Effect of Anesthetic Molecules (Halothane and Isoflurane) on the Aggregation Behavior of POE−POP−POE Triblock Copolymers

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Studies of the effect of anesthetic molecules, halothane and isoflurane, on the aggregation behavior of POE−POP−POE triblock copolymers, P84, F88, P104, in aqueous solution have been carried out using fluorescence spectroscopy and light-scattering techniques. The hydrodynamic radius of block copolymer aggregates and the I/III vibronic intensity ratio of pyrene in 5 wt % aqueous solutions of F88, P84, and P104 were obtained over a wide temperature range, 10−60 °C. Large-sized clusters form at low temperatures for P104, but they do not have a well-defined hydrophobic core. Low concentrations of the anesthetics are found to induce the aggregation of F88 and P84 at 25 °C, and this effect is similar to that of increasing the temperature. The effect of halothane and isoflurane concentration on the change of hydrodynamic radius of copolymer aggregates and the I/III vibronic ratio of pyrene in F88, P84, and P104 were investigated at 25 °C. The addition of 1 mM of anesthetic is equivalent to ca. a 1−2 °C increase in temperature. It is deduced that the anesthetic molecules are distributed in both the hydrophobic core and hydrophilic corona of the polymer micelles. However, whereas an increase in temperature removes water of hydration from around the POP and POE segments, the anesthetic molecules tend to replace water of hydration around these segments. It is inferred that anesthetic molecules could disturb the water of hydration around biological macromolecules, and it is proposed that the dehydration effect of inhalation anesthetics may play an important role in the process of anesthesia.

1. Introduction

Triblock copolymers consisting of polyoxyethylene−polyoxypropylene−polyoxyethylene (POE−POP−POE) are a series of polymeric nonionic surfactants often referred to by the trade names Pluronic or Poloxamer. In the Pluronic surfactants, POE and POP segments are considered to be hydrophilic and hydrophobic moieties, respectively. They are used extensively in industry for a variety of applications, especially in cosmetic formulations, drug delivery systems,[1−3] the extraction of proteins,[4] and corrosion protection,[5] as well as in the removal of aromatic hydrocarbons from wastewater.[6] Their physicochemical properties have been extensively reported.[7−9] Light scattering,[10−12] fluorescence spectroscopy,[13−15] NMR,[16,17] specific volume,[18,19] sound absorption,[20] microcalorimetry,[21,22] SANS,[23] SAXS,[24] and gel permeation chromatography[25] measurements have been used in an attempt to obtain new insights about the aggregation behavior of these systems. Much has been learned from these studies that has advanced our understanding of the solution properties of these triblock copolymer systems. For example, they form aggregates (micelles) at higher solution temperatures, and the micelles formed consist of a hydrophobic POP core surrounded by a corona of hydrophilic POE tails. In a previous paper,[18] we have concluded that the core contains a small amount of water, in agreement with other reports.[26,27]

The Pluronic surfactants are very sensitive to temperature changes, and this aspect has been extensively reported.[7,10,15] It is generally accepted that as the temperature is increased unimers undergo conversion into micelles over a range of temperatures. It has been observed in some of these aqueous surfactant systems that as the temperature increases the hydrodynamic radius remains approximately constant, while the aggregation number increases.[7,10,28,29] It is speculated that the dehydration of POE becomes important at higher temperatures, resulting in a reduced corona volume.[7]

There have been many studies of the effect of additives on the properties of Pluronic surfactant aqueous solutions. The additives studied have been mainly inorganic salts, and their effects have been mainly ascribed to the change in water structure caused by interactions between the inorganic salts and water. "Structure-maker" salts such as KCl and KF, which reduce the solubility of the polymer in water ("salting-out"), decrease the CMT and CMC. On the other hand, "structure-breaker" salts such as KI and KSCN, which disturb the structure of water, increase the solubility of the polymer ("salting-in")[7,30] and lead to an increase in CMT and CMC. Urea is another common additive that changes the water structure and is believed to be a "structure-breaker". It increases the CMT and CMC[31] of Pluronic copolymers. The concentration of salts and urea commonly used has been at the molar level. The following experiments show that the effect of anesthetic molecules on micellization of Pluronic copolymers is clearly evident at the millimolar level, i.e., at concentrations near to those reported for the onset of anesthesia in physiological systems.

