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Cycloadditions in weakly and highly organized aqueous media

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CHAPTER 4

Micellar Catalysis of Diels-Alder Reactions: Substrate Positioning in the Micelle

The kinetics of the Diels-Alder reactions of cyclopentadiene, 2,4-hexadien-1-ol, and 2,4-hexadienyltrimethylammonium bromide with a series of *N*-substituted maleimides are reported in micellar media. Micellar rate constants are determined and are 20–40 times lower than the respective rate constants in aqueous solution. Nevertheless, upon addition of sodium dodecyl sulfate the observed rate constants are enhanced by up to a factor of about 4.5.

The low micellar rate constants are attributed to the relatively apolar (water-poor) region of the micelle in which the reactions take place. NMR experiments indicate that the reactants usually reside near the α - or β -CH₂-groups of the surfactant molecules in the micelle. Comparison of the micellar rate constants with rate constants in water/1-propanol mixtures suggests a concentration of water of 10–15 M in the micellar region where the diene and dienophile react.

4.1 Introduction

Diels-Alder (DA) reactions can be efficiently performed using water as the reaction medium.^{1,2} Rates are usually much higher than those in common organic solvents and also the *endo/exo* ratios are often higher. Many attempts have been made to further enhance the rates of DA reactions. Instead of water, attention has been drawn to ionic liquids as possible reaction media, and a solvophobic effect similar to the hydrophobic effect of water seems to be present.^{3,4} The use of Lewis acids in aqueous media has become common in recent years. Several DA reactions proceed in water, catalysed by Lewis acids.^{5–7} By making the Lewis acid the counterion of either micelles or vesicles,

impressive rate enhancements have been realized.^{6,8} However, although the maximum observed rate constants were indeed enhanced by the use of surfactants, the rate enhancements compared to the Lewis-acid catalyzed reactions in water were only moderate (a factor of ca. 2–5).^{6,8}

Apart from these Lewis-acid catalysed DA reactions, several attempts have been made to catalyze DA reactions using micelles.⁹ Invariably, effects of added surfactant on the rates of these reactions were only modest, and both small accelerations and decelerations have been observed.

For a few reactions *micellar* rate constants have been determined,⁶ which are between one and two orders of magnitude lower than the corresponding aqueous rate constants. This retarding effect is counteracted by the general rate enhancing effect of micelles on second-order reactions, because reactants are concentrated in the micellar reaction volume (*vide infra*). Together these two factors often balance, resulting in a small overall effect on the *observed* rates constant.

In this chapter, catalysis of DA reactions in micellar media was studied systematically, in order to gain detailed insight into the various factors that together determine the observed rates. The above notion that *micellar* rate constants are between one and two orders of magnitude lower than the aqueous rate constants has been extended to a wide range of DA reactions. Nevertheless, for a few reactions, the *observed* rate constants were found to be enhanced up to a factor of about 4.5.

4.1.1 Micellar Kinetics

In 1959, Duynstee and Grunwald found that anionic surfactants inhibit while cationic surfactants enhance the rate of alkaline fading of several dyes.¹⁰ This discovery marked the beginning of the study of micellar-catalyzed reactions. A full kinetic treatment was presented for first-order reactions by Menger and Portnoy in 1967.¹¹ The latter treated micelles as enzyme-like particles, not surprisingly, as micellar catalysis was initially sometimes used as a mimic for enzyme-catalyzed reactions.¹² The effect of micelles on higher-order reactions is more complex, and led to the development of the pseudo-phase model^{13,14} and its variants,^{15,16} *vide infra*. Many processes have been studied in the presence of micelles; the reader is referred to the many reviews that have been published on this subject.^{12,13,15–19} Relatively few studies deal with bimolecular processes involving two organic reactants.^{6,10,20–25} In particular, reactions involving two neutral reactants have received little attention.^{23–25}

For a first-order reaction, the main kinetic effect of micelles stems from the specific local (micellar) reaction environment, comparable to a difference in solvation. In particular, the polarity differs from that of the bulk solution. The substrate may experience different types of microenvironments depending on its exact location within the mi-

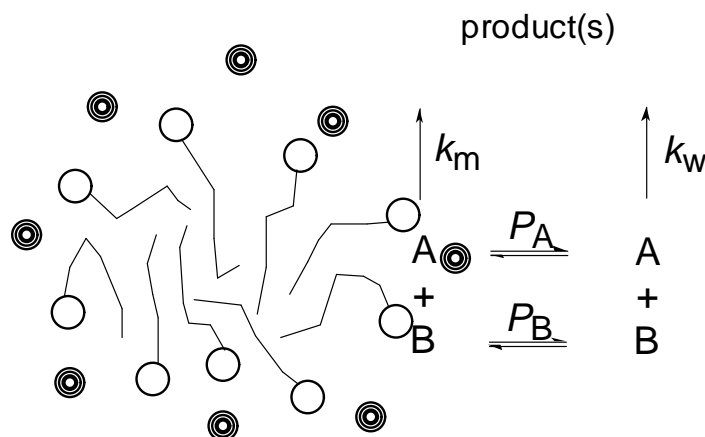


FIGURE 4.1: Schematic representation of the pseudo-phase model for a second-order reaction in micellar media (black circles represent the counterions).

celle.^{19,26} Micellar effects on reaction rate constants have been compared, for instance, with rate constants in concentrated electrolyte solutions, the latter mimicking the Stern layer.²⁷

For a bimolecular (second-order) reaction, in addition to differences in solvation in the aqueous and micellar phase, the concentrations of both reactants in the micellar reaction volume are important. Many organic substrates having an affinity for the micellar phase over the aqueous phase, concentrate in the micelles, that make up only a relatively small part of the total volume of the system. The result is a general rate enhancing effect for bimolecular reactions. The effect diminishes at higher surfactant concentrations because both reactants are diluted over increasingly more micelles. Other possible effects include a partial alignment of the reactants, which can either facilitate or complicate the reaction, and result in a shift in regio- or stereoselectivity.¹⁹

Different models have been developed to quantify the effects that micelles have on reaction kinetics. The most intuitive and easily applied model is the pseudophase model.²⁸ In the pseudophase approach, the micellar solution consists of an aqueous phase (w) and a micellar (pseudo-)phase (m). One or more reactants partition over these two phases, with partition coefficients $P_X = [X]_m/[X]_w$ (Figure 4.1). In each phase, the reaction proceeds with a particular rate, characterized by the corresponding rate constants, k_m and k_w .

A complication for second-order reactions is that either a concentration term enters the micellar rate constant, or, in order to eliminate the concentration term, the micellar reaction volume has to be estimated. In the latter case, the concentration effect is not incorporated into the micellar rate constant, but described explicitly by

