Catalysis of Diels-Alder reactions in water
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Micellar Catalysis

This chapter describes the effects of micelles on the Diels-Alder reaction that was introduced in Chapter 2. In the absence of Lewis-acid catalysts micelles induce modest retardations of this reaction, which is rather surprising in view of the usually high affinity of the Diels-Alder reactants for micellar aggregates. This intriguing lack of reactivity most likely is a result of different average binding locations of diene and dienophile. Evidence from $^1$H-NMR shift measurements and paramagnetic-ion induced relaxation rate enhancements is presented. Significantly, in the presence of Lewis-acid catalysts, micelles can induce dramatic rate enhancements, approaching enzyme-like magnitudes. The high rates of the reaction in these media is attributed primarily to an extremely efficient interaction between the dienophile and the Lewis-acid catalyst in the Stern region of the micelle.

5.1 Introduction

“Nonsense McBain!” Those words were the first reaction of the chairman of a meeting of the Royal Society of London on the lecture of McBain, wherein he suggested the existence of assemblies of surfactant molecules in aqueous solution. However, as soon became apparent, McBain was right when he postulated the spontaneous formation of dynamic aggregates by fatty acid salts, although the bilayer structure he suggested was later corrected by Hartley, who introduced the spherical structures we now know as micelles. In the years that have passed, micellar solutions have proven to be an extremely versatile topic of research. The catalytic potential of micellar aggregates has received special attention. This chapter will focus on micellar catalysis of a Diels-Alder reaction and will provide, for the first time, a link between micellar catalysis and Lewis-acid catalysis. Before elaborating on this, the physical properties and catalytic potential of micellar solutions will be briefly reviewed.

5.1.1 Micellar aggregates: structure and dynamics

Surfactant molecules (also called amphiphiles or detergents) unite a polar or ionic head and a nonpolar tail within the same molecule. The nonpolar part, which is typically made up of one or more alkyl chains, causes these compounds to be sparingly soluble in water, whereas the polar or ionic part interacts strongly with water. Upon increasing the concentration of the amphiphilic compound in water, at a certain point the solubility limit will be reached and phase separation will set in. Due to the efficient interactions between the polar headgroups and the surrounding water molecules, a complete phase separation is usually unfavourable. Instead, the process will be arrested in an intermediate stage with concomitant formation of aggregates of amphiphilic material, wherein the
nonpolar parts stick together and are shielded from water, whereas the headgroups are located in the outer regions of the aggregate. A multitude of different aggregates can be formed in this way.

The morphology of these assemblies is mainly determined by the shape of the individual surfactant molecules. Ninham and Israelachvilli have introduced the concept of the packing parameter, allowing prediction of the type of aggregate formed by considering the cross-sectional headgroup area and the length and volume of the nonpolar part of the amphiphile molecules. Surfactants containing a single alkyl chain usually form micelles when dissolved in water. A schematic representation of a spherical micelle is given in Figure 5.1. The formation of micelles sets in after a certain critical concentration of surfactant (the critical micelle concentration, $cmc$) has been reached. Beyond this concentration the addition of more surfactant molecules will result in an increase in the number of micelles, while the concentration of monomeric surfactant remains almost constant. Micellisation is usually driven by an increase in entropy, resulting from the liberation of the water molecules from the hydrophobic hydration shells of the monomeric amphiphile molecules, whereas the enthalpy change is generally close to zero.

Micelles are extremely dynamic aggregates. Ultrasonic, temperature and pressure jump techniques have been employed to study the rate constants associated with the different equilibria involved. Rates of uptake of monomers into micellar aggregates are close to diffusion controlled. The residence times of the individual surfactant molecules in the aggregate are typically in the order of $10^{-5}$ - $10^{-6}$ seconds, whereas the lifetime of the micellar entity is about $10^{-3}$ - $10^{-1}$ seconds. Factors that lower the $cmc$ usually increase the lifetimes of the micelles as well as the residence times of the surfactant molecules in the micelle. Due to this dynamic character, the size and shape of micelles are subject to appreciable structural fluctuations. Hence, micellar aggregates are polydisperse, as is demonstrated by small-angle neutron scattering data. Average aggregation numbers are typically in

![Figure 5.1. Schematic representation of a spherical micelle.](image-url)
Micellar catalysis

the range of 40 - 100\(^{12}\). The highly dynamic character has for a long time successfully misled chemists in their conception of the structure of a micelle.

Extensive discussions have focused on the conformation of the alkyl chains in the interior\(^{13}\). It has been has demonstrated that the alkyl chains of micellised surfactant 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 centre of the chain\(^{14}\). As a result, the methyl termini of the surfactant molecules can be located near the surface of the micelle, and have even been suggested to be able to protrude into the aqueous phase\(^{15}\). They are definitely not all gathered in the centre of the micelle as is often suggested in pictorial representations. NMR studies have indicated that the hydrocarbon chains in a micelle are highly mobile, comparable to the mobility of a liquid alkane\(^{16}\).

Another topic of heated debate comprised the extent of water penetration into the hydrocarbon interior\(^{13}\). Small-angle neutron scattering studies have resolved this matter by indicating that significant water penetration into the micellar core is unlikely\(^{11a,17}\). However, at the interface, extensive contact between water and the hydrocarbon chain segments definitely occurs. The headgroups of the micelle are extensively hydrated. For ionic micelles, a large fraction of the counterions are located in the vicinity of the headgroups. These counterions normally retain their first hydration shell\(^{18}\). The part of the surfactant that contains the headgroups and a variable fraction of the counterions is called the Stern region. This region comprises an appreciable electric field and a high concentration of ions (several molar) at the interface between the nonpolar interior and the aqueous exterior of the micelle and can be expected to exhibit unique properties. For pyridinium iodides the polarity of this region has been probed with the aid of the interionic charge transfer band characteristic for these species. The results indicate a somewhat reduced polarity of the Stern region compared to bulk water\(^{19}\). The important role of this region in solubilisation and micellar catalysis is reviewed in the next sections.

5.1.2 Solubilisation

One of the most important characteristics of micelles is their ability to take up all kinds of substances. Binding of these compounds to micelles is generally driven by hydrophobic and electrostatic interactions. The dynamics of solubilisation into micelles are similar to those observed for entrance and exit of individual surfactant molecules. Their uptake into micelles is close to diffusion controlled, whereas the residence time depends on the structure of the molecule and the solubilisate, and is usually in the order of 10\(^{-4}\) to 10\(^{-6}\) seconds\(^{9b,20}\). Hence, these processes are fast on the NMR time scale.

Solubilisation is usually treated in terms of the 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 solubilisate for the micelle to be quantified by a partition coefficient P. Different definitions of P can be found in the literature, differing in their description of the micellar phase. Frequently P is
expressed as a ratio of the mole fractions of solubilisate in the micellar pseudophase and the aqueous phase. However, when dealing with catalysis by micellar aggregates it is more convenient to express P as a ratio of concentrations.

The incorporation of nonionic solutes into micelles has recently been subject to multi-parameter analysis. These studies attribute a dominant role to the volume of the solubilisate in determining the partition coefficient. This suggestion was rationalised on the basis of hydrophobic interactions being more efficient for larger molecules. The hydrogen-bond acceptor capacity of the solubilisate on the other hand counteracted the uptake by the micelles, suggesting that the micellar microenvironment is a less efficient hydrogen-bond donor than bulk water. Still, quantitative understanding of solubilisation is far from complete. For instance, Hirose and Sepulveda have demonstrated that replacement of a proton in the benzene molecule with a hydrophilic group enhances its interaction with the micelle. The authors attribute this to a shift in the average binding location more towards the surface of the micelle where dipole-dipole interactions are more favourable.

The time-averaged location of different solubilisates in or at the micelle has been a topic of contention. The nature of the solubilisate largely determines its position in the aggregate. Saturated hydrocarbons show a preference for the interior of the micelle. In contrast, solubilisates that contain hydrophilic substituents, such as alcohols or amines, prefer to stay at the surface, where the hydrophilic groups can remain largely hydrated. In the case that the solubilisate has an amphiphilic character itself, the apolar parts generally are directed towards the centre of the micelle and its orientation in the aggregate resembles that of the surfactant molecules. The position of aromatic hydrocarbons has been intensively debated. Investigations have focused on the distribution of benzene in aqueous solutions of cetyltrimethylammonium bromide (CTAB) and sodium dodecylsulfate (SDS). Some authors have claimed that this solubilisate resides mainly in the interior of these micelles, whereas others have reported data that indicated binding at the interface or in both regions simultaneously. These seemingly contradictory data can be understood in terms of differences in the concentrations of solubilized benzene. At low concentrations these compounds prefer the outer regions of the micelle, whereas at higher concentrations, when the interfacial region is saturated, they penetrate deeper into the micelle with concomitant swelling of the aggregate.

