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Otto, Sijbren; Engberts, Jan B.F.N.

Published in:
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2001

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Citation for published version (APA):

Otto, S., & Engberts, J. B. F. N. (2001). Diels-Alder reactions in micellar media. In *Host Publication* (pp. 247 - 263). Marcel Dekker.

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Diels-Alder Reactions in Micellar Media

SIJBREN OTTO* and JAN B. F. N. ENGBERTS University of Groningen, Groningen,
The Netherlands

I. INTRODUCTION TO DIELS-ALDER REACTIONS

The Diels-Alder reaction is a [4+2]cycloaddition in which a diene (four-*p* component) reacts with a dienophile (two-*p* component) to provide a six-membered ring (Fig. 1). Six new stereocenters are formed in a single reaction step. Because the conformations of the double bonds are usually fully retained, the reaction is stereospecific and consequently the absolute configuration of the two newly formed asymmetric centers can be controlled efficiently. The Diels-Alder reaction is of great value in organic synthesis and is a key step in the construction of compounds containing six-membered rings [1]. A historic account of this important conversion has been published by Berson [2].

Homo Diels-Alder reactions involve only hydrocarbon fragments. If the diene or dienophile possesses heteroatoms in any of the positions a-f (Fig. 1), heterocyclic ring systems are formed (*hetero* Diels-Alder reactions).

Normal electron demand Diels-Alder reactions are promoted by electron-donating substituents in the diene and electron-withdrawing substituents in the dienophile. The opposite situation applies for *inverse electron demand* Diels-Alder reactions. *Neutral* Diels-Alder reactions are accelerated by both electron-withdrawing and electron-donating substituents.

**Current affiliation*: University of Cambridge, Cambridge, England.

Reactivity and selectivity in Diels-Alder reactions are often rationalized in terms of frontier molecular orbital (FMO) theory [3], emphasizing interactions between the highest occupied molecular orbital (HOMO) of one of the reaction partners and the lowest unoccupied molecular orbital (LUMO) of the other. During formation of the two new *s*-bonds, orbital symmetry is conserved. Therefore no intermediate is involved and the pericyclic reaction is concerted. There is ample experimental and theoretical evidence for the concerted mechanism [4]. Only in relatively rare cases does the Diels-Alder reaction take place via a nonconcerted two-step mechanism, involving either a zwitterionic or a biradical mechanism and leading to modified stereochemistry. FMO theory has been useful in analyzing possible asynchronicity in the activation process and in predicting kinetically controlled regioselectivity for Diels-Alder processes involving asymmetric dienes in combination with asymmetric dienophiles [5].

Much attention has also been given to Diels-Alder reactions that provide *endo* and *exo* cycloadducts (Fig. 2). The *endo-exo* ratio is usually the result of relatively small differences in transition state energies which appear to be primarily determined by secondary orbital interactions [6,7]. The formation of the *endo* product is associated with the most compact activated complex and exhibits the most negative volume of activation. Apart from secondary orbital interactions, other factors have been proposed for explaining the *endo-exo* ratio, including steric effects, London-dispersion interactions, and solvent effects (e.g., [8]).

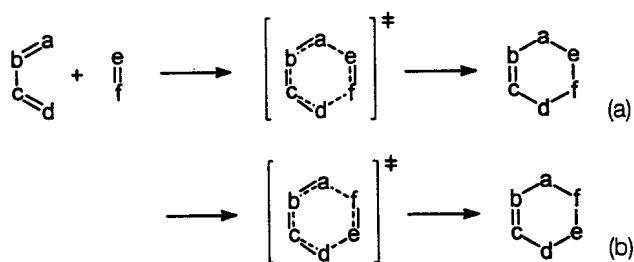


FIG. 1 Schematic representation of the Diels-Alder reaction. The versatility of the reaction is illustrated by the fact that heteroatoms are allowed at any of the positions a-f. Structures (a) and (b) indicate two regioisomeric products.

This chapter will describe micellar effects on Diels-Alder reactions with respect to both reaction rates and stereochemical aspects. For a proper understanding of the effects induced by micelles, we will first briefly review what is known about medium and catalytic effects on Diels-Alder cycloadditions.

A. Medium and Catalytic Effects on Diels-Alder Reactions

The Diels-Alder reaction is a textbook example of a reaction that is rather indifferent toward the choice of the solvent. An extreme example [9] is the dimerization of cyclopentadiene (Table 1), but for many other homo- and also for hetero Diels-Alder reactions, rate constants

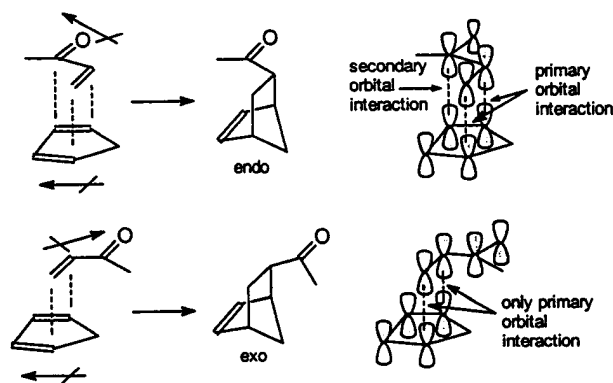


FIG. 2 *Endo* and *exo* pathway for the Diels-Alder reaction of cyclopentadiene with methyl vinyl ketone. As was first noticed by Berson, the polarity of the *endo* activated complex exceeds that of the *exo* counterpart due to alignment of the dipole moments of the diene and the dienophile [17]. The symmetry-allowed secondary orbital interaction that is possible only in the *endo* activated complex is usually invoked as an explanation for the preference for *endo* adduct exhibited by most Diels-Alder reactions.

TABLE 1 Second-Order Rate Constants k_2 for the Dimerization of Cyclopentadiene in Solution and in the Gas Phase at 25°C

Solvent/state	k_2 ($M^{-1} s^{-1}$)
Gas phase	6.9×10^{-7}
Neat	5.6×10^{-7}
Carbon tetrachloride	7.9×10^{-7}
Nitrobenzene	13×10^{-7}
Ethanol	19×10^{-7}

Source: Data from Ref. 9.

in a series of organic solvents vary only modestly. Nevertheless, attempts have been made to correlate kinetic data with solvent parameters, both for pure solvents and for binary mixtures [10,11]. Multiparameter analyses of solvent effects on Diels-Alder reactions have been carried out. For example, Gajewski [12] observed a dependence of rate constants for Diels-Alder reactions on the solvent α -parameter and the cohesive energy density. Intramolecular Diels-Alder reactions in highly viscous media have been related to the solvent density, which affects the translational motion of the reactants [13]. Rather unusual reaction media that have been employed for accelerating Diels-Alder reactions include solutions of lithium perchlorate in diethyl ether, dichloromethane, and nitromethane [14]. After considerable debate, it was argued that the substantial rate enhancements are largely due to Lewis acid catalysis by the lithium cation [15]. It is generally agreed that the small or modest solvent effects on the rates of Diels-Alder reactions are in accord with the concerted character of the cycloaddition that involves only a rather insignificant change of charge distribution during the activation process.

The effect of the reaction medium on the regioselectivity of Diels-Alder reactions can be rationalized in terms of the FMO theory [16]. In particular, the hydrogen bond donating character of the solvent, as expressed in the α -parameter, affects the orbital coefficients on the terminal atoms of diene and dienophile.

Medium effects on the *endo-exo* ratios have received extensive attention, and Berson et al. have even based an empirical solvent polarity scale [$\Omega = \log(\text{endo/exo})$] on the selectivity of the Diels-Alder reaction between methyl acrylate and cyclopentadiene [17]. Solvent effects on the diastereofacial selectivity of the Diels-Alder process have also been examined and interpreted [18].

Other factors that have been studied with the aim of increasing the rate and stereoselectivity of Diels-Alder

reactions include external pressure [19], ultrasound irradiation [20], and catalytic effects exercised by clays [21], alumina [22], silica gels [23], microporous organic crystals [24], antibodies [25], cyclodextrins [26,27], and supramolecular assemblies [28,29]. By far the most effective enhancements of rate and selectivity are induced by Lewis acids [30-33]. Studies of Lewis acid catalysis of Diels-Alder reactions have been almost completely restricted to organic solvents and binary mixtures of low water content. However, highly efficient Lewis acid catalysis has been observed for Diels-Alder reactions in purely aqueous media [34-38].