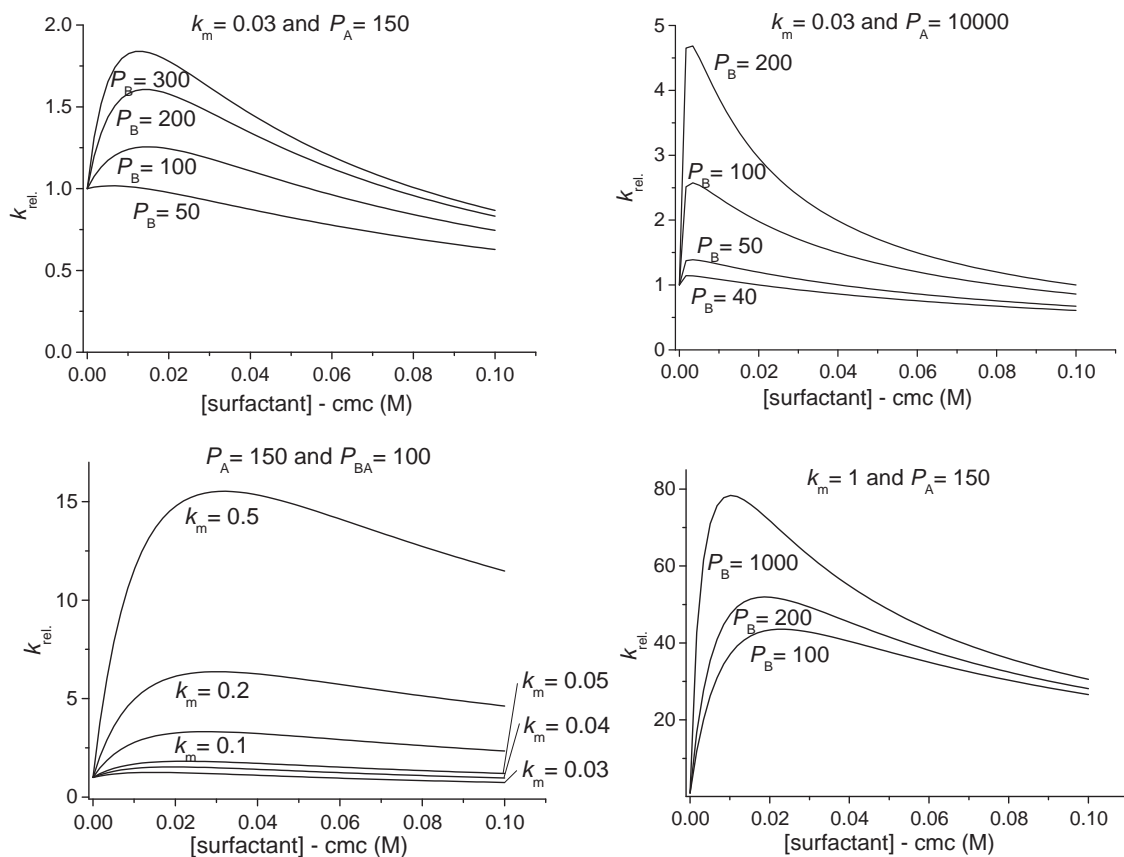


FIGURE 4.2: Illustrative examples of predictions of the observed second-order rate constants by the pseudo-phase model for various choices of k_m , P_A and P_B and with $V_m = 0.25 \text{ M}^{-1}$ and $k_w = 1$ (Equation 4.1). *Upper left:* Typical values for P for small, neutral substrates are in the order of 100. When k_m is much smaller than k_w , this results in very modest effects for the observed rate constant. *Upper right:* If one of the substrates is ionic, it will strongly bind to oppositely charged micelles, leading to high local concentrations (and larger maxima in k_{obs}) at low concentrations of surfactant; increasing the concentration of surfactant dilutes the reactant over more micelles and k_{obs} quickly drops. *Lower left and right:* When k_m and k_w are not very different, large accelerations can be accomplished, even when the binding affinities are moderate.

the model. This approach allows direct comparison between the rate constants in the aqueous and micellar phase. The observed second-order rate constant is expressed as follows (Section 4.4.5):

$$k = \frac{k_m P_A P_B C V + k_w (1 - C V)}{(1 + (P_A - 1) C V)(1 + (P_B - 1) C V)} \quad (4.1)$$

C is the concentration and V the molar volume of micellized surfactant. The molar volume of the surfactant does not always result in a good estimate of the micellar reaction volume, as discussed in Section 5.2.2. Illustrative examples of possible curves

of the apparent second-order rate constant are shown in Figure 4.2 for a bimolecular reaction, with various micellar rate constants and partition coefficients.

The most studied second-order reactions in micellar solutions involve one uncharged and one ionic, inorganic solute, the latter remaining at the micellar surface and behaving as a counter ion. For this type of reaction, the pseudophase model with ion exchange (PPIE) has been developed.¹⁵ Binding of the ionic reactant is described as an exchange process with the counterions. Few second-order reactions in micellar media that involve two uncharged organic species have been analysed using a pseudophase approach.^{23,24}

4.1.2 The Origin of the Low Micellar Rate Constants for Diels-Alder Reactions

Because reactants for DA reactions are often rather apolar, DA reactions are expected to benefit from the general rate enhancing effect of micelles for second-order reactions by means of concentrating the reactants into a small volume. However, in practise, observed rate constants are hardly influenced by the presence of micelles.⁹ Micellar rate constants (k_m) of DA reactions are relatively low ($k_m/k_w = 0.1-0.01$; k_w is the rate constant in the absence of surfactant).⁶ Moreover, data for other DA reactions⁹ also suggest that k_m is in general low.²⁹ This is surprising. Of course, the rates of many DA reactions are much larger in water than in organic solvents. Therefore, an obvious conclusion would be that the micellar reaction mainly proceeds in the apolar core. However, it is common belief that most substrates which bind to micelles remain close to the micellar surface, which is rather aqueous. Therefore, when only a difference in solvation is expected to be responsible for the difference between k_m and k_w , their values are expected to be similar. One may estimate this difference in solvation, or ‘medium effect’,³⁰ by examining concentrated solutions of salts²⁷ or organic solvents. The effect of common inorganic salts (in the order of 2–3 M) on DA reactions is rate retarding within a factor of three,³¹ and considerable concentrations of organic cosolvent are needed before a retardation by more than a factor of two is attained. For example, in mixed alcohol-water solutions, only above a mole fraction of alcohol of about 0.2 (volume fraction about 0.4–0.5) does the rate drop to values close to that of the pure alcohol.³² Furthermore, the few standard Gibbs energies, enthalpies and entropies of activation³³ and *endo/exo* ratios^{6,34} that have been reported also point towards an aqueous reaction environment. In summary, there is no unequivocal evidence supporting an ‘apolar’ micellar Diels-Alder reaction.

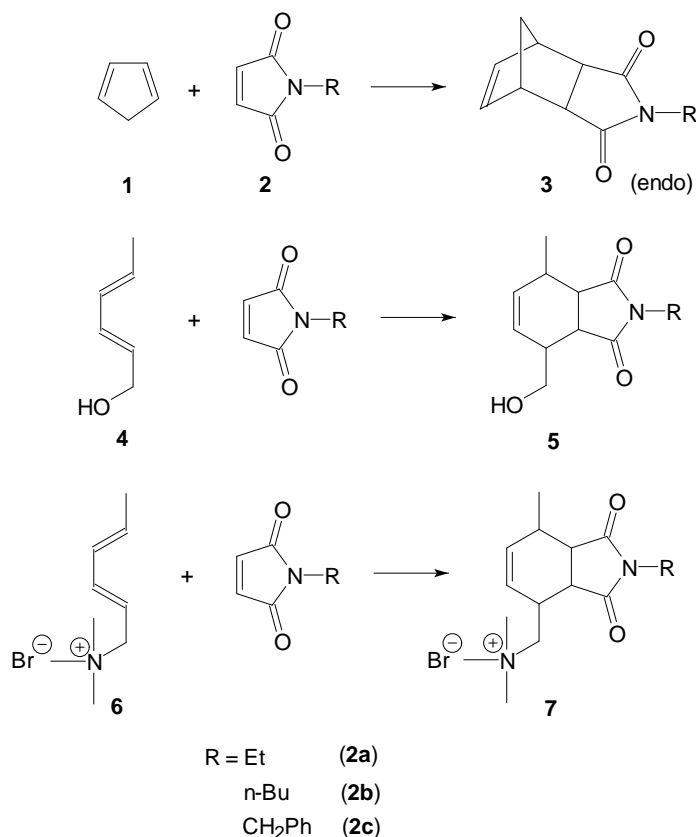
As an alternative explanation different average binding locations have been proposed;⁶ i.e. for the diene (in the micellar core), and the dienophile (at the micellar surface) for DA reactions involving the relatively apolar cyclopentadiene (**1**). Thus, upon binding, the diene and dienophile would be concentrated in *different* micellar regions,

and the number of reactive encounters would hardly increase, taking into account the reduced (micellar) reaction volume. This hypothesis has been supported NMR-relaxation experiments.⁶

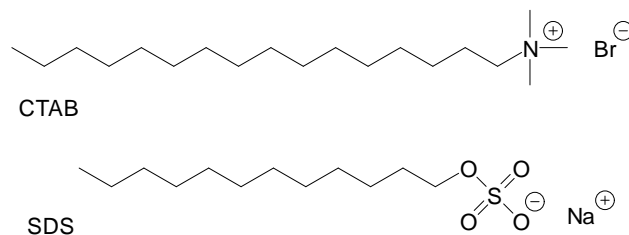
4.1.3 A Systematic Study of the 'Mismatch' in Binding Sites

To test the hypothesis of different average binding positions of diene and dienophile, a series of rather polar dienophiles, but possessing a hydrophobic group R (**2a–c**) were chosen to react with an apolar (**1**), a polar (**4**) and an ionic diene (**6**) (Scheme 4.1). Whereas the apolar cyclopentadiene (**1**) might be expected to reside mainly in the apolar micellar core, thus being only partially available to react with **2a–c**, sorbyl alcohol (2,4-hexadienol, **4**) and sorbyltrimethylammonium bromide (2,4-hexadienyltrimethylammonium bromide, **6**) are expected to bind close to the micellar surface.

