JOC Article

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

Theo Rispens and Jan B. F. N. Engberts*

Physical Organic Chemistry Unit, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

j.b.f.n.engberts@chem.rug.nl

Received June 19, 2002

We have studied the kinetics of the Diels−Alder reactions of cyclopentadiene, sorbyl alcohol, and sorbyltrimethylammonium bromide with a series of *N*-substituted maleimides in micellar media. Micellar rate constants have been determined and were found to be 20−40 times lower than the respective aqueous rate constants. Nevertheless, it was found that upon addition of sodium dodecyl sulfate the observed rate constants could be enhanced up to a factor of about 4.5. The low micellar rate constants can be 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-CH$_2$ 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.

Introduction

Diels−Alder reactions can be efficiently performed with 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. Different attempts have been made to further enhance the rates of Diels−Alder reactions. Instead of water, ionic liquids have drawn attention as a possible reaction medium, 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 more common in recent years, and also several Diels−Alder reactions were performed in water, catalyzed by Lewis acids.[5−7] By making the Lewis acid the counterion of 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-catalyzed Diels−Alder reactions, several attempts have been made to catalyze Diels−Alder reactions with micelles.[9] Invariably, effects of added surfactant on the rates of these reactions were only modest, and both small accellerations and decellerations have been observed.

For a few reactions *micellar* rate constants have been determined,[6] which are 1−2 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 of increased local concentrations of reactants in the micellar reaction volume (see below). Together these two factors often balance to only give a small overall effect on the *observed* rates.

In this work, catalysis of Diels−Alder reactions in micellar media has been studied systematically, to gain more detailed insight into the various factors that together determine the observed rates. The above notion that *micellar* rate constants are 1−2 orders of magnitude lower than the aqueous rate constants has been extended to a wide range of Diels−Alder reactions. Nevertheless, for a few reactions, the *observed* rates were found to be enhanced up to a factor of about 4.5.

(a) Micellar Kinetics. 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. For a bimolecular (second-order) reaction, in addition to this difference in solvation in the aqueous and micellar phase, also the concentrations of both reactants in the micellar reaction volume are important. Considering that many organic substrates have an affinity for the micellar phase over the aqueous phase, they will be concentrated in the micelles which

---

[1] Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic: New York, 1998.

[2] Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365−372.

[3] Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Green Chem.* **1999**, *1*, 23−25.

[4] Dubreuil, J. F.; Bazureau, J. P. *Tetrahedron* **2000**, *41*, 7351−7355.

[5] Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702−7707.

[6] Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517−9525.

[7] Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439−455.

[8] Rispens, T.; Engberts, J. B. F. N. *Org. Lett.* **2001**, *3*, 941−943.

[9] Otto, S.; Engberts, J. B. F. N. In *Reactions and Synthesis in Micellar Media*; Texter, J., Ed.; Marcel Dekker: New York, 2001; pp 247−263.

10.1021/jo0260802 CCC: $22.00

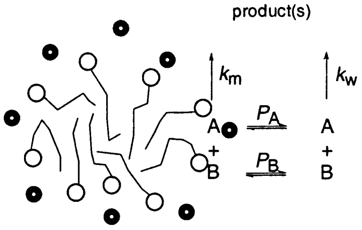


FIGURE 1. Schematic representation of the pseudophase model for a second-order reaction in micellar media (black circles represent the counterions).

together make up only a relatively small part of the total volume of the system. This results in a general rate-enhancing effect for bimolecular reactions. The effect diminishes at higher surfactant concentrations because of dilution of both reactants over increasingly more micelles.

Several models have been developed to quantify the effects that micelles have on reaction kinetics.[10,11] The most intuitive and easily applied model is the pseudophase model.[12] In the pseudophase approach, the micellar solution is described as consisting of an aqueous phase (w) and a micellar (pseudo-)phase (m), and one or more reactants partitioning over these two phases (with partition coefficients $P_X = [X]_m/[X]_w$). In each of the two phases, the reaction will proceed with a particular rate, characterized by the corresponding rate constants (k_m and k_w; Figure 1).

