Diels-Alder reactions in micellar media

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I. INTRODUCTION TO DIELS-ALDER REACTIONS

The Diels-Alder reaction is a [4+2] cycloaddition in which a diene (four-π component) reacts with a dienophile (two-π 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.

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 σ-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]).
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 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.
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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 10^8 in organic solvents. Also the endo/exo selectivity may clearly respond to the presence of Lewis acids such as AlCl_3·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.
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 donor site. 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 effects. 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 regio-selectivity.

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 $10^{-2}-10^{-1}$ 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].

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 solubilizate and is often of the order of $10^{-2}$-$10^6$ 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 solubilizate for the micelle to be quantified by a partition coefficient $P$. Frequently $P$ is expressed as the ratio of the mole fractions of solubilizate 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 solubilizates 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 unimolecular and bimolecular 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 bimolecular 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

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

(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.
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 reactions 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
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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.)

The 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 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 cycloadditions 3-(p-substituted-phenyl)-1-(2-pyridyl-2-propen-1-one

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

<table>
<thead>
<tr>
<th>Medium</th>
<th>$\Delta^oG^\ddagger$ (kJ/mol)</th>
<th>$\Delta^oH^\ddagger$ (kJ/mol)</th>
<th>$T \Delta^oS^\ddagger$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 M SDS</td>
<td>78.7</td>
<td>45.1</td>
<td>-33.6</td>
</tr>
<tr>
<td>Water</td>
<td>78.4</td>
<td>62.2</td>
<td>-16.2</td>
</tr>
<tr>
<td>0.5 M LiCl</td>
<td>77.8</td>
<td>41.9</td>
<td>-35.9</td>
</tr>
<tr>
<td>Ethanol</td>
<td>87.5</td>
<td>52.2</td>
<td>-35.3</td>
</tr>
<tr>
<td>Dioxane</td>
<td>89.1</td>
<td>48.5</td>
<td>-40.6</td>
</tr>
</tbody>
</table>

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.)
dienophiles (14a-g) with cyclopentadiene (2) [94]. The influence of micelles of cetyltrimethylammonium bromide (CTAB), SDS, and dodecyl heptaethylene ether (C12E7) 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 (C12E7), 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 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:

$$\frac{1}{k_{\text{app}}} = \frac{(2)_i}{k_{\text{obs}}} = \frac{V_{\text{mol.S}}}{[S]} + \frac{V_w}{P_2 \cdot V_i \cdot k_m \cdot \text{cmc} \cdot V_{\text{mol.S}}}$$

Herein (2)_i is the total number of moles of 2 present in the reaction mixture, divided by the total reaction volume V_i; k_{obs} is the observed pseudo-first-order rate con-
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\[
\begin{align*}
X = \text{NO}_2 & & \text{a} \\
X = \text{Cl} & & \text{b} \\
X = \text{H} & & \text{c} \\
X = \text{CH}_3 & & \text{d} \\
X = \text{OCH}_3 & & \text{e} \\
X = \text{CH}_2\text{SO}_3^- \text{Na}^+ & & \text{f} \\
X = \text{CH}_2\text{N}^+(\text{CH}_3)_2 \text{Br} & & \text{g}
\end{align*}
\]

\[14 \quad \text{X=NO}_2 \quad + \quad 2 \quad \xrightarrow{(M^{2+})} \quad 15 \quad \text{end} \quad 16 \quad \text{exo}\]

\[\text{C}^{12} \text{E}_7\]

\[\text{CTAB}\]

\[\text{SDS}\]

\[\text{M(DS)}_2 \quad \text{M = Co, Ni, Cu, Zn}\]

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

\[\text{stant}; \quad V_{\text{mol,S}} \quad \text{is an estimate of the molar volume of micellezed surfactant S; } \quad k_m \quad \text{and} \quad k_w \quad \text{are the second-order rate constants in the aqueous phase and in the micellar pseudophase, respectively; } \quad V_w \quad \text{is the volume of the aqueous phase; and } \quad P_2 \quad \text{is the partition coefficient of 2.}\]

**TABLE 3** Influence of Micelles of CTAB, SDS, and C\(_{12}\)E\(_7\) on the Apparent Second-Order Rate Constants (\(M^{-1} s^{-1}\))\(^a\) for the Diels-Alder Reaction of 14a, 14f, and 14g with 2 at 25°C\(^b\)