The unexpected preference for the interfacial region at lower concentrations of benzene has prompted speculation. It has been demonstrated that aromatic compounds are capable of forming weak hydrogen bonds with water. This ability favours uptake in the aqueous interface over solubilisation in the interior. Alternatively, some authors have attributed the binding behaviour of benzene to its weak surface activity that is amplified by the extremely high surface to volume ratio characteristic of micellar solutions. Likewise the high Laplace pressure of small aggregates has been frequently cited as cause. The high pressure in the interior of the small aggregates squeezes out the solubilisate, which then can but bind to the interface. However, as has been pointed out by Marqusee and Dill, the Laplace pressure cannot be the dominant factor, since worm-like and spherical micelles show comparable solubilisation behaviour, whereas the Laplace pressure of the former is half that of the
latter. Also the large volume of the interfacial region as compared to the core of the micelle needs to be considered, favouring binding to the interfacial region on purely statistical grounds. The binding behaviour of benzene can be extrapolated to many other aromatic compounds such as naphthalene and benzene derivatives. Interestingly, a large number of probe molecules contain aromatic rings and many of them will prefer the outer regions of micelles, whereas in bilayer systems, the same molecules prefer the interior of the aggregate. Clearly these probes cannot be used to determine polarity of the micellar interior or the extent of water penetration therein.

For ammonium surfactants there is evidence for the existence of an additional specific interaction between the headgroups of the surfactant and the aromatic solubilisate. This is in line with the observation that partition coefficients for benzene in CTAB solutions are much higher than those for SDS solutions. These cation-pi interactions have been observed in many different fields in chemistry. The importance of these specific interactions for micellar systems has been questioned by de Schryver et al.

5.1.3 Micellar catalysis - kinetic models

A micelle-bound substrate will experience a reaction environment different from bulk water, leading to a kinetic medium effect. Hence, micelles are able to catalyse or inhibit organic reactions. Research on micellar catalysis has focused on the kinetics of the organic reactions involved. An overview of the multitude of transformations that have been studied in micellar media is beyond the scope of this chapter. Instead, the reader is referred to an extensive set of review articles and monographs.

The kinetic data are essentially always treated using the pseudophase model, regarding the micellar solution as consisting of two separate phases. The simplest case of micellar catalysis applies to unimolecular reactions where the catalytic effect depends on the efficiency of binding of the reactant to the micelle (quantified by the partition coefficient, P) and the rate constant of the reaction in the micellar pseudophase (kₘ) and in the aqueous phase (kₜ). Menger and Portnoy have developed a model, treating micelles as enzyme-like particles, that allows the evaluation of all three parameters from the dependence of the observed rate constant on the concentration of surfactant.

The catalytic effect on unimolecular reactions can be attributed exclusively to the local medium effect. For more complicated bimolecular or higher-order reactions, the rate of the reaction is affected by an additional parameter: the local concentration of the reacting species in or at the micelle. Also for higher-order reactions the pseudophase model is usually adopted (Figure 5.2). However, in these systems the dependence of the rate on the concentration of surfactant does not allow direct estimation of all of the rate constants and partition coefficients involved. Generally independent assessment of at least one of the partition coefficients is required before the other relevant parameters can be accessed. Partition coefficients are usually determined using ultrafiltration or NMR or UV-vis spectroscopy. Kinetics of micelle-catalysed bimolecular reactions are generally monitored spectrophotometrically under pseudo-first-order conditions. The decrease of the absorption of one of the reactants (A) is followed in time in the presence of a more than 20-fold excess of the other
reactant (B). In the absence of surfactant, the second-order rate constant ($k_2$) follows from Equation 5.1:

$$k_2 = k_{obs} / [B]$$  \hspace{1cm} (5.1)

Herein $k_{obs}$ is the observed pseudo-first-order rate constant. In the presence of micelles, analogous treatment of the experimental data will only provide an apparent second-order rate constant, which is a weighed average of the second-order rate constants in the micellar pseudophase and in the aqueous phase (Equation 5.2).

$$k_{app} = k_{obs} / [B]$$  \hspace{1cm} (5.2)

Berezin and co-workers have analysed in detail the kinetics of bimolecular micelle-catalysed reactions.\textsuperscript{39c,44} They have derived the following equation, relating the apparent rate constant for the reaction of A with B to the concentration of surfactant:

$$k_{app} = \frac{k_m P_A P_B [S] V_{mol,S} \cdot k_w (1 - [S] V_{mol,S})}{(1 - (P_A - 1)[S] V_{mol,S})(1 - (P_B - 1)[S] V_{mol,S})}$$  \hspace{1cm} (5.3)

Herein $P_A$ and $P_B$ are the micelle-water partition coefficients of A and B, respectively, defined as ratios of the concentrations in the micellar and aqueous phase; [S] is the concentration of surfactant; $V_{mol,S}$ is the molar volume of the micellised surfactant and $k_m$ and $k_w$ are the second-order rate constants for the reaction in the micellar pseudophase and in the aqueous phase, respectively. The appearance of the molar volume of the surfactant in this equation is somewhat alarming. It is difficult to identify the volume of the micellar pseudophase that can be regarded as the potential reaction volume. Moreover, the reactants are often not homogeneously distributed throughout the micelle and

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**Figure 5.2.** Kinetic analysis of a bimolecular reaction $A + B \rightarrow C$ according to the pseudophase model.
the average location of one reaction partner may differ from that of the other. Despite these serious complications, data analysis using Equation 5.3 almost always produces reasonable results. Studies of micellar catalysis of bimolecular reactions of uncharged substrates have not been frequent\textsuperscript{41,44,45}. Dougherty and Berg performed a detailed analysis of the kinetics of the reaction of 1-fluoro-2,4-dinitrobenzene with aniline in the presence of anionic and nonionic surfactants\textsuperscript{41}. Micelles induce increases in the apparent rate constant of this reaction. In contrast, the second-order rate constant for reaction in the micellar pseudophase was observed to be roughly equal to, or even lower than the rate constant in water.

When one or more of the reaction partners of a bimolecular reaction are ionic, the kinetic analysis is further complicated. Particularly in the case when the ionic reactants are not identical to the counterions of the surfactant, estimation of the concentrations of reactive ions in the interfacial region requires a refinement of the model. There is now competition between the reactive counterions and the inert counterions with respect to binding to the micellar surface. Romsted et al. developed the pseudophase ion-exchange (PPIE) model and applied it successfully to the description of the kinetics of micellar catalysis of ionic bimolecular reactions\textsuperscript{39}. This model treats the micellar surface as a selective ion exchanger and assumes that the total fractional occupation of the surface by the counterions is constant, irrespective of the nature of these ions. For ionic bimolecular reactions, the second-order rate constant for reaction in the micellar phase is nearly always remarkably similar to the second-order rate constant in the aqueous phase, suggesting a water-like medium for the majority of micelle-catalysed bimolecular reactions\textsuperscript{12,46}. Hence, the frequently encountered increase in the apparent rate constant by several orders of magnitude results largely from the increase in the local concentrations of the reactants in the micellar pseudophase.

5.1.4 The influence of micelles on Diels-Alder reactions

On the basis of the pronounced nonpolar character of the majority of Diels-Alder reactants efficient micellar catalysis of this reaction might be anticipated. Surprisingly, accounts on this topic 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 reactions in aqueous dispersions\textsuperscript{47}. In 1983 Grieco suggested that the high efficiency of the reaction of a surfactant-like diene in aqueous solutions resulted from the formation of micellar aggregates. In the same year Breslow et al. observed a minor retardation of the reaction of cyclopentadiene with a number of dienophiles in solutions of SDS and CTAB as compared to water\textsuperscript{48}. Later, other authors obtained similar results for a number of different Diels-Alder reactions\textsuperscript{49}. The apparent rate constants of the micelle-catalysed reactions usually significantly exceed those in organic solvents\textsuperscript{50}. Interestingly, also modest accelerations in the presence of micellar aggregates compared to the reaction in water have been reported\textsuperscript{51}.

In summary, all studies on the influence of micelles on bimolecular Diels-Alder reactions indicate that the apparent rate constants in these media are strikingly similar to the rate constants in water.
Chapter 5

Unfortunately, more detailed kinetic studies aimed at the determination of the second-order rate constants in the micellar pseudophase have not been published.

Analogously, the effect of micelles on the rate of the unimolecular retro Diels-Alder reaction has been studied. Also here only a modest retardation\(^{51b}\) or acceleration\(^{51c}\) is observed. Likewise, the presence of micelles has been reported to have a modest influence on an intramolecular Diels-Alder reaction\(^ {52}\).

Studies on the endo-exo selectivity of a number of different Diels-Alder reactions in micellar media lead to comparable conclusions. Endo-exo selectivities tend to be somewhat smaller in micellar solutions than in pure water, but still are appreciably larger than those in organic media\(^ {48,50a,53}\). In contrast, in microemulsions the endo-exo selectivity is reduced significantly\(^ {48,54}\).

Jaeger and co-workers studied the regioselectivity of the reaction of a surfactant diene with a surfactant dienophile in micellar media\(^ {55}\). The orientational effects in the aggregates could result in an increase in the regioselectivity in aqueous solutions of these compounds as compared to the reaction in organic media.