Second-order reactions are more complicated in the sense that either a concentration term enters the micellar rate constant or, to eliminate the concentration term, the micellar volume has to be estimated. In the latter case, the concentration effect is not incorporated into the micellar rate constant, but described explicitly by the model. This allows a direct comparison between the aqueous and micellar rate constants. In Figure 2, illustrative examples of possible curves of the apparent second-order rate constant are shown for a bimolecular reaction, with various micellar rate constants and partition coefficients.

By far the most studied second-order reactions in micellar solutions involve one uncharged and one ionic, inorganic species, the latter remaining at the micellar surface and behaving as a counterion. For this type of reaction, the pseudophase model with ion exchange (PPIE) has been developed.[11] Few examples of second-order reactions in micellar medium that involve two uncharged organic species have been analyzed in terms of a pseudophase approach.[13,14]

(b) The Origin of the Low Micellar Rate Constants for Diels−Alder Reactions. Micellar rate constants (k_m) of Diels−Alder reactions that have been determined explicitly are relatively low ($k_m/k_w = 0.1-0.01$). Moreover, data for other Diels−Alder reactions[9] also suggest that values of k_m are low in general. The latter is based on the expected rate enhancing concentration effect (which may lead to rate accelerations up to about 100) and the observed rate constants in micellar solutions that are hardly different from those in water. This is actually a surprising phenomenon. Of course, the rates of many Diels−Alder reactions are much larger in water than in organic solvents, so an obvious conclusion would be that the micellar reaction mainly proceeds in the apolar core. However, most substrates that bind to micelles will remain close to the micellar surface, which is still 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",[15] by looking at concentrated solutions of salts[16] or organic solvents. The effect of several moles/liter of common inorganic salts on DA reactions is retarding within a factor of 3,[17] and considerable amounts of organic cosolvent are needed before a retardation by more than a factor of 2 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.[18] Furthermore, the few Gibbs energies, enthalpies, and entropies of activation[19] and endo/exo ratios[6,20] that have been determined also point toward an aqueous environment. In summary, there is no unequivocal evidence supporting an "apolar" micellar Diels−Alder reaction.

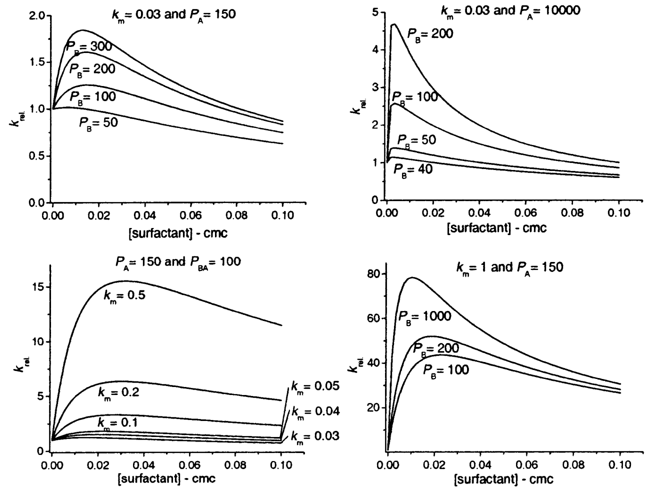


FIGURE 2. Illustrative examples of predictions of the observed second-order rate constants by the pseudo-phase model for various choices of k_m, P_A, and P_B and with $V_m = 0.25$ M^{-1} (eq 6). $k_{rel} = k_m/k_w$.

---

(10) Berezin, I. V.; Martinek, K.; Yatsimirskii, A. K. *Russ. Chem. Rev.* **1973**, *42*, 787−802.

(11) Romsted, L. S. In *Micellization, Solubilization and Microemulsions*; Mittal, K. L., Ed.; Plenum Press: New York, 1977; Vol. 2, pp 509−530.

(12) First-order reactions are most often described by a model resembling Michaelis−Menten kinetics and characterized by a binding constant and a micellar rate constant.

(13) Yatsimirski, A. K.; Martinek, K.; Berezin, I. V. *Tetrahedron* **1971**, *27*, 2855−2868.

(14) Martinek, K.; Osipov, A. P.; Yatsimirski, A. K.; Berezin, I. V. *Tetrahedron* **1975**, *31*, 709−718.