Anesthetics have been used to prevent pain during surgery for over 100 years, but the mechanism of anesthesia is still not fully understood. In early studies, the first generally recognized property of anesthetics was their high affinity for lipids, and there was a corresponding good correlation between their lipid−

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water partition coefficient and the phenomenon of anesthesia.[32] This general property was referred to as the Meyer−Overton hypothesis[33] and predicts a correlation between the potency of inhaled anesthetics and their lipophilicity, i.e., solubility in a hydrophobic phase, olive oil, considered as a model for the interior of the membrane. This hypothesis has influenced the proposed mechanism of anesthesia for many years and has led to the view that the site of anesthetic action could be the membranes of physiological systems.[34] As a result, there have been many studies focusing on the interaction between anesthetic molecules and membranes, either the lipid bilayer or membrane proteins,[35] by changing the activity of the membrane protein or the volume of the bilayer or by blocking the Na/K ion channel.[36] While there are review papers describing possible mechanisms of anesthesia,[36,37] many questions still remain unanswered. For example, with what part of the membrane, the bilayer or the membrane proteins, do anesthetic molecules interact? What is the chemical nature of the active site; is it hydrophobic or hydrophilic? The difficulty with answering these questions is that most membrane proteins function in a lipid environment. In fact, no matter whether the interactions are between the anesthetic molecules and the lipid bilayer or between the anesthetic molecules and the membrane proteins, or both, the type of interactions are hydrophobic and hydrophilic in nature. Since block copolymers consist of hydrophobic and hydrophilic segments, they have been chosen as model systems in this study to emulate the amphiphilic character of membranes. As well, they are relatively simpler and better understood than membranes, and their hydrophobic−hydrophilic ratio can be easily adjusted. An understanding of the interactions between anesthetic molecules and the block copolymer systems could improve our knowledge about the mechanism of anesthesia. This study is part of an effort to use model systems to improve our understanding of the mechanism of anesthesia.

In the first part of this report, the aggregation behavior of three triblock copolymers, F88, P84, and P104 as well as that of POE and POP polymers are described for a wide range of temperatures using the I/III vibronic ratio of pyrene and light-scattering techniques. In the second part, the aggregation behavior of these copolymers is reported as a function of anesthetic concentration using the same properties and the results are compared with those of temperature studies.

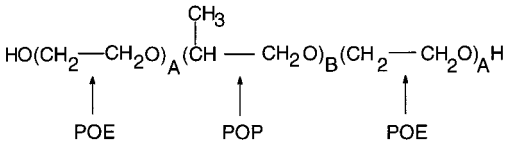
2. Experimental Section

2.1. Material. Pluronics F88, P84, and P104 were gifts from BASF. Their molecular weight distributions were checked by means of gel permeation chromatography and no impurities were detected in these samples. Their relative molar masses were estimated by acetylation and back-titration of the unreacted acetylation reagent. The percentage by mass of POE was verified by using ^{1}H NMR techniques, and the water content of each polymer was estimated by carrying out a Karl Fisher titration. The results obtained for the properties of the copolymers studied in this work confirmed the information supplied by the manufacturer. The pure polymers polyoxyethylene (POE) and polyoxypropylene (POP) were obtained from BDH. The molar masses of POE and POP are 4000 and 725 amu, respectively. The halothane and isoflurane were gifts from the Department of Anesthesiology, Royal University Hospital, University of Saskatchewan. The structures of the Pluronic surfactants, halothane, and isoflurane are shown in Scheme 1.

2.2. Solution Preparation. Aqueous solutions of block copolymers were prepared on a weight percent basis in Millipore water. The halothane and isoflurane were added to aqueous

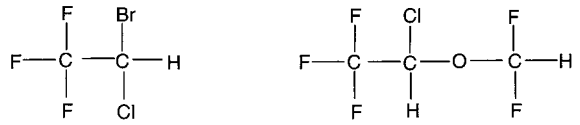
SCHEME 1

POE-POP-POE Triblock Copolymers (Pluronic)



Pluronic	Molar Mass	A	B	POP	POP/POE
P104	5410	25	56	3250	1.5
P84	3700	16	39	2250	1.5
F88	11800	108	39	2250	0.25

Halothane **Isoflurane**



solutions of block copolymers contained in small ampules using a calibrated microsyringe. The ampules were sealed at temperatures below ambient, and the dead space above the solution was made as small as possible. The solutions were shaken on a shaking bath for 1 week to achieve equilibrium. In the case of fluorescence emission measurements, pyrene was first dissolved in hexane and then the hexane solution was added into the ampule. A gentle stream of nitrogen gas was used to evaporate the hexane before addition of the block copolymer solutions.

