

MEDIUM EFFECTS OF MICELLES AS MICROREACTORS AND THE SCOPE OF THE HUGHES-INGOLD SOLVENT THEORY

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In 1935, Hughes and Ingold developed a qualitative treatment of solvent effects upon S_N reactions(1,2). An increase in solvent polarity should favor reactions in which charge increases in transition state formation and disfavor those in which charge decreases, or in which an existing charge is dispersed. Effects due to changes in net charge are the more important. The theory focuses attention on the mechanism and charge-type of reactions and provides a useful guide for a large number of nucleophilic reactions, provided that specific effects such as ion-pairing and hydrogen bonding are considered(3). This qualitative approach, with its emphasis on mechanism, can be contrasted with quantitative treatments based on linear free-energy relations, such as the Grunwald-Winstein equation and its descendants(3a, 4). It also differed from theoretical treatments that involved calculations of interactions of ions and dipoles in continuous dielectrics(5).

The meaning of polarity was left open, although Ingold drew distinctions between polar, protic, solvents, which form strong hydrogen bonds, especially with small anions, polar aprotic solvents, which solvate cations, and apolar solvents. These distinctions form the basis of quantitative treatments, such as that based on the solvatochromic scale of Kamlet, Taft, and Abraham, which sets out to quantify the factors controlling polarity(6). In many reactions, the role of specific solvent interactions, *e.g.*, hydrogen bonding to anions or anionic leaving groups, has been identified(1,3,6).

The Ingold school examined S_N reactions of non-ionic and cationic substrates and nonionic and anionic nucleophiles in testing the Hughes-Ingold solvent treat-

ment and showed that it fitted a large amount of data, although for S_N2 reactions in aqueous ethanol the presence of two potential nucleophiles was a complication(1,2).

Ingold pointed out that solvent effects are similar for aliphatic and aromatic substitutions by anions(1). Spontaneous reactions that involve charge dispersion, *e.g.*, anionic decarboxylations(7) and solvolyses of dianionic aryl phosphates(8) are inhibited by an increase in solvent polarity, especially for protic solvents where hydrogen bonding stabilizes the initial state, and solvent effects are often very large. The original theory is therefore a useful qualitative predictor of kinetic solvent effects for many organic reactions.

While this work on the relation of solvent effects to mechanism was in progress at University College, Hartley, at the School of Pharmacy, was examining properties of association colloids, for example, micelles, which are self-assemblies of surfactants (detergents), induced by operation of the hydrophobic effect(9). (Hartley's work in colloid science was started with Donnan at University College). He elucidated the source of the "colloid error," which is the effect of synthetic and natural colloids on acid-base indicator equilibria, and showed that cationic micelles increase deprotonation of weakly acidic indicators and neutralization of carbocationic dyes by OH^- , and anionic micelles have the opposite effect. The treatment was extended to equilibria involving variously charged indicators in anionic, cationic and nonionic micelles. If micelles affect equilibria they must also affect reaction rates, and Hartley's rules for indicator equilibria were

later shown to apply to reactions involving H_3O^+ and OH^- and other anions. For example, reactions of OH^- with nonionic substrates are speeded by cationic, and inhibited by anionic, micelles(10).

At first sight, there appears to be little connection between Ingold's ideas on kinetic solvent effects and Hartley's work on micellar effects on indicator equilibria, and to make the connection we must consider the structure of micelles and the way in which they control reaction rates and equilibria.

Micellar Structure

Surfactants (detergents) are amphiphilic ions or molecules that have ionic or polar head groups and apolar, hydrophobic residues, typically *n*-octyl to *n*-octadecyl groups(9,10). In dilute aqueous solution surfactants are monomeric, but above the critical micelle concentration (cmc) they associate to form micelles, which, for dilute surfactant, are approximately spherical and contain about 10^2 monomers. Micelles are thermodynamically stable, but monomers and incorporated solutes enter at near diffusion rates(11), so that equilibrium is maintained between monomer and micelle, and, for relatively slow thermal reactions, between reactants in water and in micelles.

Hydrophobic interactions cause the apolar groups to associate in a hydrocarbon-like core, with polar or ionic head groups at the surface in contact with water. Micellar structure depends on a balance between hydrophobically-driven association of the apolar groups and head group repulsions which, for ionic micelles, are reduced by association with counterions(10,12).

Ionic micelles attract counterions to their surface and repel co-ions, and they also incorporate nonionic solutes. As a result, reactant concentrations in the interfacial surface region can be much higher than in water, which increases rates of bimolecular reactions of counterions(13). Micelles also influence rates of spontaneous reactions, and we can treat them as submicroscopic reaction media, distinct from bulk solvent. It is convenient to regard micelles and water as pseudophases(10,13).