(15) By medium effect, differences in e.g. polarity or hydrogen bond-donor capacity is meant. A micellar Stern region may, for instance, be mimicked by a concentrated salt solution.[16]

(16) Buurma, N. J.; Herranz, A. M.; Engberts, J. B. F. N. *J. Chem. Soc., Perkin Trans. 2* **1999**, 113−119.

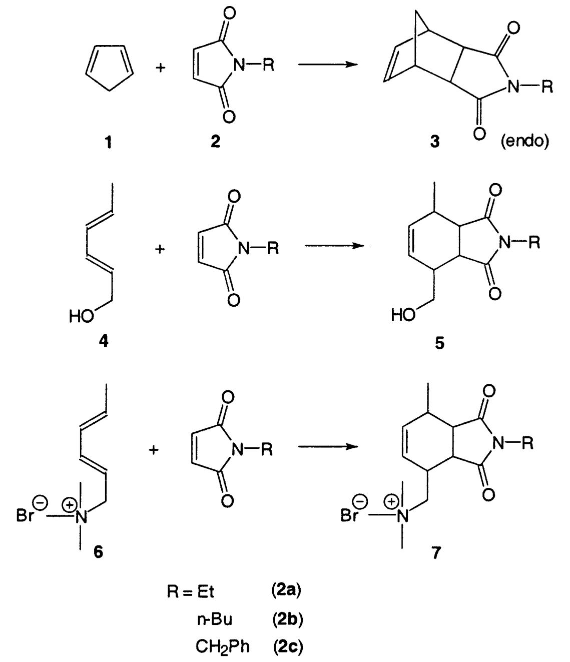
(17) Kumar, A. *Chem. Rev.* **2001**, 8801−8805.

(18) Blokzijl, W. Organic Reactivity in Mixed Aqueous Solvents. Ph.D. Thesis, University of Groningen, 1991.

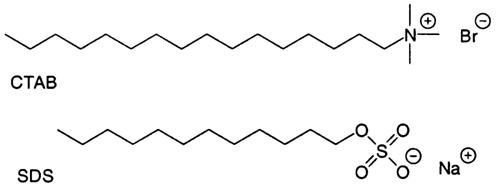
(19) Hunt, I.; Johnson, D. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1051−1056.

(20) Braun, R.; Schuster, F.; Sauer, J. *Tetrahedron Lett.* **1986**, *27*, 1285−1288.

SCHEME 1



SCHEME 2



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 by NMR-relaxation experiments.[6]

(c) 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 possesing a hydrophobic group R (**2a**−**c**), were chosen to react with an apolar (**1**), a polar (**4**), and an ionic diene (**6**) (Scheme 1). Whereas the apolar cyclopentadiene (**1**) might be expected to mainly reside in the apolar micellar core, thus being only partially available to react with **2a**−**c**, sorbyl alcohol (**4**) and sorbyltrimethylammonium bromide (**6**) are expected to bind close to the micellar surface.

The micelle-forming surfactants sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) have been used in the present kinetic study (Scheme 2).

Results and Discussion

In Table 1, the rate constants for the reactions of **1**, **4**, and **6** with **2a**−**c** in water (k_w) are listed. They hardly depend on the different substituents R of the maleimides.

TABLE 1. Aqueous Rate Constants and Results from Analyses with Use of the Pseudophase 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

Only in the case of **6** does the benzyl substituent lead 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.[21] If one compares the rate constants of **4** and **6**, the replacement of the hydroxy group by a trimethylammonium group results in a 50-fold decrease in the rate, in accordance with a much stonger inductive electron-withdrawing effect of the trimethylammonium group ($\sigma_I = 0.92$)[22] in comparison to that of the hydroxy group ($\sigma_I = 0.25$),[22] deactivating the diene.

(a) Results and Fits for SDS. In Figure 3a−c, apparent rate constants in SDS solutions are shown for the different combinations of dienes and dienophiles, relative to the rate constants in water. For **2a**, the rate with 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 looks as if the presence of SDS is hardly noticed at all.

For the other two dienophiles, the observed rate constants reach a maximum at concentrations of SDS just above the cmc and then decrease again with a further increase of the concentration of SDS. The observed rates 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 rates are higher up to a factor of 2 compared to those of **1** and **4**, the rate at higher concentrations of SDS quickly drops. This higher maximum 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 remarkably contrast with the expected better "match" in binding sites between dienes **4** and **6** and the dienophiles.