It is difficult to extract a consistent molecular picture of the influence of micelles on the Diels-Alder reaction from these rate and selectivity data. On the basis of the pronounced nonpolar character of many of the reactants, one may assume efficient binding of these compounds to micellar aggregates. However, it has been clearly demonstrated that this finding does not give rise to a significant increase in the rate of the reaction. One might argue whether or not this pattern is simply a result of the decreased efficiency of hydrogen bonding interactions and enforced hydrophobic interactions in the micellar aggregates that is compensated by an increased reactant concentration. Following this line of argument, a marked decrease of the rate of the intramolecular and retro Diels-Alder reactions is expected. However, also these processes are barely sensitive to the presence of micellar aggregates. This puzzling situation urged us to undertake a detailed investigation of the effect of micelles on a bimolecular Diels-Alder reaction.

5.2 Results and discussion

This chapter describes the effects of micelles on the Diels-Alder reaction of compounds 5.1 a-g (see Scheme 5.1) with cyclopentadiene (5.2). As far as we know, our study is the first detailed kinetic analysis of micellar catalysis of a Diels-Alder reaction.

The use of dienophile 5.1 also allows study of the effect of micelles on the Lewis-acid catalysed reaction. These studies are described in Section 5.2.2. and represent the first in-depth study of Lewis-acid catalysis in conjunction with micellar catalysis\(^ {56}\), a combination that has very recently also found application in synthetic organic chemistry\(^ {57}\).
5.2.1 Effects of micelles in the absence of Lewis acids

In this section the influence of micelles of cetyltrimethylammonium bromide (CTAB), sodium dodecylsulfate (SDS) and dodecyl heptaoxyethylene ether (C\textsubscript{12}E\textsubscript{7}) on the Diels-Alder reaction of 5.1a-g with 5.2 in the absence of Lewis-acid catalysts is described (see Scheme 5.1). Note that the dienophiles can be divided into nonionic (5.1a-e), anionic (5.1f) and cationic (5.1g) species. A comparison of the effect of nonionic (C\textsubscript{12}E\textsubscript{7}), anionic (SDS) and cationic (CTAB) micelles on the rates of their reaction with 5.2 will assess of the importance of electrostatic interactions in micellar catalysis or inhibition.

The effect of micelles of SDS, CTAB and C\textsubscript{12}E\textsubscript{7} on the apparent second-order rate constants of the Diels-Alder reaction between nonionic 5.1a, anionic 5.1f and cationic 5.1g with 5.2 is reported in Table 5.1. These apparent rate constants are calculated from the observed pseudo-first-order rate constants by dividing the latter by the overall concentration of 5.2.
For all entries the concentration of surfactant is 7.8 mM above the cmc of the particular compound. The values for the cmc have been determined under the particular reaction conditions, and were 3-14% lower than the cmc’s of the pure surfactant (see Appendix 5.1). The rate constants have been obtained by following the decrease of the absorbance of 5.1 employing UV-vis spectroscopic techniques. This technique allows use of very low concentrations of 5.1 of about 2×10⁻⁵ M so that on average there will be not more than one dienophile molecule per micelle. The overall concentration of 5.2 is 2.0 mM, which ensures that, depending on the aggregation number of the surfactant, the average number of cyclopentadiene molecules per micelle varies between 1 and 3⁸. Under these 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 5.1f in CTAB solution and for cationic 5.1g 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 favourable 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 local increased concentrations of the reactants in the micellar pseudophase. Note that also in the case where electrostatic interactions inhibit binding of the dienophile to the micelle, i.e. 5.1f in SDS and 5.1g 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 5.2 in this phase due to its partial solubilisation by the micelles.

In order to interpret the data in Table 5.1 in a quantitative fashion, we analysed the kinetics in terms of the pseudophase model (Figure 5.2). For the limiting cases of essentially complete binding of the dienophile to the micelle (5.1f in SDS and 5.1g in CTAB solution) the following expression can be derived (see Appendix 5.2):

\[
k_{\text{app}} = \frac{k_{\text{obs}}}{[5.2]}_f
\]
Herein $[5.2]_t$ is the total number of moles of $5.2$ present in the reaction mixture, divided by the total reaction volume $V_t$; $k_{obs}$ is the observed pseudo-first-order rate constant; $V_{mol,S}$ is an estimate of the molar volume of micellised surfactant $S$; $k_m$ and $k_w$ are the second-order rate constants in the aqueous phase and in the micellar pseudophase, respectively (see Figure 5.2); $V_w$ is the volume of the aqueous phase and $P_{5.2}$ is the partition coefficient of $5.2$ over the micellar pseudophase and water, expressed as a ratio of concentrations. From the dependence of $[5.2]/k_{obs}$ on the concentration of surfactant, $P_2$ and $k_m$ can be obtained. We used estimates for the molar volume of micellised CTAB$^{59}$ and SDS$^{60}$ of 0.25 M$^{-1}$ and 0.37 M$^{-1}$, respectively, and assumed $V_w/V_t = 1$, which is reasonable in view of the low concentrations of surfactant used.

Figure 5.3 shows the dependence of the apparent second-order rate constants (k_{obs}/[5.2]) on the concentration of surfactant for the Diels-Alder reactions of $5.1f$ and $5.1g$ with $5.2$. The results of the analysis in terms of the pseudophase model are shown in the inset in Figure 5.3 and in the first two

\[
\frac{1}{k_{app}} = \frac{1}{k_{obs}} + \frac{V_{mol,S}}{k_m} [S] + \frac{V_m}{P_{5.2}} + \frac{c_{mc} V_{mol,S}}{k_m} \tag{5.5}
\]

Figure 5.3. Plots of the apparent second-order rate constant, $k_{app} (= k_{obs}/[5.2]_t)$, versus the concentration of surfactant for the Diels-Alder reaction of $5.1f$ with $5.2$ in CTAB solution (†) and of $5.1g$ with $5.2$ in SDS solution (×) at 25°C. The inset shows the treatment of these data using Equation 5.5. From the slopes and the intercepts $P_{5.2}$ and $k_m$ were calculated (see Table 5.2).
The reliability of these data depends critically on the validity of the assumptions made in the derivation of Equation 5.5 and on the assumptions underlying the pseudophase model. Also the unavoidable error in the estimation of the volume of the micellar pseudophase that can be regarded as the potential site of binding and reaction will affect the reliability of the results. The system under study offers the possibility of checking the validity of some of the assumptions made during the evaluation of the partition coefficient of 5.2. By studying the reaction of 5.1f and 5.1g with 5.2 in CTAB and SDS solutions, respectively, complete binding of the dienophile to the micelles was assumed. Alternatively, the reaction of 5.1g with 5.2 in CTAB solution can be studied, in which case the dienophile is assumed to reside exclusively in the aqueous phase. Figure 5.4 shows the dependence of the apparent rate constant of this process on the concentration of CTAB. The kinetics of this process can be described using Equation 5.6 as derived in Appendix 5.3.

\[
\frac{1}{k_{app}} = \frac{k_{obs}}{k_w} \frac{P_{5.2} V_{mol,S}}{[S]} - \frac{P_{5.3} \gamma_{cmc} V_{mol,S}}{k_w} \frac{V_w}{k_w} \frac{V_f}{V_t} 
\]  

(5.6)

By plotting the reciprocal of the apparent rate constant versus the concentration of CTAB a straight line is obtained. From the slope of this line and the rate constant in the absence of surfactant (\(k_w\), see Table 5.1) the partition coefficient of 5.2 has been calculated. The result, shown in the third entry in Table 5.2, is in good agreement with the result obtained by the complementary monitoring of the reaction in the micellar phase (entry 1). Apparently treatment according to the pseudophase model as well as the assumption of complete (in case 5.1f) and negligible (in case of 5.1g) binding to CTAB micelles is justified. Note that the validity of the estimate of the volume of the micellar pseudophase cannot be judged from these data, since possible errors in this volume will influence the value for the partition coefficient to exactly the same extent in both treatments.

*Table 5.2. Analysis using the pseudophase model: partition coefficients for 5.2 over CTAB or SDS micelles and water and second-order rate constants for the Diels-Alder reaction of 5.1f and 5.1g with 5.2 in CTAB and SDS micelles at 25°C.

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Dienophile</th>
<th>(k_w) (M(^{-1})s(^{-1})) (?10%)</th>
<th>(P_{5.2}) (?10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CTAB</td>
<td>5.1f</td>
<td>5.9(10(^{-6}))</td>
<td>68</td>
</tr>
<tr>
<td>2 SDS</td>
<td>5.1g</td>
<td>3.1(10(^{-5}))</td>
<td>61</td>
</tr>
<tr>
<td>3 CTAB</td>
<td>5.1g</td>
<td>-</td>
<td>61</td>
</tr>
</tbody>
</table>
pseudophase model with those in water (Table 5.1) demonstrates a remarkable retardation induced by the micelles. This retardation would suggest that the Diels-Alder reaction experiences a rather apolar medium. This suggestion is in contrast with previous reports that indicate water-like environments for other bimolecular micelle-catalysed reactions. Moreover, 5.1f and 5.1g contain ionic moieties, which makes it unlikely that they will be dragged deeply into the micelle.

The Diels-Alder reaction provides us with a tool to probe its local reaction environment in the form of its endo-exo product ratio. Actually, even a solvent polarity parameter has been based on endo-exo ratios of Diels-Alder reactions of methyl acrylate with cyclopentadiene\(^{61}\) (see also section 1.2.3).