The remarkable effects of Lewis acids on the kinetics of Diels-Alder reactions have been known since the early 1960s [30] and may involve accelerations of 10^4 to 10^6 in organic solvents. Also the *endo/exo* selectivity may clearly respond to the presence of Lewis acids such as $\text{AlCl}_3 \cdot \text{OEt}_2$ [31]. Similarly, the regioselectivity [32] and diastereofacial selectivity [33] may be increased in the presence of Lewis acids.

The mechanism of Lewis acid catalysis can be understood with the aid of the FMO theory. Binding of the Lewis acid catalyst will lower the energy of the LUMO of the reactant to which it is coordinated. This binding will decrease the HOMO-LUMO energy difference, which will in turn increase the rate of the Diels-Alder cycloaddition. It has also been proposed that binding of the Lewis acid catalyst leads to increased secondary orbital interactions, thereby increasing the *endo/exo* ratio [39]. Other consequences of the coordination of a Lewis acid catalyst have also been considered, including an increase of asynchronicity in the formation of the activated complex [40]. Solvent effects on the efficiency of Lewis acid catalysis of Diels-Alder reactions have received relatively little attention [41]. At present, Lewis acid catalysis of Diels-Alder reactions is in everyday practice in synthetic organic chemistry.

B. Special Effects of Water on Diels-Alder Reactions

For a long time water was not a popular solvent for Diels-Alder reactions, although the pioneers Diels and Alder performed the reaction between furan and maleic acid in an aqueous medium in 1931 [42]. The latter experiment was repeated by Woodward and Baer in 1948, and a change in the *endo/exo* ratio was noted [43]. In 1973, Huisman et al. for the first time noticed a favorable aqueous effect on the rate of the same reaction, but the effect was not further explored [44]. Also, in two early patents the Diels-Alder reaction is

mentioned in connection with water as the reaction medium [45].

A breakthrough came in 1980 in the work of Breslow and Rideout [26], who observed a substantial rate increase for simple Diels-Alder reactions in pure water. In subsequent extensive research it was shown that these remarkable kinetic aqueous medium effects are a general phenomenon [46-48]. Depending on the chemical structure of diene and dienophile, rate enhancements in water relative to organic solvents may amount to factors of more than 10^4 . Rather soon after Breslow's pioneering work, synthetic applications of Diels-Alder reactions in aqueous media were explored in some detail, in particular by Grieco and his coworkers [48]. Of course, the often limited solubility of diene and dienophile is a major drawback. In elegant work, Lubineau et al. have tackled this problem by employing dienes that were rendered water soluble by the temporary introduction of a sugar moiety in the molecule [49]. The scaling up of aqueous Diels-Alder reactions has also been studied [50].

Ever since the early work of Breslow, many studies have been devoted to the identification of the special effects of the aqueous reaction medium that lead to the remarkable rate accelerations. These studies have been reviewed [46,47]. After considerable debate and controversy, it is now almost generally agreed that the enhanced reactivity in water is the result of two major effects: the *hydrogen bond donating capacity* of water and *enforced hydrophobic interactions* [51,52]. Previous suggestions that preassociation of the reactants in water played an important role were not substantiated. For example, vapor pressure measurements indicated that cyclopentadiene did not form aggregates at concentrations used in the kinetic measurements. Similar observations were made for methyl vinyl ketone, a popular dienophile in mechanistic studies of Diels-Alder reactions in water.

The peculiar nature of the Diels-Alder reaction in water was clearly revealed in a study in which Gibbs energies for the Diels-Alder reaction of cyclopentadiene with ethyl vinyl ketone over the whole mole fraction range in the mixture of 1-propanol with water were combined with Gibbs energies of transfer of the diene and dienophile from 1-propanol to the aqueous mixture and to pure water [51,53]. These data showed that the *initial state* (diene + dienophile) is significantly *destabilized* in water relative to 1-propanol (Fig. 3). By contrast, the *activated* complex has nearly equal chemical potentials in water and in 1-propanol. Consequently, in aqueous solution the hydrophobic parts of the activated complex have completely lost their nonpolar character

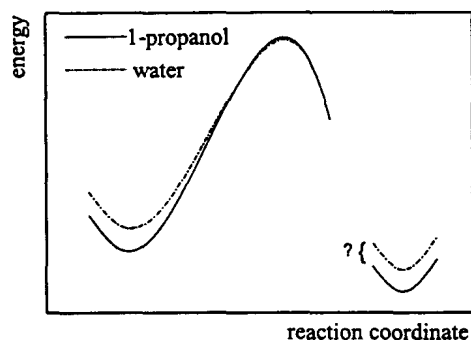


FIG. 3 Chemical potential of the initial state, the transition state, and the product of the Diels-Alder reaction between methyl vinyl ketone and cyclopentadiene in water as compared with 1-propanol. (Data from Ref. 53.)

as far as solvation is concerned. This conclusion has been confirmed in subsequent studies [52,54]. During the activation process of the Diels-Alder reaction, hydrophobic parts of the diene and the dienophile approach each other closely, a process that is particularly favorable in water (“enforced” hydrophobic interaction) compared with nonaqueous reaction media. The term “enforced” is used to stress the fact that the approximation of the nonpolar reagents is driven by the reaction and only enhanced by water. In addition, the electron redistribution that takes place during the activation process leads to an enhanced electron density at the carbonyl oxygen atom of ethyl vinyl ketone and a consequent enhanced propensity for hydrogen bond interaction with a hydrogen bond donating solvent. The small size of water molecules allows a particularly efficient interaction with hydrogen-bond acceptor sites. The medium effects on the chemical potentials, as shown in Fig. 3, are fully consistent with the operation of the hydrophobic and hydrogen-bonding effect. Beautifully detailed computational studies by Jorgensen et al. [55,56] led to similar conclusions and provided more quantitative insights into the relative importance of both solvation influences in water.

Attempts have been made to identify Diels-Alder reactions that are exclusively affected by either enforced hydrophobic interactions [57] or hydrogen-bonding effects [58]. The overall results confirmed the analysis and illustrated how the structures of diene and dienophile determine the magnitude of the aqueous rate acceleration. It appears well established now that the hydrophobicities of diene and dienophile as well as the polarizability of the activated complex play a key role in determining the acceleration of Diels-Alder reactions in water. These insights into the nature of the special

effect of the aqueous medium are also of immediate relevance for understanding the effects of water on the *endo-exo* ratios and on the diastereofacial- and regioselectivity.

Finally, we briefly note that studies in the 1990s have shown that many other organic reactions benefit from the use of water as the reaction medium [48,59-62].

II. INTRODUCTION TO MICELLAR CATALYSIS

Micelles are highly dynamic, often rather polydisperse aggregates formed from single-chain surfactants [63,64] beyond the critical micelle concentration (cmc). Micellization is primarily driven by bulk hydrophobic interactions between the alkyl chains of the surfactant monomers and usually results from a favorable entropy change [65]. The overall Gibbs energy of the aggregate is a compromise of a complex set of interactions, with major contributions from headgroup repulsions and counterion binding (for ionic surfactants) [64].

The residence times of individual surfactant molecules in the micelle are typically of the order of 10^{-5} - 10^{-6} s, whereas the lifetime of the micellar entity is about 10^{-3} - 10^{-1} s. The size and shape of micelles are subject to appreciable structural variations. Average aggregation numbers are usually in the range of 40-150. For ionic micelles, a large fraction of the counterions are bound in the vicinity of the headgroups. The overall structure of the micelle is characterized by a situation in which the ionic or polar headgroups reside at the surface of the aggregates, where they are in contact with water, with the alkyl chains in the interior of the micelle forming a relatively dry hydrophobic core [66]. The alkyl chains of micellized surfactant molecules are not fully extended. Starting from the headgroup, the first two or three carbon-carbon bonds are usually *trans*, whereas *gauche* conformations are likely to be encountered near the center of the chain. As a result, the terminal methyl moieties of the chain can be located near the surface of the micelle and may even protrude into the aqueous medium [67]. Consequently, the micellar surface has a definite degree of hydrophobicity. Nuclear magnetic resonance (NMR) studies have shown that the hydrocarbon tails in a micelle are highly mobile and comparable in mobility to the chains in a liquid hydrocarbon [68]. The degree of water penetration into the micellar interior has long been a matter of debate. Small-angle neutron scattering studies have indicated that significant water penetration into the micellar core is unlikely [69].