The solid curves in Figure 3a−c represent fits of the pseudo-phase model to these data, and the results are presented in Table 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.

The numbers for the relative micellar rate constants substantiate the above qualitative notion that the different dienes show a comparable reactivity in the micellar phase. Possible differences in binding sites are not reflected in these numbers; in particular, the relative

---

[21] Bacaloglu, R.; Bunton, C. A.; Cerichelli, G.; Ortega, F. *J. Phys. Chem.* **1989**, *93*, 1490.

[22] Chapman, N. B.; Shorter, J. *Advances in Linear Free Energy Relationships*; Plenum Press: New York, 1972.

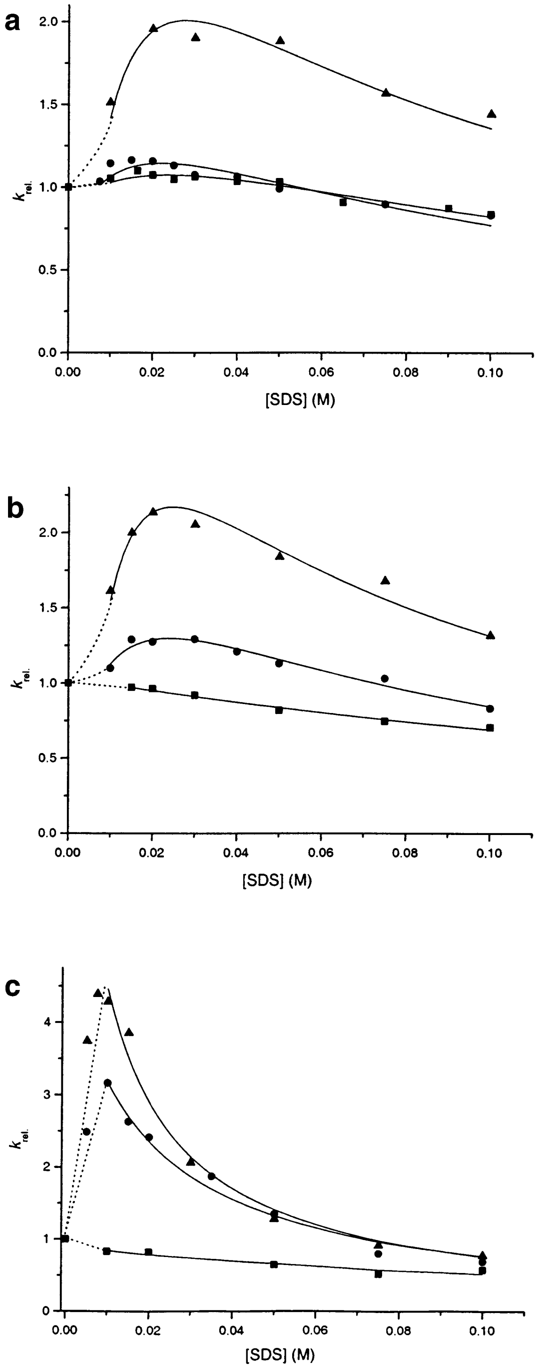


FIGURE 3. Relative apparent second-order rate constants as a function of the concentration of SDS for the reactions of **2a** (■), **2b** (●), and **2c** (▲) with (a) **1**, (b) **4**, and (c) **6** at 25 °C. The solid curves represent the fits of these data to eq 6.

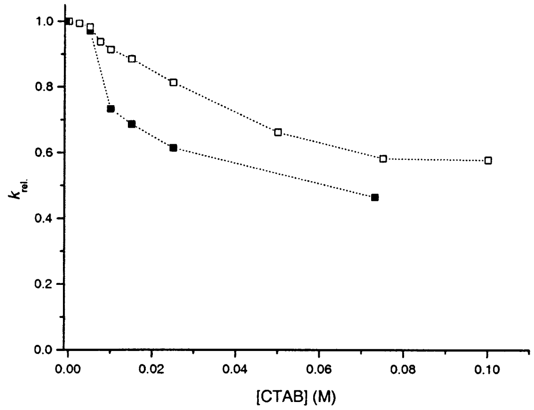


FIGURE 4. Relative apparent second-order rate constants as a function of the concentration of CTAB for the reactions of **2a** with **1** (■) and **4** (□) at 25 °C.