Polarities, or apparent dielectric constants, of micellar surfaces are estimated by examining spectral shifts of probes on their transfer from water to micelles on the assumption that spectral relations with properties of bulk solvents are applicable to submicroscopic interfaces(5,10,13-15). Based on this leap of faith, we conclude that these interfaces are less polar than water and much more polar than alkanes. Head groups are exposed to water, but its apparent activity is lower than in bulk

water(16). We can then ask whether the Hughes-Ingold solvent theory can be applied to reactions in micelles or other association colloids, but we first have to separate the overall reaction rate into the rates in the two pseudophases.

A typical cationic surfactant is a salt of the cetyltrimethylammonium ion, $\text{C}_{16}\text{H}_{33}\text{NMe}_3\text{X}$ (CTAX, X=Br, Cl, OMs). Sodium dodecyl sulfate, $\text{C}_{12}\text{H}_{25}\text{OSO}_3\text{Na}$, SDS, is the most studied anionic surfactant, and these surfactants were generally used in the work discussed here.

The Pseudophase Kinetic Model

Application of the pseudophase model to reaction rates and equilibria in association colloids requires estimation of reactant concentrations in the colloidal pseudophase, *i.e.*, analysis of the transfer equilibria(13). The problem is simple for spontaneous reactions, where we consider only transfer of the substrate. When it is fully transferred to the micelle the rate constant of the overall reaction is that in the micelle. The first order rate constant as a function of micellized surfactant (detergent) concentration, $[\text{D}_n]$, is given by(13):

$$k_{\text{obs}} = \frac{k'_w + k'_M K_S [\text{D}_n]}{1 + K_S [\text{D}_n]} \quad (1)$$

where k'_w and k'_M are first order rate constants and K_S is an association constant.

Micellar rate effects upon spontaneous reactions follow the predictions of the Hughes-Ingold solvent theory on the assumption that micellar surfaces are less polar than water. For example, for S_N1 and S_N2 hydrolyses of alkyl halides and arenesulfonates $k'_w > k'_M$ (17). There is also a charge effect of the micelle, because of charge asymmetry at its surface, so that for an S_N1 reaction of a nonionic substrate the forming positive charge in the transition state interacts unfavorably with cationic head groups. This unfavorable interaction is absent in anionic micelles, so they inhibit S_N1 reactions less than cationic micelles. In S_N2 and similar solvolyses negative charge tends to develop on the organic residue and inhibition is lower in cationic than in anionic micelles. These generalizations also apply to hydrolyses of acyl and sulfonyl chlorides(17,18). The more S_N1 -like is the transition state, the higher is the rate in anionic as compared with cationic micelles.

Spontaneous reactions that involve dispersion of an existing charge, *e.g.*, decarboxylations(19) and hydrolyses of aryl sulfate monoanions(20) and aryl phosphate dianions(21), are faster in cationic micelles than in water, as predicted by the Hughes-Ingold solvent theory.

In some cases, rate enhancements are by factors of 10^2 or more, due to changes in initial state hydration and interactions of micellar head groups with anionic transition states.

It is more difficult to analyze micellar effects upon nonspontaneous reactions because rates now depend upon concentrations of both reagents at the micellar surface(13). In some cases, the transfer equilibrium of a reagent between water and micelles can be estimated directly. This approach has been used for some ionic and nonionic organic nucleophiles, *e.g.*, amines and aryloxide ions(22) and for chloride and bromide ions(23). In other cases, *e.g.*, for reactions of OH^- , ionic concentrations are calculated by theoretical treatment of micelle-ion interactions(13,24). Provided that these concentrations can be estimated, we can write k'_w and k'_M in terms of the local concentrations of a nucleophile, Nu, in water and at the micellar surface and the second order rate constants, k_w and k_2^m

$$k'_w = k_w[\text{Nu}_w] \quad (2)$$

$$k'_M = k_2^m \text{Nu}_M \quad (3)$$

where $[\text{Nu}_w]$ is the molarity in water and Nu_M is the local molarity in the watermicelle interfacial region, not the molarity in terms of the total solution volume(13).

Micellar effects upon $\text{S}_\text{N}2$ reactions of Cl^- and Br^- with methyl naphthalenesulfonate fit the Hughes-Ingold solvent theory and k_2^m/k_w is in the range of 2-3 with several cationic micelles(23,24). Bimolecular reactions of nonionic nucleophiles with carboxylic esters and 2, 4- dinitrofluorobenzene are, as predicted, slower at micellar surfaces than in water(13,22).

For most bimolecular reactions of hydrophilic nucleophilic anions, *e.g.*, OH^- , with a variety of organic substrates, values of k_2^m are similar to, or slightly lower than, those in water(13). Some of the substrates are very hydrophobic and transfer from water to micelles lowers their free energies, which, of itself, inhibits reaction.

