated.

Table 1
Number-average molar masses and critical micelle concentrations (T = 25 °C) of E_mB_n copolymers

Copolymer	M_n (g mol^{-1})	cmc (mg dm^{-3})
$E_{110}B_{30}$	7,000	0.50
$E_{209}B_{45}$	12,400	1.70
$E_{100}B_{51}$	8,070	0.30
$E_{114}B_{56}$	9,050	0.37
$E_{155}B_{76}$	12,300	0.40

In passing we note that poly(ethylene oxide)-based copolymers with long hydrophobic blocks and high hydrophobic/hydrophilic ratios are known to form vesicles in aqueous solution. This includes E_mB_n copolymers of the type under discussion (see, e.g., Harris et al., 2002; Kelarakis et al., 2008). However, vesicles do not form at the low concentrations typical at the cmc, e.g. >0.002 g dm^{-3}, see Table 1.

4. Discussion

Combining the values of the cmc in Table 1 with previously published values (summarised in Table 2) gives the plot of log(cmc/mol dm^{-3}) against B-block length shown in Fig. 2. Variation in the temperature of determination of the cmc (see Table 1) is not a problem since, as discussed below, values of

Table 2
Published values of critical micelle concentration for E_mB_n copolymers

Copolymer	M_n (g mol^{-1})	cmc (mg dm^{-3})	Reference
$E_{27}B_7$	1690	5.8	Tanodekaew et al. (1993)
$E_{11}B_8$	1130	0.63	Chaibundit et al. (2002)
$E_{41}B_8$	2380	0.35	Yu et al. (1997)
$E_{18}B_{10}$	1510	0.063	Kelarakis et al. (2002)
$E_{24}B_{10}$	1780	0.3	Bedells et al. (1993)
$E_{50}B_{13}$	3140	0.02	Bedells et al. (1993)
$E_{106}B_{16}$	5820	0.035	Rippner et al. (2002)
$E_{96}B_{18}$	5500	0.008	Mingvanish et al. (1999)
$E_{45}B_{15}$	3080	0.0095	Elsabahy et al. (2007)
$E_{45}B_{24}$	3730	0.004	Elsabahy et al. (2007)

T = 30 °C: exception Elsabahy et al., 20 °C.

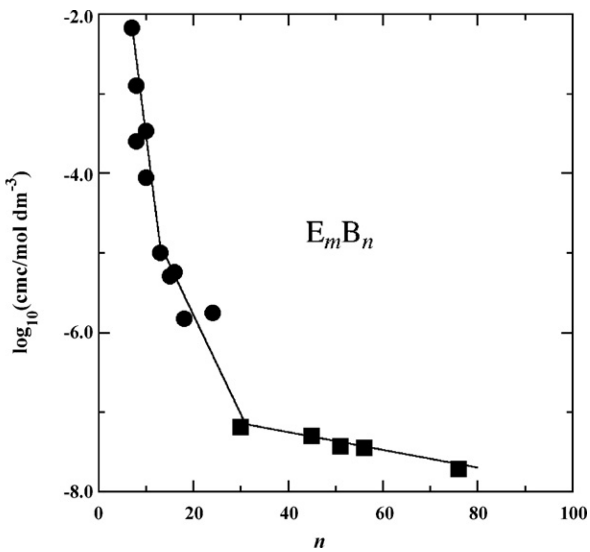

Fig. 2. Dependence of log(cmc) on the length of the B block (n) for block copolymers of poly(ethylene oxide) and poly(1,2-butylene oxide): (●) published values (see Table 2), (■) this work.

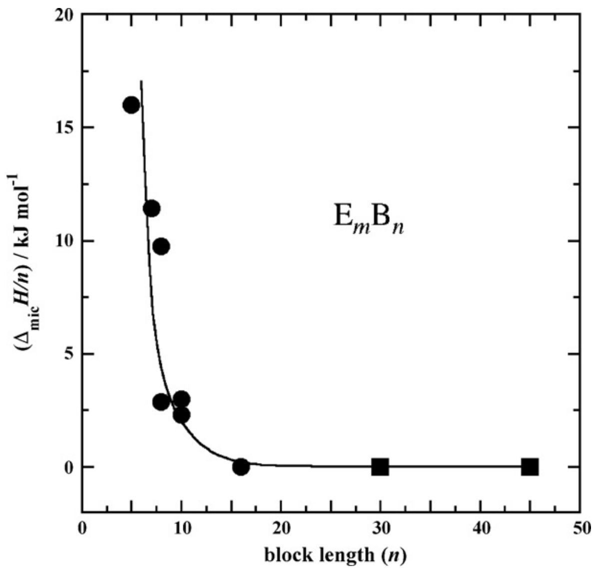

Fig. 3. Dependence of the van't Hoff enthalpy of micellisation per hydrophobic unit on block length for E_mB_n copolymers. The curve is intended to lead the eye through the data. (●) results from Bedells et al. (1993), Tanodekaew et al. (1993), Yu et al. (1997), Kelarakis et al. (1998, 2002) and Chaibundit et al. (2002), (■) present work.

the cmc of E_mB_n copolymers are insensitive to temperature when $n \geq 15$ units. Variation in the E-block length has a significant effect, and in constructing Fig. 2 we used d $\log_{10}$(cmc)/dm = 0.004 to adjust the values of the cmc (molar units) to a common number E-block length m = 100, a procedure based on results published by Alexandridis et al. (1994) and discussed previously (Booth et al., 2006). As anticipated, the data points can be satisfactorily represented by lines showing two transitions, consistent with formation of unimolecular-micelles starting at $n \approx 12$ and completion of the process at $n \approx 30$.