Micellar catalysis of organic reactions has been extensively studied [70-76]. This type of catalysis is critically determined by the ability of micelles to take up all kinds of molecules. The binding is generally driven by hydrophobic and electrostatic interactions. The take-up of solutes from the aqueous medium into the micelle is close to diffusion controlled, whereas the residence time depends on the structure of the surfactant molecule and the solubilize and is often of the order of 10^{-4} - 10^{-6} s [77]. Hence, these processes are fast on the NMR time scale. Solubilization is usually treated in terms of a pseudophase model in which the bulk aqueous phase is regarded as one phase and the micellar pseudophase as another. This allows the affinity of the solubilize for the micelle to be quantified by a partition coefficient P . Frequently P is expressed as the ratio of the mole fractions of solubilize in the micellar pseudophase and in the aqueous pseudophase. However, for micelle-catalyzed reactions, it is more convenient to express P as a ratio of concentrations.

The time-averaged location of different solubilizes in or at a micelle has been a topic of contention [78]. Apart from saturated hydrocarbons, there is usually a preference for binding in the interfacial region, that is, at the surface of the micelle [79,80]. Such binding locations offer possibilities for hydrophobic interactions and avoid unfavorable disturbances of the interactions between the alkyl groups of the surfactant molecules in the core of the aggregate. The situation is, however, complicated, and the large volume of the interfacial region as compared with the core of the micelle should also be taken into account. The preferential binding of aromatic molecules at the micellar surface has been explained at least in part by the ability of the π -system of the molecule to form weak hydrogen bonds with water [81].

A. Kinetic Models

Kinetic studies of micellar catalysis and inhibition have been largely focused on organic reactions and the field has been reviewed extensively [70-76]. In these kinetic analyses the dependence of the rate constants on the surfactant concentration has usually been rationalized in terms of the pseudophase model assuming rapid exchange of the substrate(s) between the micellar and aqueous pseudophases. Different models have been developed for *uni*- and *bi*molecular reactions. For unimolecular reactions, the kinetic micellar effect depends on partitioning of the substrate between both pseudophases and on the rate constant in water (k_w) and in the micellar pseudo phase (k_m). Menger and Portnoy [82]

developed the classic model in 1967 and this model has been successfully employed ever since. The micellar rate effect k_m/k_w depends on the local medium at the substrate binding sites where the substrate experiences specific effects due to hydrophobic segments of the alkyl chains, the polar or ionic headgroups, and the counterions in case of ionic micelles.

For *bi*molecular reactions the analysis is much more complicated, and the overall kinetic effects are now also crucially affected by the local concentration of both reactants A and B in the micellar pseudophase. A classic approach has been advanced by Berezin et al. [71,83]. Again the pseudophase model is adopted, but now an independent assessment of at least one of the partition coefficients is required before the other relevant kinetic parameters can be obtained. The overall approach is illustrated in Fig. 4.

The apparent second-order rate constant (k_{app}), which is a weighed average of the second-order rate constants in the micellar pseudophase (k_m) and in water (k_w), is given by

$$k_{app} = \frac{k_m P_A P_B [S] V_{mol,S} + k_w (1 - [S] V_{mol,S})}{(1 + (P_A - 1)[S] V_{mol,S})(1 + (P_B - 1)[S] V_{mol,S})} \quad (1)$$

in which P_A and P_B are the micelle-water partition coefficients of A and B, respectively, defined as the ratios of the concentrations in the micellar and the aqueous phase, $[S]$ is the concentration of surfactant, and $V_{mol,S}$ is the molar volume of the micellized surfactant. Accurate values of $V_{mol,S}$ are difficult to obtain, and the actual location of A and B in the aggregate may differ (see Section III.A). Usually, estimates of $V_{mol,S}$ are introduced into Eq. (1), leading to uncertainties in k_m . Despite these serious limitations, the kinetic analyses framed on the basis of Eq. (1) often produce reasonable results.

By far the most frequently analyzed types of bimolecular reactions are those involving an *ionic* reaction partner of the same charge type as the counterion

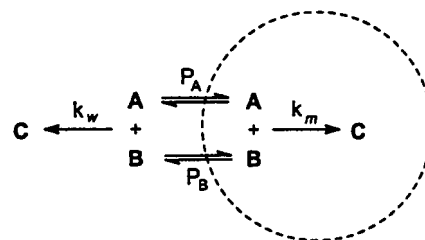


FIG. 4 Kinetic analysis of a bimolecular reaction $A + B \rightarrow C$ according to the pseudophase model.

of the ionic surfactant. Such processes are characterized by competition in binding between the reactive ion and the inert surfactant counterion. Pioneering work has been carried out by Romsted et al. [75], and the pseudophase ion-exchange model (PPIE) has been successfully applied in the micelle-catalyzed ionic bimolecular reactions. Again, it is often observed that the local microenvironment has only a modest influence on k_m/k_w and that the favorable entropic effect due to the increase of the local concentrations of both reactants in the micellar pseudophase is the dominant catalytic factor [84]. Over the years, the PPIE model has been severely tested; in particular, Romsted and his associates have advanced elegant methods for analyzing detailed aspects of counterion binding to micellar aggregates [85].

Studies of micellar catalysis of bimolecular reactions of uncharged substrates (such as most Diels-Alder reactions) have not been frequent. An example involves the reaction of 1-fluoro-2,4-dinitrobenzene with aniline in the presence of anionic and nonionic surfactants [86]. The apparent second-order rate constant (k_{app}) is increased relative to that in water as a result of compartmentalization of both reactants in the micelles. Interestingly, the second-order rate constant for reaction in the micellar pseudophase (k_m) was found to be roughly equal to or even lower than the rate constant in water. Similarly, the reaction of long-chain alkanethiols with *p*-nitrophenyl acetate [87] and the acylation of aryl oximes by *p*-nitrophenyl carboxylates [83] are catalyzed by micelles but, apart from local concentration effects, the influence of the micellar surface charge on the ionization constants of the SH and OH groups, respectively, must also be taken into account.

III. EFFECT OF MICELLES ON DIELS-ALDER REACTIONS

Because the diene and dienophile of the majority of intermolecular Diels-Alder reactions have a rather pronounced nonpolar character, efficient binding of both substrates to micelles is anticipated. This would imply that the effective reaction volume for the Diels-Alder reaction is significantly reduced, leading to micellar catalysis. Surprisingly, accounts of micelle-catalyzed Diels-Alder reactions are scarce. The first report of the influence of surfactants on Diels-Alder reactions stems from 1939, when the BASF company patented the use of detergents for promoting the yields of Diels-Alder processes in aqueous dispersions [45a]. Subsequently, more studies have appeared reporting beneficial effects of micellar systems on the yield of Diels-Alder reac-

tions [88]. More mechanistically oriented studies have focused on the effect of micelles on the kinetics (Section III.A), the *endo-exo* selectivity (Section III.B), and the regioselectivity (Section III.C) of model Diels-Alder reactions. Also, the first example of modest enantioselectivity in a micelle-catalyzed Diels-Alder reaction has been reported (Section III.D). Finally, highly efficient micellar catalysis of a Diels-Alder reaction has been found for micelles with counterions that act as Lewis acid catalysts (Section III.E).

A. Effect of Micelles on the Rate of Diels-Alder Reactions

Studies of the kinetics of Diels-Alder reactions in the presence of micelles typically reveal only modest catalytic effects, and usually the apparent rate constants in micellar media are strikingly similar to the rate constants in water. Little effort was made to obtain second-order rate constants in the micellar pseudophases. We refer here to the work of Breslow et al. [89], who observed a small (15%) acceleration of the Diels-Alder reaction of cyclopentadiene with a number of dienophiles in the presence of sodium *n*-dodecyl sulfate (SDS) micelles as compared with water. Also, a modest micelle-induced decrease in the rate constant of a Diels-Alder reaction has been reported [90].