The micelle-forming surfactants sodium dodecylsulfate (SDS) and cetyltrimethylammonium bromide (CTAB) are used in the present kinetic study (Scheme 4.2).



SCHEME 4.1.



SCHEME 4.2.

4.2 Results and Discussion

The rate constants for the reactions of **1**, **4**, and **6** with **2a–c** in water (k_w) are listed in Table 4.1. They are not significantly dependent on the substituent R of the maleimides. Only in the case of **6**, the benzyl substituent leads to a slight increase in rate, which might be attributed to a favorable interaction between the trimethylammonium group and the aryl ring in the activated complex.³⁵ If one compares the rate constants of **4** and **6**, the replacement of the hydroxy group by a trimethylammonium group results in a fifty-fold decrease in the rate constant, in accordance with a much stronger inductive electron-withdrawing effect of the trimethylammonium group ($\sigma_I = 0.92$)³⁶ in comparison to that of the hydroxy group ($\sigma_I = 0.25$),³⁶ deactivating the diene.

4.2.1 Results and Fits for SDS

Relative rate constants ($k_{rel} = k/k_w$) in SDS solutions are summarized in Figure 4.3 for the different combinations of dienes and dienophiles. For **2a**, the rate constant for the reaction involving any of the dienes is hardly influenced by the presence of SDS. In fact, the rate is influenced so little by SDS up to concentrations of 0.1 M that without further knowledge, it appears as if the presence of SDS is hardly noticed.

For the other two dienophiles, the observed rate constants reach a maximum at concentrations of SDS just above the CMC and then decrease with further increase in the concentration of SDS. The observed rate constants are enhanced up to a factor of 4.5 (**6+2c**) by the presence of micelles. The behavior of dienes **1** and **4** is remarkably similar, despite the difference in polarity of the dienes. Although for diene **6** the maximum observed rate constants are up to a factor of 2 larger compared to those of **1** and **4**, the rate at higher concentrations of SDS quickly drops. This higher maximum in rate constant is a result of the more efficient binding of **6** to the micelles already at low concentrations of SDS — not of a larger k_m . These observations contrast remarkably with the expected better ‘match’ in binding sites between dienes **4** and **6** and the dienophiles.

The solid curves in Figure 4.3a–c represent fits using the pseudo-phase model to these

TABLE 4.1: Aqueous rate constants and results from analyses using the pseudo-phase model for the DA reactions of **1**, **4** and **6** with **2a-c**.

A	B	k_w ($M^{-1}s^{-1}$)	P_A	P_B	k_m/k_w
1	2a	42.9	75	53	0.043
	2b	38.3	(60–90)	120	0.033
	2c	38.7		251	0.055
4	2a	0.0206	100	24	0.045
	2b	0.0182	(90–110)	130	0.034
	2c	0.0208		277	0.048
6	2a	4.99×10^{-4}		29	0.029
	2b	4.65×10^{-4}	ca. 1×10^4	157	0.023
	2c	8.36×10^{-4}		260	0.023

data; the results are presented in Table 4.1. For diene **6**, at concentrations well below the CMC of SDS, accelerations are observed, indicating that **6** induces micellization. These points have been left out in the fitting procedure for this reason.

The numbers for the relative micellar rate constants substantiate the above qualitative notion that different dienes show a comparable reactivity in the micellar phase. Possible differences in binding sites are not reflected in these data; in particular, the relative micellar rate constants for **1** are not different from those of **4** and **6**. For **6**, the relative rate constants are even lower than those for **1**. It is concluded that although there may be some preference of **1** to reside deeper in the micellar core compared to e.g. **4**, this preference is small and does not significantly affect the rate because of a ‘mismatch’ in binding sites.

The trend in micellar rate constants for both **1** and **4** is $k_{m,2c} > k_{m,2a} > k_{m,2b}$. This trend is also found for rate constants in 1-propanol and in mixtures of 1-propanol and water with low water content (15 or 18 M water), suggesting that in a micelle a relatively apolar environment is experienced by all these reactions.

The partition coefficients for the various compounds are in line with expectation. The partition coefficient for **1** is somewhat higher than the previously reported value of 49,⁹ but given the inherent errors of kinetically determined partition coefficients, this difference is not unanticipated. The value of 100 for **4** is in line with previously reported values of 52 and 162 for pentanol and hexanol, respectively.²⁶ The partition coefficients for the maleimides increase upon enlarging the hydrophobic group R, which is largely responsible for the binding. This is also one of the main factors that determine the observed rate constants. With increasing binding strength, the dienophile binds to the micellar phase at lower concentrations of SDS, or, will be present in a smaller micellar