Analogously we have determined the endo-exo ratio of the reaction between 5.1c and 5.2 in surfactant solution and in a number of different organic and aqueous media. These ratios are obtained from the \(^1\)H-NMR of the product mixtures, as has been described in Chapter 2. The results are summarised in Table 5.3, and clearly point towards a water-like environment for the Diels-Alder reaction in the presence of micelles, which is in line with literature observations.

This conclusion seems in conflict with the outcome of the analysis using the pseudophase model. Here we do not speculate on the origins of this discrepancy. Instead, an extensive discussion is provided in Section 5.2.3.

**Figure 5.4.** Plot of the apparent second-order rate constant, \(k_{\text{app}} = k_{\text{obs}}/[5.2]\), versus the concentration of surfactant for the Diels-Alder reaction of 5.1g with 5.2 in CTAB solution at 25°C. The inset shows the treatment of these data using Equation 5.6. From slope and intercept \(P_{5.2}\) can be calculated (see Table 5.2).
5.2.2 Effects of micelles in the presence of Lewis acids

Inspired by the many hydrolytically-active metallo enzymes encountered in nature, extensive studies have been performed on so-called metallo micelles. These investigations usually focus on mixed micelles of a common surfactant together with a special chelating surfactant that exhibits a high affinity for transition-metal ions. These aggregates can have remarkable catalytic effects on the hydrolysis of activated carboxylic acid esters, phosphate esters and amides. In these reactions the exact role of the metal ion is not clear and may vary from one system to another. However, there are strong indications that the major function of the metal ion is the coordination of hydroxide anion in the Stern region of the micelle where it is in the proximity of the micelle-bound substrate. The first report of catalysis of a hydrolysis reaction by metallomicelles stems from 1978.\(^{62}\) In the years that followed, particularly the groups of Scrimtin and Tonellato\(^ {63}\) as well as the groups of Tagaki\(^ {64}\), Engbersen\(^ {65}\) and other authors\(^ {66}\) studied these systems in detail. Apart from catalysing hydrolysis reactions, metallomicelles have also a potential in the complexation of oxygen\(^ {67}\) and in photochemical processes\(^ {68}\). Surprisingly, examples of Lewis-acid catalysis by these systems were without precedent at the time we initiated the research described in this chapter.

With the aim of catalysis of the Diels-Alder reaction of \(\text{5.1c}\) with \(\text{5.2}\) by metallo micelles, preliminary studies have been performed using the surfactants \(\text{5.5a-c}\)\(^ {69}\) and \(\text{5.6}\) (Scheme 5.2). Unfortunately, the limited solubility of these surfactants in the pH region that allows Lewis-acid catalysis of the Diels-

\[\text{Scheme 5.2.}\]

<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 C(<em>{12})E(</em>{7})</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>

Table 5.3. Endo-exo product ratios of the Diels-Alder reaction of \(\text{5.1c}\) with \(\text{5.2}\) in surfactant solution compared to water and organic solvents.
Alder reaction forced us to look for alternative surfactants. It turned out that the dodecylsulfate 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 5.1 and 5.2 (see Scheme 5.1). The physical properties of these micelles have been described in the literature$^{70}$ and a small number of catalytic studies have been reported. The influence of Cu(DS)$_2$ micelles on the kinetics of quenching of a photoexcited species has been investigated$^{71}$. Interestingly, Kobayashi recently employed surfactants in scandium triflate catalysed aldol reactions$^{57}$. Robinson et al. have demonstrated that the interaction between metal ions and ligand at the surface of dodecylsulfate micelles can be extremely efficient$^{72}$.

In this section the catalytic efficiency of Co(DS)$_2$, Ni(DS)$_2$, Cu(DS)$_2$ and Zn(DS)$_2$ micelles as well as the effect of CTAB and C$_{12}$E$_7$ on the copper-ion catalysed Diels-Alder reaction between 5.1 and 5.2 is described.

The pronounced shift of the UV-vis absorption spectrum of 5.1 upon coordination to a metal ion allows investigation of the complexation behaviour of these compounds in the presence of micelles. Figure 5.5 shows the spectra of nonionic 5.1c as well as the anionic and cationic counterparts 5.1f and 5.1g in water and in surfactant solutions containing copper(II) ions. The shifts of the absorption bands primarily reflect the extent of coordination of the dienophile to the copper ions. Binding to micelles has a negligible influence on the spectrum. Addition of C$_{12}$E$_7$ to a 10 mM Cu(NO$_3$)$_2$ solution containing the ionic dienophiles 5.1f and 5.1g leaves the absorption spectra essentially unchanged. Apparently 5.1f and 5.1g have little affinity for C$_{12}$E$_7$ micelles. A similar picture emerges for cationic 5.1g, which resides preferentially in the aqueous phase rather than binding to cationic CTAB micelles. In contrast, 5.1c has some affinity for C$_{12}$E$_7$ and CTAB micelles, resulting in a decreased coordination to the copper ions in the presence of these surfactants. Interestingly, all three

### Table 5.4

<table>
<thead>
<tr>
<th>metal ion</th>
<th>k$_{app}$ (M$^{-1}$s$^{-1}$)</th>
<th>k$_2$ (M$^{-1}$s$^{-1}$)</th>
<th>k$_{app}$ / k$_2$</th>
<th>K$_a$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co$^{2+}$</td>
<td>0.137</td>
<td>8.40$\times$10$^{-2}$</td>
<td>1.6</td>
<td>1.17$\times$10$^2$</td>
</tr>
<tr>
<td>Ni$^{2+}$</td>
<td>0.152</td>
<td>9.46$\times$10$^{-2}$</td>
<td>1.6</td>
<td>6.86$\times$10$^2$</td>
</tr>
<tr>
<td>Cu$^{2+}$</td>
<td>5.95</td>
<td>2.56</td>
<td>2.3</td>
<td>1.16$\times$10$^3$</td>
</tr>
<tr>
<td>Zn$^{2+}$</td>
<td>0.176</td>
<td>1.18$\times$10$^{-1}$</td>
<td>1.5</td>
<td>7.28$\times$10$^1$</td>
</tr>
</tbody>
</table>

$^a$ The concentration of surfactant was 3.89 mM above the cmc in each case. $^b$ Values taken from Chapter 2 and determined at a constant ionic strength of 2.0 M using KNO$_3$ as background electrolyte.
dienophiles, even anionic 5.1f, bind more efficiently to the copper ions in the presence of Cu(DS)$_2$ micelles than in a solution containing twice the overall concentration of copper ions. This result is in line with literature observations that revealed an increased interaction between transition-metal ions and chelating organic molecules in the presence of anionic surfactants$^{72}$. Further evidence for an increased efficiency of complexation in the presence of micellar aggregates with bivalent metal counterions is presented in Table 5.4. The apparent rate constants of the reaction of 5.1c with 5.2 in the presence of micelles of Co(DS)$_2$, Ni(DS)$_2$, Cu(DS)$_2$ and Zn(DS)$_2$ are compared to the rate constants for the corresponding bivalent metal ion - dienophile complexes in the absence of micelles. The latter data are not dependent on the efficiency of the formation of the catalyst - dienophile complex whereas possible incomplete binding will certainly be reflected in the former. The good correlations between $k_{app}$ and $k_2$ and the absence of a correlation between $k_{app}$ and

![Figure 5.5. UV spectra of 5.1c, 5.1f and 5.1g in water (a) compared to those in solutions containing: 10 mM Cu(NO$_3$)$_2$ (b); 5 mM Cu(DS)$_2$ (c); 10 mM CTAB plus 10 mM Cu(NO$_3$)$_2$ (d) and 10 mM C$_{12}$E$_7$ plus 10 mM Cu(NO$_3$)$_2$ (e).](image)
**Kₐ** demonstrate that the equilibrium constant of binding of the dienophile to the metal ion has little influence on the apparent rate constant of the Diels-Alder reaction in the micellar solutions. Hence, we contend that binding of the dienophile to the metal ions is essentially complete in the presence of M(DS)₂ micelles.

The enhanced binding predicts a catalytic potential for these solutions and prompted us to investigate the influence of the different types of micelles on the rate of the copper-ion catalysed reaction. Table 5.5 summarises the results, which are in perfect agreement with the conclusions drawn from the complexation studies.
In all surfactant solutions 5.2 can be expected to prefer the nonpolar micellar environment over the aqueous phase. Consequently, those surfactant/dienophile combinations where the dienophile resides primarily in the aqueous phase show inhibition. This is the case for 5.1f and 5.1g in C_{12}E_7 solution and for 5.1g in CTAB solution. On the other hand, when diene, dienophile and copper ion simultaneously bind to the micelle, as is the case for Cu(DS)_2 solutions with all three dienophiles, efficient micellar catalysis is observed. An intermediate situation exists for 5.1c in CTAB or C_{12}E_7 solutions and particularly for 5.1f in CTAB solution. Now the dienophile binds to the micelle and is shielded from the copper ions that apparently prefer the aqueous phase. This results in an overall retardation, despite the possible locally increased concentration of 5.2 in the micelle.