More detailed analyses have been performed by Hunt and Johnson [91], who studied the kinetics of the homo Diels-Alder reaction of 1,2-dicyanoethylene (**1**) with cyclopentadiene (**2**) as a function of the concentration of sodium dodecyl sulfate (SDS) surfactant. The presence of micelles induces a modest decrease of the rate of this reaction (Fig. 5). Enthalpies and entropies of activation of the reaction in micellar medium have been determined and compared with those in water, aqueous salt solutions, and organic solvents (Table 2). Gibbs energies, entropies, and enthalpies of activation for the reaction in micellar solutions resemble those in 0.5 M LiCl more than those in organic solvents or water. This seems to point toward the Stern region of the micelles as the prominent site for this Diels-Alder reaction.

Wijnen and Engberts [58] have studied the effect of SDS on another homo Diels-Alder reaction between 1,4-naphthoquinone (**4**) and cyclopentadiene (**2**). The results were compared with a structurally related retro Diels-Alder reaction (Fig. 6). Close to the cmc a modest acceleration of the former bimolecular Diels-Alder reaction was observed, whereas micelles induced a small inhibition of the retro Diels-Alder. However, this

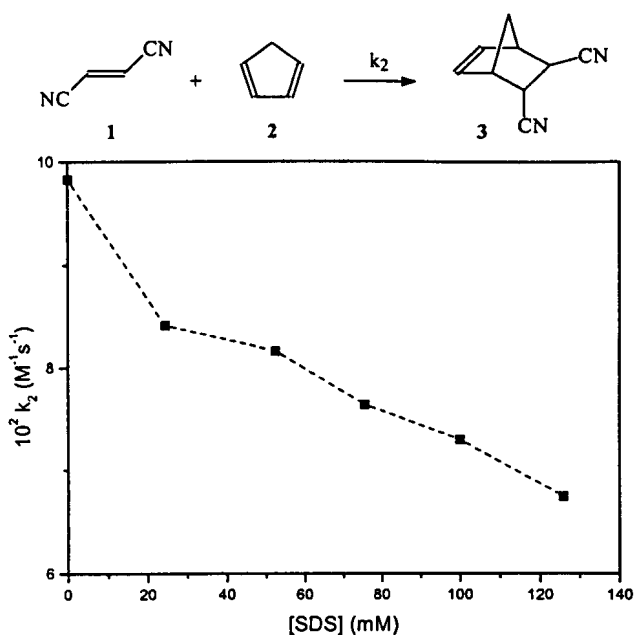


FIG. 5 Second-order rate constants for the Diels-Alder reaction of **1** with **2** at different concentrations of sodium dodecyl sulfate (SDS). (Data from Ref. 91.)

process is still considerably faster than that in organic solvents [58].

The same authors have studied a reversible hetero Diels-Alder reaction and compared it with an irreversible analogue (Fig. 7) [92]. This time the rates of both retro and bimolecular Diels-Alder reactions experienced a modest beneficial influence of the presence of SDS micelles. The equilibrium constant is somewhat displaced toward the adduct. This particular reaction is classified by Desimoni et al. [11] as a *type C* Diels-Alder reaction, signifying that it is almost insensitive to hydrogen bonding effects and that its rate is mainly governed by enforced hydrophobic interactions. This

TABLE 2 Gibbs Energies, Enthalpies, and Entropies of Activation for the Diels-Alder Reaction of **1** with **2** in Different Media

Medium	$\Delta^q G^\ddagger$ (kJ/mol)	$\Delta^q H^\ddagger$ (kJ/mol)	$T \Delta^q S^\ddagger$ (kJ/mol)
0.05 M SDS	78.7	45.1	-33.6
Water	78.4	62.2	-16.2
0.5 M LiCl	77.8	41.9	-35.9
Ethanol	87.5	52.2	-35.3
Dioxane	89.1	48.5	-40.6

Source: Data from Ref. 91.

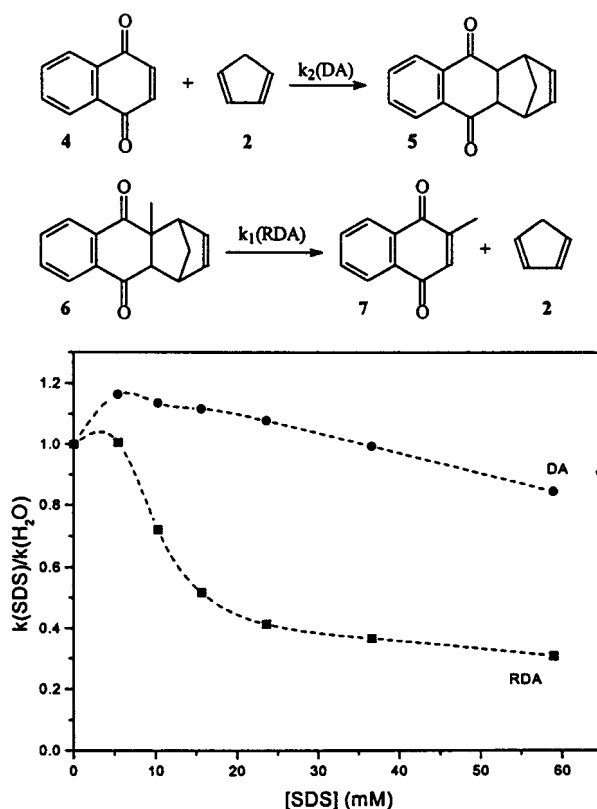


FIG. 6 Relative rate constants for the retro Diels-Alder reaction (■) of **6** and the bimolecular Diels-Alder reaction (●) of **4** with **2** at different concentrations of sodium dodecyl sulfate (SDS). (Data from Ref. 58.)

suggests that enforced hydrophobic interactions are slightly more efficient in the Stern region of the SDS micelles than in bulk water.

Van der Wel, Wijnen, and Engberts [57] have studied the influence of surfactants on the hetero Diels-Alder reaction of a cationic dienophile **12** with cyclopentadiene (Fig. 8). A 10-fold acceleration is induced by anionic SDS micelles, whereas nonionic Triton X-100 and cationic 1-*N*-dodecyl-4-methylpyridinium bromide have only modest effects on the rate of the reaction. The efficient catalysis by SDS most likely results from electrostatically enhanced binding of the dienophile to the micelles.

The presence of micelles does not lead to a significant alteration of the efficiency of an intramolecular Diels-Alder reaction [93] as compared with the process in pure water. The most detailed kinetic investigation of the effect of micelles on Diels-Alder cycloadditions has focused on the homo Diels-Alder reaction between 3-(*p*-substituted-phenyl)-1-(2-pyridyl-2-propen-1-one

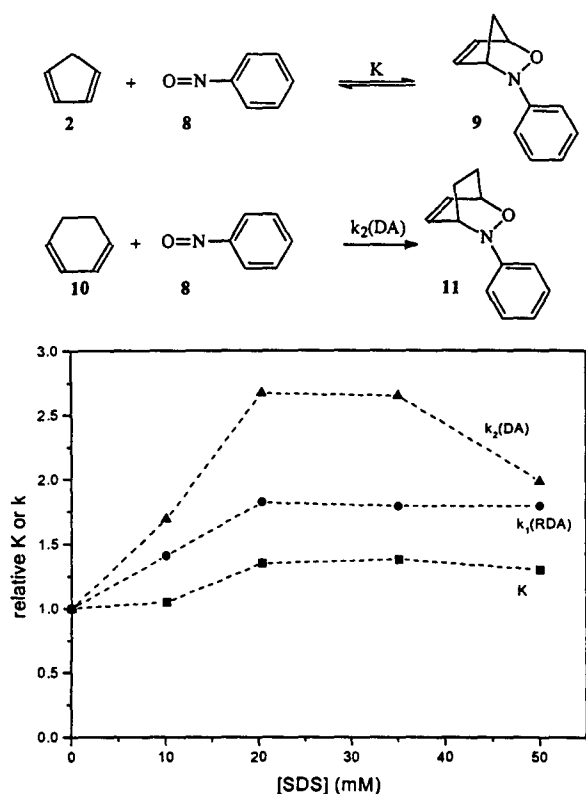


FIG. 7 Relative equilibrium constants for the reversible hetero Diels-Alder reaction of **8** with **2** (■), relative second-order rate constants of the addition of **8** to **10** (▲), and relative first-order rate constants for the retro Diels-Alder reaction of **9** (●) at different concentrations of sodium dodecyl sulfate (SDS). (Data from Ref. 92.)

dienophiles (**14a-g**) with cyclopentadiene (**2**) [94]. The influence of micelles of cetyltrimethylammonium bromide (CTAB), SDS, and dodecyl heptaoxyethylene ether (C_{12}E_7) on this process has been studied (Fig. 9). Note that the dienophiles can be divided into nonionic (**14a-e**), anionic (**14f**), and cationic (**14g**) species. A comparison of the effect of non ionic (C_{12}E_7), anionic (SDS), and cationic (CTAB) micelles on the rates of their reactions with **2** enabled assessment of the importance of electrostatic interactions in micellar catalysis or inhibition. The most important results of this study are summarized in Table 3.

