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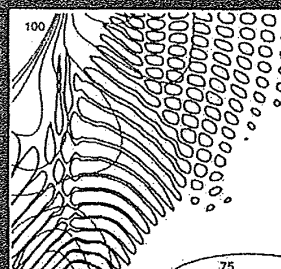
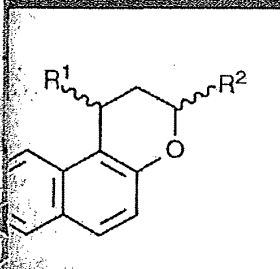
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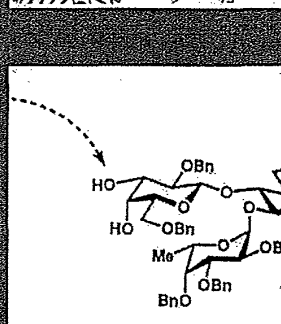
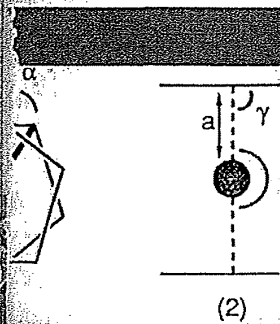
Volume 23 Issue 6

Pages 363-442

December 1994



Benzotriazole-mediated Arylalkylation and Heteroarylalkylation
By Alan R. Katritzky and Xiangfu Lan 363

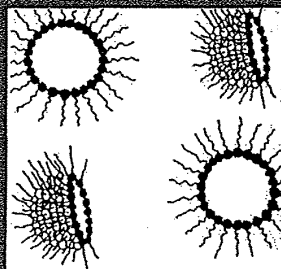
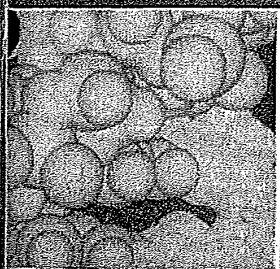


LIVERSIDGE LECTURE. The Dynamics of Photodissociation
By Richard N. Dixon 375

Molecular Mechanics Force Fields for Cyclopentadienyl Complexes
By Brice Bosnich 387

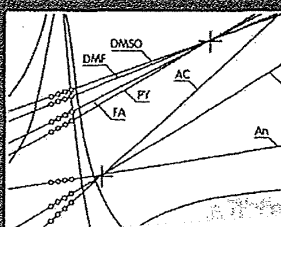
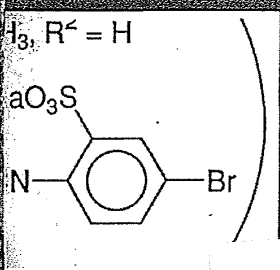
HAWORTH MEMORIAL LECTURE. Experiments Directed Towards Glycoconjugate Synthesis
By Tomoya Ogawa 397

Pericyclic Key Reactions in Biological Systems and Biomimetic Syntheses
By Ulf Pindur and Günter H. Schneider 409



Surfactant Systems: Their Use in Drug Delivery
By M. Jayne Lawrence 417

Biological Activity, Reactivity, and Use of Chromotropic Acid and its Derivatives
By Jan Duda 425



Mechanistic and Structural Investigations Based on the Isokinetic Relationship
By Wolfgang Linert 429

1994 Indexes 439

ISSN 0306-0012

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Surfactant Systems: Their Use in Drug Delivery

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1 Introduction

Molecules or ions which are amphiphilic, that is, contain both a hydrophobic and hydrophilic part, in aqueous solution frequently assemble at interfaces and self-associate in an attempt to sequester their apolar regions from contact with the aqueous phase. This self-association gives rise to a rich variety of phase structures (Figure 1). Aggregation is not, however, just limited to aqueous solution; it is sometimes observed in non-aqueous polar solvents such as ethylene glycol and non-polar solvents such as hexane (in the latter case giving rise to inverse structures).