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**. Therefore, we conclude 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 $k_{\mathrm{m},\mathbf{2c}} > k_{\mathrm{m},\mathbf{2a}} > k_{\mathrm{m},\mathbf{2b}}$. This trend is also found for the 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 found for the various compounds are in line with expectation. The value found for **1** is somewhat higher than the previously reported value of 49,[9] but given the errors that are inherent to these numbers, when determined kinetically, this is not unanticipated. The value of 100 for **4** is in line with previous reported values of 52 and 162 for pentanol and hexanol, respectively.[23] 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 rates. With increasing binding strength, the dienophile will bind to the micellar phase already at lower concentrations of SDS, or it will be present already in a smaller micellar volume, so that the reaction benefits more from the locally increased concentrations of reactants. This means that the observed maximum rate constant shifts to a higher value, which will in principle be reached at a lower concentration of SDS.

(b) Results for CTAB. In Figure 4, relative rate constants in CTAB solutions are shown for the reaction of **2a** with **1** and **4**. Compared to SDS, there is a more pronounced retardation of these reactions. Since organic substrates generally bind stronger to CTAB micelles than to SDS micelles,[23] comparison with the results for SDS learns that the micellar rate constants are lower for CTAB than for SDS. This could be due to the difference 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, has a nearly equal effect on the rate (Table 2). Instead, the reactants may experience a less polar, less water-rich environment in CTAB micelles. We have tried to mimick this situation using water/1-propanol mixtures, which will be discussed below.

(c) Average Binding Locations As Determined by NMR. On the basis of changes in relaxation times induced by paramagnetic ions, it was concluded by Otto et al.[6,24] that cyclopentadiene resides on average more

---

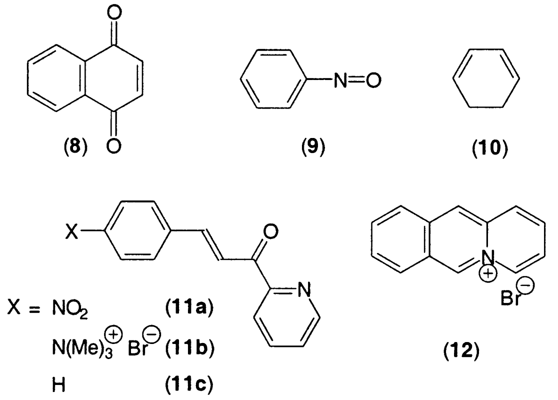
(23) Sepulveda, L. *Adv. Colloid Interface Sci.* **1986**, *25*, 1−57.
(24) Otto, S. Catalysis of Diels−Alder Reactions in Water. Ph.D. Thesis, University of Groningen, 1998.

TABLE 2. Relative Rate Constants for 1 + 2a in Different Media

medium	k/k_w[a]	$[H_2O]$ (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 M^{-1} s^{-1}). [b] From ref.32. [c] Tetramethylammonium bromide. [d] Sodium methyl sulfate.

SCHEME 3



deeply inside the micellar core, whereas the dienophiles **11b** and **11c** (Scheme 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 to these ions, the induced rates relative to groups close to the micellar surface (α-CH_2) provide estimates about average binding positions.[25] 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, we recalculated the induced relaxation rates, taking into account that the fraction of cyclopentadiene that is not bound to the micelles will not be influenced by the paramagnetic ions. The recalculated values reveal that differences in binding sites for the different substrates are only minor (Figure 5a).