Under the reaction conditions, the effect of micelles on the rate of the Diels-Alder reaction is obviously small and invariably results in a slight *inhibition* of the reaction. The most significant effect occurs for anionic **14f** in CTAB solution and for cationic **14g** in SDS solution. These are the two combinations for which one would expect essentially complete binding of the

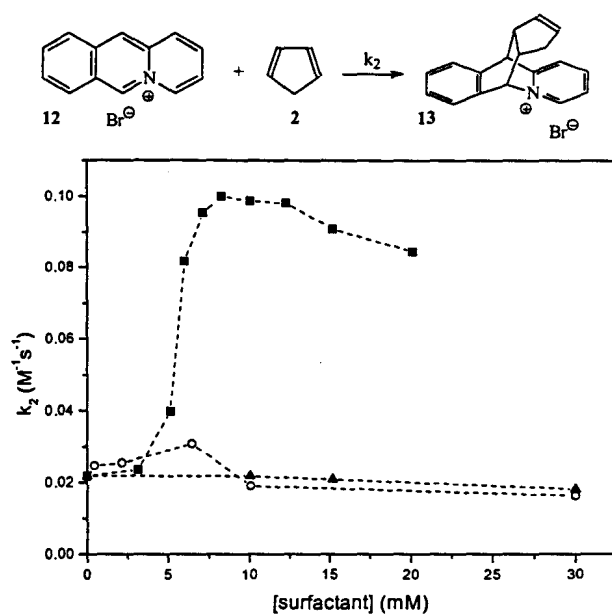


FIG. 8 Second-order rate constants for the reaction of **12** with **2** in aqueous solutions of sodium dodecyl sulfate (SDS) (■), Triton X-100 (○), and *N*-dodecyl-4-methylpyridinium bromide (▲). (Data from Ref. 57.)

dienophile to the micelle as a result of favorable electrostatic interactions in addition to the hydrophobic interactions. Apparently, reaction in the micellar environment is slower than reaction in the bulk aqueous phase, despite the anticipated locally increased concentrations of the reactants in the micellar pseudophase. Also, in the case where electrostatic interactions inhibit binding of the dienophile to the micelle, i.e., **14f** in SDS and **14g** in CTAB solution, a retardation of the reaction is observed. In these cases the dienophile will most likely reside mainly in the aqueous phase. The retardation will result from a decrease in the concentration of **2** in this phase due to its partial solubilization by the micelles.

The kinetics of the aforementioned reactions have been analyzed in terms of the pseudophase model (Fig. 4). For the limiting cases of essentially complete binding of the dienophile to the micelle (**14f** in CTAB and **14g** in SDS solution) the following expression [95] was used:

$$\frac{1}{k_{\text{app}}} = \frac{[\mathbf{2}]_t}{k_{\text{obs}}} = \frac{V_{\text{mol,S}}}{k_m} [\text{S}] + \frac{V_w}{P_2 \cdot V_t \cdot k_m} - \frac{\text{cmc} \cdot V_{\text{mol,S}}}{k_m} \quad (2)$$

Herein $[\mathbf{2}]_t$ is the total number of moles of **2** present in the reaction mixture, divided by the total reaction volume V_t ; k_{obs} is the observed pseudo-first-order rate con-

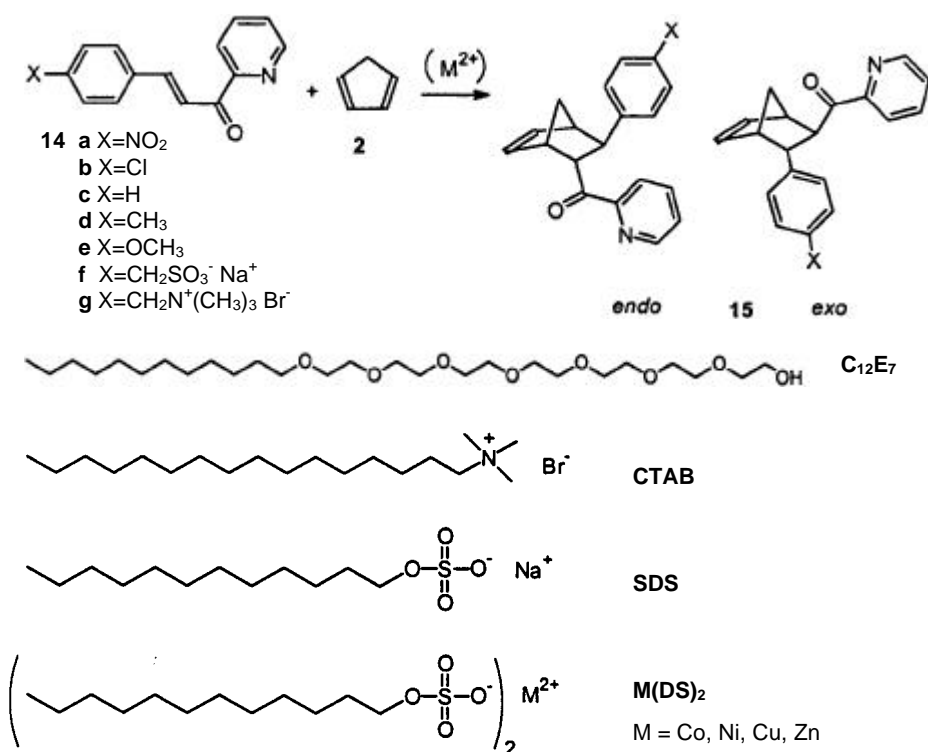


FIG. 9 A Diels-Alder reaction that is subject to Lewis acid catalysis in water.

stant; $V_{\text{mol,S}}$ is an estimate of the molar volume of micellized surfactant S; k_{m} and k_{w} are the second-order rate constants in the aqueous phase and in the micellar pseudophase, respectively; V_{w} is the volume of the aqueous phase; and P_2 is the partition coefficient of **2**

TABLE 3 Influence of Micelles of CTAB, SDS, and C₁₂E₇ on the Apparent Second-Order Rate Constants ($\text{M}^{-1} \text{s}^{-1}$)^a for the Diels-Alder Reaction of **14a**, **14f**, and **14g** with **2** at 25°C^b

Medium ^c	14a	14f	14g
Water	4.02×10^{-3}	1.74×10^{-3}	2.45×10^{-3}
SDS	3.65×10^{-3}	1.44×10^{-3}	1.47×10^{-3}
CTAB	3.61×10^{-3}	0.283×10^{-3}	2.01×10^{-3}
C ₁₂ E ₇	3.35×10^{-3}	1.62×10^{-3}	2.05×10^{-3}

^aThe apparent second-order rate constants are calculated from the observed pseudo-first-order rate constants by dividing the latter by the overall concentration of **2**.

^b[**14**] $\approx 2 \times 10^{-5}$ M; [**2**] = 2.0×10^{-3} M.

^cAll solutions contain 1.0×10^{-4} M EDTA in order to suppress catalysis by trace amounts of metal ions. The concentration of surfactant is 7.8 mM above the cmc of the particular amphiphile under reaction conditions.

Source: Data from Ref. 94.

over the micellar pseudophase and water expressed as a ratio of concentrations. From the dependence of $[2]_{\text{t}}/k_{\text{obs}}$ on the concentration of surfactant, P_2 and k_{m} were obtained. Table 4 shows that the partition coefficients of **2** over SDS or CTAB micelles and water are similar. Comparison of the rate constants in the micellar pseudophase calculated using the pseudophase model with those in water (Tables 3 and 4) demonstrates a remarkable retardation induced by the micelles.