Clearly, very promising results were obtained for the Cu(DS)_2 solutions. We have analysed this system in some detail. Figure 5.6 shows the dependence of the rate of the Diels-Alder reaction of 5.1c, 5.1f, and 5.1g with 5.2 on the concentration of Cu(DS)_2. For all three dienophiles the apparent second-order rate constant for their reaction with 5.2 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 dominate the behaviour. Together, these two effects result in the appearance of a rate maximum at a specific concentration of surfactant that is typical for micelle-catalysed bimolecular reactions. The position of the maximum depends primarily on the micelle-water partition coefficient of the dienophile. For instance, cationic 5.1g reacts fastest almost at the cmc, because of its very high affinity for the anionic Cu(DS)_2 micelles.

<table>
<thead>
<tr>
<th>medium</th>
<th>5.1c</th>
<th>5.1f</th>
<th>5.1g</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mM Cu(NO_3)_2</td>
<td>1.11</td>
<td>1.38</td>
<td>2.13</td>
</tr>
<tr>
<td>5 mM Cu(DS)_2</td>
<td>5.95</td>
<td>5.50</td>
<td>15.3</td>
</tr>
<tr>
<td>CTAB b + 10 mM Cu(NO_3)_2</td>
<td>0.401</td>
<td>0.150</td>
<td>1.84</td>
</tr>
<tr>
<td>C_{12}E_7 b + 10 mM Cu(NO_3)_2</td>
<td>0.630</td>
<td>1.08</td>
<td>1.71</td>
</tr>
</tbody>
</table>

*a [1] = 2\times10^{-5} \text{ M}; [2] = 1.0\times10^{-3} \text{ M} \quad \text{b The concentration of surfactant is 3.89 mM above the cmc.} \quad \text{c The concentration of surfactant is 7.8 mM above the cmc of the particular compound under the reaction conditions.}
Formation of a complex with a copper cation only further stimulates this behaviour. As a result, 5.1g is almost completely bound to the micelles, even at low concentrations of Cu(DS)$_2$. By contrast, the reaction of 5.1f still benefits from an increasing surfactant concentration at 10 mM of Cu(DS)$_2$. In fact, it is surprising that the reaction of this anionic compound is catalysed at all by an anionic surfactant. Probably it is the copper complex of 5.1f, being overall cationic, that binds to the micelle. Not surprisingly, the neutral substrate 5.1c shows intermediate behaviour.

Interestingly, at very low concentrations of micellised Cu(DS)$_2$, the rate of the reaction of 5.1a with 5.2 was observed to be zero-order in 5.1a and only depending on the concentration of Cu(DS)$_2$ and 5.2. This is akin to the turn-over and saturation kinetics exhibited by enzymes. The acceleration relative to the reaction in organic media in the absence of catalyst, also approaches enzyme-like magnitudes: compared to the process in acetonitrile (Chapter 2), Cu(DS)$_2$ micelles accelerate the Diels-Alder reaction between 5.1a and 5.2 by a factor of $1.8\times10^6$. This extremely high catalytic efficiency shows how a combination of a beneficial aqueous solvent effect, Lewis-acid catalysis and micellar catalysis can lead to tremendous accelerations.

**Figure 5.6.** Plots of the apparent second-order rate constant ($k_{app}$) versus the concentration of Cu(DS)$_2$ for the Diels-Alder reaction of 5.1c ( ), 5.1f (†) and 5.1g (œ) with 5.2 at 25°C. The inset shows the treatment of the data for the reaction of 5.1g according to the pseudophase model.
Chapter 5

The essentially complete binding of 5.1g to the Cu(DS)₂ micelles allows treatment of the kinetic data of Figure 5.6 using the pseudophase model. Since it is very likely that 5.1g binds in the Stern region (vide infra), complete binding to the copper ions can be assumed. Using Equation 5.5, the Cu(DS)₂-water distribution coefficient of 5.2 is obtained as well as the second-order rate constant for reaction in the micellar pseudophase (see inset in Figure 5.6). Unfortunately no literature data exist for the molar volume of Cu(DS)₂ that is required for the kinetic analysis. We have used an estimate of the molar volume of micellised Cu(DS)₂ of 0.50 M⁻¹, twice as large as the number that we have used previously for SDS.

Calculations using this value afford a partition coefficient for 5.2 of 96 and a micellar second-order rate constant of 0.21 M⁻¹s⁻¹. This partition coefficient is higher than the corresponding values for SDS micelles and CTAB micelles given in Table 5.2. This trend is in agreement with literature data, that indicate that Cu(DS)₂ micelles are able to solubilize 1.5 times as much benzene as SDS micelles. Most likely this enhanced solubilisation is a result of the higher counterion binding of Cu(DS)₂ micelles (89% versus 60%, see Appendix 5.1), which reduces headgroup repulsion and allows a tighter packing of the headgroups resulting in decreased water penetration and an increased nonpolar character of the micellar interior as compared to SDS micelles.

Comparison of the micellar second-order rate constant of 0.21 M⁻¹s⁻¹ with the rate constants for the reaction in acetonitrile (0.472 M⁻¹s⁻¹) and ethanol (0.309 M⁻¹s⁻¹), again points to 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.

In order to obtain more insight into the local environment for the catalysed reaction, we investigated the influence of substituents on the rate of this process in micellar solution and compared this influence to the corresponding effect in different aqueous and organic solvents. Plots of the logarithms of the rate constants versus the Hammett \( \rho \)-value show good linear dependences for all

<table>
<thead>
<tr>
<th>medium</th>
<th>( \rho )</th>
</tr>
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<tbody>
<tr>
<td>10 mM Cu(DS)₂</td>
<td>0.86</td>
</tr>
<tr>
<td>10 mM Cu(NO₃)₂ in acetonitrile</td>
<td>0.96ᵇ</td>
</tr>
<tr>
<td>10 mM Cu(NO₃)₂ in ethanol</td>
<td>1.00ᵇ</td>
</tr>
<tr>
<td>10 mM Cu(NO₃)₂ in waterᵃ</td>
<td>0.82ᵇ</td>
</tr>
</tbody>
</table>

ᵃ Ionic strength 2.00 M (KNO₃).ᵇ Data taken from Chapter 2.
media. The resulting \( ? \)-values are shown in Table 5.6. The \( ? \)-value in Cu(DS)\(_2\) solution resembles that in aqueous solution more than those in organic solvents. It appears that the outcome of the analysis using the pseudophase model is not in agreement with experimental observations. Apparently, one (or more) of the assumptions of the pseudophase model is not valid for the system studied here. In particular, the treatment of the micellar pseudophase as a homogeneous “solution” might not be warranted. Therefore we contend that diene and dienophile, on average, reside in different parts of the micelle. Surely, this would impede the reaction. This arrangement would also explain the absence of a large catalytic effect in cases where diene and dienophile bind efficiently to the micelle. In order to check this hypothesis, we probed the binding sites of diene and dienophile using \( ^1H \)-NMR techniques.

5.2.3 Average binding sites and their implications

NMR methods have been regularly employed in the study of micellar solutions\(^\text{74}\). The most frequently encountered technique to probe the binding location of aromatic compounds in micelles makes use of changes in the chemical shifts in the \( ^1H \)-NMR spectrum of the surfactant induced by the ring current of the aromatic moiety of the solubilisate\(^\text{27a,34c,35a,75}\). In general, protons located above or below the plane of the aromatic ring are shielded and, hence, experience upfield shifts. Protons in plane with the aromatic ring, on the other hand, are deshielded and shift downfield. In the absence of any specific interactions or orientational constraints, the shielding effect of the aromatic ring of one compound on the proton chemical shifts of another is dominant and results in an upfield shift\(^76\). Note that any preference for a specific orientation is reflected in the magnitude of the ring-current induced shifts. Consequently, interpretation of shift data in terms of binding locations is somewhat hazardous.

Studies on a large number of aromatic compounds have revealed that for CTAB the largest shift occurs for the alkyl chain protons near the surfactant headgroup, whereas in SDS nearly all proton signals are shifted significantly\(^75b-e\). For SDS, the most pronounced shifts are observed for protons around the centre of the chain. This result has been interpreted in terms of deeper penetration of aromatic compounds into SDS micelles relative to CTAB micelles\(^75b-e\).

The aromatic shifts that are induced by 5.1c, 5.1f and 5.1g on the \( ^1H \)-NMR spectrum of SDS, CTAB and Zn(DS)\(_2\) have been determined. Zn(DS)\(_2\) is used as a model system for Cu(DS)\(_2\), which is paramagnetic. The \( \text{cmc} \) and counterion binding for Cu(DS)\(_2\) and Zn(DS)\(_2\) are similar and it has been demonstrated in Chapter 2 that Zn(II) ions are also capable of coordinating to 5.1, albeit somewhat less efficiently than copper ions. Figure 5.7 shows the results of the shift measurements. For comparison purposes also the data for chalcone (5.4) have been added. This compound has almost no tendency to coordinate to transition-metal ions in aqueous solutions. From Figure 5.7 a number of conclusions can be drawn. (1) The shifts induced by 5.1c on the NMR signals of SDS and CTAB
show the characteristics usually observed for benzene derivatives. Comparison of the shifts induced by 5.1c on the proton resonances of CTAB with dodecyltrimethylammonium bromide (Figure 5.7j) demonstrates that the differences between SDS and CTAB with respect to the solubilisation of 5.1c are only partly due to a difference in chain length. There seems to be an intrinsic difference between the interaction of the sulfate and the ammonium headgroup with the aromatic solubilisate, in line with literature evidence for a specific cation-arene interaction (see Section 5.1.2). (2) Introduction of an ionic group in the dienophile (compare Figure 5.7e with 5.7h and 5.7f with 5.7i) causes this compound to reside on average closer to the headgroups of the surfactant. (3) Chelation of the dienophile to a zinc(II) ion has little effect on its location in the micelle (compare Figure 5.7a with 5.7d). (4) The presence of the pyridine nitrogen atom influences the binding location only to a minor extent (compare Figure 5.7b with 5.7e and 5.7c with 5.7f).