2.3. Fluorescence Emission Measurements. A SPEX Fluorolog 2 spectrophotometer was used. The spectra were recorded in the S/R mode in 0.50 nm steps, integrating counts for 1 s at an excitation wavelength of 335 nm. The slit widths were 1 mm for all measurements.

2.4. Dynamic Light Scattering (DLS). Light scattering measurements were conducted at a scattering angle of 90° using a Brookhaven model 9025 instrument equipped with a 150 mW argon-ion laser operated at 488 nm. Dynamic light scattering data were analyzed as described previously.[38]

3. Results and Discussion

3.1. Effect of Temperature on the Micellization of Block Copolymers. *Fluorescence Probing of Pluronic Aqueous Solutions.* Pyrene is a widely used fluorescence probe because the relative intensities of the vibrational fine structure (five bands) of its fluorescence spectra have been found to be sensitive to the polarity of its environment, the so-called Ham effect.[16,26,39] In the present study, the pyrene probe was used to monitor the formation of micelles with increasing temperature and increasing concentrations of halothane and isoflurane. The I/III intensity ratios of pyrene in water, aqueous 5% POE solution, liquid POP, 0.5% aqueous POP, and several POE−POP−POE triblock copolymer aqueous solutions as a function of temperature are shown in Figure 1. The I/III intensity ratios of pyrene in 5% aqueous solutions of F88, P84, and P104 experience a sharp decrease at a certain temperature which is evidence of micelle formation in these polymer solutions. It is seen that, at lower temperatures, the I/III intensity ratio of pyrene in 0.5% aqueous POP is the same as in water and aqueous 5% POE, and then it starts to deviate negatively from the lower temperature trend at 30 °C. This observation suggests that the POP polymer dissolves in water at lower temperatures but at higher temperatures begins to form a hydrophobic aggregate into which the pyrene locates.

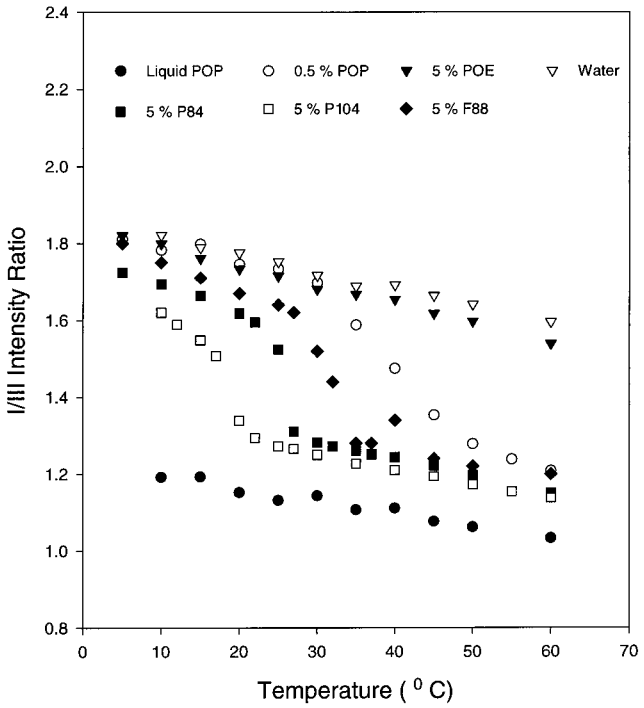


Figure 1. I/III vibronic intensity ratio of pyrene in water, liquid POP, 0.5% POP, 5% POE, 5% P84, 5% P104, and 5% F88 as a function of temperature.

This is in agreement with the fact that the POP polymer is more soluble in water at lower temperatures.[26] It is also seen that the I/III intensity ratio of pyrene in 0.5% POP does not decrease to the value for pyrene in liquid POP, which suggests that the aggregates formed by the POP in water are somewhat hydrated. The relative order of the magnitude of the I/III intensity ratio (Figure 1) of pyrene at lower temperatures is F88 > P84 > P104. This indicates that the state of the block copolymer unimers may not quite be the same. Unimers may exist in a coiled state and provide a slightly different hydrophobic environment for pyrene.[7,40] Figure 1 shows that, after the formation of micelles at elevated temperatures, the magnitude of the I/III intensity ratio of pyrene also follows the order F88 > P84 > P104, which indicates that the cores of the micelles formed by these block copolymers have different polarities. The fact that the I/III intensity ratio of pyrene does not approach the value in liquid POP in all of the block copolymers studied here suggests that their hydrophobic cores, including that of the aggregates formed by 0.5% POP, are hydrated to a different degree. The environment of pyrene in P84, P104, and F88 is very close to pyrene in 0.5% POP in water rather than liquid POP. This means that POP aggregates formed in water may be a better model than liquid POP for the core of block copolymer aggregates.