This retardation is unlikely to be a result of a micellar medium effect. Information concerning the mi-

TABLE 4 Analysis Using the Pseudophase Model: Partition Coefficients for **2** over CTAB or SDS Micelles and Water and Second-Order-Rate Constants for the Diels-Alder Reaction of **14f** and **14g** with **2** in CTAB and SDS Micelles at 25°C

Surfactant	Dienophile	P_2 ($\pm 10\%$)	k_{m} ($\text{M}^{-1} \text{s}^{-1}$) ($\pm 10\%$)
CTAB	14f	65 ^a	5.9×10^{-6}
SDS	14g	49 ^a	3.1×10^{-5}

^aCorrected data; see Ref. 95.

Source: Data from Ref. 94.

croenvironment experienced by the Diels-Alder reactants was obtained from analysis of the *endo-exo* ratio of the reaction between **14c** and **2** in surfactant solution and in a number of different organic and aqueous media [94] (see also Section III.B). The results of the study clearly point toward a waterlike environment for the Diels-Alder reaction in the presence of micelles. The inhibitory effect of micelles is suggested to result from the fact that diene and dienophile are on average located in different parts of the micelles. The diene seems to prefer the hydrophobic center of the micelle, whereas the dienophile has a stronger affinity for the Stern region. Evidence comes from ¹H-NMR relaxation time studies in which paramagnetic ions are added to the micellar solutions [38,94]. Multivalent ions were used with a charge opposite to that of the surfactant headgroup, ensuring strong binding of these species to the Stern region of the micelles. As these paramagnetic ions enhance the relaxation of the protons in their vicinity, species bound to the Stern region will experience a more enhanced rate of relaxation from those residing in the core of the micelle. Comparison of Fig. 10 and Fig. 11 indeed demonstrates that the relaxation rate enhancement experienced by the diene is significantly smaller than that experienced by the dienophile.

In conclusion, the fact that micelles have a rather limited influence on the rate of bimolecular as well as retro and intramolecular Diels-Alder reactions suggests (1) that the micellar medium experienced by the reactants is not too different from water and (2) that concentration effect of the reactants in the micelles is not too efficient. The latter effect is probably a result of the fact that diene and dienophile prefer different binding sites in the micelle.

B. Effect of Micelles on the *Endo-Exo* Selectivity

Few detailed studies have been performed regarding micellar effects on *endo-exo* selectivities. Diego-Castro and Hailes [96] have studied the influence of micelles on the Diels-Alder reaction of cyclopentadiene with several alkyl acrylates of different chain lengths (methyl, ethyl, pentyl, heptyl, and nonyl). *Endo-exo* ratios in micellar media were strikingly similar to those in water irrespective of the length of the alkyl group in the dienophile. Unfortunately, the reactions were performed using a surfactant concentration close to the cmc, where solubilization of the reactants by the micelles is rather inefficient and the reaction is more likely to take place in bulk water than in the micelles.

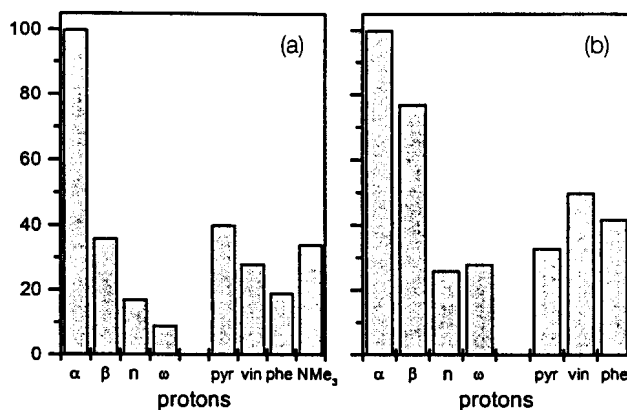


FIG. 10 Paramagnetic ion-induced spin-lattice relaxation rates (r_p) of the protons of **14c** (a) and **14g** (b) in SDS solution and of SDS in the presence of **14c** or **14g**, normalized to r_p for the surfactant α -CH₂. The solutions contained 50 mM SDS, 8 mM **14c** or **14g**, and 0 or 0.2 mM DyCl₃ and 0 or 0.6 mM cyclen. (Data from Ref. 94.)

Braun, Schuster, and Sauer [97] have studied the *endo-exo* ratio of the reaction of cyclopentadiene with acrylonitrile and butyl acrylate in micellar media. The *endo-exo* ratios were significantly larger than in organic solvents, which seems to point toward a highly polar micellar reaction medium. Unfortunately, no comparisons were made with the *endo-exo* selectivity in pure water. Otto et al. [94] have studied the effect of micelles of SDS, CTAB, and C₁₂E₇, on the *endo-exo* ratio of the Diels-Alder reaction of **14c** and **2** (Fig. 9). Com-

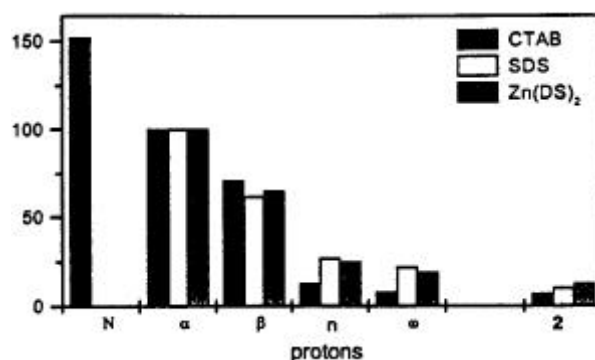


FIG. 11 Paramagnetic ion-induced spin-lattice relaxation rates (r_p) of the protons of **2** in CTAB, SDS, or Zn(DS)₂ solution and of these surfactants in the presence of **2**, normalized to r_p for the surfactant α -CH₂. The solutions contained 25 mM Zn(DS)₂, 50 mM CTAB or SDS, 3 mM **2**, and 0 or 0.4 mM [Cu(EDTA)]²⁻ for CTAB solutions and 0 or 0.2 mM Cu(NO₃)₂ for SDS and Zn(DS)₂ solutions. (Data from Ref. 94.)

TABLE 5 *Endo-Exo* Product Ratios of the Diels-Alder Reaction of **14c** with **2** in Surfactant Solutions Compared with Water and Organic Solvents

Medium	% <i>Endo</i> -% <i>exo</i>
100 mM CTAB	86-14
100 mM SDS	88-12
100 mM C ₁₂ E ₇	85-15
Water	84-16
Ethanol	77-23
Acetonitrile	67-33

parison of the results with those obtained for organic solvents and pure water (Table 5) demonstrates that the beneficial solvent effect of water is still present in the micelle-mediated reaction.

In summary, *endo-exo* selectivities in micellar media tend to be comparable to those in pure water [89] and significantly larger than those in organic solvents. Apparently, surfactants can be used in order to improve the solubility of the Diels-Alder reactants in water, without significant deterioration of the selectivity as compared with pure water. Interestingly, in microemulsions the *endo-exo* selectivity is reduced significantly [89,98].

C. Micellar Effects on the Regioselectivity

Significant work in this area has been carried out by Jaeger et al. An interesting issue that was addressed in the early days of micellar catalysis involves the question of how binding to specific sites in micelles could affect the stereochemistry of the reactions. For example, extensive structural changes in substrates were expected to influence the depth of penetration of the substrate into the micellar core with a concomitant change in the efficiency of the micellar catalysis. This expectation was not borne out in practice [99,100].

In fact, one could ask how "micellar binding sites" can be defined with sufficient precision to allow conclusions about the details of the relevant microenvironment and orientation of the substrate. In view of the micellar structure, it is more appropriate to consider a range of binding situations of small differences in Gibbs energy of binding and involving a range of substrate orientations. Most substrates in micelle-catalyzed reactions contain at least one polar substituent that prefers to bind at or close to the micellar surface and at least partly in direct contact with water. Solely apolar molecules, such as alkanes, will preferentially bind in

the hydrophobic core of the micelle, assuming orientations that lead to a minimal disturbance of the chain packing of the surfactant molecules.