Over the years several of the phase structures produced by surfactants have been of interest to the pharmaceutical scientist, either as drug vehicles/carriers or more recently as targeting systems. In the former application the surfactant system takes no part in the biodistribution of the drug it carries, acting purely as the vehicle. In the second case the surfactant system in some way 'conveys' the drug to the desired (or target) site in the body and deposits it. Targeting can take one of two forms; namely 'passive' targeting which relies on the natural biodistribution of the carrier, or 'active' targeting in which the carrier is in some way directed to the desired site, frequently by the use of targeting ligands expressed on the surface of the carrier. Both types of targeting have the advantage of protecting the body from any unwanted side-effects of the drug, while at the same time achieving the desired concentration of drug at the target site.

By far the majority of work examining the potential of surfactant systems in drug delivery has explored their use as drug carriers; for example non-ionic micelles have been widely investigated as a means of producing a clear stable solution of a poorly water-soluble drug suitable for intravenous or oral administration.^{1,2} However, during the past twenty years or so, as the importance of drug targeting has been realized, a number of surfactant systems, such as phospholipid or non-ionic surfactant vesicles, have been extensively investigated as targeting systems.³

Despite all the research into the potential use of surfactant phase structures for drug delivery, such phase structures have not made much of an impact on the formulation scene; there are

only a few marketed preparations that could be considered to be drug-containing surfactant systems in either the United Kingdom or the United States. Consequently, the true potential of surfactant formulations, particularly of non-ionic surfactants, has perhaps not been fully realized. In order to appreciate the potential and also the limitations of such systems an understanding of the phase behaviour of surfactants is essential. The following account therefore describes the phase behaviour of surfactants with reference to their physico-chemical properties relevant to their use as drug delivery systems. It also details some of the work performed to date investigating the use of surfactant systems – in particular, those produced from the less toxic non-ionic surfactants – for drug delivery.¹

2 Phase Behaviour of Surfactants

2.1 Equilibrium Phase Structures

Although surfactants self-associate in a wide variety of solvents, their state of aggregation varies considerably between solvents (Table 1). As water or a buffered aqueous solution is the usual continuum for most drug delivery systems, it is important to understand (and predict) the range of equilibrium phase structures commonly encountered in such solutions. Mention will be made of the phase structures encountered in other solvents where appropriate.

When a surfactant is dispersed in water just above the limit of its aqueous solubility (*i.e.* above its critical micelle concentration, cmc) it generally aggregates, depending upon its molecular geometry,⁴ into one of four types of structure, namely the isotropic micellar phase and the liquid crystalline hexagonal, lamellar, and cubic phases. The aforementioned phases, with the exception of the lamellar phase, can either be in a normal or reverse orientation. Recently, in addition to these commonly encountered phase structures, there has been an increasing number of more unusual aggregates, such as helical bilayers⁶ and fibre gels⁷ reported.

Upon increasing the surfactant concentration well above the cmc there are generally changes in aggregate or phase structure. The order of phase structures formed upon increasing surfactant concentration generally follows a well-defined sequence (Figure 2) with a 'mirror plane' through the lamellar phase, such that normal phase structures can be considered to be 'oil-in-water', while reverse structures can be thought of as 'water-in-oil'.⁸ Most surfactants, however, exhibit only a portion of this sequence, depending upon the aggregate type initially formed at the cmc and the resulting interaggregate forces experienced.⁹ Although the same phase structures are observed in other non-aqueous polar solvents, the sequence of phases is sometimes very different and appears to depend both upon the molecular geometry and the nature of the polar head-solvent interactions.