<table>
<thead>
<tr>
<th>Medium(^c)</th>
<th>14a</th>
<th>14f</th>
<th>14g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>4.02 \times 10^{-3}</td>
<td>1.74 \times 10^{-3}</td>
<td>2.45 \times 10^{-3}</td>
</tr>
<tr>
<td>SDS</td>
<td>3.65 \times 10^{-3}</td>
<td>1.44 \times 10^{-3}</td>
<td>1.47 \times 10^{-3}</td>
</tr>
<tr>
<td>CTAB</td>
<td>3.61 \times 10^{-3}</td>
<td>0.283 \times 10^{-3}</td>
<td>2.01 \times 10^{-3}</td>
</tr>
<tr>
<td>C(_{12})E(_7)</td>
<td>3.35 \times 10^{-3}</td>
<td>1.62 \times 10^{-3}</td>
<td>2.05 \times 10^{-3}</td>
</tr>
</tbody>
</table>

\(^a\)Corrected data; see Ref. 95.

\[^b\]Corrected data; see Ref. 95.

\[^c\]All solutions contain 1.0 \times 10^{-3} 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.

**TABLE 4** Analysis Using the Pseudophase Model: Partition Coefficients for 2 over CTAB of 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

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Dienophile</th>
<th>(P_2 \ (\pm 10%))</th>
<th>(k_m \ (M^{-1} s^{-1}) \ (\pm 10%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTAB</td>
<td>14f</td>
<td>65(^a)</td>
<td>5.9 \times 10^{-6}</td>
</tr>
<tr>
<td>SDS</td>
<td>14g</td>
<td>49(^a)</td>
<td>3.1 \times 10^{-5}</td>
</tr>
</tbody>
</table>

\(^a\)Corrected 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 $^1$H-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 $\alpha$-CH$_3$. The solutions contained 50 mM SDS, 8 mM 14c or 14g, and 0 or 0.2 mM DyCl$_3$ and 0 or 0.6 mM cyclen. (Data from Ref. 94.)](image)

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 C$_{12}$E$_7$, 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 $\alpha$-CH$_3$. 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(NO$_3$)$_2$ for SDS and Zn(DS)$_2$ solutions. (Data from Ref. 94.)](image)


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

<table>
<thead>
<tr>
<th>Medium</th>
<th>%Endo-%exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mM CTAB</td>
<td>86-14</td>
</tr>
<tr>
<td>100 mM SDS</td>
<td>88-12</td>
</tr>
<tr>
<td>100 mM C12E7</td>
<td>85-15</td>
</tr>
<tr>
<td>Water</td>
<td>84-16</td>
</tr>
<tr>
<td>Ethanol</td>
<td>77-23</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>67-33</td>
</tr>
</tbody>
</table>

The microwave catalysis for Alder reactions was observed in water, with significant differences leading to the stereochemistry of the reactions being affected. In view of the increasing size of the substituents in micellar media, it is more appropriate to consider a range of binding situations of small differences in the micellar structure, it is more appropriate to consider a range of binding situations of small differences in the efficiency of the micellar catalysis. This expectation was not borne out in practice [99,100].

In another series of studies, Jaeger et al. [101] examined how monohalogenation of alkyl phenyl ethers C6H5OR (R = n-C8H17, n-C9H19, and n-C12H25) by chlorine and bromine in micellar solutions of SDS and in vesicular solutions to give 4-OC6H4OR and 2-OC6H4OR exhibits ortho/para ratios and reaction rates different from those in aqueous buffer solutions in the absence of surfactants. Indeed, in the micelles the ortho preference 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 ortho preference.

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 micelles 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-C8H17, n-C9H19, and n-C12H25) by chlorine and bromine in micellar solutions of SDS and in vesicular solutions to give 4-OC6H4OR and 2-OC6H4OR exhibits ortho/para ratios and reaction rates different from those in aqueous buffer solutions in the absence of surfactants. Indeed, in the micelles the ortho preference 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 ortho preference.
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-nonly 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 reactions 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.
increases dramatically when the concentration of Cu(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 × 10$^{-5}$ M$^{-1}$ s$^{-1}$), Cu(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 Cu(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 Cu(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 assumed, which was supported by ultraviolet-visible analysis [94]. Using Eq. (2), a Cu(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 M$^{-1}$ s$^{-1}$. Comparison of this rate constant with those for the reaction in acetonitrile (0.472 M$^{-1}$ s$^{-1}$) and ethanol (0.309 M$^{-1}$ 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
\( \rho \) 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 \(^1\)H-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.

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95. In the original paper [94] Eq. (2) and the data calculated with it contained a small error. This has now been corrected. We gratefully acknowledge Prof. P. Walde for pointing this out.