If one assumes that the I/III intensity ratio can be treated as a sum of contributions of pyrene in water and in liquid POP, then the water content of the core can be calculated from the following equation:

$$(\mathrm{I/III})_{\mathrm{Core}} = (1 - X_{\mathrm{Water}})(\mathrm{I/III})_{\mathrm{POP}} + \mathrm{X}_{\mathrm{Water}}(\mathrm{I/III})_{\mathrm{Water}} \qquad (1)$$

where $(\mathrm{I/III})_{\mathrm{Core}}$ is the experimental value of the I/III intensity ratio in Pluronic solutions after the formation of micelles, $(\mathrm{I/III})_{\mathrm{POP}}$ and $(\mathrm{I/III})_{\mathrm{Water}}$ are the I/III intensity ratios of pyrene in liquid POP and in water, respectively, and X is the mole fraction of water associated with the POP core. Replacing $(\mathrm{I/III})_{\mathrm{Core}}$ with the I/III intensity ratio in 5% of F88, P84, P104 and replacing $(\mathrm{I/III})_{\mathrm{POP}}$ and $(\mathrm{I/III})_{\mathrm{Water}}$ with the I/III intensity ratio in liquid POP and water, respectively, at 60 °C, the mole fractions of water in the cores of the block copolymers at this temperature were estimated and the results are shown in Table 1. It is seen that the water content of the core follows the order F88 > P84 > P104, and is consistent with their relative hydrophobicity.

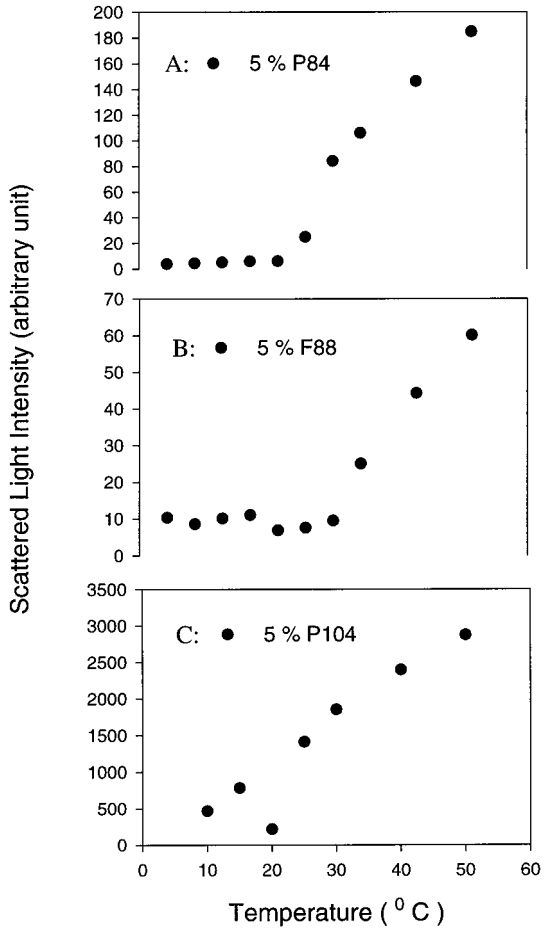


Figure 2. Scattered light intensity in aqueous Pluronic solutions as a function of temperature.

TABLE 1. Mole Fraction of Water in the Core of Polymer Micelles at 60 °C

Pluronics	5% F88	5% P84	5% P104
X_{Water}	0.29	0.21	0.19

Light Scattering Study of Block Copolymer Aqueous Solutions. The scattered light intensity results of these three systems as a function of temperature are shown in parts A−C of Figure 2. Estimates of the CMTs for 5% aqueous solutions of F88, P84, and P104 obtained from these data are 35, 27.5, and 17.5 °C, respectively. The scattered light intensity for P104 shows that it behaves differently from P84 and F88 at low temperatures. It appears to decrease sharply with rising temperature just before it reaches the CMT. Dynamic light scattering results of this system will show (below) that P104 appears to form clusters before forming micelles, while F88 and P84 do not. The hydrodynamic radii of micelles formed in 5% aqueous solutions of F88, P84, P104 are shown in Table 2. The micelle radius obtained for F88 in the present work is slightly greater than that previously reported[12] for some of the temperatures. The micelle radius for P104 is 7.5 nm at 40 and 50 °C and 8.5 nm at 25 °C, in good agreement with previously reported values.[11,15] Table 2 provides the hydrodynamic radii for P104 and P84 over

