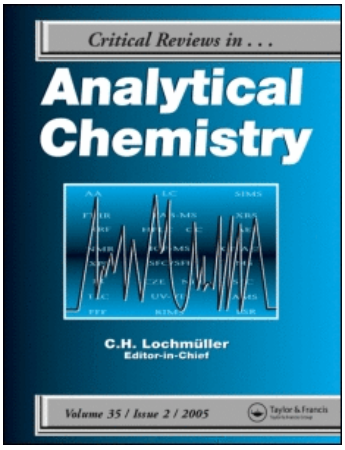

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Micelles in Analytical Chemistry

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Micelles in Analytical Chemistry

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I. INTRODUCTION

Molecules which possess both hydrophilic and hydrophobic structures may associate in aqueous media to form dynamic aggregates commonly called micelles. Interest in these aggregates has grown over the years from the original work of Hartley,[1] which describes what is still accepted as a functional model of the geometry of micelles. Fortunately, our understanding of the geometry as well as other features of micelles has increased markedly over the intervening years as evidenced by the abundance of reviews concerning micelles just since 1980 (over 350 reviews as searched via online CAS). While most of these papers deal with micelle structure, catalysis, or dynamics, this report continues a tradition of reviews concerning the utility of micelles in analytical chemistry.

Actually, the field of micelles in analytical chemistry has grown to the point where it is now difficult to contain all of the required areas of analytical technology within one review. Several of the subspecialties of analytical chemistry deserve and have received their own reviews regarding the utility of micelles within those disciplines. Armstrong[2] has written an excellent review concerning the area of separations and micelles, while the field of micelles in electrochemical measurements has recently been reviewed by McIntire.[3] Additionally, earlier reviews encompassing the entirety of analytical chemistry with respect to the utility of micelles have been published.[4-6] Given these reports regarding the usefulness of micelles in analytical chemistry, one might well ask, why is there a need for yet another review of this topic? Two major reasons stand out as justification for another review of this field. First, the last major review of the utility of micelles in analytical chemistry[4] appeared in 1985, having been prepared in 1984. Incidently, this is an excellent article covering virtually all areas of analytical chemistry with respect to micelles and other organized assemblies. Even so, there has been a significant time lapse since that offering and new reports have appeared which could be of importance to the researcher in these areas. Second, reviews of micelles in analytical chemistry to date have tended towards summations of results from the literature without detailed critical assessment of the reports of the work being reviewed.[4-6] The primary thrust of this report is the critical assessment of the state of micelles in analytical chemistry: both current status and future potentials. For these reasons, this report should be of value to those interested in the field of micelles in analytical chemistry.

As stated before,[7] it is impossible to comprehend the action of micelles in a given analytical method or to accurately predict the results of incorporating micelles into a new method of analysis without an understanding of micelles. This includes effects arising from the molecular structure of the amphiphile from which the micelle is derived and possible effects of the various substrates which might be present in the solution upon the architecture of the organized assembly. Furthermore, the catalytic abilities of micelles must be recognized by the analyst as so much of the observed benefits of the use of micelles in analytical chemistry comes from these abilities.[7] There are many other properties of micelles which would be of some importance to the researcher desiring to use them in an analytical method; yet, a detailed understanding of these properties is not absolutely necessary for the intelligent application of these agents in analytical situations. Thus, although some time will be spent discussing micelles in this review, that time is designed to provide a feeling for the actions of micelles in given situations. It is hoped that the interested reader will follow the literature references to detailed reviews and original articles to ferret out the unique properties of importance in his or her own situation.[2-15]

Given an understanding of micelles, the analyst is then in a position to make an intelligent start regarding the utility of micelles within a specific analytical application. This appreciation of micelle characteristics together with knowledge of the mechanism of the chemical reaction occurring within the method of analysis itself can lead to benefits with respect to analysis time and sensitivity. In any case, the correct immediate application of micelles to a specific analytical situation cannot be carried out without some experimental investigation of the system of interest and its interactions with the micellar solution. Attempts with anionic, cationic, and even nonionic micelles within a given analytical framework should be made in spite of predictions regarding optimum interactions with a specific charge type of micelle. The results can be both surprising and enlightening, and lead to enhancements not predicted from first principles.

This review does not attempt to catalog the literature with respect to micelles in analytical chemistry. Rather, the thrust is to illustrate the utility of these microheterogeneous systems in analytical situations through discussion of examples from the literature with enough reference to earlier reviews and articles that the interested individual can proceed further on his or her own initiative. Necessarily, the first section of this report deals with micelles and the properties and characteristics of micelles. This brief review attempts to prepare the uninitiated reader for further discussions regarding the interactions between micelles and substrates. This section is lengthy although

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the text is descriptive and heavily referenced for the reader's benefit. Following that, various areas of analysis and the use and potential for use of micelles within these areas are discussed in some detail. Again, heavy reference to original articles is provided for the reader's edification. Finally, a summary is offered to draw together the important aspects of that which has preceded.

Together, it is hoped that this is a soothing document which serves to encourage the analyst to try micelles in his or her own particular situation. It should also provide enough references and examples so that his or her foray into this area will be comforted by the work of others. The potential of micelles in the area of analytical chemistry is only exceeded by the time available for the examination of their utility. Micelles can benefit spectroscopic methods of analysis by affording automation which in this era of high sample throughput is a significant advantage.[4,6] Even areas as unlikely as atomic spectroscopy[16,17] have shown benefits from the use of micelles within their analytical procedures. From this pedagogical introduction, we begin.

II. UNDERSTANDING MICELLES

As pointed out previously, the intelligent application of micelles to a particular analytical situation requires some understanding of these microheterogeneous systems. This section attempts to provide that level of understanding within the analytical context germane to this report.

A. Micelle Characteristics

Micelles are dynamic aggregates of amphiphilic molecules.[13] An amphiphilic molecule possesses well-defined regions of hydrophobic and hydrophilic character. In the absence of qualifiers, the designation "micelle" or "normal micelle" indicates a system of surfactant dissolved in an aqueous medium. With respect to these normal micelles, the nonpolar portion of the molecule is commonly referred to as the (hydrophobic) tail, while the polar structure of the amphiphile is known as the (hydrophilic) head group. When the concentration of these molecules in solution is increased above a characteristic value known as the critical micelle concentration (cmc), they associate to form relatively well-defined aggregates known as micelles. This phenomenon can be observed by following changes in any of several physical properties of the solution with increasing concentration of amphiphile (Figure 1).[7] The cmc is often referred to as a single concentration while, in fact, it is a narrow range of concentrations over which these physical solution properties are altered. At concentrations above the cmc, the concentration of free amphiphile (i.e., not in micellar form) remains fairly constant with added surfactant, a feature which is reflected in the near constant conductance of ionic micellar solutions above the cmc (Figure 1). It is important to realize that the concentration of free amphiphile does slowly

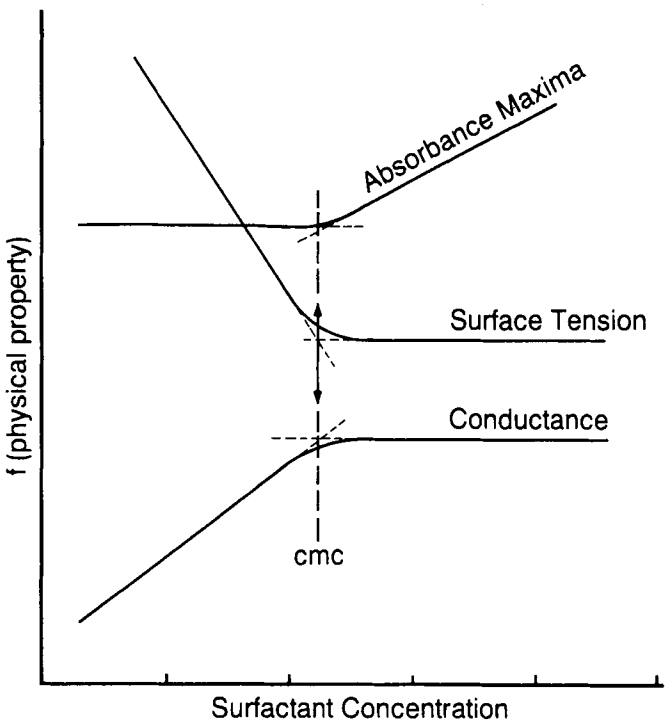

FIGURE 1. Some examples of possible physical property changes with increasing concentration of surfactant. Note that conductance changes are only observed for ionic surfactants and that conductance generally continues to increase above the cmc rather than becoming constant as shown schematically in this figure.[7]

increase above the cmc although the change is often small enough so as to be unobtrusive to the analytical technique at hand. This feature has important consequences in the use of micellar mobile phases in separations as pointed out by Armstrong[2] and Khaledi and Dorsey.[18]

As shown in Figure 2, these aggregates of amphiphiles assemble such that the tails of the molecules are packed together in the interior, or core, of the micelle while the polar head groups form a boundary zone between the nonpolar core of the micelle and the isotropic (polar) aqueous solution beyond. The charged interfacial zone is referred to as the Stern Layer of ionic micelles. Nonionic micelles do not have charged head groups, rather polar structures such as polyoxyethylene groups are presented to the bulk solution. The polyoxyethylene head groups of the nonionic micelles are referred to as a sheath. The microscopic order provided to the solution by micelles gives rise to perhaps the most important characteristic of micellar solutions, that is the ability to solubilize otherwise water insoluble molecules in what is essentially an aqueous matrix.

The geometry of micelles continues to be a subject of much debate.[15,19] One school of thought is that the micelle is essentially a droplet of hydrophobic phase within the bulk aqueous system.[15] These results stem largely from NMR measurements regarding line widths and relaxation times. This model does not allow for deep penetration of water into the micelle interior

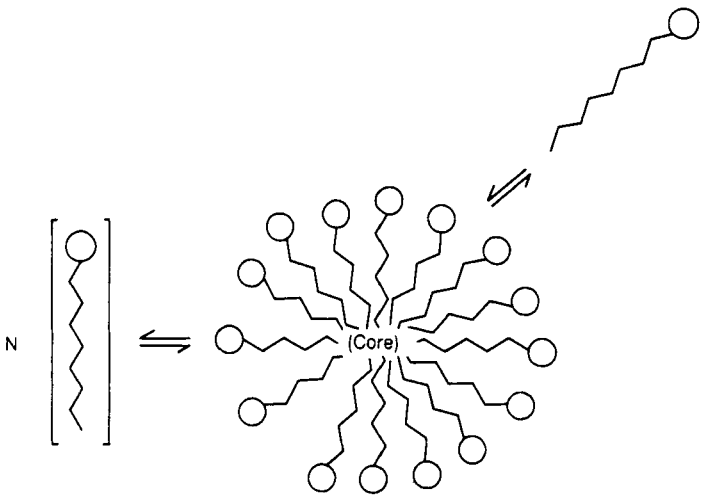

FIGURE 2. The aggregation of N monomers to form a normal, aqueous micelle. The open circles represent polar head groups and may be anionic, cationic, nonionic, or zwitterionic.

and hence has been called the reef model of micelle structure. The other prevailing hypothesis which is based upon molecular models and fluorescence measurements suggests that the micelle affords rather deep channels into the very core of the aggregate.[19] This model has thus been labeled the fiord model for obvious reasons. Finally, statistical treatments of micelle structure have come up with results which seem to explain much of what both previous models attempt to explain.[5] This work by Dill and others[20,21] follows from earlier models of polymer conformations and provides for both the significant amount of water contact with structures often viewed as sequestered within the interior of the micelle and the ability of micelles to solubilize very nonpolar molecules. Nonetheless, the discussion continues with some of the best reports coming from the work of Menger and associates.[19,22] The subject promises to be with us for some time.