2.1.1 Implications for Drug Delivery

An understanding of the phase behaviour of surfactants is essential for the efficient use of surface active systems in drug delivery. For example, after introduction into the body the surfactant system may, depending upon its route of administration, undergo a large dilution. If the surfactant is diluted below its cmc, precipitation of transported drug may occur. This precipitation may have very serious consequences, especially if

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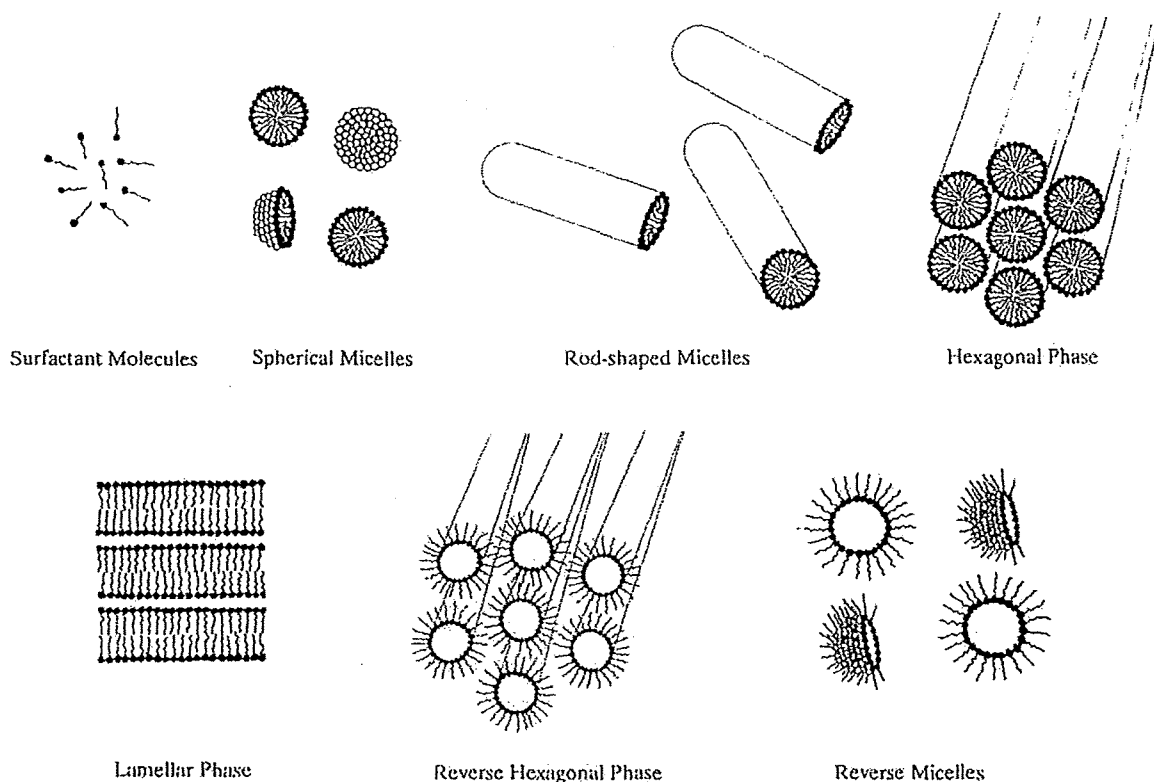


Figure 1

Table 1 Self-association in solvents

Class of solvents	Example of class	Type of Aggregate
Class A	Water, glycerol, ethylene glycol	Normal
Class B	Hexane, benzene, cyclohexane	Reverse
Class C	Methanol, ethanol	No aggregate formation

the drug is being administered intravenously. Ideally therefore the cmc should be as low as possible in order to avoid such problems. Surfactants that form lamellar phases at their cmc generally do so at much lower concentrations than those surfactants which initially form micelles. Since non-ionic surfactants generally exhibit lower cmc's than ionic surfactants they are preferred for the purposes of drug delivery, especially when a micellar solution is being investigated as the drug delivery vehicle. In a similar vein, if a concentrated surfactant solution is administered it may experience a sufficient dilution to induce a phase change, say for example from an hexagonal to a micellar phase. As the drug-carrying capacity of each aggregate type may differ, such a phase change could have very serious implications

such as dose dumping within the body. When considering using a surfactant system as a drug delivery vehicle it should also be borne in mind that phase transitions can also be induced by a change in temperature and that normal human body temperature is typically 12 degrees above ambient. Other problems to be aware of are hysteresis effects. These are particularly common in cubic phases and may have important consequences for drug delivery. For example, certain cubic phases have been shown to be pseudo-stable for very long periods at temperatures at which some other form of aggregate would normally be formed.⁶

A knowledge of the various biological surface-active agents which the surfactant aggregate may encounter *in vivo* is also essential as these may alter or even destroy the aggregate. For example the endogenous micelle-forming bile salts encountered in the small intestine have been shown to solubilize orally administered liposomes, thereby releasing any water-soluble solute trapped inside the carrier.