Jaeger et al. [101] examined how monohalogenation of alkyl phenyl ethers C₆H₅OR (R = *n*-C₅H₁₁, *n*-C₉H₁₉, and *n*-C₁₂H₂₅) by chlorine and bromine in micellar solutions of SDS and in vesicular solutions to give 4-XC₆H₄OR and 2-XC₆H₄OR exhibits *ortho/para* ratios and reaction rates different from those in aqueous buffer solutions in the absence of surfactants. Indeed, in the micelles the *o/p* ratio decreases with increasing length of R, whereas the second-order rate constant decreases in the series. These regioselectivity and kinetic data can be rationalized by assuming different solubilization sites for the aromatic ethers depending on the length of the R substituent. These differences lead to different reaction environments and concomitant kinetic differences. Lengthening of R is proposed to lead to solubilization "deeper" in the micelle and changes in the *o/p* preference.

In another series of studies, Jaeger et al. examined regioselectivity control of Diels-Alder reactions for cases in which the diene or both the diene and dienophile were amphiphilic molecules themselves. In a Diels-Alder process involving a cationic surfactant 1,3-diene with a neutral non surfactant dienophile, the orientational effects within the micellar aggregates were not sufficiently strong to overcome the intrinsically preferred regioselectivity of the reaction [102]. Modest regioselectivity was found for a Diels-Alder reaction of another cationic surfactant diene with cationic surfactant dienophiles [103,104]. The reactions were performed at 100°C, most likely decreasing the organizational abilities of the aqueous aggregate compared with those at lower temperatures.

A substantially larger regioselectivity [105] was found in a study employing amphiphilic diene **16** (cmc = 1.0 × 10⁻⁴ M) and amphiphilic dienophile **17** (cmc = 4.4 × 10⁻³) (Fig. 12). The cycloadducts **18** and **19** were formed, which were separated by preparative reverse-phase HPLC and characterized by ¹H-NMR spectroscopy.

Since the substituents at carbons 1 and 2 in **17** are close to being electronically and sterically equivalent with respect to the dienophile reaction center, no regiochemical preference is anticipated in the absence of interfacial orientational effects in the mixed micelles formed from **16** and **17**. Evidence for this assumption was also obtained from an analysis of the regioselectivity of the Diels-Alder reaction of **20** and **21** in toluene. As expected, the two analogous cycloadducts were obtained in equal amounts. Interestingly, the re-

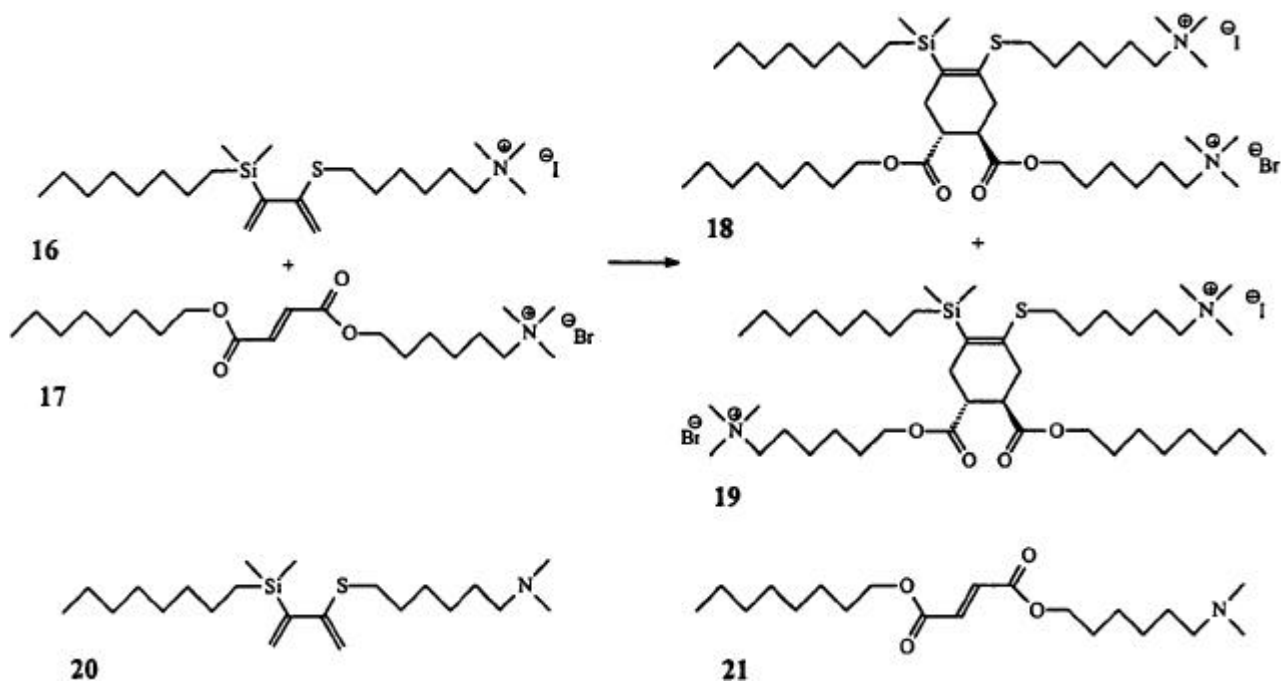


FIG. 12 A regioselective Diels-Alder reaction between a surfactant diene and a surfactant dienophile.

actions of **16** with **17** at concentrations above their cmc values gave an **18:19** ratio of 6.6:1. Therefore it is clear that interfacial and related orientational effects that result from surfactant aggregation can induce significant regioselectivity in a Diels-Alder reaction in aqueous solution.

D. Micellar Effects on the Enantioselectivity

Recently, a report appeared that described the first Diels-Alder reaction in aqueous chiral micellar media [106]. The novel (s)-leucine-derived chiral micellar amphiphile **22** was used as a catalyst for the Diels-Alder reaction of cyclopentadiene with *n*-nonyl acrylate (**23**) (Fig. 13).

Preferential formation of the *R*-endo isomer was observed. Using a surfactant concentration of 11 mg L⁻¹ and in the presence of 4.86 M LiCl, the yield was 75%, with an *endo/exo* ratio of 2.2 and an enantioselectivity of 15% (*R*). This result may be compared with the maximum enantioselectivity (21%) found for Diels-Alder reactions in the presence of cyclodextrins. In the absence of surfactant, the reaction in water gave a yield of 70% and an *endo/exo* ratio of 1.7. Further optimization of the structure of the chiral micellar catalyst might well lead to improved enantioselectivities. In this context it may be noticed that aqueous Diels-Alder re-

actions catalyzed by chiral Lewis acids may exhibit enantioselectivities up to 74% [36,37].

E. Effects of Micelles with Catalytically Active Counterions

The most efficient means of accelerating Diels-Alder reactions is catalysis by Lewis acids. In aqueous media this process is hampered by the strong interaction of the catalysts with water [62]. However, one example has been reported where this difficulty was overcome by modification of the dienophiles so that they can form a chelate with the catalyst ions (Fig. 9) [35-37].

The reaction of these dienophiles with cyclopentadiene in the *absence* of Lewis acid catalysts has been described in Section III.A. In that case introduction of micelles into the aqueous reaction mixture induced a modest retardation of the reaction.