Micelle characteristics vary with the nature of the amphiphile as well as with the composition of the solution. Micelles may be categorized as anionic, cationic, nonionic, or zwitterionic depending upon the nature of the polar head group of the amphiphile.[7] Examples of amphiphiles with anionic head groups include alkali and alkaline earth metal salts of carboxylic acids, sulfuric acids, and phosphoric acids. Cationic micelles usually contain quaternary nitrogren head groups due to the stability of these materials as well as their commercial availability. The polar head groups of nonionic micelles generally consist of polyoxyethylene or polyoxypropylene chains.[23] The micelle characteristics of several of these amphiphile systems are presented in Table 1. More detailed and extensive tabulations of surfactant properties can be found in the literature.[4,6-8,14,15] Ionic micellar systems include counterions or gegenions which partially neutralize the charged surface of the micelle. The nature of the counterion can have a dramatic effect on the physicochemical properties of the micelle. For example, sodium dodecyl sulfate (SDS) is very soluble in aqueous media at 30°C. Alteration of the counterion from sodium to potassium results in potassium dodecyl sulfate (KDS), which is not soluble at 30°C. This result follows from an examination of the values of the Krafft points for these two surfactants. The Krafft point is that temperature below which the solubility of the monomeric amphiphile is less than the value of the cmc. Thus, micelles cannot exist below such a temperature. If a micellar solution is brought below its respective Krafft point, precipitation will occur until the concentration of the monomeric amphiphile is reduced to the level of solubility in that solution at that temperature.

The nature of the counterion also affects the value of the cmc. Although defined as a discrete concentration, the cmc is actually a narrow range of concentrations over which the cooperative aggregation of amphiphile monomers occurs.[2,7] Just as alteration of the counterion of ionic micelles can alter the cmc, so can changes in the length or structure (e.g., branching, unsaturation) of the hydrophobic tail affect the properties of the resulting micelles. In addition, changes in pressure, temperature, and ionic strength can affect the properties of micelles as well.[2,7,15] Although these effects must be somewhat controlled, they can be beneficial in that they afford relative ease of variation of the components of the ordered system.

Surfactants can associate in nonaqueous media, forming reverse or inverse micelles.[7] The hydrophobic tails of the amphiphiles are extended into the bulk nonpolar solvent, while the head groups are drawn together to form the hydrophilic core of these aggregates (Figure 3). The size and characteristics of these structures are critically dependent upon the water content of the solution. The water present tends to accumulate within the core to form an isolated pool of water which may exhibit unique properties. At low ratios of water to surfactant, the activity of the water is greatly diminished from that of bulk water. This occurs due to secondary structure formation resulting from hydrogen bonding and from solvation of the closely spaced ionic head groups. As more water is added to the system, the properties of the pool become more like those of bulk aqueous media.[2,7,13] These properties have made these inverse structures useful in a number of special techniques, several of which are discussed by Pelizzetti and Pramauro.[4]

The vast majority of analytical applications of micelles have been demonstrated using normal micelles while relatively few have been examined with inverse micelles. A notable exception to this has been in the area of chemiluminescence, where the inverse micelle structure provides unique advantages to mixed enzyme-lumophore systems.[6] This lack of emphasis upon the inverse systems is understandable when it is considered that a proposed advantage of micellar systems is their use as an inexpensive substitute for nonaqueous media. Given this as a

Table 1
Characteristics of Three Commonly Used Surfactants[2,7]

Name	Abbreviation	cmc[a]	N[b]	Radius[c]	KP[d]
Sodium dodecyl sulfate	SDS	8.1×10^{-3}	62	25	16
Cetyltrimethylammonium bromide	CTAB	9.2×10^{-4}	61	48	22
Polyoxyethylene-23-Lauryl ether[e]	Brij-35	$\sim 7 \times 10^{-5}$	40	>50	100[f]

[a] Values given in moles per liter are from Reference 7.
[b] N = aggregation number; the preferred number of monomers per micelle.[7]
[c] Values in Angstroms are from Reference 45.
[d] Krafft Point in degrees centigrade from Reference 2.
[e] The advantage in using Brij-35 for analytical measurements lies in the absence of an aromatic functionality which opens UV absorbance as a detection method.
[f] For nonionic surfactants, the corresponding temperature is called the cloud point.

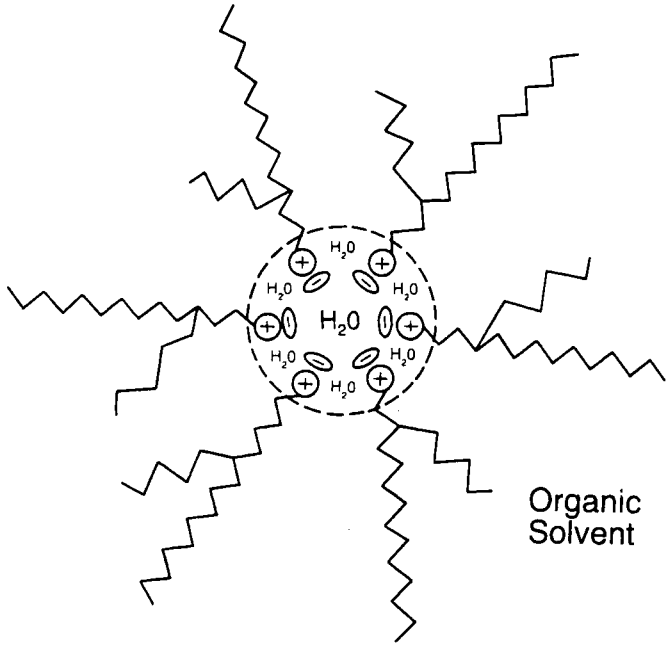

FIGURE 3. Schematic representation of an inverse micelle. The hydrophobic tail of the amphiphile is a branched chain in this example as these two-tailed surfactants are often used for these systems.

major consideration at the outset, it does not make sense to then undertake a study based in a nonaqueous medium. Nevertheless, these ordered media have demonstrated and will continue to provide unique advantages for particular analytical systems which will render them the systems of choice for a variety of analyses.

B. Micelle Substrate Interactions

Incorporation of a substrate into an aqueous micellar solution affects both micelle and substrate properties. Inclusion of hydrophobic substrates into micellar solutions generally causes a decrease in the cmc of the system.[2,4,5,7-10,15] Solubilization of relatively large amounts of nonpolar molecules can also alter the aggregation number (N) of the micelle.[7-10,15] Thus, substrate solubilization may result in the aggregation of fewer or greater numbers of amphiphiles per micelle and hence, alteration of the size of the micelle. In contrast to what might be expected, uptake of nonpolar substrates does not follow a rigid stoichiometric formula (i.e., × substrate molecules per micelle), rather the distribution of substrate molecules among the micelles present has been found to follow a Poisson distribution in a number of studies (Figure 4).[24,25] This indicates that a finite number of micelles are unoccupied and that a finite number of micelles contain multiple substrate molecules whenever a molecule is solubilized within micelles. Thus, if a second order reaction pathway is to be avoided (i.e., disproportionation), then the ratio of substrate concentration to micelle concentration must be less than approximately 0.1 so as to guarantee single occupation of those micelles which are occupied by substrate molecules.[25]

The location of solubilized substrates within the micelle may be in any or all of several regions of the aggregate. Ionic species oppositely charged from the head groups of the micelle may bind tightly to those functionalities via coulombic attraction.[2-5,26,27] Nonpolar species possessing polarizable electrons (e.g., aromatics) have been found to reside near the polar head groups rather than deep within the core of the micelle,[28,30] while alkanes are thought to interact with the core of the micelle.[2-5,31] Substrates having amphiphilic character may exhibit a special interaction with micelles and align themselves with the more polar end of the molecule directed outward towards the head groups of the micelle and the tail directed inward towards the core of the micelle.[28,31,32]

These interactions between micelles and solubilized substrates are highly dynamic. Micelles themselves are transient in nature with the lifetime of a single monomer within a micelle being on the order of 10 μs, while micelles exist on the millisecond time scale before they dissolve and reform.[2-8,10,33] The

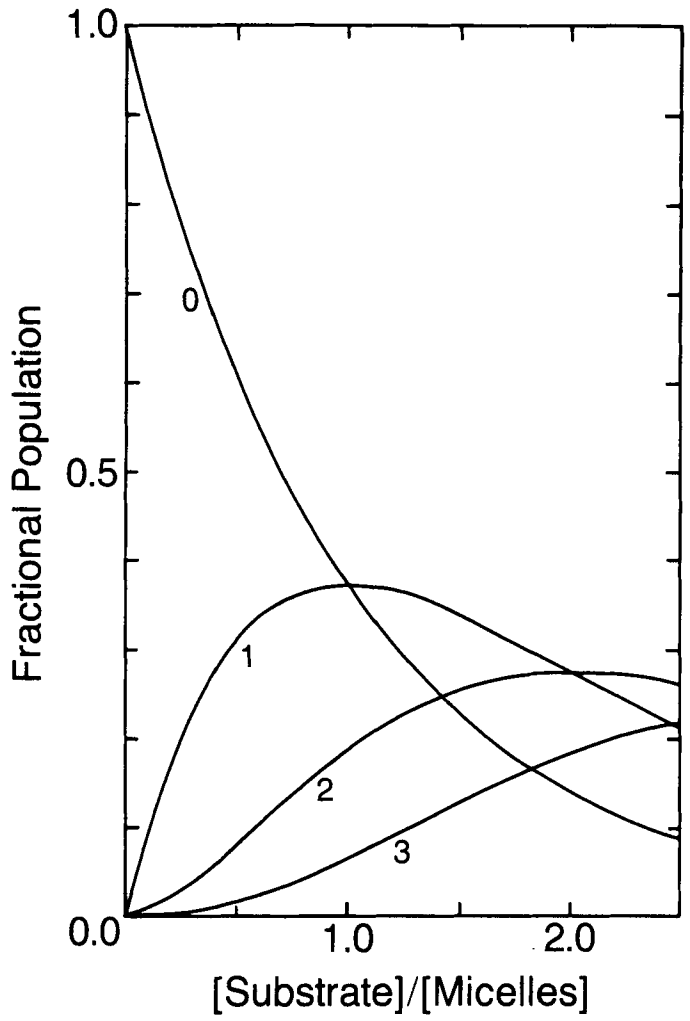

FIGURE 4. Distribution of a solubilized substrate among normal micelles with increasing substrate concentration as described by the Poisson distribution.