Provided that transfer equilibria between water and micelles are taken into account, micellar rate effects on many bimolecular nucleophilic reactions are as predicted for a medium that is somewhat less polar than water. The charge on the micellar surface markedly affects transfer equilibria, especially of hydrophilic ions, but has little effect upon free energies of activation at the micelle-water interface. This generalization also applies reasonably well for reactions involving electrophilic cations, *e.g.*, H_3O^+ , where overall reaction rates are increased by anionic micelles(13).

The situation is completely different for reactions of electrophilic anions, *e.g.*, oxidations of sulfides by

IO_4^- and HSO_5^- (25) and reactions of alkenes with Br_3^- (26). Cationic micelles concentrate these anions in the interfacial region, which should increase reaction rates; but rate enhancements are very small, or nonexistent(25, 26). Based on estimation of reactant concentrations in the micellar pseudophase, k_2^m is smaller than k_w by two to three orders of magnitude. This behavior is very different from that seen for reactions of nucleophilic anions.

Although ionic micelles repel co-ions, they have a small, but finite concentration in the interfacial region at the micellar surface, and it can be estimated, based on a theoretical model(27). This calculation has been made for IO_4^- in micelles of SDS, and values of k_2^m for sulfide oxidations are lower than k_w by factors of 3-5(25b). This small inhibition is as expected because of the lower polarity of an SDS micelle relative to water(14). This striking difference in kinetic behaviors of cationic and anionic micelles can be ascribed to interactions between micellar head groups and the transition state. In sulfide oxidation, an electron is transferred from sulfur to the anionic oxidant with development of positive charge on sulfur(25,28). Interaction of this charge with a cationic micellar head group strongly inhibits oxidation, but this unfavorable interaction disappears for oxidation at the surface of an anionic micelle, although the overall reaction is slow because of the very low concentration of IO_4^- at the anionic micellar surface.

The same unfavorable charge effect applies to bromination by Br_3^- at cationic micellar surfaces where the forming bromonium ion interacts unfavorably with the head groups(26). The reaction of Br_3^- cannot be examined in solutions of SDS where equilibrium between the brominating agents favors Br_2 .

Conclusions

Rate constants in the interfacial region at surfaces of aqueous micelles depend upon the properties of this region as a submicroscopic reaction medium and the mechanism and charge type of the reaction(13,17-24). For bimolecular reactions of nonionic nucleophiles, decreases in the second-order rate constants, relative to those in water, are consistent with the Hughes-Ingold solvent theory and the lower polarities of micellar surfaces relative to water(22). Similar considerations apply to $\text{S}_\text{N}2$ reactions of halide ions with methyl arenesulfonates which are slightly faster at cationic micellar surfaces than in water(23,24b).

The theory also predicts the lower first-order rate constants of $\text{S}_\text{N}1$ and $\text{S}_\text{N}2$ hydrolyses of nonionic substrates at micellar surfaces relative to water. However,

because the interfacial region is electrically asymmetrical it is necessary in S_N1 reactions to consider interactions between the dipolar transition state and the micellar head groups(17). This problem of electrical asymmetry also complicates analysis of micellar rate effects upon oxidations or brominations by anionic electrophiles(25,26).

I do not believe that Ingold ever considered the extent to which association colloids might affect reaction rates and equilibria, and systematic study of reactivity in these systems required the availability of readily usable spectrophotometers for rate measurement(10). The success of the Hughes-Ingold solvent theory, as applied to micellar rate effects, shows how well-considered ideas on the factors that control reactivity in one set of conditions, or one type of reaction, can generally be applied over a much wider range of conditions. The generalizations that Hartley developed to explain micellar structure and effects on indicator equilibria(9) have also stood the test of time; and the two sets of ideas come together to explain the behavior of association colloids as reaction media.

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Note added in proof: The solvatochromic scale has been extended to aqueous micelles. M. H. Abraham, H. C. Chadha, J. P. Dixon, C. Rafols, and C. Treiner, *J. Chem. Soc. Perkin Trans. 2*, **1995**, 887; F. H. Quina, E. O. Alonso, and J. P. S. Farah, *J. Phys. Chem.*, **1995**, *99*, 11708. Local concentrations of nucleophiles in micellar surfaces can be estimated by dediazonization trapping, J. H. Yao and L. S. Romsted, *J. Am. Chem. Soc.*, **1994**, *116*, 11779.

A biography covering details of Ingold's early life, education, and professional accomplishments, together with extensive information about Hilda Usherwood Ingold and E. D. Hughes, has been published since the ACS Symposium: K. T. Leffek, *Sir Christopher Ingold, A Major Prophet of Organic Chemistry*, Nova Lion Press, 980 Kentwood Terrace, Victoria, BC, Canada, V8Y 1A6.