Figure 5.7k shows the shifts of the proton signals of C₁₂E₇ as induced by 5.1c. All parts of the surfactant experience an appreciable shift. The strongest shifts are observed near the interface between the alkyl chains and the ethyleneoxide part, suggesting that 5.1c prefers the interfacial region of the nonionic micelles.

Surprisingly, the shifts observed in the NMR spectrum of Zn(DS)₂ as caused by 5.1g seem to point towards a relatively deep penetration of this compound into the micelle, which is extremely unlikely. 5.1g, when bound to Zn(DS)₂ micelles, will coordinate to a Zn(II) ion. The resulting complex will now have three positive charges: two of the zinc ion at one end of the complex and one of the trimethylammonium group at the other end. It is hard to imagine that this very hydrophilic complex will penetrate into the micellar interior. Still the shifts indicate a short distance between the n-protons of the surfactant and the aromatic rings of 5.1g. The most likely explanation for this behaviour, is bending of the alkyl chain of the surfactant towards the aromatic parts of the dienophile.

This demonstrates that an interpretation of shift data solely in terms of depth of penetration into the micelle is hazardous. The observed shifts of surfactant protons merely indicate a proximity of aromatic groups and, strictly, do not provide direct information about the location where this encounter occurs. Still, from the data in Figure 5.7 it may be concluded that, on average, the dienophile is not in the core of the micelle.

In a second attempt to obtain more insight into the binding location of the dienophile and now also the diene, we have made use of the influence of paramagnetic ions on the spin-lattice relaxation rates of species in their proximity. Close to these ions the spin-lattice relaxation rate is dramatically enhanced. This effect is highly distance-dependent as is expressed by Equation 5.7, describing the spin-lattice relaxation time in the absence of inner-sphere coordination.

\[
\frac{1}{T_1} = \frac{\gamma^2}{\hbar} \frac{D}{d^6} \left( \frac{6\gamma_z^2}{1} + \frac{2\gamma_x^2}{\gamma_z^2} \right) \left( \frac{14\gamma_z^2}{1} + \frac{2\gamma_x^2}{\gamma_z^2} \right) \]

(5.7)
Figure 5.7. Aromatic solubilisate-induced changes in the chemical shifts (upfield) of the $^1$H-NMR signals of micellised surfactant. Figures a-f show the effect of 5.4 and 5.1c on the proton resonances of Zn(DS)$_2$ (25 mM), SDS (50 mM) and CTAB (50 mM). Figure g and h show the corresponding effect of 5.1g on Zn(DS)$_2$ (25 mM) and SDS (50 mM), respectively. Figure i depicts the effect of 5.1f on the CTAB (50 mM) resonances. Figure j shows the shifts induced by 5.1c on the DTAB (50 mM) resonances and Figure k the corresponding effect on C$_{12}$E$_7$ (50 mM). The concentrations of the solubilisate were 2.0 (†), 5.0 (‡) or 8 (§) mM. N stands for the protons at the three headgroup methyl moieties of CTAB, ? and ? for the methylene protons at the ? and ? positions relative to the headgroup. ? represents the terminal methyl group protons and n the protons between the ? and ? positions.
Here $T_1$ is the spin-lattice relaxation time due to the paramagnetic ion; $d$ is the ion-nucleus distance; $D$ is a constant related to the magnetic moments, $\gamma_1$ is the Larmor frequency of the observed nucleus and $\gamma_s$ is the Larmor frequency of the paramagnetic electron and $\gamma_s$ its spin relaxation time.

Paramagnetic relaxation techniques have been employed in investigations of the hydrocarbon chain conformation of micellised surfactant\textsuperscript{78,79}, in estimations of the viscosity of the micellar surface\textsuperscript{80} and of the counterion binding\textsuperscript{81} and in solubilisation studies\textsuperscript{42,75d,e,82}. Generally, one can select the charge of the paramagnetic ion so that it will be a counterion to the micellar system under study, which ensures that it will be located primarily in the Stern region of the micelle. Consequently, compounds bound to the outer regions of the micelle will experience a much larger influence of these paramagnetic ions than compounds located in the interior of the micelle. The relaxation rate induced by the paramagnetic ion ($r_p$) can be assessed by subtracting the observed relaxation rates in the absence of these ions from those obtained in the presence of the paramagnetic species. The exact magnitude of $r_p$ is strongly dependent upon the local concentration of the paramagnetic ions at the micelle. Consequently, normalisation of the $r_p$ values is required before comparisons between separately prepared solutions can be made. Hence, throughout this study the $r_p$ values will be expressed as a percentage of the $r_p$ value of the methylene group next to the surfactant headgroup.

We have used the paramagnetic relaxation technique to study the binding locations of 5.1c, 5.1f, 5.1g and 5.2 in CTAB, SDS and Zn(DS)\textsubscript{2} solutions, employing [Cu(EDTA)]\textsuperscript{2-}, Cu\textsuperscript{2+} (for 5.2) or Dy\textsuperscript{3+} (for 5.1) as paramagnetic species. Figure 5.8 shows the values of $r_p$ for 5.1c and 5.1f in CTAB solution.

\textbf{Figure 5.8.} Paramagnetic ion-induced spin-lattice relaxation rates ($r_p$) of the protons of 5.1c and 5.1f in CTAB solution and of CTAB in the presence of 5.1c or 5.1f, normalised to $r_p$ for the surfactant $\text{-CH}_2$. The solutions contained 50 mM of CTAB, 8 mM of 5.1c or 5.1f and 0 or 0.4 mM of [Cu(EDTA)]\textsuperscript{2-}.

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relative to $r_p$ for the surfactant -methylene protons. In order to provide a frame of reference, also the relative paramagnetic relaxation rates of the CTAB protons are depicted. The latter show a clear decrease upon going from the headgroup towards the end of the hydrocarbon chain. The values for both dienophiles are of a magnitude somewhere between those of the $^7$ and the $^n$ methylene protons of CTAB. Consequently, on average they are somewhat farther away
from the paramagnetic ions than the ? protons, but not as far as the n protons. Interestingly, the introduction of an ionic group (compare 5.1f with 5.1c) results in a modest decrease of the average distance to the paramagnetic ion. Presumably, two counteractive effects are operative. The presence of a charged group might well result in a strong shift of the average binding location towards the outer regions of the micelle, resulting in an increased influence of the paramagnetic ion on the rate of relaxation. On the other hand, the electrostatic repulsion between the charged substituent and the paramagnetic counterion will result in a decrease of the effect of this ion on the relaxation rate.

**Figure 5.10.** Paramagnetic ion induced spin-lattice relaxation rates ($r_p$) of the protons of 5.1c (a) and 5.1g (b) in SDS solution and of SDS in the presence of 5.1c or 5.1g, normalised to $r_p$ for the surfactant -CH$_2$. The solutions contained 50 mM of SDS, 8 mM of 5.1c or 5.1g and 0 or 0.2 mM of DyCl$_3$ and 0 or 0.6 mM of cyclen.
Analogous studies on dienophiles 5.1c and 5.1g in SDS and Zn(DS)$_2$ lead to essentially the same conclusions. Figure 5.9 shows the relaxation data for 5.1g in Zn(DS)$_2$ solutions. The corresponding data for 5.1c could not be measured due to solubility problems. Analogously, Figure 5.10 shows the relaxation data of 5.1c and 5.1g in SDS solutions.

In conclusion, for all dienophile / surfactant combinations the average distance between the Diels-Alder reagent and the paramagnetic ion is intermediate between the corresponding distances of the ? and the n protons of the surfactant. Hence, the dienophile resides in the outer regions of the micelle.

The effects of paramagnetic ions on the relaxation rate of diene 5.2 in CTAB, SDS and Zn(DS)$_2$ solutions are illustrated in Figure 5.11. In this case the relative value of $r_p$ is invariably smaller than the corresponding effect on the ?$^{77}$ methyl protons of the surfactant. This trend clearly demonstrates that diene 5.2, in contrast to the dienophiles, is located in the interior of the micelle and spends little time at the surface.