The temperature dependence of log(cmc) gives a value of the van't Hoff enthalpy of micellisation from

$$\Delta_{\text{mic}}H_{\text{VH}} = \frac{R\,\text{d}\ln(\text{cmc})}{\text{d}(1/T)}$$

For large values of the micelle association number ($N \geq 50$, Hall, 1987) $\Delta_{\text{mic}}H_{\text{VH}}$ is a true value of the standard enthalpy of micellisation, the usual situation when n is large. For smaller values it is to be regarded as an apparent value of the standard enthalpy which, nevertheless, correctly describes the temperature dependence of the cmc. Plotting values of the van't Hoff enthalpy per B unit ($\Delta_{\text{mic}}H_{\text{VH}}/n$) against block length brings the data for E_mB_n copolymers into acceptable correspondence; see Fig. 3. Very low values, essentially $\Delta_{\text{mic}}H_{\text{VH}} = 0$, are characteristic of E_mB_n copolymers with $n \geq 15$, as might be expected for transfer of a copolymer molecule with a collapsed coil to a micelle core. As noted above, values of the cmc which are independent of temperature, i.e., consistent with a van't Hoff enthalpy of micellisation of zero, have been found for other block copolymers with long hydrophobic blocks (e.g. Yamamoto et al., 2002).

Present results for E_mB_n copolymers are compared with the results for E_mL_n and E_mCL_n copolymers in Fig. 4 where, for clarity, they are represented by the lines drawn through the data points. The results for E_mL_n and E_mCL_n copolymers are taken directly from the review by Attwood et al. (2007), where they are corrected to a common E-block length, m = 100. As described previously (Attwood et al., 2007), for values of n below that required for formation of unimolecular micelles, effectively for $\log(\text{cmc/mol dm}^{-3}) > -5$, superposition of results by scaling n leads to the following ranking of hydrophobicities per chain unit:

L : B : CL = 1 : 1.5 : 2

If the effect of unimolecular–micelle formation on cmc depended only on hydrophobicity (defined in this way) then the level of the lines at high values of n should fall in order $E_mL_n > E_mB_n > E_mCL_n$. While the results for the two copolymers with polyester blocks fit this pattern, that for E_mB_n copolymers does not.

Accordingly, we seek an explanation which takes account of the chemical difference between the polyether and polyester blocks. Small-angle neutron scattering (SANS) has been used to show that the micelle cores of E_mB_n copolymers contain water, an effect ascribed to association with the ether oxygens of the B-block and also to its terminal hydroxyl group (Derici et al., 1999; Castelletto et al., 2002, 2004). The hydrophobic blocks of E_mL_n and E_mCL_n copoly-

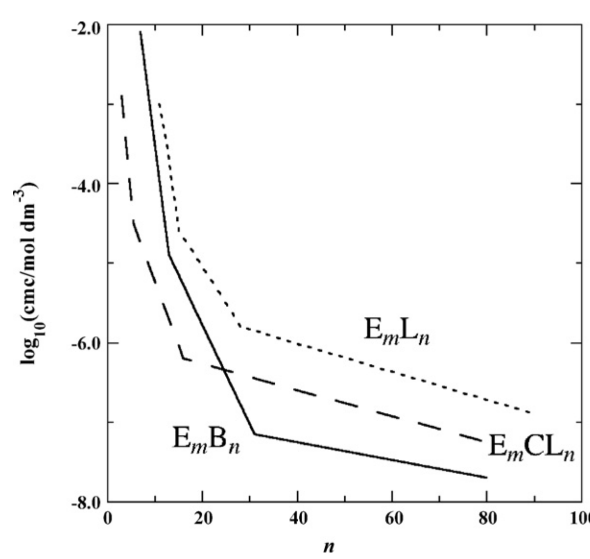

Fig. 4. Dependence of log(cmc) on hydrophobic-block length for the length for E_mL_n, E_mCL_n and E_mB_n copolymers, as indicated. The lines summarise the results displayed in Fig. 1 and in Attwood et al. (2007).

mers have ester oxygens, and terminal hydroxyl groups, and SANS has been used to study micellar solutions (Vangete et al., 2004; Riley et al., 2003), but not with a view to detection of water in the micelle core. As it happens, methylation of the hydroxy-end group of E_mB_n copolymers is known to make little or no difference to values of the cmc of copolymers with short block lengths ($E_{18}B_{10}$ and $E_{11}B_8$) forming large micelles ($N > 60$ at 25 °C) (Kelarakis et al., 2002; Chaibundit et al., 2002). However, the formation of unimolecular micelles ($N = 1$) is likely to be particularly affected by inclusion of water molecules in the collapsed coil, including water binding to the oxygens of the ether or ester linkages, and the seemingly anomalous result for the E_mB_n copolymers may well be a consequence of a differences in this interaction.

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