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REACTIVITY CONTROL IN MEMBRANE MIMETIC SYSTEMS

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Abstract - Aqueous and reversed micelles, microemulsions, monolayers, bilayers, vesicles, host-guest systems and polyions - collectively termed as membrane mimetic systems - provide unique environments for reactivity control. Properties of the different membrane mimetic systems, kinetic theories governing reactivities therein, and the application of reactivity control in synthetic chemistry, stereochemistry and isotope enrichment will be discussed.

INTRODUCTION

Physical organic chemists have long recognized the important role the reaction media plays in controlling rates, product distributions and stereochemistry. Attention has been focussed recently on aqueous and reversed micelles, microemulsions, monolayers, bilayers, vesicles, host-guest systems and polyions as reaction media (Ref. 1). These systems, often referred to as organized assemblies or membrane mimetic agents (Ref. 2), have many functions in addition to merely providing unique reaction media. They are expected to (a) solubilize, concentrate, compartmentalize, organize, and localize reactants and products; (b) maintain reactant gradients; (c) alter dissociation constants, oxidation and reduction properties; (d) stabilize (or destabilize) reactants, intermediates, transition states, and products; (e) affect chemical pathways and rates; and (f) separate products and/or charges (Ref. 3). Naturally, not all membrane mimetic agents fulfill all these expectations or are useful in all applications. Judicious selection of a given system for a given application requires a sufficient understanding of the properties of membrane mimetic agents themselves and those of the substrate interactions therein. Much information has been obtained through the kinetic investigations of reactions occurring in the environment of organized assemblies. Although kinetic treatments have been described for reactions occurring in aqueous micelles they appear to be generally applicable to all systems. Concurrent with kinetic investigations, membrane mimetic agents, particularly micelles, have been used advantageously for controlling reaction pathways. The current state of art in reactivity control in membrane mimetic systems will be the subject of this presentation. Subsequent to a brief description of the different membrane mimetic systems, kinetic treatments and applications will be discussed.

MEMBRANE MIMETIC SYSTEMS

Membrane mimetic agents can conveniently be divided into those assembled from surfactants, those acting as hosts, and those having ionized groups on polymer backbones (Ref. 2). Aggregation behavior of surfactants depends upon their chemical structures, on the nature of the media and on the method of preparation. Opposing forces of repulsion between the polar headgroups and of association between the hydrocarbon chains of the surfactants are responsible for aggregation in water. Dipole-dipole interactions provide the driving force for association in apolar solvents. Formation of reversed micelles requires at least traces of water. These systems can be considered, therefore, to be surfactant entrapped water pools in hydrocarbon solvents. Increasing the concentration of entrapped water, i.e., the size of the water pools, at a given surfactant concentration results in the formation of larger aggregates. If the water concentration is further increased, water-in-oil, w/o, microemulsions begin to appear. Spreading an organic solution of a surfactant on water results in monolayer formation at the air-water interface. There are two types of bilayers. The first type, the planar black (or bilayer) lipid membrane, the BLM, is formed on the orifice of a small pinhole. The second type, the closed bilayer vesicle, is formed by the swelling of lipids.

Bilayer vesicles are smectic mesophases of phospholipids (liposomes) or surfactants (surfactant vesicles) with water interspaced between them.

Figure 1 is a schematic representation of the structures formed from surfactants. These structures are, it must be realized, gross oversimplifications. There are substantial morphological differences between the different classes of membrane mimetic agents. Aqueous micelles are spherical entities having 30-60 Å diameters. Reversed micelles have similar dimensions. Micellar dimensions can

appreciably increase upon the solubilization of large molecules. Microemulsions and vesicles are considerably larger than micelles. Their diameters range between 50-1,000 Å and 300-5,000 Å, respectively. Consequently, water-in-oil, w/o, microemulsions contain considerably larger water pools than reversed micelles. Cavities provided by crown ethers, cryptands, cyclodextrins, and related hosts are small by comparison. They complex uni and divalent metal ions, NH_4^+, and small aromatic compounds. Dimensions of monolayers depend on the surface area of the subphase and on the surface pressure; BLMs are confined within a relatively small pinhole; and weight averaged molecular weights of polyions can be several million.