We also determined the induced relaxation rates for substrates **4** and **6** (Figure 5b). If we compare the relaxation rates of **11c**, **1**, and **4** with those of SDS, it seems that **11c** and **4** reside on average near the β-CH_2 group of SDS, or just slightly more to the inside. For **1**, the position may be anywhere near the n-CH_2 groups of the SDS molecules in the micelle: the values for n-CH_2, ω-CH_3, and **1** are nearly equal, and because it is known[25] that the ω-CH_3 group can be found anywhere between the innermost part and the surface of the micelle, the same might be true for **1** as well. 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 is assumed in the pseudophase model.[10]

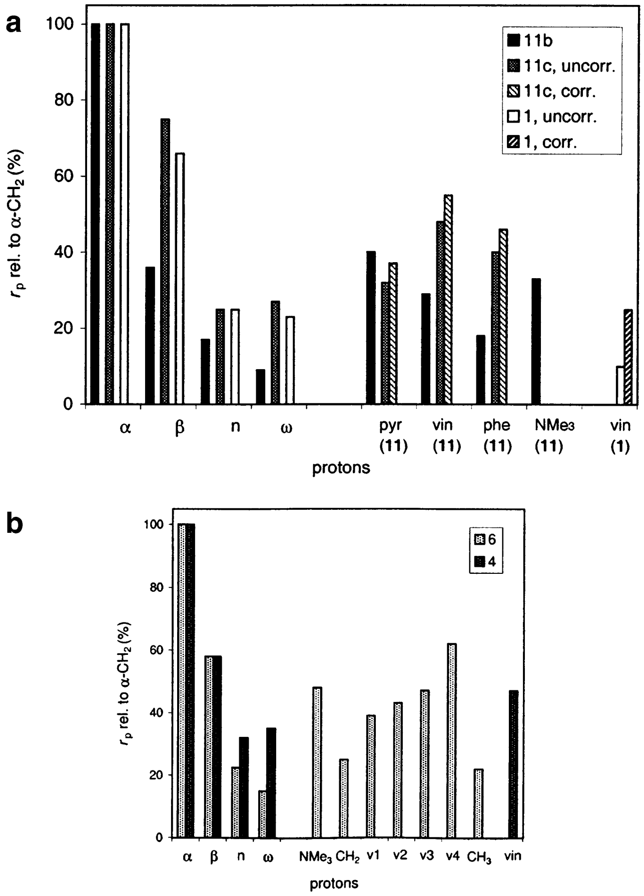


FIGURE 5. Paramagnetic ion-induced spin–lattice relaxation rates (r_p) of the protons of SDS and of (a) **1**, **11b**, and **11c**[6,24] and (b) **4** and **6**. All data are relative to those of the α-CH_2 group of SDS. For compounds **1** and **11c**, both corrected and uncorrected values are shown (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**; NMe_3, substituent on phenyl ring; (**4**) vin, vinylic hydrogens; (**6**) self-explenatory, except for v1–v4: (vinylic hydrogens) numbered from NMe_3 group onward.

For the cationic substrates **11b** and **6**, the 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. The induced relaxation rates therefore most likely do not reflect the average binding locations of these substrates and other techniques are required to estimate these.

A complication in interpreting these data and connecting them to kinetic experiments is that they do not give

---

(25) Cabane, B. *J. Phys.* **1981**, *42*, 847–859.

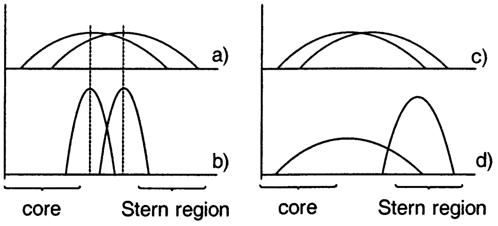


FIGURE 6. (Left) Two substrate distributions with a different mean value. When the distributions are broad (a), there is considerable overlap, whereas tight distributions (b) have little overlap. (Right) Situation c illustrates how two noncharged substrates may be distributed over a micelle: broad distributions with a mean value close to the edge between the core and the Stern layer. In situation d, one of the noncharged 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.

an indication of the width of the distribution. This width is crucial in determining whether differences in average binding location have a small or large influence on the rate (Figure 6).

Information about the width of the distribution may be obtained from NOESY experiments. For example, Hawrylak and Marangoni[26] showed that 1-butanol remains close to the micellar surface, with the α-CH_2 of 1-butanol near the α-CH_2 of SDS, and the tail pointing inward. Benzene, on the other hand, was found to distribute itself throughout the micelle with no preference for a particular region. In a similar study,[27] ethanol was found to reside in a phosphocholine bilayer mainly near the α- and β-CH_2 groups of the tails. The picture that emerges from all these experiments is that organic substrates which possess polar groups mainly reside near the first few CH_2 groups of the surfactant tails. Vinylic or aromatic apolar substrates such as benzene or cyclopentadiene may be found throughout the micelle.