residence times of a variety of substrates within anionic SDS micelles have been determined and range up to approximately 50 μs. It must be remembered that even though the spectral and electrochemical responses of solubilized substrates may appear to reflect a constant microenvironment, the location and microenvironment of the molecule of interest are constantly in a state of flux between the aqueous phase and the micellar phase.[3-7,25,34]

A final note regarding the capacity of micelles to solubilize other molecules. It has long been accepted that cationic micelles are able to solubilize more of a given substrate than are anionic and nonionic micelles. The reason for this is that the cationic systems have "softer" head groups, which allow a smaller interhead group separation and therefore a larger volume of hydrophobic character with which to accept organic substrates.[7] If one varies the nature of the substrate rather than the surfactant, the trends are less clear. In general, however, the ability of a given micellar system to solubilize substrates varies from very hydrophobic molecules (i.e., alkanes) much less than polarizable molecules (i.e., aromatics) less than amphiphilic molecules (i.e., surface active agents such as nitrobenzene). These trends are consistent with the view of Dill et al.[20,21] and others[15,19,22] that the architecture of the micelle provides for significant contact between the bulk aqueous media and the hydrocarbon portions of both the surfactants and the incorporated substrates (*vida supra*).

C. Micellar Catalysis

The phenomenon of micellar catalysis deserves individual mention at this point inasmuch as the vast majority of analytical benefits derived from the use of micelles arise from just this feature of these microheterogeneous systems. Many reviews have been written about the action of micelles with respect to the catalysis of reactions.[7,8,13,35-38] These works deal in great detail with the mechanism of specific reactions and the actions of micelles in those systems. Fendler and Fendler[7] even deal with the catalytic action of inverse micelles. For the purpose of this report, the general aspects of micellar catalysis are more important. In that light, the following is brief and very superficial given all the work that is extant within the literature on this subject, but informative enough to give a feeling as to how this process affects reactants and reactions in a micellar solution.

It is generally accepted that one frequently observed mechanism of micellar catalysis arises from concentration of the reagents into a very small volume, thereby increasing the observed rate of reaction simply by boosting the concentration terms within the rate equation. That is to say that the intrinsic rate constant for a given reaction is not affected by the organization of the medium. For example, given a reaction between A and B, if A is solubilized within the micelle, then B must also interact with that system or the reaction will be inhibited rather than catalyzed. If, however, B is attracted to the surface of the micelle either via coulombic attraction or through hydrophobic interactions of its own character, the reaction will be catalyzed because the effective concentration of the reactants within the reaction volume will be much greater than the concentration of either reactant in the total volume of solution. Thus, if both reactants are solubilized near the head groups of the micelle system, it is not inconceivable to see rate enhancements of as much as 1000-fold simply by effective concentration increases. Thus, if the reactants will interact with the micellar phase, analytical benefits may be observed.

There are exceptions to these general statements regarding micellar catalysis. If the micellar system results in a different reaction pathway, then the rate constant necessarily is altered by the use of such systems. For example, if one of the reactants undergoes disproportionation, inclusion of that reagent into the micellar phase will result in catalysis of that process, which may or may not be the reaction of interest. Furthermore, the addition of an ionic reagent to the system which interacts with the micelle surface may result in the alteration of the micelle

system itself, causing transitions from spheroidal aggregates to rod-like structures having much less surface area and thus less reaction zone for the catalysis of the reaction of interest. While these pitfalls must be avoided, in general, micelles can provide acceleration of desired reactions especially at the low levels of reactants usually employed in analytical situations.

III. THE ANALYTICAL UTILITY OF MICELLES

The analytical utility of micelles is evident in a wide variety of analytical techniques from instrumental to classical wet chemical methods of analysis.[2-4,6] As more studies are reported, more investigators are convinced to attempt the use of micelles in their particular areas of interest. It is beyond the scope of this work to detail each avenue of research into micellar utility in analysis. Thus, three major areas of analysis have been selected to illustrate the nature of the interactions, benefits, and utility of micelles in analytical chemistry. These areas are also the most heavily reported and reflect the greatest amount of activity with respect to micelles in analysis. This section is opened with a discussion of electrochemical measurements in the presence of micelles, an area of great promise and increasing interest. A discussion of the effects of micelles upon spectral analyses follows, including micelle-enhanced luminescence and absorption effects. The last section deals with the effects of micelles in analytical separations, including the relatively new area of micellar electrokinetic chromatography (MECC). As mentioned earlier, these discussions cannot possibly touch all of the uses of micelles in analytical chemistry, but they do discuss many of the major effects with emphasis upon the types of interactions which can be expected in these systems. Knowledge of these interactions can prepare the analyst to apply micelles to his or her own particular analytical situation.

A. Electrochemical Measurements

The use of micelles in electrochemical investigations has recently been reviewed.[3,4] Micelles have found utility as organized media for a variety of electrochemical research efforts, including mimetic membranes for redox studies,[3,27] energy storage,[32,39,40] and electrocatalysis.[41-44] Electrochemical measurements are being used to estimate micelle size as derived from diffusion coefficients of solubilized probe molecules and the Stokes-Einstein equation.[28,44-46,49] Yet, their use in analytical measurements has hardly exceeded the traditional addition of surfactant to polarographic media for maxima suppression. As pointed out by Pelizzetti and Pramauro,[4] electrochemists tend to view nonelectroactive substances as simply that — not important to the electrochemical response of interest. Yet, work has appeared that suggests several potential analytical benefits could be derived from the use of micelles in specific electroanalytical applications.

As reviewed by McIntire,[3] the possible utility of micelles in electroanalytical chemistry can be divided into several categories. They include electrochemical masking, electrocatalysis, and the provision of a low-cost and nontoxic alternative to nonaqueous solvents. Furthermore, micelles have also been used in a variety of electrochemical research venues other than classical electroanalytical studies.[3,5,26,28,32,34,45] While progress continues in these areas,[30,44,46-50] work in the analytical arena remains largely in the recent past.

It can happen that the electroanalytical utility of a given molecular system is less than optimal due to electrochemical irreversibility. That is to say that the act of transferring an electron from the electrode to the redox molecule in solution can be a kinetically limiting process. Normally, almost all electroanalytical techniques are governed by diffusion such that the rate of heterogeneous electron transfer has no impact upon the observed signal. Gundersen and Jacobsen[51] have reported that the addition of surfactant to solutions may catalyze the redox process of interest and therefore enhance the utility of the system. Their work centered upon the three-electron reduction of bismuth 1,2-diaminocyclohexanetetraacetic acid (DCTA). This negatively charged complex undergoes a single, clean reduction to bismuth metal at a mercury electrode in the absence of surfactant. Upon the addition of a cationic surfactant (dodecylammonium perchlorate), the reduction peak shifts to less extreme potentials and provides a greater peak current value. This behavior is exactly as expected for enhanced rates of heterogeneous electron transfer. Further evidence of surfactant catalysis was reported by these authors in that when an anionic surfactant was added to the system, the peak potential was shifted to much more extreme values and the peak became lower and broader than in the absence of surfactant (Figure 5). Such behavior is suggestive of inhibition of the transfer of electrons between the electrode and the solution-resident molecule. It is interesting to note that although the presence of micelles in solution is not directly addressed, the authors point out that these effects are the result of a modified surface layer upon the electrode and that the addition of a high molecular weight cationic surfactant can totally inhibit any electron transfer at all.[51] This indicates that the effects noted in their report are due to a reorganization of the electrical double layer on the electrode surface such that the charge experienced by the substrate is either enhanced or diminished from that felt in the absence of surfactant. As pointed out before,[52] electrochemistry is a heterogeneous technique and only responds to the activity of the redox substrate at the electrode surface. Therefore, the presence of micelles in the bulk solution cannot directly affect the act of electron transfer other than to regulate the rate at which materials diffuse toward the electrode given that those materials interact with the micellar phase and to modify the electrode surface through adsorption of either monomer or hemimicelles.

An area of electroanalysis in which micelles can effect the analytical utility of the redox system is the use of these structures as psuedocatalysts. In these systems, the micellar phase

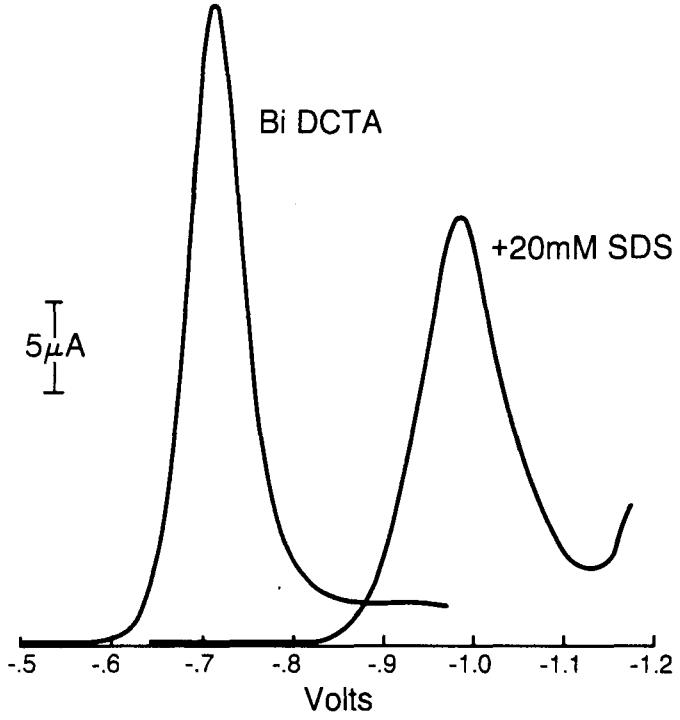

FIGURE 5. The differential pulse voltammetric reduction of bismuth DCTA with and without SDS micelles present. The voltammetry was carried out at a hanging mercury drop electrode with a pulse amplitude of 25 mV, a scan rate of 1 mV/s and a drop time of 1s.

serves to solubilize either the actual catalyst itself or the substrate or both. Rusling et al.[41-44] have worked extensively in this area which may have been first studied by Yeh and Kuwana[53] in 1976. These systems can be further illustrated by example.