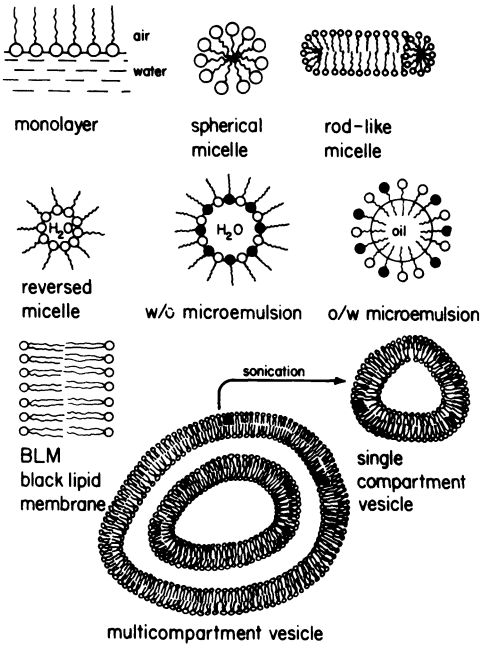


Fig. 1. An oversimplified representation of organized structures of surfactants.

The inherent stability of a given membrane mimetic agent is an important consideration. For all practical purposes polyions, synthetic and naturally occurring hosts are stable species. On the other hand, one can only talk about kinetic stabilities of micelles, microemulsions and vesicles. Micelles are in dynamic equilibrium with monomeric surfactants. The timescale for the release of a single surfactant molecule and its subsequent reincorporation, i.e., that for the dissociation of the micelle, is in the order of microseconds. The stepwise dissolution of micelles to monomers and the subsequent reassociation, i.e., the dissolution of micelles, occurs on the millisecond timescale. Behavior of microemulsions is quite analogous. Conversely, surfactant residence times in vesicles are of the order of minutes to hours. Micelles, microemulsions and vesicles can remain stable for weeks subsequent to their formation. Monolayers, under appropriate conditions, can be kept for an equally long time. BLMs, however, rarely last longer than a couple of hours.

Phase transition is an important property of monolayers, BLMs and vesicles. Depending on the surface area - pressure isotherm, monolayers may be in a gaseous, fluid or solid state. Thermotropic phase transitions of BLMs and vesicles involve changes in the arrangements of lipids without altering the gross structural features of the bilayers. Below the phase transition temperature, the surfactant constituents of BLMs and vesicles are in highly ordered "solid" states, with their alkyl chains in all-trans conformations. Above the phase transition temperatures, lipids become fluid as the result of gauche rotations and kink formation. Micelles and host systems do not usually have temperature induced phase transitions. Polyions can undergo, however, conformational changes which may result in altered secondary and tertiary structures. There are additional motions of surfactants within the BLMs and vesicles. Surfactants may undergo segmental and rotational motions, lateral diffusion and flip-flop.

Recognizing the need for enhanced stabilities and controllable permeabilities leads to the development of polymeric surfactant vesicles (Ref. 4-8). Large numbers of anionic, cationic, zwitterionic and redox active polymerizable surfactants have been synthetized, purified and characterized (Ref. 4-8). Depending on the position of the double bond, vesicles can be polymerized either across their bilayers or across their headgroups (Fig. 2).

Furthermore, vesicles having double bonds on their headgroups can be "zipped-up" either at their inner or at their outer surfaces or alternatively be polymerized both at their inner and outer surfaces (Fig. 2). Interestingly, sizes of vesicles are retained upon polymerization. Polymeric vesicles are considerably more stable than their unpolymerized counterparts. They show no sign of fusion or deterioration over months. They remain stable in up to 25% alcohol!