Micellar catalysis of this reaction in combination with Lewis acid catalysis has been studied in detail [94]. The dodecyl sulfate surfactants Co(DS)₂, Ni(DS)₂, Cu(DS)₂, and Zn(DS)₂ containing catalytically active counterions are extremely potent catalysts for the Diels-Alder reaction between **14** and **2**. Figure 14 shows the dependence of the rates of the Diels-Alder reactions of **14c**, **14f**, and **14g** with **2** on the concentration of Cu(DS)₂. For all three dienophiles the apparent second-order rate constant for their reaction with **2**

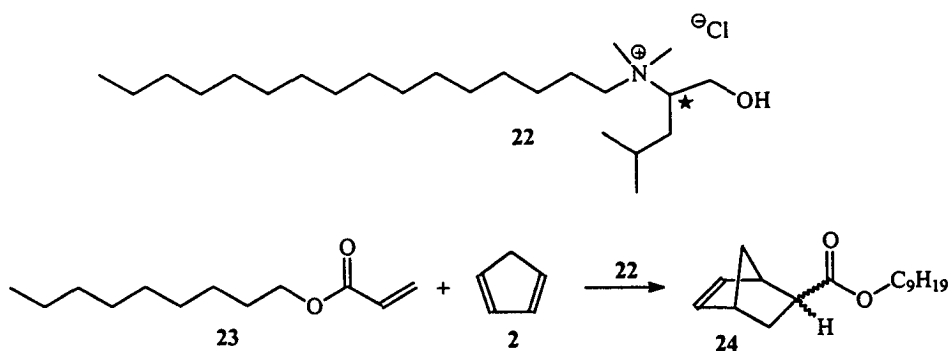


FIG. 13 The first example of enantioselectivity induced by a chiral surfactant in a micelle-catalyzed Diels-Alder reaction.

increases dramatically when the concentration of $\text{Cu}(\text{DS})_2$ reaches the cmc (1.11 mM). Beyond the cmc, the dependence of the rate on the surfactant concentration is subject to two counteractive influences. At higher surfactant concentration, a larger fraction of dienophile will be bound to the micelle, where it reacts faster than in bulk water, resulting in an increase in the rate of the reaction. At the same time, the concentration of diene in the micellar pseudophase will drop with increasing surfactant concentration due to the increase in the volume of the micellar pseudophase. At higher surfactant concentrations the dienophile will be nearly completely bound to the micelles and the dilution effect will start to dominate the behavior. Together, these two effects result in the appearance of a rate maximum at a specific concentration of surfactant that is typical for micelle-catalyzed bimolecular reactions (see also Fig. 8). The position of the maximum depends primarily on the micelle-water partition coefficients of diene and dienophile.

Interestingly, the acceleration relative to the reaction in organic media in the absence of catalyst approaches enzymelike magnitudes: compared with the process in acetonitrile (second-order rate constant = $1.40 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$), $\text{Cu}(\text{DS})_2$ micelles accelerate the Diels-Alder reaction between **14a** and **2** by a factor of 1.8×10^6 .

Also the effects of cationic (CTAB) and non ionic (C_{12}E_7) surfactants on the Cu^{2+} -catalyzed reaction have been studied. However, these systems were much less efficient than $\text{Cu}(\text{DS})_2$, suggesting that a local high concentration of catalyst ions in the Stern region of the micelles is a prerequisite for a highly efficient interaction with the dienophile.

The essentially complete binding of **14g** to the $\text{Cu}(\text{DS})_2$ micelles allowed treatment of the kinetic data of Fig. 14 using the pseudophase model. Furthermore, complete binding of **14g** to the copper ions was as-

sumed, which was supported by ultraviolet-visible analysis [94]. Using Eq. (2), a $\text{Cu}(\text{DS})_2$ -water distribution coefficient for **2** of 86 was obtained [95]. The second-order rate constant for reaction in the micellar pseudophase was calculated to be $0.21 \text{ M}^{-1} \text{ s}^{-1}$. Comparison of this rate constant with those for the reaction in acetonitrile ($0.472 \text{ M}^{-1} \text{ s}^{-1}$) and ethanol ($0.309 \text{ M}^{-1} \text{ s}^{-1}$) seems to indicate a relatively apolar medium for the Diels-Alder reaction. This conclusion is hard to reconcile with the ionic character of two of the three reaction partners involved.

More insight into the local environment for the catalyzed reaction was obtained from the influence of substituents on the rate of this process in micellar and in different aqueous and organic solvents. The Hammett

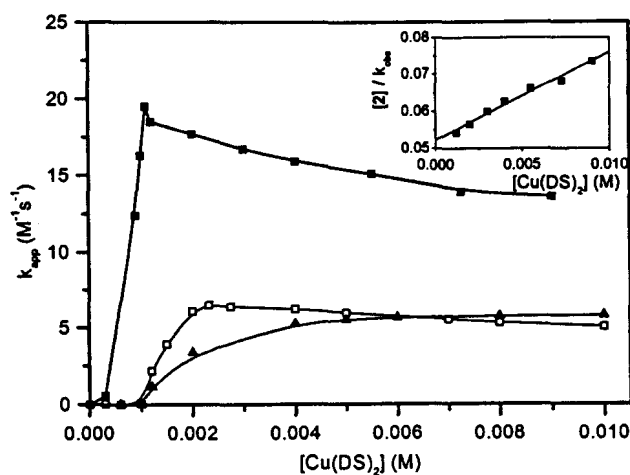


FIG. 14 Plots of the apparent second-order rate constant (k_{app}) versus the concentration of $\text{Cu}(\text{DS})_2$ for the Diels-Alder reaction of **14c** (\square), **14f** (\blacktriangle), and **14g** (\blacksquare) with **2** at 25°C . The inset shows the treatment of the data for the reaction of **14g** according to the pseudophase model. (Data from Ref. 94.)

r value in Cu(DS)₂ solution was found to resemble closely that in aqueous solution rather than those in organic solvents, suggesting an aqueous microenvironment for the reaction [94].

It appears that the outcome of the analysis using the pseudophase model (a rather apolar reaction environment) is not in agreement with experimental observations (an aqueous reaction environment). Apparently, the assumptions of the pseudophase model are not valid for the Diels-Alder reaction studied. In particular, the treatment of the micellar pseudophase as a homogeneous "solution" might not be warranted. As noted in Section III.A, there are strong indications that the diene and the dienophile reside on average in different parts of the micelle, the diene preferring the core and the dienophile the Stern region of the micelles. Additional paramagnetic ¹H-NMR relaxation rate studies of the binding location of the reactants in Zn(DS)₂ micelles further support this suggestion [38,94]. Surely, spatial separation of diene and dienophile will impede their reaction.

In summary, the use of anionic micelles with bivalent metal ions as catalytically active counterions can lead to accelerations of suitable Diels-Alder reactions of enzymelike magnitude. The high efficiency of these systems mainly results from the efficient interaction between dienophile and catalysts in the Stern region of the micelles, where both species are present in high local concentration. Even larger accelerations are anticipated upon modification of the diene so that this species also binds to the Stern region rather than in the core of the micelle. Examples of similar micellar systems have found application in synthetic organic chemistry [107].

IV. SUMMARY AND OUTLOOK

It is now well established that many Diels-Alder reactions, both of normal electron demand and of inverse electron demand, can be substantially accelerated by using water as the reaction medium. Also, *endo/exo* ratios are usually improved for aqueous media. These findings had important implications for further extending the versatility of Diels-Alder reactions in organic synthesis and for providing a stimulus for detailed studies of medium effects on pericyclic reactions. These interesting developments called for studies of Diels-Alder reactions in micellar solutions. By concentrating the diene and dienophile in the micellar reaction volume, further enhancements were anticipated. Furthermore, solubilization of the Diels-Alder reaction partners in the micelles could offer a solution for

improving the otherwise limited solubility of diene and dienophile in water. Finally, effects on the Diels-Alder stereochemistry were expected. Specific binding could lead to regioselectivity, whereas the use of chiral micelle-forming surfactants would provide a possibility for obtaining enantioselectivity in appropriate Diels-Alder processes. Studies have illustrated the potential power to bring about these appealing results. Micellar catalysis of Diels-Alder reactions has been pursued and could indeed induce significant accelerations. Examples have been shown in this chapter. However, it is a requisite that diene and dienophile bind to rather similar binding sites in the micelle. In the case of, for example, an apolar diene and a moderately polar dienophile, the diene will preferentially reside in the core of the micelle and encounters with the dienophile, preferentially sitting at the micellar surface, will be hampered. The overall result will then be micellar inhibition rather than catalysis. Extreme rate enhancements can be obtained by combining micellar and Lewis acid catalysis. However, a specially designed dienophile is required for such a catalytic process.

Binding of dienes and dienophiles to micellar aggregates will certainly improve their solubilities in water and extend the potential for using aqueous reaction media for Diels-Alder reactions. The use of micelles with the aim of inducing favorable regioselectivity and enantioselectivity has had only modest success. However, it is anticipated that challenging developments in this area are possible through variation of the structural architectures of diene, dienophile, and micelle-forming amphiphile.

ACKNOWLEDGMENT

The authors gratefully acknowledge Miss H. E. Wolters for typing the manuscript.

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