TABLE 2. Micelle Size as a Function of Temperature

Pluronic		10 °C	15 °C	20 °C	25 °C	30 °C	35 °C	40 °C	45 °C	50 °C	60 °C
5% F88	R_h (nm)							22.0	15.2	12.1	8.9
5% P84	R_h (nm)				25.5	10.8	7.5	7.3	6.5	6.5	6.5
5% P104	R_h (nm)	104.3	102.3	16.5	8.5	7.0		7.5		7.5	

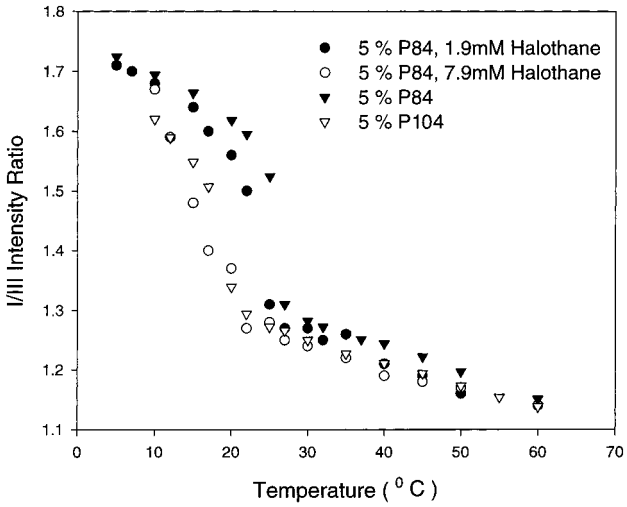


Figure 3. I/III vibronic intensity ratio of pyrene in 5% P84 as a function of temperature in the presence of halothane.

a wider range of temperatures than previously reported. As the temperature increases, both F88 and P84 form larger micelles at the critical micelle temperature. They decrease in size upon further increase in temperature, e.g., from $R_h = 22$ nm at 40 °C to 8.9 nm at 60 °C for F88 and from $R_h = 25.5$ nm at 25 °C to 6.5 nm at 60 °C for P84. The same is true for P104 above the CMT. The decrease in micelle size with increasing temperature suggests that the degree of dehydration of the POE segment is enhanced by increasing the temperature.

In the case of an aqueous 5% P104 solution, clusters form at lower temperatures with a radius of ca. 100 nm. The magnitude of the vibronic I/III intensity ratio at low temperatures (Figure 1) suggests that the clusters appear not to have a well-defined hydrophobic core. As temperatures approach the CMT, micelles start to form and the clusters disappear. These clusters are not well characterized but could be some kind of network of P104 unimers. More work needs to be done to understand these clusters. In summary, it is found from the I/III vibronic intensity ratio data of pyrene in 0.5% POP that POP in water would be a better model for the micelle core of these block copolymers. Large clusters of P104 exist at lower temperatures, but no well-defined hydrophobic environment appears to be associated with them.

3.2. Effect of Anesthetic Molecules on the Micellization of Block Copolymers. *Temperature Dependence of the I/III Vibronic Intensity Ratio of Pyrene in Aqueous Pluronic Solutions in the Presence of a Fixed Amount of Halothane.* Figure 3 shows the temperature dependence of the I/III vibronic intensity ratio of pyrene in aqueous 5% P84 solutions in the presence of 1.79 and 7.9 mM halothane. It is evident that a small amount of halothane significantly affects the micellization process of P84, reducing the CMT and lowering the onset of the transition temperature. Since the micellization process in the absence of additive is driven by the dehydration of POP,[30,41,42] the halothane appears to enhance the dehydration of POP. The fact that a very small amount of halothane is required is very striking. It suggests that the halothane molecules do not act as a "structure-maker" or "structure-breaker". Rather they act directly on the block copolymer. The values of the I/III vibronic intensity ratios of pyrene in aqueous P84 solution follow the order P84 (stock solution) > P84 (1.98 mM halothane) > P84 (7.9 mM halothane). This suggests that the environment for pyrene in P84 in the presence of halothane is more hydrophobic than in its absence. When compared with the magnitude of the I/III intensity ratio of pyrene in 5% P104, the presence of halothane makes the environment of the core of P84 as hydrophobic as that of P104. This indicates that the addition of halothane removes water from the core of micelles formed by P84.