Proton and hydroxide ion permeabilities in polymerized vesicles are much slower than those in their unpolymerized analogues. Permeabilities of these ions in dimethyldioctadecylammonium chloride surfactant vesicles are instantaneous. Conversely, hydroxide permeates into polymerized surfactant vesicles with half lives ranging from 5 - 20 min. Significantly, permeation into completely polymerized vesicles is slower than that into vesicles which have been "zipped-up" only on their outer surfaces.

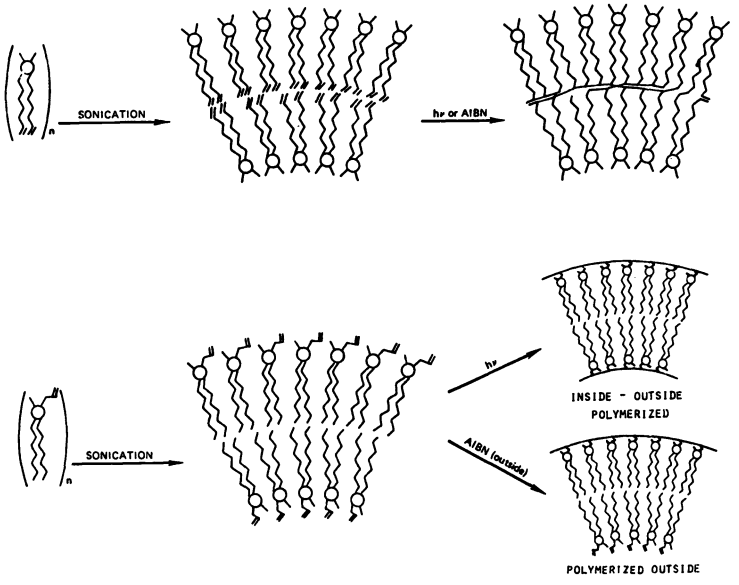


Fig. 2 Schematics of Polymeric Vesicle Formation

KINETIC TREATMENTS OF REACTIONS OCCURRING IN THE PRESENCE OF MEMBRANE MIMETIC AGENTS

Kinetic treatments of reacting substrates are intimately related to the stability of the membrane mimetic system acting as the host. Reactivities in aqueous micelles illustrate this point. Processes occurring at rates comparable to the dissolution or dissociation of micelles (Ref. 9-12) are treated in terms of substrate entry or exit (Ref. 13-14). Alternatively, a stochastic approach can be used (Ref. 15). Processes occurring at timescales slower than the dissolution of dissociation of micelles, on the other hand, are treated in terms of regular rate equations familiar to physical organic chemists.

Most treatments (Ref. 16-20) considers reactivities to be the sums of reactions occurring in the bulk aqueous (R_w) and in the pseudophase provided by the membrane mimetic agent (R_M):

$$R_{Total} = R_w + R_M \qquad (1)$$

For unimolecular reactions, partitioning of only one substrate needs to be considered. Assuming that the substrate does not perturb the equilibria of the system, unimolecular reactions in membrane mimetic systems are described by:

$$\begin{array}{ccc} S + M & \overset{K_S}{\rightleftharpoons} & SM \\ \downarrow k'_w & & \downarrow k'_M \\ \text{Products} & & \text{Products} \end{array} \qquad (2)$$

where S is the substrate, M is the membrane mimetic agent, SM is the substrate - host complex, and k'_w and k'_M are the first order rate constants in the two phases. The observed first order rate

constant for the reaction, k_{obs} is described by:

$$k_{obs} = \frac{k'_w + k'_M K_s[M]}{1 + K_s[M]} \quad (3)$$

Recognizing the analogy between equation 3 and the Michaelis-Menten equation for enzyme catalyzed reactions allowed the treatment of data by:

$$\frac{1}{k'_w - k_{obs}} = \frac{1}{k'_w - k'_M} + \frac{1}{(k'_w - k'_M)K_s[M]} \quad (4)$$

which is similar to the Lineweaver-Burke equation of enzyme kinetics. Equation 4 well describes the kinetics of both inhibited and catalyzed unimolecular processes. Its validity is substantiated by the good agreement between kinetically and independently determined substrate - host binding constants (Ref. 21).