Kuwana was involved in the study of the redox chemistry of large biomolecules (i.e., cyctochrome c and cytochrome c oxidase) which were thought to be kinetically limited in their intrinsic rates of heterogeneous electron transfer at solid electrodes.[54,55] They overcame this apparent problem by using ferrocene as a mediator titrant[56] or electron shuttle from the electrode to the solution resident biomolecule (Figure 6). Mediator titrants are not a new concept, and the properties of a variety of these molecules have been tabulated.[57] Yet, the use of micelles to solubilize the titrant (i.e., the ferrocene) was new and spoke to the questions of effects of micelles upon electron transfer to micelle-resident species. It was demonstrated that the electron transfer characteristics of the micelle-solubilized ferrocene were unchanged from those observed in the absence of micelles in mixed aqueous-nonaqueous media. In the limit, it is conceivable that such a technique could be used to analyze for the biomolecule of interest in an electrocatalytic method. This technique would essentially look at the current due to the redox process of the ferrocene at the electrode and how it is impacted by the presence of large, electrochemically irreversible biomolecules in solution. Such work remains in the realm of speculation outside of the exciting experiments ongoing at the University of Connecticut.[41-44]

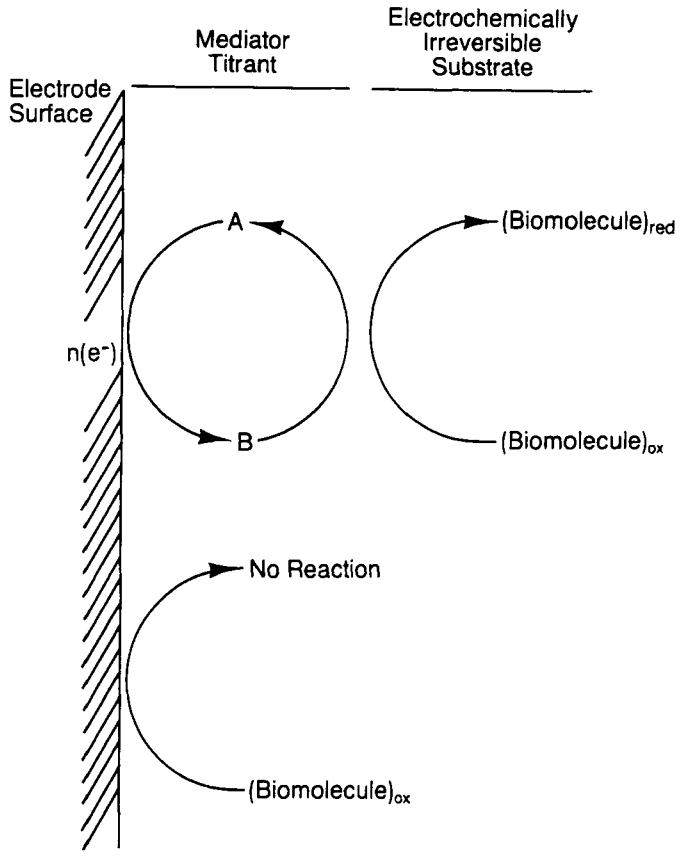

FIGURE 6. Graphical illustration of the utility of mediator titrants.

More recently, the use of micelle-solubilized catalysts to enhance the electron transfer characteristics of molecules of low water solubility has been studied by Rusling et al.[44] As pointed out by these authors, their methods are potentially useful in the areas of electroorganic synthesis, biological electron transfer modeling, and electroorganic analysis in nontoxic media.[41-43] From an analytical standpoint, clearly the last topic is of the greatest interest. The utility can be described as follows. Given a micelle-solubilized catalyst, then the current derived from the reduction (or oxidation) of that species can be enhanced by the presence of a selective substrate. Such processes are often labeled ECcat reaction schemes by electrochemists,[52] as illustrated by the sequence of reaction steps shown here:

(at electrode)
$A \rightarrow B + n(e^-)$
$B + (\text{biomolecule})_{ox} \rightarrow A + (\text{biomolecule})_{red}$
$(\text{biomolecule})_{ox} + n(e^-) \rightarrow$ does not occur
(at electrode)

where the A/B redox couple is the mediator titrant (catalyst). Note that A is regenerated by the homogeneous transfer of electrons to the oxidized form of the biomolecule of interest, thus, the description as catalytic. This regeneration process

gives rise to a current which is strictly related to the amount of biomolecule present in the reaction layer near the electrode and hence the bulk solution. As long as the electrochemical measurement is rapid and does not perturb the distribution of biomolecule, this current enhancement can be related to the concentration of the substrate, thereby providing an analysis of the quantity of material added. While this is much too simplistic to describe the work which has been carried out, the goal remains to provide easier analyses of trace organic materials without extended sample workup or nonaqueous solvents.

A number of reports concerning the ability of surfactants to selectively mask the electrochemical response of a variety of materials without blocking that of the analyte of interest have appeared.[51,58-60] As an example, the addition of gelatin to a solution of metal ions generally suppresses the polarographic responses of all, with the exception of thallium and silver.[60] This was extended to the report of a detailed electroanalytical method for thallium in the presence of many interfering ions.[61] Furthermore, it has been demonstrated that the addition of 0.1% Triton X-100 to a solution of mixed iron and copper diethylenetriaminepentaacetic acid (DTPA) complexes results in the complete masking of the copper complex while the reduction of the iron complex is unimpeded.[58]

It is interesting to note that thallium and silver are just the ions integral to the recent phenomenon of micelle-stabilized room temperature phosphorescence.[2,4,5] This topic is covered in depth in the following section of this review. Furthermore, the heterogeneous nature of electrocatalysis is illustrated again by the use of surface-active agents to selectively inhibit the response of a variety of ions at the electrode surface. While this entire area was pioneered by Reilly et al. in 1956, little has been reported in the following years.[62] Potential uses of this technology can readily be imagined. For example, flow injection analysis of water samples for possibly toxic levels of thallium using electrochemical detection and surfactant masking of interfering ions would be a logical extension of these reports. Ions could be selectively determined in ion chromatography using masking with surfactants. Unfortunately, this area remains the domain of the few experimenters with knowledge in the fields of electrochemistry, micelles, and analysis.

In summary, of all the areas in which micelles have been examined with respect to analytical utility, electrochemical methods have received the least analytical effort and continue to provide empirical results at best. Yet, reports concerning photophysical electron transfer processes in micelles, homogeneous electron transfer reactions in micelles, and fundamental electrochemical studies of micelle-solubilized redox substrates continue to appear at a steady rate. This dichotomy will not be resolved until a more ordered investigation of the effect of surface-active agents upon the electrical double layer is completed affording some measure of predictability to the use of these agents in electroanalysis. Until that time, the use of micelles (i.e., surface-active agents) in electroanalysis will remain at the present low levels.

B. Micelles in Spectroscopy

The utility of micelles in spectroscopic methods of analysis is perhaps the most popular and oldest area of micellar application in analytical chemistry. Hinze[6] first reviewed this area in 1978. Since that time, the number of reports in this area has continued to grow at a faster rate than in either electroanalytical methods or psuedophase (micellar) separations. Clearly, the requirement for sophisticated equipment is not present in this area of research such that any laboratory possessing a spectrophotometer can profitably investigate the effects of adding surfactants to a given colorimetric method of analysis. Furthermore, more instrumentally involved methods of analysis respond to the addition of micelles just as well as do normal spectrophotometric analyses. Without a doubt, this concentration of effort will continue in the forseeable future.

The utility of micelles in spectroscopic measurements is derived from several possible effects upon the system of interest. The well-documented effects of micellar systems upon acid-base chemistry of even slightly associated molecules can enhance (or degrade) the analytical quality of a given method.[4,7,8,38,63] In the field of metal ion complexation, much work has been carried out which suggests that the surfactant (within the micelle) takes part in the formation of a ternary complex with concomitant shifts in the wavelength of absorption.[4,6,64] Finally, as always, the ability of the micellar system to solubilize slightly insoluble or even very insoluble complexes and/or ligands has been used to enhance the analytical merit of given methods.[4,6,65,66] Several of the effects mentioned earlier result in part from ion exchange or acid-base properties of micellar solutions such that this section is introduced with a discussion of this pertinent subject.

1. Acid-Base Considerations

The effects of micelles upon the acid-base properties of a variety of indicator acids were noted early on by Hartley[67] and expanded upon by Hartley and Roe.[68] While elegant theories have been developed to rationalize these types of observations since that time, it is sufficient here to note that apparent pK_a alterations arise primarily from a combination of electrostatic and microenvironmental affects of the micelle.[4,38,69-74] Thus, even nonionic micelles can effect apparent pK_a shifts for incorporated acids (Table 2). Analytically, these shifts can allow determinations of organic acids in the presence of equal pK_a inorganic acids by moving the equivalence points apart. Furthermore, incorporation of weak acids can result in their determination in aqueous media as opposed to nonaqueous titrations. For example, Staroscik et al,[63] demonstrated the effective analysis of a variety of barbituates in cationic micelles as opposed to "official" nonaqueous titrations. In this case,

Table 2
pK_a Shifts of Various Species as a Function of Surfactant Charge Type

Species	Alone	With surfactant		
		Cationic	Anionic	Nonionic
Phenol Red, pK_{a2}	7.68	7.66[a]		
Bromophenol Blue, pK_{a2}	3.89	3.02[a]		
Bromocresol Green, pK_{a2}	4.58	4.08[a]		
8-Quinolinol, pK_{a1}	5.02	4.26[b]	5.72[c]	5.02[d]
pK_{a2}	9.67	9.35[b]	10.29[c]	9.76[d]
Quinine, pK_{a1}	4.13	4.20[b]	5.35[c]	
pK_{a2}	8.52	7.57[b]	9.79[c]	
Methyl Red, pK_{a1}	4.95	3.67[e]	6.63[c]	5.20[d]
4-Nitrophenol, pK_{a1}	7.15			7.11[d]

[a] Carbethoxypentadecyltrimethylammonium bromide.
[b] Dodecyltrimethylammonium chloride.
[c] Sodium dodecyl sulfate (SDS).
[d] Triton X-100.
[e] Dodecyltrimethylammonium bromide.