Figure 3 shows that halothane lowers and broadens the onset of the transition region in comparison to when halothane is absent. In the latter case, the transition temperature range is about 5 °C (22−27 °C), whereas it is 8 (17−25 °C) and 12 °C (10−22 °C) in the presence of 1.98 and 7.9 mM halothane, respectively. This indicates that the POP segment is more hydrophobic in the presence of halothane than in its absence, but still not hydrophobic enough to induce micelle formation at low temperatures. A possible explanation for this is that, although the acidic hydrogen, see Scheme 1, in halothane can hydrogen bond with the ether oxygen of POP and make POP less hydrated, the halothane molecules themselves are hydrated at lower temperatures. It may also be said that the hydrophobic interactions between halothane and the POP segment are not strong enough to induce micellization at low temperatures. However, as temperature is further increased, the hydration water is removed from both halothane and POP and the hydrophobic interactions become strong enough to induce the formation of micelles.

Dependence of the I/III Vibronic Intensity Ratio of Pyrene in Aqueous Pluronic Surfactant Solutions as a Function of Anesthetic Concentration at Constant Temperature. Parts A and B of Figure 4 illustrate the I/III vibronic intensity ratio of pyrene in 5% aqueous solutions of F88 and P84 as a function of halothane and isoflurane concentrations at 25 °C. The effect of the addition of anesthetic is equivalent to that of an increase in temperature. As the concentration of anesthetic increases, the I/III intensity ratio of pyrene decreases sharply at a critical concentration of the anesthetic which is an indication of micelle formation. This concentration is about 0.5 mM in P84 for both halothane and isoflurane. If one compares the concentration range of anesthetic with the temperature range required to complete the transition, then 1.0 mM of isoflurane and 1.0 mM halothane are equivalent to ca. a 1.4 and 1.1 °C temperature increase, respectively. In the case of F88, 1 mM of isoflurane and 1 mM of halothane are equivalent to a 1.5 and 1.3 °C temperature increase, respectively. It is seen that the effect of isoflurane is slightly greater than that of halothane, and this will be discussed later.

Scattered Light Intensity of Aqueous Pluronic Surfactant Solutions as a Function of Anesthetic Concentration at 25 °C. Figure 5A shows the scattered light intensity of a 5% P84 aqueous solution as a function of anesthetic concentration at 25 °C. It is seen that the intensity increases dramatically with an increase of anesthetic concentration. Only a small concentration of anesthetic is needed to induce the aggregation process of the system (cf. Figure 5A, inset). Both the I/III ratio and light scattering data show similarities between the addition of anesthetics and an increase in temperature and strongly suggest that the addition of anesthetic molecules dehydrates block

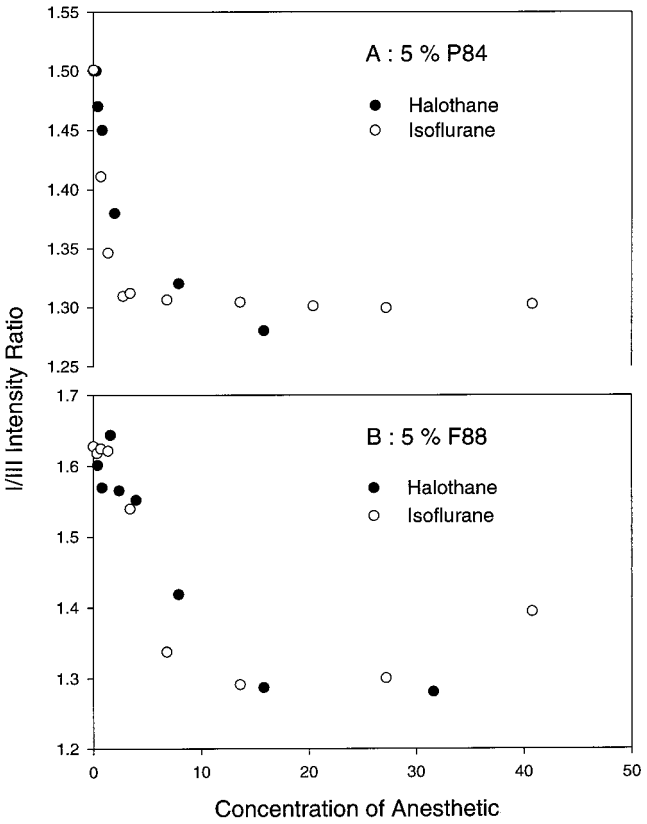


Figure 4. I/III vibronic intensity ratio of pyrene in 5% aqueous solutions of P84 and F88 as a function of halothane and isoflurane concentration (mM).