Equation 3 does not adequately describe the kinetics of bimolecular reactions in membrane mimetic systems. Partitioning of both reactants (A and B) between the bulk and the pseudo phase of the membrane mimetic agent has to be considered (Ref. 16,17):

$$(A + B)_w \xrightarrow{k'_w} \text{Products} \quad (5)$$

$$(A + B)_M \xrightarrow{k'_M} \text{Products}$$

where the subscripts w and M refer to the bulk water and the pseudo phase of the host. The overall rate, described by equation 1 is modified to:

$$R_{Total} = k'_M[B]_M[A]_M[M]\bar{V} + k'_w[A]_w[B]_w(1-[M]\bar{V}) \quad (6)$$

where $\bar{V}$ is the molar volume of the host surfactant and the concentrations of reagents A and B are given by material balances:

$$[A]_{Total} = [A]_M[M]\bar{V} + [A]_w(1 - [M]\bar{V}) \quad (7)$$

$$[B]_{Total} = [B]_M[M]\bar{V} + [B]_w(1 - [M]\bar{V}) \quad (8)$$

If the chemical reaction 5 does not affect the partition equilibria:

$$[A]_w \underset{}{\overset{P_A}{\rightleftharpoons}} [A]_M \quad (9)$$

$$[B]_w \underset{}{\overset{P_B}{\rightleftharpoons}} [B]_M \quad (10)$$

the observed second order rate constant for reactions in the presence of membrane mimetic agents is given by:

$$k_2 = \frac{k_M P_A P_B[M]\bar{V} + k_w(1 - [M]\bar{V})}{(1 + (P_A-1)[M]\bar{V})(1 + (P_B-1)[M]\bar{V})} \quad (11)$$

If both A and B bind strongly to the host ($P_A >> 1$ and $P_B >> 1$) and if $[M]\bar{V} << 1$ then equation 11 simplifies to :

$$k_2 = \frac{(k_M/\bar{V})K_A K_B[M] + k_w}{(1 + K_A[M]\bar{V})(1 + K_B[M])} \quad (12)$$

where the binding constants are expressed by:

$$K_A = (P_A - 1)\bar{V} \quad (13)$$

$$K_B = (P_B - 1)\bar{V}$$

Equations 11 and 12 have been found to describe well several bimolecular reactions in aqueous (Ref. 21,22) and reversed (Ref. 23) micelles as well as in surfactant vesicles (Ref. 24,25). The experimental data on the dependence of k_2 on [M] can be used to calculate k_M, K_A, and K_B. For this purpose equation 12 is transformed to:

$$\frac{[M]}{k_2 - k_w} = x + y[M]\frac{k_2}{k_2 - k_w} + z[M]^2\frac{k_2}{k_2 - k_w} \quad (14)$$

where,

$$x = \frac{\bar{V}}{K_M K_A K_B} \quad (15)$$

$$y = x(K_A + K_B) \quad (16)$$

$$z = x(K_A K_B) \quad (17)$$

A plot of the data according to equation 14 gives a value for the intercept, x. This value allows further analysis in terms of rearranged equation:

$$\left[\frac{1}{k_2} - \frac{x}{M}\right]\left[1 - \frac{k_w}{k_2}\right] = y + z[M] \quad (18)$$

which in turn, provides numerical values for y and z and hence for k_M, K_A, and K_B. Figure 3 illustrates the treatment of the kinetic data for the reaction of sodium ascorbate with a stable free radical on the surface of dioctadecyldimethylammonium chloride surfactant vesicles (Ref. 24).