From Diaz-Garcia, M. E. and Sanz-Medel, A., *Talanta*, 33, 255, 1986. With permission.

the attraction of the cationic headgroups for hydroxide ions from the bulk aqueous solution effectively lowers the apparent pK_a of the barbituates, making them stronger acids and thus more amenable to titrametric analyses. Interestingly, these titrations could be carried out visually using thymolphthalein as an indicator or potentiometrically with a conventional glass electrode. This is in contrast to a number of earlier reports wherein the potentiometric route was not analytically viable due to slow electrode response and/or fouling.[75-78] Alternatively, thermometric titrations have been used to avoid these documented problems in some micellar systems.[79]

The observed variations in acid-base properties in micellar systems can be analytically beneficial as demonstrated earlier. In fact, many shifts in absorbance maxima of various dyes upon incorporation into micelles result from such acid-base equilibria.[7,9] Yet, it should be noted that these same effects could potentially inhibit desired reactions upon micellization, thereby diminishing the analytical utility of that particular method. Nevertheless, these micellar effects can and have been used to great advantage.

2. Surfactant Ligand Effects

A growing application of micelles in analytical chemistry involves the beneficial alteration of metal ion-ligand complex spectral properties via surfactant association. The addition of micelles to these chelates can affect both the wavelength of choice and increase the absorbance (fluorescence) of the resulting species over that of the normal binary complex.[64,80-82] The literature in this area has been reviewed by Hinze[6] and more recently by Pelizzetti and Pramauro.[4] Yet, in spite of these reviews and the increasing amount of work in these areas, little effort has been directed towards understanding the mechanism(s) of these effects. Cermakova[80] has summarized those efforts together with his own work in the area of triphenylmethane dyes. His work suggests that the observed spectral alterations result from micelle effects upon the ionization equilibria of the ligand dyes rather than actual complexation of the metal ion itself by the surfactant. This is in concert with the comments of Pelizzetti and Pramauro[4] regarding the effects of competing ions, different surfactants, and pH in these systems. Furthermore, these results speak to the relative ineffectiveness of anionic surfactants in these systems as discussed later. In any case, these effects have been shown to be useful in many analyses and a few selected examples are cited next.

Most of the reported work in this area deals with the effects of cationic micelles on complexes of negatively charged ligands with metal cations.[4,80] An interesting example involves a study of the effects of hexadecylpyridinium chloride (HPC) upon the spectral properties of the binary complex of scandium(III) with *o*-hydroxyhydroquinonephthalein (Qnph)[64] (Figure 7). As reported previously in studies of this type, the addition of HPC results in a significant spectral shift relative to the absorbance of the dye-surfactant solution alone such that quantitation of the metal ion of interest becomes possible. The complex exhibits greater absorbance and increased stability relative to that observed in the presence of a nonionic surfactant. It is interesting that this particular complex takes advantage of both micellar-induced spectral changes and micelle solubilization to

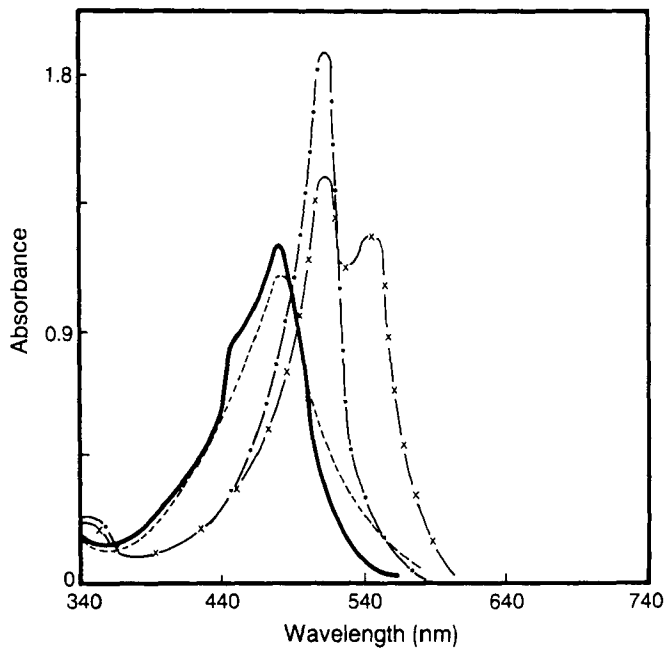

FIGURE 7. Absorption spectra of scandium(III)-Qnph and of Qnph alone in the presence of hexadecylpyridinium chloride (HPC) and in the presence of a conventional nonionic surfactant, LT-221. —— = Qnph alone in LT-221; ----- = Qnph-scandium(III) in LT-221; —·—·— = Qnph alone in HPC; and —x— = Qnph-scandium(III) in HPC solution.[81]

yield the observed analytical benefits. More is stated about solubilization in the next section.

Although the majority of work in this area concerns cationic surfactants, anionic micelles have also demonstrated analytical utility in similar ways.[4,83,84] The ternary complex of SDS with zirconium and 2-(6-bromo-2-benzothiazolylazo)-5-diethylaminophenol results in a more sensitive analysis than comparable methods using cationic surfactants.[83] SDS has also been shown to enhance the analysis of fluoride ion by altering the absorbance characteristics of the ligand and not those of the analytical complex itself (Figure 8).[84] In spite of these reports, the general utility of anionic micelles with respect to metal ion determinations will remain low due to direct surfactant-metal ion interactions which inhibit metal ion-dye complex formation and by Krafft point effects[7] due to the action of the metal ions in question as counterions for the anionic headgroups of the negatively charged surfactants.

3. Solubilization Effects

Sections III.B.1. and III.B.2. have dealt with what can be described as ionic or head group effects of micelles upon various analytical methods. These effects are significant and are an important part of understanding micellar effects in general.[3-9,70-75] This section addresses the other major factor in the utilization of micelles in analytical chemistry, that is, the ability

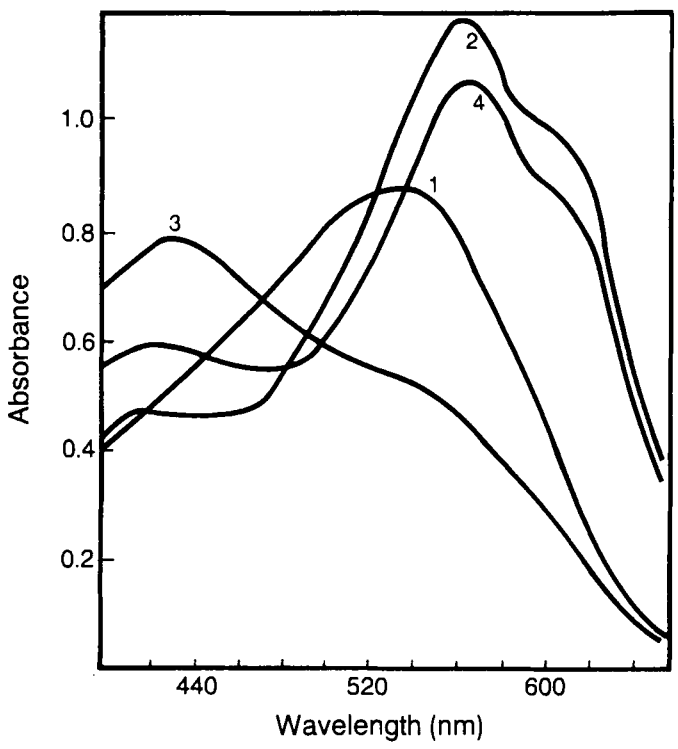

FIGURE 8. Absorption spectra: (1) La(III)-Alizarin Fluorine Blue (AFB); (2) F——La(III)-AFB; (3) La(III)-AFB in SDS; (4) F—— La(III)-AFB in SDS. Conditions: 1.2 mg/l fluoride, 20% (v/v) acetone, 1.5×10^{-4} M La(III)-AFB, pH 4.6, 17.0 mg/ml SDS when used, and all measured against a water reference.[84]

of these microheterogeneous systems to solubilize normally water-insoluble moieties in an essentially aqueous matrix such that the resulting solution appears homogeneous on a macroscopic scale. While this section discusses systems wherein the effects of interest are related to this ability, it is a mistake to think that the important effects of sections III.B.1. and III.B.2. can be understood solely upon the basis of ionic interactions or that the effects discussed in this section are devoid of interfacial components. Complete understanding can only result from recognition of all the possible and applicable effects of micelles on solution-resident molecules and complexes.

The ability of micelles to solubilize analytically useful complexes can obviate the need for nonaqueous extraction steps in a given analysis.[4,6,63,75-79] This may not appear to be a major advantage until one considers automation of these analyses. Aihara et al.[66] demonstrated the flow injection fluorometric analysis of europium(III) using thenoyltrifluoroacetone and trioctylphosphine oxide in nonionic micellar media. This technique is an extension of earlier studies regarding the utility of nonionic micelles relative to solvent extraction with respect to the analysis of rare earth metal ions.[85,86] They have extended this work to the analysis of terbium(III).[87] Other fundamental reports concerning the analysis of neodymium,[65] silicon as the molybdosilicate complex,[88] cadmium and nickel,[89] and beryllium[90] in the presence of nonionic micelles rather than via solvent extraction speak to the generic utility of this approach.

4. Micelles in Fluorescence, Phosphorescence, and Chemiluminescence

Fluorescent probe molecules have been used for many years to study micelle dynamics, solute distributions, micellar microenvironments, and micellar effects upon reaction kinetics.[4-7,13,15,24,25,91] These systems are particularly attractive with respect to micelle dynamics because the temporal dependence of the fluorescence event is sufficiently fast that it exceeds all of the micelle kinetic processes. Thus, fluorescent probes can be used to estimate the dynamics of surfactant monomer entry and exit from the micellar aggregate, substrate entry and exit (residence times), and micelle dissolution.[24,25,91] Micelles have turned the tables and become the vehicle rather than the subject with respect to the analytical utility of fluorescent methods. These microheterogeneous systems present several advantages over conventional homogeneous solution techniques including increased sensitivity, reduced interferences, and enhanced experimental convenience.[92] These effects are observed in both ionic and nonionic micelles with charge-charge interactions being important in some cases and not in others. Conversely, nonionic micelles may enhance fluorescence in one system and actually quench these emissions in others and these effects may vary from one type of nonionic micelle to another.[93] It is clear, however, that the micelle enhancement of fluorescence is just that — micellar! The concentration of surfactant must exceed the cmc to observe these effects.[93-94] This is in contrast to some electrochemical and spectral methods where sub-cmc concen-

trations of surfactant may affect analytical systems.[3,4,6] The requirement for intact micelles supports a strong dependence upon micelle solubilization rather than direct surfactant ligand interactions as the source of these effects.