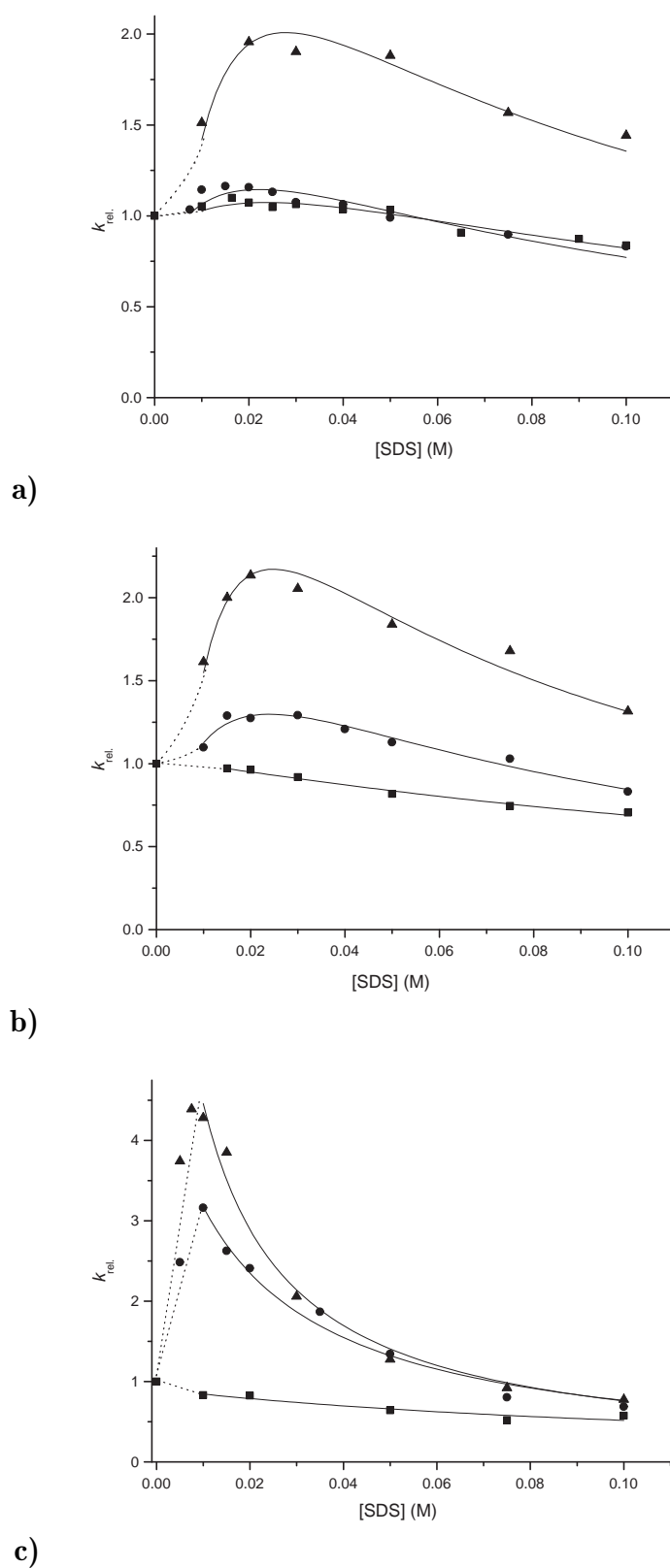


FIGURE 4.3: Relative second-order rate constants ($k_{\text{rel}} = k/k_w$) as a function of the concentration of SDS for the reactions of **2a** (■), **2b** (●), and **2c** (▲) with **a) 1**, **b) 4** and **c) 6** at 25 °C. The solid curves represent the fits of these data to Equation 4.7.

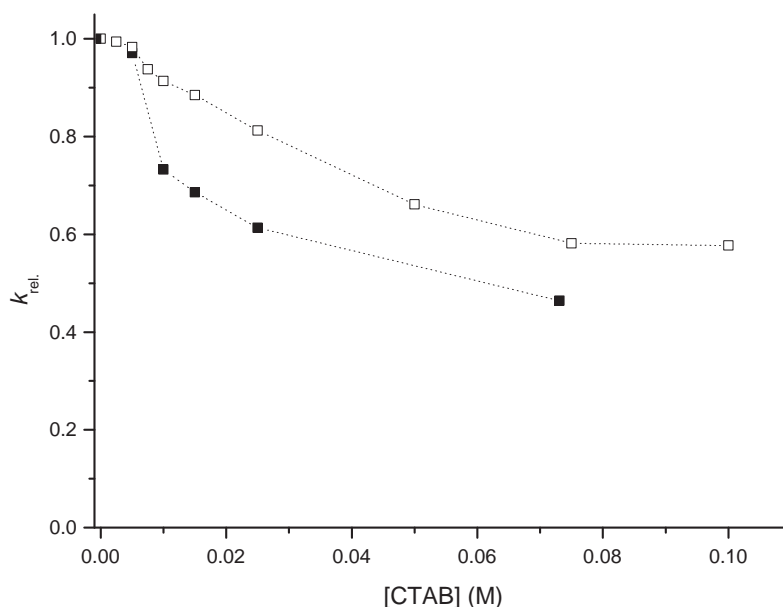


FIGURE 4.4: Relative second-order rate constants ($k_{\text{rel}} = k/k_w$) as a function of the concentration of CTAB for the reactions of **2a** with **1** (■) and **4** (□) at 25 °C.

volume, so that the reaction benefits more from the locally increased concentrations of reactants. Hence, the observed maximum rate constant increases and is reached, in principle, at a lower concentration of SDS.

4.2.2 Results for CTAB

In Figure 4.4, relative rate constants are shown for the reaction of **2a** with **1** and **4** in CTAB solutions. Compared to SDS, there is a more pronounced retardation of these reactions. Organic substrates generally bind stronger to CTAB micelles than to SDS micelles.²⁶ Partition coefficients for *N*-alkylsubstituted maleimides for CTAB are equal to or larger than those for SDS (Chapter 5). Hence, comparison with the results for SDS shows that the micellar rate constants are lower for CTAB than for SDS. This trend could be due to the change in headgroups. However, 2 M of either tetramethylammonium bromide (TMAB) or sodium methyl sulfate (SMS) — mimicking the effect of the headgroups of CTAB and SDS, respectively — have a nearly equal effect on the rate constant (Table 4.2). Instead, the reactants may experience a less polar, less water-rich environment in CTAB micelles. This situation has been mimicked using water/1-propanol mixtures. The results are discussed below.

TABLE 4.2: Relative second-order rate constants for **1** + **2a** in different media.

Medium	k/k_w^a	$[\text{H}_2\text{O}]$ (M)
water	1	55.5
ethanol	0.0075	
1-propanol	0.0084 ^b	
3 M 1-propanol	0.68	43
6 M 1-propanol	0.18	31
9 M 1-propanol	0.060	18
12 M 1-propanol	0.028	6
2 M TMAB ^c	0.68	42
2 M SMS ^d	0.74	48
3 M SMS	0.55	44
3 M SMS/3 M 1-propanol	0.27	32
2.7 M SMS/3.5 M 1-propanol	0.18	31.5
1 M SMS/6 M 1-propanol	0.10	27
micellar rate constant in SDS	0.043	

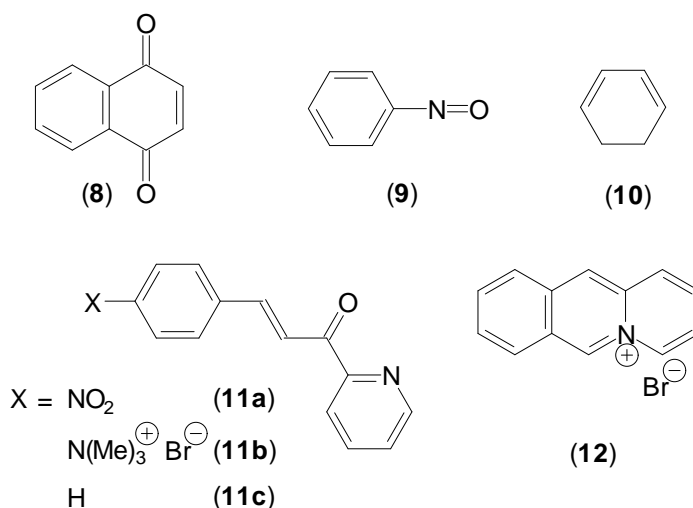
a) Rate constant relative to the rate constant in water ($42.9 \text{ M}^{-1}\text{s}^{-1}$).

b) From Ref. 37. *c)* Tetramethylammonium bromide. *d)* Sodium methyl sulfate.

4.2.3 Average Binding Locations as Determined by NMR

On the basis of changes in relaxation times induced by paramagnetic ions, Otto et al.^{6,38} concluded that cyclopentadiene resides on average more deeply inside the micellar core, whereas the dienophiles **11b** and **11c** (Scheme 4.3) remain closer to the micellar surface. In these experiments, paramagnetic ions are present in low concentration and bind strongly to the oppositely charged micelles. As the induced relaxation rates depend strongly on the distance of the hydrogen atoms to these ions, these induced rates relative to groups close to the micellar surface ($\alpha\text{-CH}_2$) provide information concerning average binding positions.³⁹ However, careful examination of the experimental conditions reveals that only part of the cyclopentadiene is bound to the micelles in these experiments, which was not taken into account in the previous analysis. On the basis of the partition coefficients found previously and found in this work, the induced relaxation rates have been recalculated, taking into account that the fraction of cyclopentadiene not bound to the micelles is not influenced by the paramagnetic ions. The recalculated values reveal that differences in binding sites for the different substrates are only minor (Figure 4.5a).