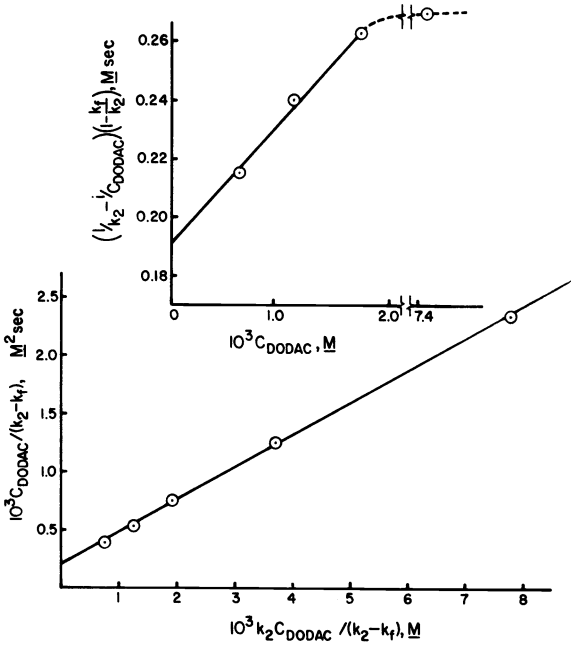


Fig. 3. Kinetic treatment of catalysis in surfactant vesicles according to equation 14.

Useful as it may be, equation 12 is inadequate for treating ionic reactions in the presence of charged micelles and for accounting for electrolyte effects on the rates of micelle catalyzed reactions (Ref. 21). The pseudophase model is apparently insufficient for these systems. There are two recent modifications of equation 11. The first, developed by Romsted (18), incorporates counterion distributions in the micellar Stern layer in unbuffered solutions. The second, the ion exchange model (Ref. 20), allows for estimations of micelle bound and free ions in the presence of buffers and electrolytes.

The model developed by Romsted (18) considers the micellar Stern layer to be saturated by hydrophilic counterions. The degree of ionization (i), reflecting the counterion distribution between the aqueous

and micellar pseudophases, is assumed to be independent of the surfactant concentration and the ionic strength at constant temperature. The hydrophilic ionic reagent, X, and the nonreactive micellar counterion Y, exchange rapidly between the two phases:

$$X_M + Y_w \rightleftharpoons X_w + Y_M \tag{19}$$

where the subscripts M and w refer to micelles and water. The selectivity coefficient for the ionic reagent at the Stern layer,

$$K_{X/Y} = \frac{X_w Y_M}{X_M Y_w} \tag{20}$$

determines the concentration of the hydrophilic reagent in the micellar phase. It is quite feasible, therefore, to obtain high X_M concentrations even when the stoichiometric concentration of Y far exceeds that of X. The observed second order rate constant between a neutral reagent A and a hydrophilic reagent in the presence of an ionic micelle is described by the modified equation 12 (Ref. 18):

$$k_2 = \frac{K_M i' D K_A [M]}{(1 + K_A[M])(X_t + Y_t K_{X/Y})} + \frac{k_w}{K_A[M] + 1} \tag{21}$$

where i' is the degree of counterion binding to the Stern layer (i' = 1 - i), D is the molar density of the micellar phase expressed in moles of surfactant per liter of micellar phase, $X_t = [M] + [BY]$ is the concentration of added salts. Equation 20 has successfully predicted the kinetic behavior of a large number of second order reactions in ionic micelles as well as salt effects therein (Ref. 19-21). One critical test using reactive counterion surfactants succeeded initially then, produced some interesting failures of the model (Ref. 21). This model cannot, however, be applied to buffered systems.

The ion exchange model has provided quantitative rationalizations for (a) the binding of a reactive ion to the micelle in the absence or presence of buffers: (b) the first order reaction of an ionic substrate in the micelle; (c) the second order reaction of a neutral substrate with an ionic reagent; (d) the effect of micelles on dissociation of weak acids and bases and (e) the binding of OH^- to cationic micelles (Ref. 20). This model assumes that (a) the distribution of aggregate sizes can be presented in terms of most probable aggregation number $\bar{N}$; (b) ion - ion and ion - headgroup - headgroup interactions are noncooperative; (c) degrees of ionization (i's) of the individual micellar species are the same; (d) ion - ion exchange rates are rapid compared to the lifetime of the micelle and (e) activities of micellar and ionic species can be treated in terms of their concentrations. With these assumptions the selectivity coefficient for a reactive counterion X^- in B^+X^-, in micelle forming detergent D^+Y^-, in the absence or in the presence of an added common salt, B^+Y^-, is given by:

$$K_{X/Y} = \frac{X_M^-}{(X_T^- - X_M^-)} \frac{i[M] + CMC + X_M^- + [B^+Y^-]_T}{(1 - i)([M] - X_M^-)} \tag{22}$$

where the subscripts T and M refer to total concentrations of the appropriate species and to those present in the micellar pseudophase. At high detergent concentration

$$K_{X/Y} = \frac{i}{1 - i} \frac{X_M^-}{X_w^-} \tag{23}$$

equation 23 predicts that X_M^-/X_w^- tends to a limiting value and it allows, therefore, the assessment of K_{X^-/Y^-}. Addition of a buffer maintains X_w^- rather than X_M^-. Rate constants for the reaction of a univalent ionic substrate, S^-, in an oppositely charged micelle, D^+Y^-, is given by:

$$k_{obs} = \frac{k'_M K_{S^-/Y^-}(Y_M^-/Y_w^-) + k'_w}{1 + K_{S^-/Y^-}(Y_M^-/Y_w^-)} \tag{24}$$

Equation 24 should be compared to equation 3. The selectivity of micelle bound ions rather than substrate partitioning is expressed in equation 24. Similarly, incorporation of the concepts of ion exchange theory in treating bimolecular reactions in micelles (see equation 12) leads to equation 25 and 26 for reactions between S and an oppositely charged X in the absence and in the presence of buffers, respectively (Ref. 20).

$$k_2 = \frac{X_T[(k_M/\bar{V})(K_S K_{X/Y})(Y_M^-/Y_w^-) + k_w]}{(1 + K_S[M])\,[1 + K_{X/Y}(Y_M^- Y_w^-)]} \quad (25)$$

$$k_2 = \frac{X_w[(k_M/\bar{V})(K_S K_{X/Y})(Y_M^-/Y_w^-) + K_w]}{(1 + K_S[M])} \quad (26)$$

It should be noted that the assumptions are the same in the Romsted-Bunton (Ref. 21) and the ion exchange (Ref. 20) treatments. They only differ in the mathematical treatments and experimental tests. The main difference between the two approaches is that equations in the former are derived in terms of stoichiometric quantities of materials including hydrophilic ions,while the ion exchange equations are expressed in terms of the concentration of the hydrophilic ions in the aqueous phase which have to be determined independently.

Distribution of reactive counterions, discussed in terms of micellar surface potentials (Ref. 26), has led to equations similar to those based on the ion exchange model.

Regardless of the model used, rate enhancements for bimolecular reactions appear to be the mere consequence of concentrating the reagents in the membrane mimetic agents. Media effects can only be operational for unimolecaular reactions. In spite of this conclusion, kinetic studies of catalysis in micellar and macromolecular systems had been exceedingly useful. They provided much needed insight into these fascinating systems which, in turn, made their rational exploitation feasible.

APPLICATION OF REACTIVITY CONTROL IN MEMBRANE MIMETIC SYSTEMS

Different features of a given system should be carefully considered in designing experiments for synthetic or other applications. It should be realized that micelles and liposomes have been investigated in considerably greater detail than microemulsions, monolayers or synthetic surfactant vesicles. Similarly, host-guest interactions are better understood than those occurring in polyions. The available sites for interaction and the amount of substrate that can be incorporated into one aggregate are important to consider. For example, in energy transfer and photochemical experiments there is often need to compartmentalize no more than one substrate molecule per aggregate. The relatively small aqueous micelles meet this requirement best. A point of illustration is the efficient energy transfer from micellar sodium dodecyl sulfate, SDS, solubilized naphthalene to terbium choride (Ref. 27). In the absence of micelles there is no energy transfer. If the system is arranged such that there is less than one naphthalene molecule in each micelle while a large number of terbium cation is attached electrostatically to the surface of each negatively charged SDS micelle, energy transfer becomes highly efficient. The role of micelles is to obviate naphthalene - naphthalene triplet - triplet annihilation which precludes energy transfer. Subsequent to excitation, naphthalene singlets intersystem cross into the triplet domain. These species, in turn, transfer their energies to terbium chloride located on the micellar surface. In the absence of micellar cages naphthalene triplets react with each other in preference to transferring energy to terbium (Ref. 27).