Increases in fluorescent sensitivity in micelle solutions are thought to arise from a number of interactions.[92] Removal of the fluorophore from the bulk aqueous medium into the micellar microenvironment(s) can diminish vibrational quenching from the hydrogen bond network of water. Furthermore, the relatively high viscosity of these microenvironments can inhibit quenching by molecular oxygen by affecting diffusion rates.[25] Finally, intrinsic photophysical properties can be altered within the micellar medium.[24]

Micellar diminution of interferences results from the same properties which afford micellar catalysis only in reverse. That is that micelles can be used to inhibit some ionic interferences. For example, the use of a cationic micelle can inhibit the interference of pyridinium ion while anionic micelles inhibit the deleterious action of iodide ion in the fluorescent analysis of anthracene.[92,94] Clearly, like charges repel and result in diminished interferences. Interestingly, nonionic micelles are somewhat effective against many different interferences either charged or neutral.[92] Thus, while charge effects do modulate the relative inhibition of the various interferences, certainly the order provided by the possible micelle microenvrionments provides a significant proportion of the observed protection.

While experimental convenience is in the opinion of the analyst, it does appear that micelles offer several potential advantages over traditional analytical fluorimetry techniques. Perhaps the most obvious advantage arises from micelle solubilization of either reagent(s) or products, thereby eliminating requirements for nonaqueous media. It is noteworthy that these normally sensitive fluorescent methods are a very good match for micelles in that enhanced solubilities of the already small quantities of analyte can be achieved at concentrations of surfactant just sufficient to provide normal micelles, i.e., above the cmc. Furthermore, solubility limits are generally not approached in these micelle systems before the dynamic range of the analysis is exceeded at the high end. Relative to absolute amounts of material, these methods are perhaps the best suited to the microheterogeneous micellar medium.

Other conveniences include avoidance of oxygen removal from solution and possible catalysis of derivatization reactions. As mentioned before, micelles have been observed to diminish quenching due to oxygen.[92] Thus, homogeneous systems which often require oxygen removal may not require this step in micellar systems, which is in itself a major convenience,[95] not to mention the time savings and associated cost considerations. Always a possibility, micellar catalysis can be used to enhance derivatization reactions either in reaction time[92,94] or in extent of reaction.[7] These results can increase throughput and/or sensitivity, and may afford the utility of these methods in flow injection instrumentation[66,87,96] as well as clinical applications.[97]

A great deal of work regarding the effects of micelles upon metal chelate fluorescence has been reported.[4,6,9,66,81,85-87,92-95,98-100] Sanz-Medel et al. summarized much of this work regarding the effects of both cationic and nonionic micelles upon analyte fluorescence. In addition, their work demonstrated that in the absence of charge effects, the nature of the surfactant monomer is critical to the resulting analytical enhancements. For example, the presence or absence of aromatic groups or of branched aliphatic chains can significantly affect micelle fluorescence enhancements (Table 3).[93] Nithipatikom and McGown[101] have pursued an interesting new area of study in these respects. Their work with sodium taurocholate micelles and heavy metal ion fluorescence enhancement may well lead to improved, more convenient metal ion analyses in the future.

Phosphorescence has not achieved marked success in routine analysis due to restrictive sample preparation requirements. Samples are normally immobilized in either low temperature glasses or upon solid supports (i.e., filter paper). In either case, the experiments are not convenient and often suffer from unwanted fluorescence and a need for sophisticated instrumentation. The introduction of micelle-stabilized room temperature phosphorescence (MSRTP) by Cline-Love in 1980 offered a dramatically altered method of phosphorescence analysis.[102] Their work demonstrated the room temperature phosphorescence of deoxygenated micelle solutions of various polycyclic aromatic hydrocarbons (PAH). The requirements for MSRTP include having concentrations of surfactant present sufficient to guarantee micelles, the presence of heavy atoms

Table 3
Effect of Surfactant Structure upon Fluorescence Enhancement Using the Niobium-Lumogallion-Tartrate System

Surfactant	Micelle Enhancement Factor
Triton X-114[a]	16.0
TritonX-100	19.5
Triton-X-405	14.7
Nemol K-36[b]	19.3
Nemol K-1032	19.3
Nemol K-1035	19.2
Nemol K-2030	25.5
Nemol K-3030	24.1
Genapol PF-10[c]	4.9
Genapol PF-20	3.9
Genapol PF-40	5.5
Genapol PF-80	3.3

[a] Tritons are tert-Octylphenols condensed with ethylene oxide.
[b] Nemols are nonylphenols condensed with ethylene oxide.
[c] Genapols are ethylene oxide-propylene oxide condensates.

From Sanz-Medel, A., Fernandez-Perez, M. M., DeLaGuardia-Cirugeda, M., and Carrion-Dominguez, J. L., *Anal. Chem.*, 58, 2161, 1986. With permission.

to promote intersystem crossing, and the exclusion of oxygen from the solution.[103] Initially, these systems involved solubilization of PAH in anionic SDS micelles which had been altered by the addition of either thallium or silver ions to the counterion field about the headgroups of the micelles. The proximity of these heavy metal ions to the micelle-solubilized PAH results in enhanced intersystem crossing to the triplet state from the initial excited singlet state, thereby increasing phosphorescence at the expense of interfering fluorescence processes. Interestingly, silver and thallium are those metal ions which are not masked by surfactants at electrode surfaces (*vida supra*). For some years, this was the only MSRTP system reported. Recently, Sanz-Medel et al. reported the MSRTP of metal chelates as applied to the determination of niobium using cationic micelles and bromoform as the heavy atom rather than thallium or silver.[104] They demonstrated that sodium sulfite can be used to scavenge oxygen in these systems with no deleterious effects upon the resulting MSRTP, thus avoiding any foaming or sudsing problems associated with nitrogren purging. Finally, room temperature phosphorescence can be achieved via both colloidal dispersions[105] and cyclodextrin complexes,[106] yet, MSRTP would appear to be a somewhat generic approach to room temperature phosphorescence in liquids and may lead to more sensitive and selective analyses in the future.[107,108]

Inverted micelles have demonstrated advantages in some chemiluminescence measurements. Igarashi and Hinze[109] have reported that the use of hexadecyltrimethylammonium chloride (CTAC) in a mixed chloroform-cyclohexane solvent system affords the opportunity to carry out the enzymatic generation of hydrogen peroxide and the luminol-peroxide chemiluminescence detection scheme simultaneously.[109] Normal bulk aqueous methods require preliminary peroxide generation, followed by pH alterations for subsequent luminescence detection. These types of systems have also been used to detect copper(II) at subpicogram levels in tap water in a flow injection analysis setting.[110,111] The extreme sensitivity of these methods together with the potential for automation suggests that this will be an area of interest for some time.

5. Other Spectroscopic Methods

The utility of micelles has been reported in several other areas. Both atomic absorption[16,17] and emission[112] have been carried out in micelle solutions with some advantages. It is not clear at this time what exactly governs these responses. Analyte could be concentrated at the interface of solution droplets in a sort of micellar catalysis, or the size of the droplets could be optimized by the effects of surfactant upon surface tension.[17] In any event, it is not yet feasible to predict how micelles will affect a given analysis in these areas.

Micelles have also been cited as useful in Raman spectroscopy for the same reasons they are useful in phosphorescence. That is, unwanted fluorescence can be quenched via the use of heavy atoms or other micelle-catalyzed quenching reactions.[113] Thus, analyte-generated fluorescence is removed from the Raman emissions, providing an enhanced spectrum. Furthermore, insoluble materials can be accessed in an aqueous medium using micelles. Water is a good solvent for Raman spectroscopy, while nonaqueous solvents are less than optimal. This area of potential micelle utility will certainly grow in the future.

C. Micelles in Analytical Separations

Micelles have been employed in a wide range of analytical techniques which can be grouped under this heading.[2,4] In fact, this subspecialty of micellar analytical utility has produced several reviews[2,114-118] and a monograph[119] indicative of the level of interest in this particular application of micelles. While micelles have been used in a variety of separation applications, three areas currently stand out in terms of importance. These are (1) micelles in extraction processes, (2) micelles in chromatography, and (3) micelles in electrokinetic separations. Each of these is addressed, in turn, starting with a discussion of micelles in extraction processes as a logical extension of micelle solubilization discussed in Section III.B.3. Interested readers are directed to earlier reviews[2,4-6,114,118,119] and original papers discussed therein for more detail regarding other micelle-enhanced separation applications.

1. Micelles in Analytical Extraction Processes

The ability of micelles to solubilize normally water-insoluble metal chelates and organic analytes has been discussed earlier regarding spectrophotometric and fluorometric methods of analysis (see Sections III.B.1. to 4.). Such *in situ* solubilization offers several advantages over conventional mixed solvent schemes, including experimental convenience, cost, ease of waste disposal, and, in some cases, enchanced spectroscopic signals.[118] The analytical utility of these systems can be further increased when they are used to extract the insoluble complex or substrate from the bulk aqueous medium into a much smaller volume phase consisting almost entirely of surfactant. The resulting concentration of the molecular system of interest affords increased sensitivity of analysis.

These separations depend upon a particular physical property of the surfactant. For example, nonionic surfactants go through a critical point upon increasing the solution temperature known as the cloud point. Above this temperature, the nonionic micelle phase separates from the bulk aqueous medium, taking the already solubilized analyte into that phase as well. Assuming a 100:1 ratio of water volume to surfactant volume, this results in a 100-fold increase in analyte concentration with the obvious attendant benefit of increased sensitivity. Watanabe and co-workers have reported the use of nonionic micelles for just such enhanced analyses of metal chelates.[120-123] The metal ion is first complexed and solubilized within the nonionic micelle. The solution is then heated above the cloud point to afford phase separation, followed by analysis of the surfactant

rich layer. Hinze[118] has summarized these applications (see Table 10, Reference 118). He has also pointed out that these complex systems will require a great deal of fundamental research before they can move away from the current state of empiricism.

Ionic surfactants can also phase separate although the effect is normally generated with solution additives such as high levels of salt. While this area has seen limited activity, it would seem to offer all of the advantages of the nonionic systems and a much broader range of metal surfactant interactions.[118] Some work has been carried out involving the extraction of metal chelates into conventional organic phases from micellar solutions.[46] These systems can be enhanced via surfactant alteration and the addition of functional groups directly to the surfactant to increase the efficiency of the extraction process.[4] Mechanistically, these systems would appear to be an extension of classical phase transfer catalysis with metal-surfactant complexation in the aqueous phase as the rate limiting step.