The induced relaxation rates for substrates **4** and **6** were also determined (Figure 4.5b). If the relaxation rates of **11c**, **1** and **4** are compared with those of SDS, it seems that **11c** and **4** reside on average near either the $\beta\text{-CH}_2$ -group of SDS, or just slightly more to the inside. For **1**, the position may be anywhere near the $n\text{-CH}_2$ -groups



SCHEME 4.3.

of the SDS molecules in the micelle: the relaxation rates for n -CH₂, ω -CH₃ and **1** are nearly equal. It is known that the ω -CH₃-group can be found anywhere between the innermost part and the surface of the micelle.³⁹ The same might be true for **1**. It therefore seems unlikely, that there would be a drastic decrease in the number of reactive encounters between the diene and dienophile in the micellar phase compared to the situation, in which the reactants distribute themselves homogeneously over the micellar reaction volume, as assumed in the pseudo-phase model.¹³

For the cationic substrates **11b** and **6**, interpretation of the data is hampered, because the repulsion between the paramagnetic cation and the substrates interferes with the distance-to-surface dependent relaxation rate. Therefore, the induced relaxation rates most likely do not reflect the average binding locations of these substrates and other techniques are required to identify the binding locations.

A complication in interpreting these data and connecting them to kinetic experiments is that they do not indicate the width of the distribution of the reactants within the micellar phase. This width is crucial in determining whether differences in average binding location have either a small or large influence on the rate (Figure 4.6). Information concerning the width of the distribution can be obtained from NOESY experiments. For example, Hawrylak and Marangoni⁴⁰ showed that 1-butanol remains close to the micellar surface, with the α -CH₂ of 1-butanol near the α -CH₂ of SDS, and the tail pointing inward. Benzene, on the other hand, distributes throughout the micelle with no preference for a particular region. In a similar study,⁴¹ ethanol was found to reside in a phosphocholine bilayer mainly near the α - and β -CH₂-groups of the tails. The picture that emerges from these experiments is that organic substrates

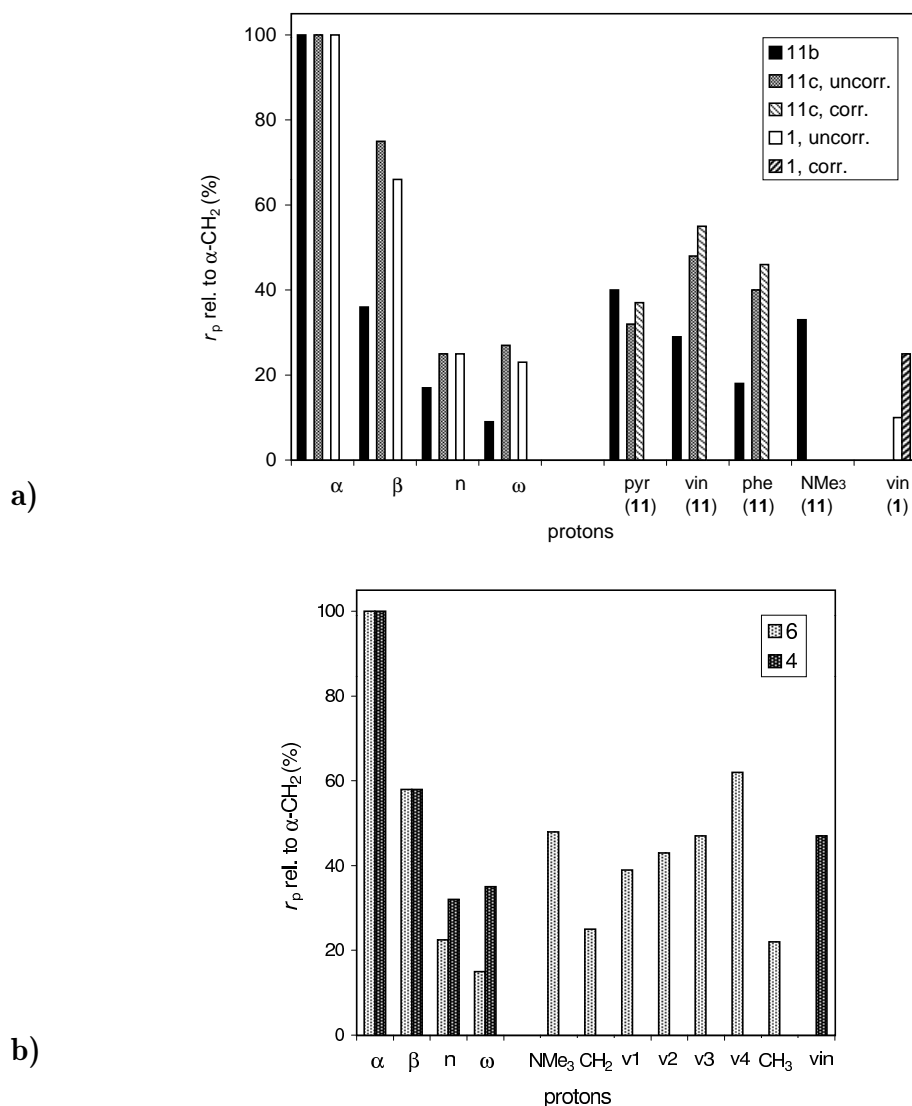


FIGURE 4.5: Relative paramagnetic ion-induced spin-lattice relaxation rates (r_p) of the protons of of a) **1**, **11b**, and **11c**^{6,38} and b) **4** and **6**. For each substrate, values are also given for the hydrogens of SDS; the signal for the α -CH₂-group of SDS is set equal to 100% in each case. The values for SDS serve as an internal reference, and at the same time show that the structure of the aggregate is not completely unaffected by the presence of the substrate (compare the cationic substrates **6** and **11b** with the other substrates). For compounds **1** and **11c**, both corrected and uncorrected values are shown (see text). Legend: SDS) n: hydrogens at C3–C11; **1**) vin: vinylic hydrogens; **11b**) vin: vinylic hydrogens, phe: hydrogens on phenyl ring, pyr: hydrogens on pyridine ring; **11c**) same as **11b**, NMe₃: substituent on phenyl ring; **4**) vin: vinylic hydrogens; **6**) self explanatory, except for v1–v4: vinylic hydrogens, numbered from NMe₃-group onwards.

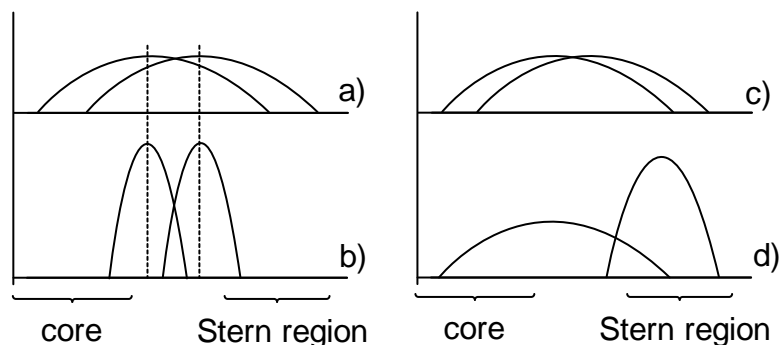


FIGURE 4.6: *Left drawing:* two substrate distributions with a different mean value. When the distributions are broad (a), there is considerable overlap, whereas tight distributions (b) have little overlap. *Right drawing:* situation c illustrates how two non-charged substrates may be distributed over a micelle: broad distributions with a mean value close to the edge between the core and the Stern layer; in situation d, one of the non-charged substrates has been displaced by a charged one, which will bind tightly to the outer part of the micelle, resulting in less encounters between the two substrates.

which possess polar groups reside mainly near the first few CH_2 -groups of the surfactant tails. Vinylic or aromatic apolar substrates such as benzene and cyclopentadiene may be found throughout the micelle.

4.2.4 Micellar Rate Constants Estimated from Water/Salt/Alcohol Mixtures

To obtain further insight into the origin of the low micellar rate constants, the reaction of **1** with **2a** was carried out using solutions containing sodium methyl sulfate (SMS), 1-propanol, or both (Table 4.2). The underlying idea was that the Stern region of an ionic micelle resembles a concentrated salt solution,²⁷ but also possesses hydrophobic character. In fact, if a solute enters a micelle, the outer region closely resembles a concentrated salt solution. However, deeper inside the micelle, the concentrations of both headgroups and water decrease — judging from molecular dynamics simulations, these concentrations reach zero rapidly^{42–45} — and the apolar character of the hydrophobic core becomes more and more apparent.