2.3 Modified Phase Structures

In addition to the equilibrium phase structures mentioned above, there are a few non-equilibrium and modified surfactant phase structures that are currently finding application in drug delivery.

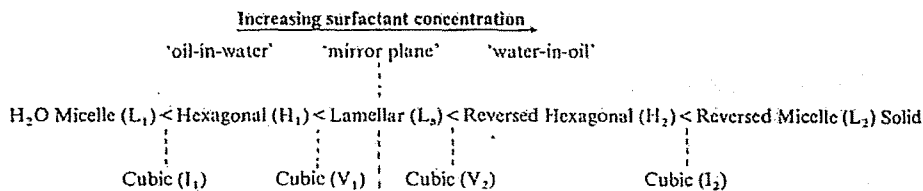


Figure 2 Idealized phase sequence in surfactant-water systems. (Modified from reference 6; terminology as in reference 7.)

2.3.1 Vesicles

Vesicles are generally formed by dispersing lamellar phases in an excess of water¹¹ (or non-aqueous polar solvents such as ethylene glycol, dimethylformamide), or in the case of reversed vesicles in an excess of oil.¹² The resulting vesicles are approximately spherical structures dispersed in a water or an oil continuum. Vesicles produced from phospholipids have been widely investigated as drug delivery vehicles. Unlike the phase structures mentioned earlier, however, these non-equilibrium structures are prepared using methods such as sonication and will eventually re-equilibrate back into the lamellar phases from which they originate.¹¹ This inherent instability has caused considerable problems with the wide-spread commercial exploitation of vesicular delivery systems. For a few surfactants, however, the vesicular phase is an equilibrium structure; for example, the ionic ganglioside GM3, a glucosidic amphiphile of biological origin, forms vesicles spontaneously in water,¹³ while some combinations of non-ionic surfactants have been shown to form reversed vesicles spontaneously.¹⁴

2.3.2 Polymerized Aggregates

Attempts have been made to use polymerization to stabilize various nascent phase structures, for example micelles,¹⁵ cubic phases,¹⁶ and vesicles.¹⁷ With the exception of micelles (which as yet it has not proven possible to polymerize) polymerization of these structures gives aggregates exhibiting the significant advantage that they do not suffer break down upon dilution *in vivo*. However, because of their size (ranging from tens to hundreds of nm) these aggregates can cause problems as they are not readily excreted from the body; hence such systems will probably have limited clinical use, although they may have a use in oral administration. In an attempt to overcome the problem, biodegradable polymerized aggregates are presently being investigated.¹⁸ When preparing drug-containing polymerized aggregates it is important to choose the appropriate stage for drug addition; adding the drug before polymerization may cause the drug to be irreversibly bound in the aggregate, while addition of the drug after polymerization may lead to low levels of entrapment.

2.4 Drug Aggregates

A number of drugs are themselves amphiphilic and may aggregate into various structures, most frequently small-micellar type structures.¹ In these cases the drug aggregate could act as its own vehicle, if the drug loading were not too high. It has been postulated that the formation of vesicles consisting of pure drug (pharmacosomes) should also be feasible.¹⁹ Unfortunately most drugs are not lipophilic enough to form vesicles easily without derivatization with materials like fatty acids.¹⁹ However with certain drugs it may be possible to produce vesicles over a narrow pH range using the appropriate ratio of amphiphilic salt to free drug. The tight control over pH that would be necessary, however, means that such vesicles are unlikely to provide useful drug delivery systems. An alternative approach to producing pharmacosomes has recently been reported in which a biodegradable micelle-forming drug conjugate has been synthesized from the hydrophobic drug adriamycin and a polymer composed of polyoxyethylene glycol and polyaspartic acid.²⁰ This approach has the benefit that while it may be possible to dilute out the micelle, the drug will probably not precipitate because of the water solubility of the monomeric drug conjugate. Since neither of these types of derivatized drug structures consist of drug alone, they can therefore not be considered to be true drug aggregates.