These types of extractions can be used to analyze surfactant levels in environmental water samples.[4] Nonionic, polyoxyethylene surfactants have been analyzed spectrophotometrically in methylene chloride after extraction from the aqueous sample as a picrate ion complex.[124] These polyoxyethylene-type surfactants can be thought of as linear crown ethers in that they can interact with a variety of metal ions via the unpaired electrons of the regularly spaced oxygen atoms. Thus, when potassium picrate is added to the aqueous sample of nonionic surfactant, the potassium ion is "chelated" with the polyoxyethylene groups. This cationic complex interacts tightly with the picrate anion to form a net neutral, colored complex which can then be concentrated by extraction into a nonaqueous solvent.[124,125] As reviewed by Pelizzetti and Pramauro,[4] this area of analysis has direct commercial importance although it does not involve micelles per se.

2. Micelles in Chromatography

The ability of micelles to selectively interact with a variety of molecules affords the possibility of using these materials to carry out separations of those same species.[2,4,114,118,119] This is the essence of chromatography and broadly describes the use of micelles in this area. From the first reported use of micelles in the separation of transfer RNAs in 1977,[126] there has been rapidly increasing interest in this field as evidenced by the reviews mentioned earlier.[2,4-6,114,118,119]

Micelle or psuedophase chromatography has been described as the effect of adding an additional partitioning process to traditional separations systems.[2] For example, in reversed-phase chromatography, retention is related to the magnitude of substrate partitioning into the organic stationary phase with more hydrophobic molecules being retained the longest. A second and third partition process are available when micelles are added to the mobile phase. The available partition pathways become (1) between water and the stationary phase, (2) between water and the micellar phase, and (3) directly between the micellar phase and the stationary phase (Figure 9).[2,118,119] Thus, the potentials for interaction are increased dramatically when micelles are present. Substrate molecules can interact with both the stationary phase and the micellar phase via partitioning. Further, substrates may interact with the micelle phase through coulombic attraction, adsorption, coassembly of amphiphilic substrates with surfactant monomers, etc.[114] The number of possible interactions makes the addition of micelles much more than just another liquid phase.

This three-phase model of micellar chromatography has been described in quantitative terms and has been examined relative to a number of separations.[127,128] One form of the derived expressions is shown here for HPLC using micellar mobile phases.

$$\frac{1}{k'} = \frac{1}{\varphi}\frac{C_M V(K_{MW} - 1)}{K_{SW}} + \frac{1}{K_{SW}} \qquad (1)$$

where k' is the observed capacity factor, φ is the volume ratio of stationary phase to the void volume, C_M is the concentration of micelles, K_{MW} is the partition coefficient between the micellar phase and the aqueous phase, K_{SW} is the partition coefficient between the stationary phase and the aqueous phase, and V is the molar volume of surfactant. Equation 1 predicts that k' decreases with increased micelle concentration as does the retention time. These effects have been observed in a variety of separations.[2,118,119,127,128] The multiple forms and initial derivations of the mathematical description of this model have

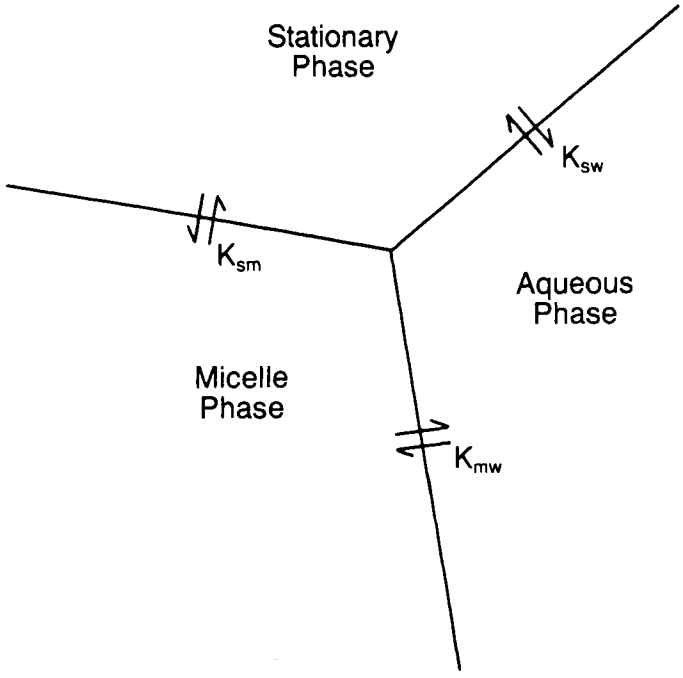

FIGURE 9. The possible partitioning in micellar chromatography.[2,118,119]

been reviewed in detail by Armstrong.[2] He has also pointed out the assumptions made in those derivations and has noted that surfactant concentrations in large excess of the cmc, the addition of organic modifiers, and other solution components may result in deviations from these expressions. For example, the addition of an organic modifier gives rise to a system in which micelle structure, the cmc, solute micelle interactions, and solute stationary-phase interactions are disturbed in often unpredictable ways.

Quite often these types of systems will not adhere to the derived three-phase model. A specific example occurs in the case of an ionic micellar mobile phase and a like-charged solute. Rather than no observed effect upon the retention of these species which was predicted from a presumed lack of substrate micelle interaction, the micellar mobile phase actually retards their elution. The mechanism of this interaction is proposed to be the result of an excluded volume effect arising from the charge on the micellar phase actually forcing the like-charged substrate into the stationary phase in greater amounts than dictated by the intrinsic partition coefficient. This example serves to point out that a full theoretical description of these systems remains to be carried out.

Micelles exhibit enhanced selectivity which permits their use in separations to begin with. On the other hand, they have yet to achieve the efficiencies observed in traditional chromatographies.[2,4-6,118,119] Dorsey et al. have examined these systems and found that the addition of a small amount of organic modifier (i.e., *n*-propanol) gives rise to enhanced efficiencies which can equal those observed in classical systems.[129] As pointed out by Armstrong,[2] these mixed organic micelle systems are complex and probably exhibit efficiencies approaching normal chromatographies due to disruption of the micellar system, thereby becoming analogous to ion pair chromatography. Recent work points to slow mass transfer between the stationary phase and the aqueous phase as a primary cause of the reduced efficiencies. A number of workers have proposed carrying out micellar separations at higher temperatures and concentrations of surfactant slightly above the cmc to enhance this mass transfer process and achieve the equilibrium status necessary for improved capacity.[129,130] Dorsey suggests that the addition of small amounts of organic modifier results in the solvation of the stationary phase, thereby increasing the rate limiting mass transfer and resulting in improved efficiencies.[119] While it has been demonstrated that the addition of small amounts of various alcohols can significantly increase the efficiency of micellar chromatographic separations, these ill-defined systems have not demonstrated improved separation efficiencies over traditional separations methods.

Given that micelle chromatographic separation efficiencies are at best equal to those achieved in traditional separations, what are the attractions for the use of this technique? Clearly, unique and modifiable selectivities obtainable in these systems is a major advantage. Khaledi has examined the selectivities of a number of micellar mobile phases and contrasted the results with traditional hydroorganic systems to find that the micelle systems do indeed offer selectivity advantages.[131] Landy and Dorsey have examined both the efficiencies and selectivities of anionic, cationic, and nonionic micellar mobile phases. Their results demonstrate how selection of the surfactant can alter the observed selectivity of the separation. In their work, the elution order of acetophenone and phenol is reversed on going from anionic SDS to cationic cetyltrimethylammonium bromide (CTAB). Phenol may well exist in a deprotonated form in the cationic micelles which are known to attract hydroxide ions to their surface as counterions.[7] It was also demonstrated that the cmc of the micelle system can be determined via chromatographic results. The array of possible interaction mechanisms of substrates with micelles provides the interaction possibilities which result in the observed selectivity advantage.

Micelles can also offer the possibility of enhanced detection in separations. These systems can enhance fluorescence and can afford stabilized room temperature phosphorescence.[2,114,119] Even micelle-enhanced chemiluminescence is a possibility. Another area of enhanced detection involves electrochemical detection. Traditional gradient separations often exhibit unstable electrochemical baselines due to continuous electrical double layer alterations and varying solution resistance as the gradient changes. Gradient micelle separations can be detected electrochemically because a fundamental property of micelles results in stable bulk-phase conditions.[18] That property is that the concentration of free monomer remains constant above the cmc with additions of further surfactant. Thus, as the concentration of surfactant is increased during the gradient, the concentration of free monomer remains unchanged with excess surfactant going to increase the numbers of micelles and the volume of the micellar phase.[132] This is a unique advantage of micellar separations.

The use of micelles in separations can provide many other advantages over traditional separations. Micelles can be a low cost substitute for organic mobile phases both at purchase and at disposal. Micelles are less toxic than most organic media and can offer improved selectivity as mentioned earlier. Gradient elution is more rapid due to less time required between runs for reequilibration. This results directly from the constancy of free monomer concentration at surfactant levels in excess of the cmc. That is, the stationary phase is saturated with adsorbed surfactant at all micelle concentrations. Nonionic micelles have been reported to deviate from this behavior at higher concentrations.[2] In fact, Borgerding et al. have examined the retention mechanisms of a homologous series of alkylbenzenes in nonionic micellar mobile phases and found that unlike other micelle systems, direct micelle-stationary phase substrate partitioning is important.[133] Finally, micelles are easily prepared, reproducible, and afford direct injection of complex matrices such as serum.[114] The use of micelles in the mobile phase can obviate the need for protein precipitation and

removal before serum analysis can be carried out, which is certainly the case with traditional reverse-phase HPLC. Furthermore, the use of surfactants can even free analyte from any interfering proteins or particles upon which it may be adsorbed, thus giving rise to increased recovery and more complete analysis.[114] These types of benefits can amount to large savings in time and expense whenever multiple samples must be run. It can be expected that greater and greater use of these separation systems will be observed in this type of high-volume sample throughput situations in the future.