The data show that the reaction is inhibited by adding salt up to 3 M (estimates of the concentration of headgroups run from 3–5 M;²⁷ although recent experiments suggest a lower value⁴⁶). Nevertheless, the reaction is still much slower in the micellar phase. It is clear that this effect alone cannot account for the low micellar rate constants.

The effect of adding 1-propanol alone is also rate retarding, and solutions containing

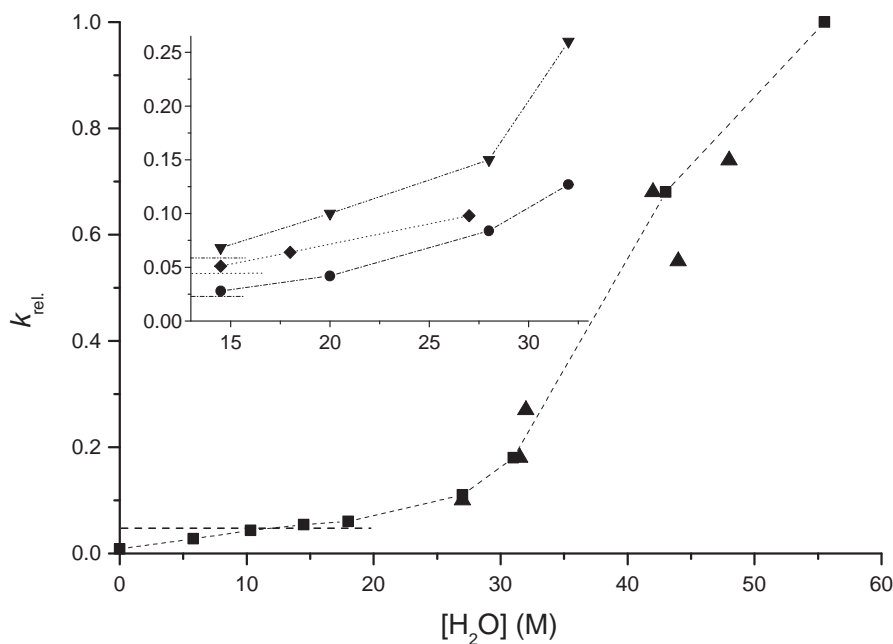


FIGURE 4.7: Relative second-order rate constants ($k_{\text{rel}} = k/k_w$) for **1** + **2a** as a function of the concentration of water for 1-propanol/water mixtures (■) and salt or salt/1-propanol solutions (▲; see Table 4.2. salts are TMAB and SMS). Inset: relative rate constants in 1-propanol/water mixtures for **1** + **8** (●),³² **4** + **2a** (◆) and **10** + **9** (▼).⁴⁷ The lines on the lower left part of the graphs indicate the corresponding relative micellar rate constants.

both SMS and 1-propanol (saturated in 1-propanol for the amount of SMS present) also show rate constants lower by a factor of 4–10 than those in water. In Figure 4.7, these rate constants are plotted as a function of the concentration of water. The amount of water that is present in these solutions is the most important parameter in determining the rate. If these mixtures mimic a micelle upon going from the surface to the inner core, these data suggest that the reaction takes place mainly in a region of the micelle where the concentration of water is already quite low (10–15 M). Comparison with other Diels-Alder reactions (inset of Figure 4.7) shows that in all cases the corresponding micellar rate constants match a propanol/water mixture with a concentration of water of about 10–15 M.

The above observations lead to the suggestion, that many dienes and dienophiles are actually situated on average between the Stern region and the apolar core and are in a relatively apolar (non-aqueous) environment, but still more ‘water-like’ than pure propanol. Therefore, the ‘small’ micellar rate constants mainly originate from the rela-

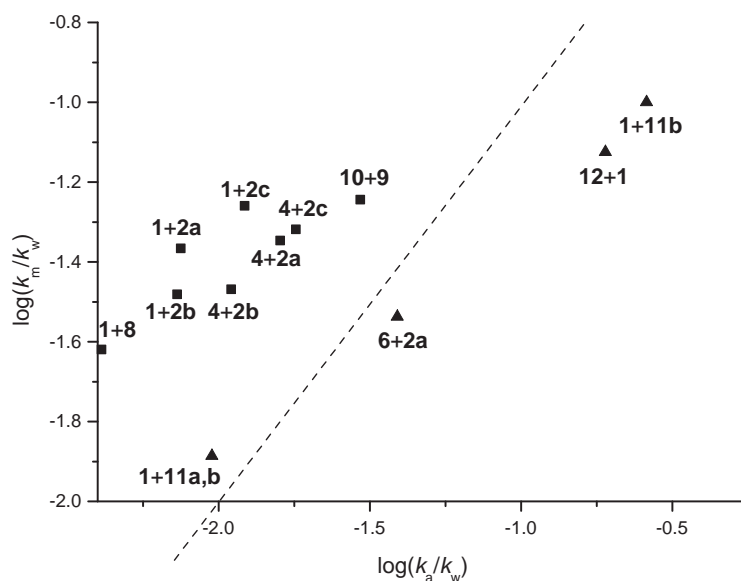


FIGURE 4.8: Relative second-order rate constants in ethanol or propanol (k_a/k_w) versus relative rate constants in the micellar phase (k_m/k_w) for a range of Diels-Alder reactions. The upper triangles (\blacktriangle) correspond with reactions involving an ionic substrate. They form a distinct group, for which the micellar rate constant is much lower (even lower than the rate in alcohol). The dashed line is a guide to the eye and indicates where k_m/k_w and k_a/k_w are equal.

tively apolar medium, not of a ‘mismatch’ between diene and dienophile. Nevertheless, the binding locations are important parameters, because they determine the exact nature of the environment that the reactants experience.

Apparently, none of the substrates used in this study binds to the outermost part of the micelles. This condition was expected for ionic reagents. However, ionic reagents behave in a more complicated way, as will be discussed below.

4.2.5 Solvent Sensitivity and Micellar Rate Constants

In Figure 4.8, micellar rate constants (for SDS) are plotted against rate constants in ethanol or 1-propanol (all relative to water) for a collection of Diels-Alder reactions.⁵⁰ The reactions include those studied in this chapter as well as previously studied reactions. In Table 4.3 and Scheme 4.3, details of the reactions and of the analysis are given.

The generally lower value of k_m/k_w is noted for reactions in which one of the reactants is (positively) charged (indicated in Figure 4.8 with upper triangles). For most cases

TABLE 4.3: A comparison between the relative micellar rate constants and the relative rate constants in organic solvents.

Diene	Dienophile	k_w ($M^{-1}s^{-1}$)	k_{ac}/k_w^a	k_a/k_w^b	k_m/k_w^c
1	8	4.92 ^d		0.00041 ^d	0.024 ^e
1	2a	42.9	0.0029 ^f	0.0075	0.043
1	2b	38.3	0.0026 ^f	0.0073 ^f	0.033
1	2c	38.7		0.0122	0.055
1	11a,b	0.00402 ^g /0.00245 ^h	0.0035 ^{i,g}	0.0095 ^{i,g}	0.013 ^{i,h}
1	11b^j	2.1 ⁱ	0.24 ⁱ	0.26 ⁱ	0.10 ⁱ
4	2a	0.0208	0.0084	0.016	0.045
4	2b	0.0182		0.011	0.034
4	2c	0.0206		0.018	0.048
6	2a	4.99 × 10 ⁻⁴		0.039	0.029
12	1	0.214 ^k	0.11 ^k	0.19 ^k	0.075 ^l
10	9	0.425 ^m		0.0294 ^m	0.057 ⁿ

a) k_{ac} is rate constant in acetonitrile. b) k_a is rate constant in 1-propanol or ethanol. c) k_m is the micellar rate constant – All values were fitted using a CMC for SDS of 0.007 M and a molar volume of 0.25 L/mole. d) Ref. 32. e) Value from the fit of the data given in ref. 32, using a value for $P_1 = 70$; resulting in $P_8 = 330$. f) Ref. 37. g) Value for **11a**. h) Value for **11b**. i) Ref. 6, 48. j) Cu²⁺-catalysed reaction. k) Ref. 49. l) Value from the fit of the data given in Ref. 49, assuming complete binding of **12** thus neglecting the reaction in the aqueous phase (Equation 4.8); resulting in $P_1 = 65$. m) Ref. 47. n) Value from fit of the data given in Ref. 47, using a value for $P_{10} = 250$ (this value gave the best fit, also, compared to **1**, **10** has one extra CH₂ unit, which, in general, gives a 3–4 times higher binding constant to SDS,²⁶ which is in agreement with this value; resulting in $P_9 = 93$).