Similar principles have been employed in altering photochemical pathways. Photodecarbonylations have been investigated most extensively. Photodecarbonylation of dissymmetrical dibenzylketones in homogeneous solution results in statistical product formation (Ref. 28):

$$\underset{\text{ACB}}{\text{PhCH}_2\overset{\overset{\text{O}}{\|}}{\text{C}}\text{CH}_2\text{Ar}} \xrightarrow{h\nu} \underset{\text{AA}}{\text{PhCH}_2\text{CH}_2\text{Ph}} + \underset{\text{AB}}{\text{PhCH}_2\text{CH}_2\text{Ar}} + \underset{\text{BB}}{\text{ArCH}_2\text{CH}_2\text{Ar}} \quad (27)$$

25% 25% 25%

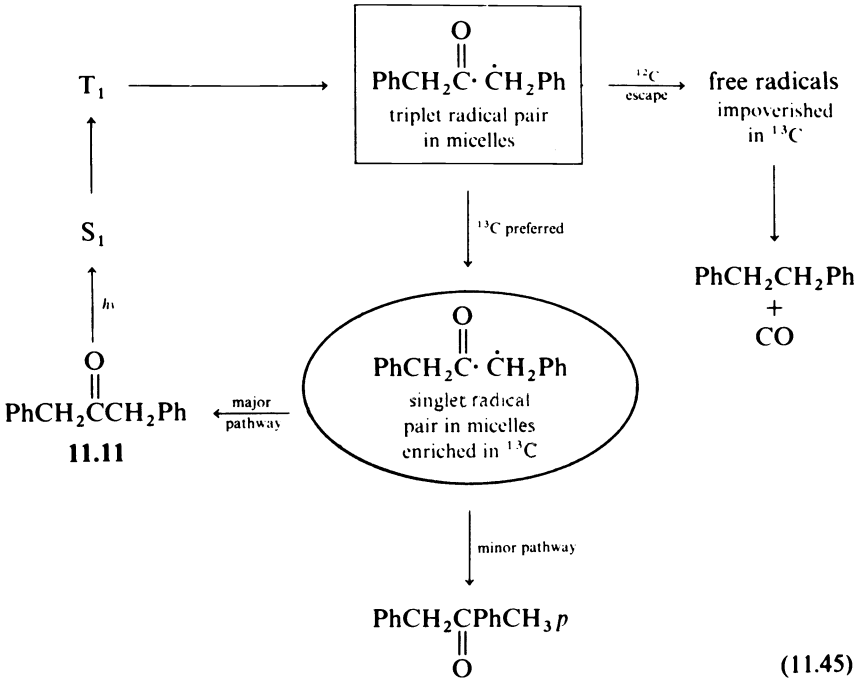
Product distribution is dramatically altered in the presence of micellar hexadecyltrimethlyammonium chloride, CTACl. Increasing the surfactant to ketone ratios results in a sigmoidal increase of the cross products, AB, at the expense of coupled products AA and BB. When there is less than one reactant per micelle, AB becomes the exclusive photoproduct. Under this condition the photolytically generated A· and ·B readily react with each other prior to their escape from the micellar cage. Conversely, in homogeneous solution there is nothing to prevent the radicals from reacting with each other in a statistical manner (Ref. 28).