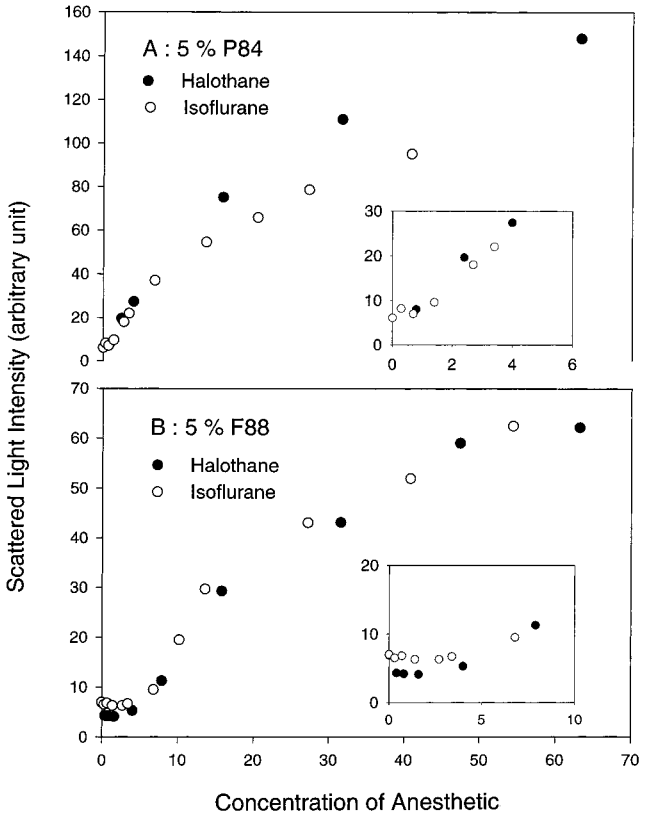


Figure 5. Light scattering intensity in 5% aqueous solutions of P84 and F88 as a function of halothane and isoflurane concentration (mM).

copolymers and induces aggregation of these block copolymers. The variation in aggregate size in 5% P84 solution as a function of anesthetic concentration is shown in Tables 3 and 4. Less than 1 mM of isoflurane induces micelle formation, whereas about 2 mM of halothane is required. Again, it is seen that isoflurane is slightly more effective than halothane. It is possible that the difference in their size or hydrophobicity is responsible for the difference in their effect on the micellization of block copolymers. Hydrogen bond formation between the acidic proton of the anesthetic and POP could be a chemical driving force for the interaction. Such bonding can also occur between anesthetic molecules and POE. However, the preference of anesthetic molecules to interact with the POP rather than POE segments can be explained by the two following factors. One is that the interactions between water molecules and the POP segments are weaker than that between water molecules and POE segments and it is easier for these anesthetic molecules to replace water molecules around the POP segments. The other factor is that anesthetic molecules and POP segments are hydrophobic and the hydrophobic interactions between them lead to greater energy stabilization. Hydrophobic interactions between anesthetic molecules and POP are considered to be the dominant physical driving force for the binding of anesthetics to block copolymers.

TABLE 3. Micelle Size as a Function of Halothane Concentration

5% F88	halothane (mM)	7.9	15.8	31.6	47.4	63.2	
	R_h (nm)	18.1	16.8	14.0	12.8	11.2	
5% P84	halothane (mM)	2.4	4.0	7.9	15.8	31.6	63.2
	R_h (nm)	10.0	11.0	10.5	10.5	9.7	8.0
5% P104	halothane (mM)	0.0	0.8	4.0	7.9	15.8	79.0
	R_h (nm)	8.5	9.0	8.5	8.5	8.0	8.5

A 5% aqueous solution of F88 has a higher CMT than that of P84, and it is expected that it should take more anesthetic to induce the micellization of F88. This is confirmed from the results shown in Figure 5B. The inset of Figure 5B shows that the scattered light intensity is independent of concentration of anesthetic up to about 7 mM. Recall that the CMT for F88 in the absence of anesthetic is about 37.5 °C. Therefore, 7 mM of anesthetic decreases the CMT by 12.5 °C which is equivalent to a ~1.8 °C temperature rise per millimolar of anesthetic.