the micellar rate constant is actually lower than that for the reaction in ethanol. At this stage, only ad hoc explanations can be invoked. Possibly the ionic substrates remain in a relatively small region at the micellar surface, strongly held in place by ionic interactions — as opposed to neutral substrates, which may be situated in a larger part of the micelle (but not so much at the surface). For reactions involving one neutral and one ionic reactant, differences in binding location may become important and affect the activation process for the cycloaddition reaction (Figure 4.6). The pseudo-phase model might be modified to describe this effect, by distinguishing between three regions (core, Stern region, and bulk water). The cationic substrate will not enter the micellar core, whereas the neutral substrate can be found both in the core and the Stern region. This topic is discussed in more detail in Section 6.2.

At this stage, we contend that Diels-Alder reactions catalyzed by SDS micelles may be divided into two groups, one involving only neutral species, and the other involving a (cat)ionic species. For the first group of reactions, the micellar rate constants correspond

to rate constants in a propanol/water mixture with a concentration of water of about 10–15 M, which suggests that the reactions mainly take place in the region of the micelle where water penetration is limited. No evidence was obtained that a difference in average binding location is an important factor in determining these micellar rate constants. For the second group of reactions, this ‘solvent effect’ most likely also influences the rate in the micelle, but this effect alone does not fully explain these (low) rate constants. Other micellar effects also must play a role (*vide supra*).

4.3 Conclusions

Despite the relatively low micellar rate constants, Diels-Alder reactions nevertheless can be accelerated by adding surfactant, depending on the binding properties of the substrates to the micelles.

No evidence emerges for differences in average binding location being responsible for the low micellar rate constants. All combinations of dienes and dienophiles with different binding characteristics lead to micellar rate constants that are substantially lower than the respective aqueous rate constants, but higher than those in, for instance, 1-propanol (the latter with the exception of reactions involving ionic species).

We suggest that in most cases the reaction in the micellar phase mainly takes place in the region between the core and the Stern layer, thereby still experiencing a polar environment, which, however, is not sufficiently aqueous ($[\text{H}_2\text{O}] \approx 15 \text{ M}$) as to attain aqueous rates.

4.4 Experimental

4.4.1 Materials

Cyclopentadiene was prepared from its dimer immediately before use. Demineralised water was distilled twice in a quartz distillation setup. *n*-Butylmaleimide has been synthesised previously.³⁷ Sorbyl alcohol (2,4-hexadien-1-ol, **4**) has been prepared using a literature procedure.⁵¹ All other chemicals were obtained from commercial suppliers and were of the highest purity available, unless indicated otherwise.

Sorbyltrimethylammonium bromide (2,4-hexadienyltrimethylammonium bromide, **6)**

The first step involves a modified literature procedure,⁵² for the second step the procedure for preparing allyltrimethylammonium bromide⁵³ has been adapted.

7.6 g of PBr_3 in 8 ml of ether was added to a mixture of 4.7 g (0.049 mol) of sorbyl alcohol, 1.2 ml of pyridine (dry) and 40 ml of ether under cooling. A yellow precipitate slowly formed. After one hour the mixture was poured on ice-water and extracted with ether. The ethereal layers were washed subsequently with a sodium bicarbonate solution and brine and then dried with sodium sulfate. After removal of the ether, distillation yielded 4.3 g of a pale yellow liquid (bp. 60–75 °C/5 mm Hg). H-NMR indicated it to be a mixture of the product and unknown side products. In the liquid a precipitate forms in minutes upon standing, so it was used immediately in the next step.

A mixture of 4.3 g of sorbyl bromide (previous step) and 11 ml of 25% trimethylamine in methanol was stirred at room temperature for two days in the absence of light. A little precipitate had formed, which was filtered off. The methanol was evaporated and the remaining yellow-white solid material was washed with ether and acetone. Of this crude material, 1.5 g was recrystallized from ethanol (2 ml, 80 to –20 °C). The precipitate was filtered off (H-NMR in D_2O : δ 2.7 (s)). The filtrate was concentrated and the remaining solid material was recrystallized from acetone (2 ml, 56 to 7 °C), yielding a white solid, which was dried in vacuo at 50 °C (220 mg, 10%). Upon concentrating the filtrate a second, less pure batch was obtained. H-NMR (D_2O): δ 6.40 (m, 1H), 6.05 (m, 1H), 5.85 (m, 1H), 5.52 (m, 1H), 3.72 (d, $J = 8$ Hz, 2H), 2.88 (s, 9H), 1.62 (d, $J = 6.5$ Hz, 3H). m.p. 135–137 °C. Anal. calcd. C: 49.1, H: 8.24, N: 6.36, found C: 48.9, H: 8.35, N: 6.45.

4.4.2 Product Analysis

For compounds **3a** and **3b**, see Ref. 37. Compound **3c**⁵⁴ has been prepared analogously. Mainly the *endo* product is formed.³⁷

2-Alkyl-4-(hydroxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione (5). In a typical procedure, about 0.5 mmol of the maleimide (**2a–c**) and 0.5 mmol of sorbyl alcohol (**4**) were dissolved in water and stirred for several days at room temperature. The mixture was extracted with ether, the ethereal layers washed with brine, dried (magnesium sulfate) and evaporated; the remainder (oils, that after some time solidified) was analysed by H-NMR and contained besides product traces of starting materials, that could be removed by column chromatography (silica/ether). Products (mixtures of isomers, not individually identified) were obtained in quantitative yields.

2-Ethyl-4-(hydroxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione (5a).⁵⁵ H-NMR (CDCl_3): δ 5.77 (dt, ⁵⁵ $J = 9, 3$ Hz, 1H), 5.66 (dt, ⁵⁵ $J = 9, 3$ Hz, 1H), 3.98 (m, 2H), 3.50 (q, $J = 7$ Hz, 2H), 3.30 (m, 2H), 3.05 (dd, $J = 9, 10$ Hz, 1H), 2.55 (broad, 1H), 2.43 (broad, 1H), 1.49 (d, $J = 8$ Hz, 3H), 1.09 (t, $J = 8$ Hz, 3H).

2-Butyl-4-(hydroxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione (5b). H-NMR (CDCl_3): δ 5.85 (m, 1H), 5.64 (m, 1H), 3.95 (m, 2H), 3.46 (t, $J =$

7 Hz, 2H), 3.33 (m, 2H), 3.04 (dd, $J = 9, 10$ Hz, 1H), 2.57 (broad, 1H), 2.42 (broad, 1H), 1.48 (d, 3H; m, 2H), 1.13 (m, 2H), 0.88 (t, $J = 7$ Hz, 3H).

2-Benzyl-4-(hydroxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3-(2H)-dione (5c).⁵⁶ H-NMR (CDCl₃): δ 7.22 (m, 5H), 5.68 (dt, $J = 9, 3$ Hz, 1H), 5.58 (dt, $J = 9, 3$ Hz, 1H), 4.53 (s, 2H), 3.89 (m, 2H), 3.26 (m, 2H), 3.02 (dd, $J = 8.5, 9$ Hz, 1H), 2.52 (broad, 1H), 2.37 (broad, 1H), 1.41 (d, $J = 8$ Hz, 3H).