**Figure 5.11.** Paramagnetic ion induced spin-lattice relaxation rates ($r_p$) of the protons of 5.2 in CTAB, SDS or Zn(DS)$_2$ solution and of these surfactants in the presence of 5.2, normalised to $r_p$ for the surfactant ?-CH$_2$. The solutions contained 25 mM of Zn(DS)$_2$, 50 mM of CTAB or SDS, 3 mM of 5.2 and 0 or 0.4 mM of $[\text{Cu(EDTA)}]^2-$ for CTAB solutions and 0 or 0.2 mM of Cu(NO$_3$)$_2$ for SDS and Zn(DS)$_2$ solutions.
Careful analysis of the influence of the character of the solubilisate on the relaxation data of the surfactant led to another interesting observation. Figure 5.12 summarises these data. The frontal row of bars represents the relative $r_p$ values of the different surfactant protons in the absence of any solubilisate. The second and third row show the corresponding effects in the presence of 8 mM of $\mathbf{5.1c}$, $\mathbf{5.1f}$ or $\mathbf{5.1g}$. The relative paramagnetic relaxation rates are similar to those of the pure surfactant. Hence, the introduction of these compounds into a micellar solution does not lead to a significant perturbation of the alkyl chains of the micelle. Yet, when $\mathbf{5.2}$ is added to solutions of SDS and Zn(DS)$_2$, significant increases in the relative paramagnetic relaxation rates of the ?, the n and the ? protons are observed. Apparently, the presence of a nonpolar solute in the interior of these micelles forces the alkyl chains of the individual surfactant molecules towards the surface. Curiously, for CTAB this effect is completely absent. This might be a result of the increased length of the alkyl chain of this surfactant compared to the two anionics, ensuring an increased tolerance towards incorporation of a solubilisate. In the literature, studies comparing the solubilisation in SDS micelles with that in CTAB solutions, likewise, suggest a significantly more pronounced perturbation of the structure of SDS micelles.$^{75c}$

**Figure 5.12.** Effect of the solubilisate on the paramagnetic ion-induced spin-lattice relaxation rates ($r_p$) of the protons of CTAB, SDS or Zn(DS)$_2$, normalised to $r_p$ of the surfactant -CH$_2$. The solutions contained 25 mM of Zn(DS)$_2$, 50 mM of CTAB or SDS, 3 mM of $\mathbf{5.2}$ and 8 mM of $\mathbf{5.1c}$, $\mathbf{5.1f}$ or $\mathbf{5.1g}$ and 0 or 0.4 mM of [Cu(EDTA)]$^{2-}$ for CTAB solutions and 0 or 0.2 mM of Cu(NO$_3$)$_2$ for SDS and Zn(DS)$_2$ solutions.
In summary, the NMR studies indicate different average binding locations for diene and dienophile. The diene resides preferentially in the interior of the micelles, which is not surprising in view of its pronounced nonpolar character. The dienophiles, on the other hand, are located more towards the surface of the aggregates. This behaviour has important implications for the rationalisation of the kinetic data. Clearly, when the Diels-Alder reagents are not homogeneously distributed over the micellar pseudophase, analysis according to the pseudophase model will provide erroneous results. Using this model, a second-order rate constant in the micellar pseudophase will be obtained that is too low. However, the partition coefficients that are produced using this model are still useful, as long as one bears in mind that they represent the ratio of the average concentrations of solubilisate in the micellar phase and in the aqueous phase.

Another consequence of the above analysis is, that the surprising inefficiency of micellar aggregates to catalyse Diels-Alder reactions can now be rationalised. Obviously, micelles are able to bind diene and dienophile efficiently but in different parts of the micelle. The reactions seems to take place at the surface of the micelle in a rather aqueous environment, where the concentration of diene is low.

The only micellar system that shows efficient catalytic behaviour is Cu(DS)$_2$. These micelles concentrate dienophile and copper ion at their surface, thereby promoting complexation of these compounds. Since Cu(DS)$_2$ aggregates are also capable of binding 5.2 better than CTAB and SDS micelles, the local concentration of 5.2 at the surface of the Cu(DS)$_2$ micelles is apparently high enough to allow a modest rate enhancement compared to the situation of fully complexed dienophile in pure water. Note that at concentrations slightly higher than the cmc of Cu(DS)$_2$, very efficient coordination of the dienophile to copper can take place, which, in the absence of the surfactant, requires copper ion concentrations which are orders of magnitude higher.

In retrospect, this study has demonstrated the limitations of two commonly accepted methods of analysing solubilisation and micellar catalysis, respectively. It has become clear that solubilisate ring-current induced shifts need to be interpreted with due caution. These data indicate a proximity of solubilisate and parts of the surfactant and, strictly, do not specify the location within the micelle where the encounter takes place. Also the use of the pseudophase model for bimolecular reactions requires precaution. When distribution of the reactants over the micelle is not comparable, erroneous results are likely to be obtained.

### 5.3 Conclusions

The Diels-Alder reaction of dienophiles 5.1a-e, containing neutral, cationic or anionic substituents, with diene 5.2 in the absence of Lewis acids is retarded by micelles of CTAB, SDS and C$_{12}$E$_7$. In the situation where the dienophile does not bind to the micelle, the reaction is inhibited because uptake of
5.2 in the micelles lowers its concentration in the aqueous phase. However, retardations are most pronounced when there is essentially complete binding of the dienophile to the micelle. In this case the reaction is likely to take place at the micellar surface, where it still experiences a water-like environment. The retardation mainly results from a significant difference in the binding locations of 5.1 and 5.2, with the dienophiles preferring the outer regions of the micelle and the diene residing in the interior. Evidence comes from solubilisate-induced aromatic shifts in the proton spectrum of the surfactants as well as from paramagnetic ion-induced relaxation rate enhancements of the $^1$H-NMR signals of the solubilisate. The latter experiments also show that 5.2, in contrast to 5.1, perturbs the micelles of SDS and Cu(DS)$_2$. In the situation of inhomogeneous distribution of 5.1 and 5.2 over the micelle, kinetic analysis using the pseudophase model, that has been so successful for many other bimolecular micelle-catalysed processes, will lead to erroneous estimates of the second-order rate constant in the micellar pseudophase.

In contrast to the situation in the absence of catalytically active Lewis acids, micelles of Cu(DS)$_2$ induce rate enhancements up to a factor $1.8 \times 10^6$ compared to the uncatalysed reaction in acetonitrile. These enzyme-like accelerations result from a very efficient complexation of the dienophile to the catalytically active copper ions, both species being concentrated at the micellar surface. Moreover, the higher affinity of 5.2 for Cu(DS)$_2$ compared to SDS and CTAB (P$_{5.2}$ = 96 versus 61 and 68, respectively) will diminish the inhibitory effect due to spatial separation of 5.1 and 5.2 as observed for SDS and CTAB.

5.4 Experimental section

Materials.

Trans-chalcone (5.4) (mp 57.1 - 57.7 °C) was obtained from Aldrich and recrystallised from ethanol. Cyclopentadiene (5.2) was prepared from its dimer (Merck-Schuchardt) immediately before use. Demineralised water was distilled twice in a quartz distillation unit. Cu(NO$_3$)$_2$·3H$_2$O (Merck), DyCl$_3$·6H$_2$O (Aldrich), KNO$_3$ (Merck), cetyl trimethylammonium bromide (CTAB, Merck), sodium dodecylsulfate (SDS, BDH Chemicals), dodecyl heptaoxyethylene ether (C$_{12}$E$_{7}$, Nikko) and ethylenediaminetetraacetic acid tetrasodium salt trihydrate (EDTA, Aldrich) were of the highest purity available. 1,4,7,10-Tetraazacyclododecane (cyclen) has been kindly provided by Erik Keller. Cu(DS)$_2$ and Zn(DS)$_2$ have been prepared following literature procedures$^{70a}$ and were crystallised from water. Compounds 1a-g have been prepared by an aldol condensation of the corresponding substituted aldehyde with 2-acetylpyridine as has been described in Chapter 2. $^1$H-NMR
measurements were performed in D$_2$O (99.9% D, Aldrich). Stock solutions of 5.1c and 5.4 were prepared in methanol-d$_4$ (99.8% D, CIL).

**Endo-exo ratios.**
Endo-exo ratios of the micelle-catalysed reactions have been determined by adding 0.25 mmol of 5.1c and 0.5 mmol of 5.2 to a solution of 5 mmol of surfactant and 0.005 mmol of EDTA in 50 ml of water in carefully sealed 50 ml flasks. The solutions were stirred for 7 days at 26 °C and subsequently freeze-dried. The SDS and CTAB containing reaction mixtures were stirred with 100 ml of ether. Filtration and evaporation of the ether afforded the crude product mixtures. Extraction of the Diels-Alder adducts from the freeze-dried reaction mixture containing C$_{12}$E$_7$ was performed by stirring with 50 ml of pentane. Cooling the solution to -18 °C resulted in precipitation of the surfactant. Filtration and evaporation of the solvent afforded the adduct mixture. Endo-exo ratios were obtained from the crude product mixtures using $^1$H-NMR as described in Chapter 2.

**Kinetic measurements.**
All kinetic measurements were performed using UV-vis spectroscopy (Perkin Elmer ?2, ?5 or ?12 photospectrometers) as described in Chapter 2.