Hinze and Armstrong have nicely summarized recent analytical separations applications,[118,119] and they are not repeated here. Several works have appeared since those references including a study of reversed micelle solutions as the mobile phase in normal chromatography. It was determined that the reversed micelles eliminated the variations in retention with varying mobile-phase water content although a loss in efficiency was observed.[134] Kim and Brown have reported the use of micellar-mobile phases on a polyvinyl alcohol (PVA) column for the separation of adenosine from theobromine in cacao[135] and the study of the retention behavior of nucleosides.[136] The PVA column afforded a much wider pH range than traditional reverse-phase columns while micelles gave more rapid separation times. Berthod et al. studied the retention of various solutes on five stationary phases with two micellar-mobile phases. They determined that substrate-stationary-phase partitioning is a function of the nature of the stationary phase and is not strongly influenced by the micellar-mobile phase.[137,138]

This necessarily brief overview of some of the important features of micelles in separations has not addressed some of the relatively important areas of separations where micelles have been tried and have shown advantage. Planar chromatography can derive many of the same benefits from the use of micelles that are observed in HPLC applications.[2,118,119] Gel filtration separations were the initial systems studied involving the use of micelle-mobile phases and can provide interesting alterations of predicted elution behavior.[2] Micelle-enhanced ultrafiltration is a relatively new technique wherein organic substrates are solubilized within a micellar phase prior to filtration. When the solution is passed through a very small pore-size filter, the micelles are retained along with the organic substrate thereby concentrating that substrate for subsequent analysis.[119] Finally, in addition to the analytical benefits discussed earlier,[114] the emerging area of biotechnology has received some help in the form of reverse micelles for recovery of the products of protein production. Amstrong and Li demonstrated that a liquid membrane permeated with reverse micelles can be used to selectively recover a variety of proteins.[139] The selectivity can be modulated via the solution conditions on the receiver side of the membrane. Hatton has further reviewed these techniques with respect to extractions of proteins and amino acids.[140] This particular area may well provide the next avenue for rapid growth of the use of micelles in both analytical and preparative situations as a logical extension of that which has gone before.[114,118]

3. Micellar Electrokinetic Chromatography

Electrophoresis has been and continues to be a critical method for the analysis of proteins, peptides, oligonucleotides, and other biologically important materials.[141] Recently, the extension and miniturization of this technique to afford electrophoretic separations in small-diameter open tubes has been demonstrated to be as useful in these analyses as are classical electrophoretic methods.[142-147] Although originally proposed and demonstrated in open glass capillaries of 200 to 500 μm internal diameter by Virtanen in 1974,[148] the technique of capillary zone electrophoresis (CZE) was certainly reduced to practice by Jorgenson and Lukacs[149-152] to the dimensions and separations extant in the literature today.

As originally proposed, CZE is a superb technique for the separation of ionic species in that only charged molecules migrate through the capillary at different rates. However, neutral species coelute at a rate equal to the migration of the mobile phase; a process alternately called electroosmosis or electroendosmosis. This solvent flow is the result of high voltage across the capillary and is a function of the double layer established along the capillary wall.[142-145] If strong enough, anions which are electromigrating towards the anode will be swept through the capillary to the cathode by this solvent flow. Thus, the overall order of elution is cations, then neutrals in one peak, followed by anions.

In 1984, 10 years after the initial report by Virtanen,[148] Terabe et al. introduced the use of micelles in CZE.[153] For the same reasons which micelles exhibit excellent selectivity in traditional separations, they provide for enhanced separations in CZE. That is the differential partitioning and selective interactions of various substrates with the micellar phase results in improved separations for both neutral and ionic species. These processes are most readily apparent when the substrates of interest possess finite water solubility of their own. Totally hydrophobic substrates tend to coelute with the micelle velocity as they are only resident within that phase. Thus, separations of these materials require either very long columns, modified capillaries, high voltages, or perhaps all of these adjustments.[143]

As pointed out by Cohen et al.[143] and Burton et al.,[154] MECC exhibits a limited peak capacity. The elution "window" lies between that of an unretained neutral species, t_o, and that of a totally retained species, t_m, which is also the retention time of the micelle. Burton et al. have reported t_o and t_m values for several micellar mobile phases at several voltages (Table 4).[154] If the number of peaks which can be eluted within the available window is given by

$$n = 1 + N/4(\ln(t_m/t_o)) \quad (2)$$

and easily achievable values of N are assumed to be 200,000,

Table 4
Values of t_o and t_m with Three Surfactants at Several Voltages

Surfactant	Voltages 15 kV	20 kV	30 kV
Sodium dodecyl sulfate			
t_o	16.8	12.0	7.0
t_m	51.6	36.2	19.7
Dodecyltrimethylammonium chloride			
t_o	16.8	11.8	6.2
t_m	39.6	28.2	14.4
Cetyltrimethylammonium chloride			
t_o	23.0	17.2	10.2
t_m	64.0	44.4	24.2

Data, in minutes, were taken from Burton, D. E., Sepaniak, M. J., and Maskarinec, M. P., *J. Chromatogr. Sci.*, 25, 514, 1987. With permission.

then the number of peaks attainable within the window listed in Table 4 for SDS at 20 kV would be 124! Their work goes on to suggest that capacity and selectivity can be tailored by the choice of surfactant within limits established to avoid excessive Joule heating and solubility problems. Interestingly, when cationic micelles are used, the direction of the solvent flow is reversed and moves from the cathode to the anode.[155] This results from adsorption of the cationic surfactant upon the capillary walls, altering the net charge from the normal negative silanol groups to the positive nature of the adsorbed surfactant. Normally, this is easily accommodated by reversing the power supply polarity. The limited elution window remains a (minor) concern even in these systems although cationic MECC appears to have greater capacity for more hydrophobic substrates. In any case, just as in traditional micellar chromatography, selectivity often obviates the apparent problem of limited capacity and elution window.

Unlike micellar chromatography, the utility of these micellar systems for enhanced detection has not been reported in MECC. Given the small amounts of sample, this would appear to be a natural advantage of micelles in these separations. It may well be that detection is sufficiently rigorous in these capillaries that advantages due to micelles have not been observed or recognized. Yet, micelle-enhanced fluorescence, room temperature phosphorescence, and chemiluminescence would seem to be useful in these systems as smaller and smaller samples are examined. Extremely sensitive electrochemical detection has been reported in these systems and successfully used to detect a series of borate-complexed catechols.[156]

It is clear that these systems will continue to increase in utility with the onset of commercial instrumentation[157-158] and with further study of the specific substrate micelle interactions which will increase the effectiveness of these mobile phases in these elegant separations. Karger has extended MECC to the analysis of oligonucleotides[143] and to the capillary version of SDS polyacrylamide gel electrophoresis.[159] In fact, the separation of dansylated methylamine from dansylated methyl-(d_3)-amine has been carried out using micelles as a psuedo-stationary phase within the capillary.[160] The almost universal utility of micelles in this area is certain to maintain this as one of the most rapidly growing fields of micelles in analytical chemistry.

IV. SUMMARY

The utility of micelles in analytical chemistry has grown since the initial review of the area in 1976.[6] They have been used in almost every avenue of analysis with demonstrated advantages.[4,119] These advantages result either from micellar catalysis of analytically important reactions or micellar inhibition of deleterious effects such as fluorescence quenching and phosphorescence quenching.[5] Other areas of demonstrated benefit include titrimetric analyses, spectral analyses of many types, electrochemical analysis by selective ion masking, traditional separations through both enhanced detection capabilities and unique selectivities, and generic separations of neutrals by MECC. Even highly instrumented methods of analysis can benefit from the use of micelles. For example, the utility of micelles in Raman for removal of interfering molecular luminescence by the same route used for micelle-stabilized room temperature phosphorescence. Many of the uses of micelles in analysis are summarized in Table 5. It is worth noting that several important references concerning flow injection analysis, chemiluminescence, and micellar chromatography have been added to this table in proof. While several of these articles were in press during the preparation of this review, their content is certainly germane to the subject at hand and therefore they are included in this review (i.e., References 164 to 170). Clearly, the use of micelles in analytical chemistry is on the verge of becoming ubiquitous.

The growth in the use of micelles in analytical chemistry will continue especially in those countries where instrumentation is restricted or unavailable for whatever reason. The emphasis upon chemistry rather than instrumentation to increase analytical merit is reasonable in those areas and should be expected. There is a major effort concerning spectral effects of micelles in China where several reviews[161-163] and a number of individual articles have recently been published.[82,83,88,89] Another major center for this area of analytical micellar applications is in Spain.[9,81,93,104] Much work has been carried out in France in the area of micelles in electrochemistry[30,48-50] and Italy regarding titrations and general analytical utility.[4,76,77] Of course Japan is contributing much to this area of study[64,66,85-87,90,98] as is the rest of the scientific community around the world. This area of study, micelles in analytical chemistry, has truly become a universal effort with each discovery in one group supporting those of others and leading the

Table 5
Micelles in Analytical Chemistry: A Technique-Oriented Approach

Technique	Description	Ref.
Spectroscopy	General reviews	4, 6
UV-Vis absorbance	Overview of dye surfactant interactions	9
	Triphenylmethane dye-metal chelate interactions	80
	Micelle solubilization and spectral enhancement	64
	Anionic surfactant in the analysis of Zr	83
Fluorescence	An analytical review	92
	Avoidance of the requirement to remove oxygen	95
	Summary of metal chelate-micelle fluorescence	93
	Sodium taurocholate micelles with heavy metal ion effects	101
Phosphorescence	An overview	103
	Polycyclic aromatic hydrocarbons	102, 103
	Metal chelates	104
Chemiluminescence	An analytical review	164
	Copper determination in tap water	110, 111
	Micelles and the Lucigenin hydrogen peroxide system	165
	Reactive OH^- counterions and chemiluminenscence	166
Flow injection analysis	An analytical review	167
	of neodymium	65, 168
	of europium(III)	66
	of terbium(III)	87
	of silicon	88
	of nickel	89
	of beryllium	90
Other spectroscopies		
Raman	Reduction of luminescence interferences	113
Atomic	Absorption	16, 17
	Emission	112
EPR	A brief overview	15, 31
NMR	A brief overview	15
Separations	General reviews	2, 4-6, 114, 118, 119, 169
Analytical extraction	Increased sensitivity	120 (118)
Pseudophase chromatography	General reviews	2, 114, 118, 119, 169
	Biotechnology applications	114, 139, 140
	Effects of temperature	129, 130
	Effects of stationary-phase type	137, 138
	Effects of varying nonionic surfactant type	133
	Effects of different surfactant-charge type	7, 169
	With polyvinyl alcohol columns	135, 136
	With organic modifiers	2, 129, 169
	Selectivity advantages	131
	Reverse phase (inverse micelles)	134
	Polycyclic aromatic hydrocarbons	170
Micellar electrokinetic chromatography (MECC)	Reviews of capillary electrophoresis	141, 142, 145
	Available migration window	143, 154
	Effects of cationic surfactant	155
	Electrochemical detection (catechols)	156
	Oligonucleotides	143
	Polyacrylamide gel-filled capillaries	159
Micelle-enhanced ultrafiltration		119
Titrations	A general review	4
	Review of dye surfactant interactions	9
	Micelle solubilization vs. nonaqueous titrations (barbituates)	63
	Thermometric titrations	79
Electrochemistry	A general review	3, 4
	Redox studies in mimetic membranes	27
	Energy conversion studies	32, 40
	Electrocatalysis of the reduction of allyl halides	41, 42
	Diffusion coefficient measurements	28, 44, 46
	Electrochemical reversibility, analysis of BiDCTA	51
	Micelle-solubilized mediated titrations	57
	Electrochemical masking	60, 61

way to new and more unique ways to utilize these microheterogeneous systems. It will surely be interesting and important to watch and take part in the future of this research.

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