2-Alkyl-7-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)-N,N,N-trimethylmethanaminium bromide (7). In a typical procedure, about 0.12 mmol of sorbyltrimethylammonium bromide (**6**) and 0.12 mmol of maleimide (**2**) in 0.7 ml of methanol were shielded from light and allowed to react for 1–4 weeks. Then the methanol was evaporated and the remainder was analysed by NMR. None of the reactions was yet complete, as there were still small percentages of starting materials left. Attempts to recrystallize the compounds (ethanol) failed. No further attempts were made to purify the compounds. Products are mixtures of isomers, not individually identified.

2-Ethyl-7-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)-N,N,N-trimethylmethanaminium bromide (7a). H-NMR (CD₃OD): δ 5.77 (dt, $J = 10, 3$ Hz, 1H), 5.68 (dt, $J = 10, 3$ Hz, 1H), 4.06 (d, $J = 14$ Hz, 1H), 3.8 (dd, $J = 9, 14$ Hz, 1H), 3.28 (m, 2H), 3.22 (m, 2H), 3.08 (s, 9H), 2.77 (broad, 1H), 2.52 (broad/m, 1H), 1.30 (d, $J = 8$ Hz, 3H), 0.90 (t, $J = 8$ Hz, 3H).

2-Butyl-7-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)-N,N,N-trimethylmethanaminium bromide (7b). H-NMR (CD₃OD): δ 5.80 (dt, $J = 9, 3$ Hz, 1H), 5.69 (dt, $J = 9, 3$ Hz, 1H), 4.06 (d, $J = 14$ Hz, 1H), 3.84 (dd, $J = 8, 14$ Hz, 1H), 3.28 (m, 2H), 3.20 (m, 2H), 3.10 (s, 9H), 2.79 (broad, 1H), 2.55 (broad/m, 1H), 1.29 (d, 8 Hz, 3H; m, 2H), 1.1 (m, 2H), 0.77 (t, $J = 7.5$ Hz, 3H).

2-Benzyl-7-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)-N,N,N-trimethylmethanaminium bromide (7c). H-NMR (CD₃OD): δ 7.18 (m, 5H), 5.76 (dt, $J = 8.5, 3$ Hz, 1H), 5.63 (dt, $J = 8.5, 3$ Hz, 1H), 4.42 (s, 2H), 4.06 (d, $J = 14$ Hz, 1H), 3.83 (dd, $J = 10, 14$ Hz, 1H), 3.32 (m, 1H), 3.10 (s, 9H), 2.79 (broad, 2H), 2.55 (broad/m, 1H), 1.27 (d, $J = 7$ Hz, 3H).

4.4.3 Kinetic Measurements

Kinetic measurements were performed using UV-VIS spectroscopy (Perkin Elmer $\lambda 2$, $\lambda 5$ or $\lambda 12$ spectrophotometer) at 25.0 °C. All reactions were followed at 298 nm (disappearance of the dienophile). The diene was present in excess. Either the dienophile (in case of cyclopentadiene as the diene) or the diene was dissolved, the solution was allowed to equilibrate, and subsequently the second reactant was added and the measurement started. Reactants were added by injecting a known amount (2–10 μ l) of a concentrated stock solution in acetonitrile (water in case of **6**). The rates of the faster reactions were

followed for at least four half-lives and pseudo-first-order rate constants were obtained using a fitting program. The rate constants of the slower reactions were obtained using initial rate kinetics. Typical conditions were: [diene]= 1–5 mM, [dienophile]= 0.05–0.1 mM. For the slower reactions possible competition of the hydrolysis of the maleimides⁵⁷ was excluded by measuring under slightly acidic conditions (pH 3–3.5). Rate constants were generally reproducible to within 3%.

4.4.4 NMR Measurements

Paramagnetic relaxation times were determined using an inversion-recovery pulse sequence. The T_1 values were calculated using a least-squares fitting procedure available on the Varian software. Solutions contained 50 mM of SDS, 5 mM of either **4** or **6** and 0 or 0.2 mM of CuCl_2 . For compound **4**, reliable values for T_1 could not be determined for the CH_3 and CH_2 groups, because their signals nearly coincided with those of SDS. Relaxation rates for compound **4** were calculated taking into account that **4** is only partly bound to micelles under the conditions used. Experiments using 100 mM of SDS rather than 50 mM yielded the same, corrected values.

4.4.5 Kinetic Analysis Using the Pseudo-phase Model

Details of the pseudo-phase model have been described in detail,^{13,14} and are summarized here. The micellar solution is assumed to consist of an aqueous (w) and a micellar (m) phase. The reagents are distributed over two phases (Figure 4.1). Partitioning is described by the partition coefficients:

$$P_A = [A]_m/[A]_w \quad (4.2)$$

$$P_B = [B]_m/[B]_w \quad (4.3)$$

Rate constants in the aqueous and micellar phase are k_w and k_m , respectively. The overall reaction rate is the weighted average of reaction rates in aqueous (v_w) and micellar (v_m) phases:

$$\begin{aligned} v &= k[A]_t[B]_t = v_m CV + v_w(1 - CV) \\ &= k_m[A]_m[B]_m CV + k_w[A]_w[B]_w(1 - CV) \end{aligned} \quad (4.4)$$

C is the concentration of surfactant minus the CMC. V is the molar volume of the surfactant. Combination of Equation 4.2–4.4 together with

$$[A]_t = [A]_m CV + [A]_w(1 - CV) \quad (4.5)$$

$$[\text{B}]_{\text{t}} = [\text{B}]_{\text{m}}CV + [\text{B}]_{\text{w}}(1 - CV) \quad (4.6)$$

results in the following expression for the apparent second-order rate constant:

$$k = \frac{k_{\text{m}}P_{\text{A}}P_{\text{B}}CV + k_{\text{w}}(1 - CV)}{(1 + (P_{\text{A}} - 1)CV)(1 + (P_{\text{B}} - 1)CV)} \quad (4.7)$$

which is the same as Equation 4.1. In deriving Equation 4.7, it is assumed that the reagents do not affect the properties, in particular the CMC, of the surfactant. This assumption will break down when the ratio [reagent]/[surfactant] becomes too high. For the dienophiles, the concentrations are well below the surfactant concentrations, but for the dienes, this is not the case. For dienes **1** and **4**, with moderate affinity for the micellar phase, uptake of diene in the micellar phase with increasing concentration of surfactant is such that the model may be safely applied. However, for diene **6**, micellization is induced at concentrations well below the CMC of SDS and binding is essentially already complete at these low surfactant concentrations. This problem was circumvented by only taking into account data with concentrations of SDS higher than 10 mM, such that $[\mathbf{6}]/[\text{SDS}] < 0.3$. This also applies to the reaction between **12** and **1**.

Fits were performed using Microcal Origin 6.0,⁵⁸ using the Levenberg-Marquardt algorithm. Data were fitted to Equation 4.7. For V_{SDS} , a value of $0.25 \text{ dm}^3 \text{ mol}^{-1}$ was used.²⁶ Because of the mutual dependency of P_{A} and P_{B} , only one of these parameters could be obtained in a single fit. Therefore, fits were performed with different fixed values for P_{diene} . This resulted in sets of values for $P_{\text{dienophile}}$ as a function of values for P_{diene} , from which the most consistent values were taken. These most consistent values of P_{diene} appear in Table 4.1, with the corresponding values for $P_{\text{dienophile}}$ and $k_{\text{m}}/k_{\text{w}}$. From the variation in the numbers for the different parameters, the accuracy is estimated to be better than 20% for the partition coefficients (except for **2a**) and 5–10% for the micellar rate constants.

For diene **6**, because of the high affinity to SDS micelles, it was assumed that all of the diene was present in the micellar phase. This, together with a high value of $P_{\mathbf{6}}$ (10^4 – 10^5) leads to Equation 4.8:

$$k = \frac{k_{\text{m}}P_{\text{A}}}{1 + (P_{\text{A}} - 1)CV} \quad (4.8)$$

which was used in fitting the results for **6**. The value for $P_{\mathbf{6}}$ is based on fits with use of equation 4.7 with fixed values for $P_{\mathbf{2a-c}}$.

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