**Conductivity measurements.**
Conductivity measurements were performed using a Wayne-Kerr Autobalance Universal Bridge B642 fitted with a Philips electrode PW 95121/01. The solution in the cell was stirred magnetically and thermostatted at 25 (?0.1) °C. The surfactant was added from a stock solution in water in portions of 50 ?l and the conductivity was measured. $C_{mc}$ were obtained from the intersection of the tangents drawn before and after the break in the conductivity versus concentration plot. The degree of counterion binding is taken as one minus the ratio of these tangents.

**NMR measurements.**
Routine spectra were taken on a Varian VXR 200 MHz or Varian VXR 300 MHz spectrometer. The aromatic shift measurements and the paramagnetic relaxation measurements were performed on a Bruker AC 250 MHz spectrometer. Proton chemical shifts were determined relative to the signal of HOD (4.63 ppm). Paramagnetic relaxation times were determined using the inversion recovery experiment. The variable delay times between the 180° and the 90° pulse were chosen so that they cover the relaxation process during the time-span of minimally five times $T_1$. The 10-16 different delay times were in a random order so as to minimise systematic errors that might result from fluctuations of the strength of the magnetic field during the experiment. The delay time between
subsequent pulse sequences was at least five times $T_1$. The $T_1$ values were calculated using a least squares fitting procedure available on the Bruker software.

In a typical experiment 5-10 μl of a stock solution of the 5.1 or 5.2 in D$_2$O or CD$_3$OD was added to a 50 mM surfactant solution in D$_2$O, resulting in a concentration of dienophile and diene of 8.0 and 3.0 mM, respectively. After determination of the proton spin-lattice relaxation times, a stock solution of the paramagnetic species in D$_2$O was added and the relaxation time measurements were repeated. For CTAB solutions, [Cu(EDTA)]$^{2-}$, prepared in situ from Cu(NO$_3$)$_2$·3H$_2$O and 1.2 equivalent of Na$_4$EDTA·3H$_2$O, served as paramagnetic species in 0.4 mM concentration. For measurements on 5.2 in Zn(DS)$_2$ and SDS solutions, Cu(NO$_3$)$_2$ was added, resulting in a 0.2 mM concentration. For measurements on 5.1 in Zn(DS)$_2$, DyCl$_3$·6H$_2$O was added at 0.2 mM concentration. For SDS micelles, three equivalents (relative to Dy$^{3+}$) of cyclen was added to prevent direct interaction between Dy$^{3+}$ and the dienophile.

**Appendix 5.1**

Critical micelle concentrations and counterion binding (?) of cetyltrimethylammonium bromide (CTAB), sodium dodecylsulfate (SDS) and cobalt, nickel, copper and zinc didodecylsulfate (M(DS)$_2$) in pure water and under reaction conditions, as determined by conductivity measurements at 25°C:

<table>
<thead>
<tr>
<th>surfactant</th>
<th>cmc (mM)</th>
<th>? (%)</th>
<th>cmc (mM)</th>
<th>? (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTAB</td>
<td>0.89$^b$</td>
<td>81$^b$</td>
<td>0.87</td>
<td>71</td>
</tr>
<tr>
<td>SDS</td>
<td>8.14$^b$</td>
<td>60$^c$</td>
<td>7.58</td>
<td>61</td>
</tr>
<tr>
<td>Co(DS)$_2$</td>
<td>1.17</td>
<td>90</td>
<td>1.04</td>
<td>88</td>
</tr>
<tr>
<td>Ni(DS)$_2$</td>
<td>1.19</td>
<td>92</td>
<td>1.09</td>
<td>90</td>
</tr>
<tr>
<td>Cu(DS)$_2$</td>
<td>1.20</td>
<td>89</td>
<td>1.11</td>
<td>87</td>
</tr>
<tr>
<td>Zn(DS)$_2$</td>
<td>1.24</td>
<td>86</td>
<td>1.10</td>
<td>84</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: [5.2] = 1.0$\times$10$^{-3}$ M; [1-propanol] = 9.9$\times$10$^{-2}$ M; [5.1c] = 2.2$\times$10$^{-5}$ M. $^b$ Data taken from reference 12. $^c$ Data taken from reference 84.

**Appendix 5.2**

Assuming complete binding of the dienophile to the micelle and making use of the pseudophase model, an expression can be derived relating the observed pseudo-first-order rate constant $k_{obs}$ to the concentration of surfactant, [S]. Assuming a negligible contribution of the reaction in the aqueous phase to the overall rate, the second-order rate constant in the micellar pseudophase $k_m$ is given by:

(A2.1)
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\[ k_m \approx \frac{k_{obs}}{[5.2]_m} \]

Next, \([5.2]_m\) can be expressed as a function of the partition coefficient \(P_{5.2}\) and the concentration of surfactant in the equations:

\[ P_{5.2} \approx \frac{[5.2]_m}{[5.2]_w} \]

\[ [5.2]_w \approx \frac{n_{5.2.w}}{V_w} \approx \frac{n_{5.2,m}}{V_m} \approx \frac{n_{5.2,t}}{V_t} \approx [5.2]_m \cdot \frac{V_m}{V_t} \]

(A2.3)

Where \(n_{5.2.w}, n_{5.2,m}\) and \(n_{5.2,t}\) are, respectively, the number of moles of 5.2 in the aqueous phase, the micellar phase and the total of the two. \(V_w\) and \(V_m\) are the volumes of the aqueous phase and the micellar pseudophase.

Substitution of A2.2 in A2.3 and solving for \(1/[5.2]_m\) gives:

\[ \frac{1}{[5.2]_m} \approx \frac{V_w}{P_{5.2}\cdot n_{5.2,t}} \]

(A2.4)

The volume of the micellar pseudophase can be estimated from the molar volume of the micellised surfactant \(V_{mol,S}\):

\[ V_m \approx ((S) \cdot cmc) \cdot \frac{V_t}{V_{mol,S}} \]

(A2.5)

Substituting A2.5 in A2.4 and substituting \(n_{5.2,t}\) with \([5.2]/V_t\) yields:

\[ \frac{1}{[5.2]_m} \approx \frac{V_w}{P_{5.2}\cdot [5.2]/V_t} \cdot \frac{V_t}{[5.2]/V_t} \]

(A2.6)

Combining A2.6 and A2.1 gives the final equation from which \(k_m\) and \(P_{5.2}\) can be obtained by plotting \(1/k_{app}\) versus \([S]\).

\[ \frac{1}{k_{app}} \approx k_{obs} \cdot \frac{V_{mol,S}}{[S]} + \frac{V_m}{P_{5.2}\cdot [5.2]/V_t} \cdot \frac{V_t}{[5.2]/V_t} \cdot \frac{cmc \cdot V_{mol,S}}{k_m} \]

(A2.7)

**Appendix 5.3**

When the dienophile does not bind to the micelle, reaction will take place exclusively in the aqueous phase so that the second-order rate constant of the reaction in this phase \(k_w\) is directly related to the ratio of the observed pseudo-first-order rate constant and the concentration of diene that is left in this phase.

\[ k_w \approx \frac{k_{obs}}{[5.2]_w} \]

(A3.1)
The partition coefficient of \(5.2\) \((P_{5.2})\) can be expressed in terms of the concentration of \(5.2\) in the aqueous phase \([5.2]_w\), the total number of moles of \(5.2\) in the reaction mixture \(n_{5.2,t} = n_{5.2,w} + n_{5.2,m}\), as well as the volumes of the aqueous phase \(V_w\) and the micellar phase \(V_m\).

\[
P_{5.2} = \frac{[5.2]_m}{[5.2]_w} \frac{1}{n_{5.2,t}} \frac{n_{5.2,w}}{V_m} \frac{[5.2]_w}{V_w} \frac{1}{n_{5.2,w}} \frac{n_{5.2,t}}{V_m} \frac{V_w}{V_m} \quad (A3.2)
\]

Rewriting and substitution of A2.5 and substitution of \(n_{5.2,t}\) with \([5.2]_t/V_t\) gives:

\[
\frac{1}{[5.2]_w} \frac{P_{5.2} \times V_{mol,S} \times [S]}{[5.2]_t} - \frac{P_{5.2} \times c_{mc} \times V_{mol,S} \times k_w}{[5.2]_t} \frac{V_w}{V_t} \quad (A3.3)
\]

Combining A3.1 and A3.3 and rewriting results in:

\[
\frac{1}{k_{app}} \frac{k_{obs}}{k_w} \frac{[5.2]_w}{[5.2]_t} \frac{P_{5.2} \times c_{mc} \times V_{mol,S} \times k_w}{k_w} \frac{V_w}{V_t} \quad (A3.4)
\]

Using Equation A3.4, the partition coefficient of \(5.2\) can be obtained from the slope of the plot of the apparent second-order rate constant versus the concentration of surfactant and the independently determined value of \(k_w\).

Acknowledgements

The \(^1\)H-NMR shift and relaxation measurements have been performed in cooperation with Prof. Dr. J. C. T. Kwak at Dalhousie University, Halifax, Canada. We gratefully acknowledge the Dutch Organisation for Scientific Research (NWO) for a travel grant to S.O. Theo Rispens is most gratefully acknowledged for the synthesis and purification of \(5.5a-c\).

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