Comparing data in Table 2 with data in Tables 3 and 4, one can see that the micelle size at high temperatures is smaller than that at high concentrations of anesthetic. This can be explained by the difference in the mechanism of dehydration. At elevated temperatures, POP is less stabilized by hydration water, leading to micelle formation. On the other hand, the anesthetic molecules replace the water of hydration around the POP segment and make POP more hydrophobic and hence induce the formation of micelles. The anesthetic molecules may remain in the core, and this might cause the micelles to be larger than at higher temperatures. Pyrene is considered to locate in the core of the micelles formed by the Pluronic surfactants and the observation that the I/III vibronic intensity ratio of pyrene in aqueous block copolymer solutions is similar to that in aqueous 0.5% POP is evidence for this argument.

In the present study, the emission of fluorescence from pyrene was quenched by halothane. There are two mechanisms of quenching, i.e., collisional or short-range quenching and Coulombic interaction or long-range quenching. In long-range quenching, the absorbance spectrum of the quencher must overlap the emission spectrum of the probe. Since halothane does not absorb light in the 300−500 nm region, the quenching mechanism must be short range, and hence the quenching of pyrene by halothane is evidence that halothane is located near to pyrene, for example, at the periphery of the core of the micelle. It has been previously reported that halothane quenched

TABLE 4. Micelle Size as a Function of Isoflurane Concentration

5% F88	isoflurane (mM)	6.8	10.2	13.6	27.2	40.8	54.4			
	R_h (nm)	37.8	26.1	21.6	18.0	13.8	13.5			
5% P84	isoflurane (mM)	0.3	0.7	1.4	2.7	3.4	6.8	13.6	20.4	27.2	40.8
	R_h (nm)	20.2	13.1	13.8	11.5	10.6	9.8	8.9	9.3	8.1	8.0

the fluorescence emission of a protein component located in a hydrophobic environment, and this quenching phenomenon was used as evidence that halothane is located in a hydrophobic environment.[43]

A comparison of the hydrodynamic radii of micelles in 5% P84 and F88 solutions in the presence of halothane and isoflurane shows that, as the concentration of anesthetic increases, the micelle size decreases. This is similar to the effect of a temperature increase. As the temperature increases, the extent of dehydration around the POE segment increases and the size of the micelle becomes smaller since the micelle becomes more compact. Consequently, as the concentration of anesthetic increases, anesthetic molecules replace water around POE and repel water molecules in the vicinity of them to further dehydrate the POE. It appears that the anesthetic molecules do locate in both the core and the corona and thus the size of the micelles induced by the anesthetics is larger than that induced by a temperature increase. The nearly constant size of micelles formed by P104 as a function of halothane concentration supports this argument. The hydrodynamic radius of the P104 micelles is around 8.5 nm, and as the concentration of halothane increases, the size remains the same up to 80 mM of halothane. If the anesthetic molecules were to simply locate in the core without replacing the water molecules around the POE, the size of micelle should increase as the concentration of anesthetic increases. This is inconsistent with experimental results for F88 and P84 in the presence of both halothane and isoflurane and for P104 in the presence of halothane. Therefore it is concluded that the anesthetic molecules are distributed throughout the corona and within the core, perhaps at the periphery.

Conclusion

The effect of anesthetics on the micellization of Pluronic copolymers F88, P84, and P104 is found to be analogous to the effect of increasing the temperature. Very small amounts of halothane and isoflurane are found to enhance the dehydration of Pluronic surfactants and induce the formation of micelles. A 1 mM concentration of halothane or isoflurane is equivalent to a temperature increase of 1−2 °C. The common feature of the structure of these anesthetics is that they contain an acidic hydrogen which can increase their ability to form hydrogen bonds with their surroundings. The anesthetic molecules are considered to distribute in the core as well as in the corona of the micelles formed by Pluronic surfactants. Halothane and isoflurane appear to replace the water around POP and POE. The results of this study indicate that Pluronic copolymers are good systems to use to study the effect of third components on dehydration of these systems. An important result obtained in the present study is that the addition of only very small amounts of halothane or isoflurane (approaching physiological conditions for anesthesia) are found to induce the formation of micelles in these systems. There are two driving forces for the interaction between anesthetic molecules and block copolymers, i.e., hydrogen bonding and hydrophobic interaction.

One further point needs to be emphasized. Water enclosed within the solvation shell present in the immediate vicinity of biomolecules is termed "biological water".[44] Without this solvation sheath, biological molecules would be inactive. The current experimental results show that anesthetic molecules have the ability to disturb this water of hydration. If this observation is true of biological systems, then it suggests that part of the mechanism of anesthesia may involve dehydration of the bilayer or protein by the anesthetic molecules.

References and Notes

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