A significant extention of the cage principle is the utilization of micelles for the enrichment of magnetic isotopes (Ref. 29). The underlying principle is based on the radical pair model of chemically induced dynamic nuclear polarization, CIDN P (Ref. 30). According to this theory the chemical reactivity of radical pairs is expected to depend on the hyperfine interactions of the orbitally

uncoupled electrons of the radical pair with nuclear spins (magnetic isotope effect) or laboratory magnets (magnetic field effects). It should be feasible, therefore, to separate magnetic isotopes from nonmagnetic ones in photochemical reactions involving suitable radical pairs. The function of micelles is to compartmentalize appropriate radicals, alter their microenvironments and act as boundary to reflect overshot dibenzylketones to crucial geometries required for intersystem crossing from the triplet to the singlet potential surface (Ref. 29). Photolysis of dibenzylketone in aqueous CTACl micelles results in the formation of 1,2-diphenylethane and carbon monoxide in high quantum yields ($\Phi \sim 0.8$). The mechanism involves the formation of a triplet radical pair within the micellar cage (equation 28). The triplet radical pair, containing ^{13}C nuclei undergoes nuclear hyperfine coupling induced intersystem crossing to a singlet radical pair which, in turn, regenerates dibenzylketone or forms phenyl-p-acetophenone. Since the ^{12}C nucleus is non-magnetic it cannot undergo nuclear hyperfine coupling induced triplet radical pair to singlet radical pair conversion. Consequently, cage products are formed faster for ^{13}C than ^{12}C nuclei with the resultant ^{13}C enrichment of dibenzylketone. Isotope enrichment as high as 5.6% have been reported (Ref. 29).

In contrast to aqueous micelles, microemulsions and vesicles serve well the need for organizing high concentrations of polar and apolar molecules in each aggregata. These systems are more suitable, therefore, in photochemical solar energy conversion and in target directed drug deliveries (Ref. 2). Membrane mimetic systems have also been used in synthetic chemistry either by virtue of their "catalytic" power or by their ability to control product formation in competing reactions. Ease of separation of reactants from products and from the membrane mimetic agents is an essential requirement. Early work favored hosts and polyions, along with phase transfer catalysts since they can be readily separated from the reaction products. The very amphiphatic nature of surfactants renders product separation from micelles difficult. Products cannot be extracted since surfactants tend to form emulsions. More recently functionally modified micelles have been developed to overcome this problem. Surfactants have either immobilized on gels or made destructable by the introduction of suitable labile bonds. The latter system allows the destruction of the micelle forming surfactants subsequent to product formation to small non surface active fragments, which render product extraction feasible (Ref. 31).

Utilizing membrane mimetic systems for promoting stereoselectivities, chiral recognition and asymmetric inductions has been a long standing and fascinating problem (Ref. 1,2). Maximum stereospecificities are to be expected for systems which provide relatively rigid and specific binding sizes for a given substrate and its reactive transition state. Free energies of binding and/or reactivities of the enantiomers should be different to bring about chiral discriminations. Cavities of functionalized optically active cyclodextrins and crown ethers are expected to provide more rigid and hence energetically more favorable binding sites for chiral discrimination than those available in micelles. This expectation is borne out by the substantially greater stereoselectivities observed in host - guest systems than in micelles. Racemic amino acids have been resolved by the selective transport of amino acid salt in a "catalytic amino acid resolving machine" using (RR) and (SS)-dimethyl substituted naphthyl crown ethers (Ref. 32).



(28)

(11.45)

The synthetic utility of functionalized crown ethers is beautifully demonstrated by the asymmetric reduction of ketones (Ref. 33). Carbonyl group reduction is facilitated by binding to the magnesium complex of an optically active 1,4-dihydropyridine containing crown ethers. Ketones have been reduced to the corresponding S-alcohol in up to 82% chemical and in up to 86% optical yields. Since the pyridinium salt of the host crown ether is easily reconverted to 1,4-dihyropyridine by $Na_2S_2O_4$, the crown ether acts as a cyclic catalyst for asymmetric reduction (Ref. 33).

Only selected examples of reactivity control in membrane mimetic systems have been provided in this brief survey. We can confidently expect exponential growth of applications. It is up to us to exploit the vast potential membrane mimetic chemistry provides.

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