2.5 Influence of Oil

When oil is added to a binary mixture of surfactant and water a whole variety of phase structures may be formed. Several of these structures currently have a use in drug delivery, for

example microemulsions, macroemulsions, and multiple emulsions.¹ Others such as self-emulsifying systems²¹ and vesicles encapsulated in water-in-oil emulsions are at present under investigation.²²

3 Choice of Phase Structure for Drug Delivery

When choosing a phase structure for drug delivery a number of factors need to be considered, in particular, how the physico-chemical properties of the phase structure relate to the intended application. If, for example, a surfactant system is required for topical use the phase structure chosen should be of sufficiently high viscosity to enable the preparation to be retained on the skin surface, while at the same time allowing it to be spread readily over the surface of the skin. In contrast, if a system is intended for administration intravenously it should be of sufficiently low viscosity not to cause pain upon injection. Another important factor to be considered is the capacity of the aggregate for the drug to be incorporated. Micellar solutions, by virtue of low surfactant concentrations, generally exhibit the lowest capacity for drug, while in contrast cubic and other liquid crystalline phases can frequently tolerate very high drug loadings.^{23,24} Recently it has been realized that the toxicity of a particular surfactant may depend upon the nature of its aggregate. For example, the same surfactant has been shown to exhibit a significantly reduced toxicity when present in a vesicular as opposed to a micellar solution.

Table 2 gives some of the physico-chemical characteristics important for formulation purposes together with the possible pharmaceutical applications of each phase structure. It should be noted that while Table 2 gives the average properties of each phase, the variations in each case may be quite significant. For example, while solutions containing spherical micelles generally exhibit low viscosities, those containing long rod shaped micelles frequently exhibit very high viscosities. Similarly, cubic phases can display a wide range of stiffness; some samples are as hard as plexiglass, while in others the phases are sufficiently flexible that they almost flow.⁶

It is important when considering the use of surfactant phase structures as delivery vehicles to remember that a surfactant aggregate cannot be considered an *inert* carrier, and that the drug and indeed other additives such as preservatives and flavourings* may (depending upon the amount present) dramatically alter the cmc and, in some cases, the type and range of aggregates formed. Unfortunately very little work has been performed in this area and is difficult to predict the effect of a drug (or indeed any other additive) on a phase structure as it is expected to vary according to whether the additive (a) is water soluble, (b) adsorbs at the aggregate surface, (c) co-aggregates with the surfactant, or (d) resides in the interior of the aggregate. Evidence suggests, however, that the phase structure experiences the most disruption when the additive is itself surface active. For example, the presence of the drug lignocaine hydrochloride at concentrations greater than about 5 wt% converts the cubic structure formed from 10 wt% monolein in water into a lamellar phase.¹⁰ The influence of the presence of drug is further complicated because most drugs are administered as salts, hence the amount of amphiphilic salt to lipophilic free drug varies according to pH. Consequently the effect of the drug on the phase structure may vary with the pH of the surrounding environment. This effect is more likely to be significant if ionic surfactants are used. Yet another complication is that if the drug promotes a phase transition, this transition may conceivably be reversed as the release of a surface-active drug from the aggregate proceeds.¹⁰ This phase reversal may lead to two different patterns of drug release.

* Flavourings are very important if surfactants are to be given orally; surfactants do not taste very pleasant. Also, because of their effect on membranes, surfactants may numb the patient's mouth.

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