(d) Micellar Rate Constants Estimated from Water/Salt/Alcohol Mixtures. To obtain more insight into the origin of the low micellar rate constants, the reaction of **1** with **2a** was performed in solutions containing sodium methyl sulfate (SMS), 1-propanol, or both (Table 2). The underlying idea is that the Stern region of an ionic micelle resembles a concentrated salt solution,[16] but that it also possesses hydrophobic character. In fact, if a solute enters a micelle, the outer region will closely resemble a concentrated salt solution. However, deeper inside the micelle, the concentrations of both headgroups and water will decrease—judging from molecular dynamics simulations, these concentrations will reach zero rapidly[28,29]—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 to 5 M, although recent experiments suggest a lower value[30]), but is still much faster than in the micellar phase. It is clear that this effect alone cannot account for the low micellar rate constants.

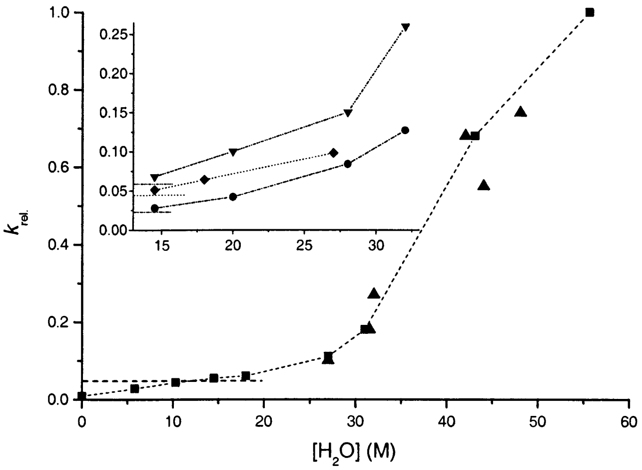


FIGURE 7. Relative rate constants for **1** + **2a** as a function of the concentration of water for 1-propanol/water mixtures (■) and salt or salt/1-propanol solutions (▲; see Table 2; salts are TMAB and SMS). Inset: relative rate constants in 1-propanol/water mixtures for **1** + **8** (●), **4** + **2a** (◆), and **10** + **9** (▼).[42] The lines on the lower left part of the graphs indicate the corresponding relative micellar rate constants.

The effect of adding 1-propanol alone also is rate retarding, and solutions containing both SMS and 1-propanol (saturated in 1-propanol for the amount of SMS present) also show rates 4−10 times lower than those in water. In Figure 7, these rates are plotted as a function of the concentration of water. It is obvious that 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, this suggests that the reaction mainly takes place 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 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 leads to the suggestion that many dienes and dienophiles are actually situated on average at the edge between the Stern region and the apolar core and are in a relatively apolar environment, but still more "water-like" than propanol. The "low" micellar rate constants therefore mainly originate from the relatively apolar medium, not of a "mismatch" between diene and dienophile. The binding locations are important parameters though, because they determine the exact nature of the environment that the reactants experience.

Apparently none of the used substrates binds to the outermost part of the micelles. This could be expected for ionic reagents. However, they behave in a peculiar manner, as will be discussed below.

(e) Solvent Sensitivity and Micellar Rate Constants. In Figure 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

---

[26] Hawrylak, B. E.; Marangoni, D. G. *Can. J. Chem.* **1999**, *77*, 1241−1244.

[27] Feller, S. E.; Brown, C. A.; Nizza, D. T.; Gawrisch, K. *Biophys. J.* **2002**, *82*, 1396−1404.

[28] Tieleman, D. P.; van der Spoel, D.; Berendsen, H. J. C. *J. Phys. Chem. B* **2000**, *104*, 6380−6388.

[29] Wymore, T.; Gao, X. F.; Wong, T. C. *J. Mol. Struct.* **1999**, *485*, 195−210.

[30] Buurma, N. J.; Engberts, J. B. F. N. To be submitted for publication.

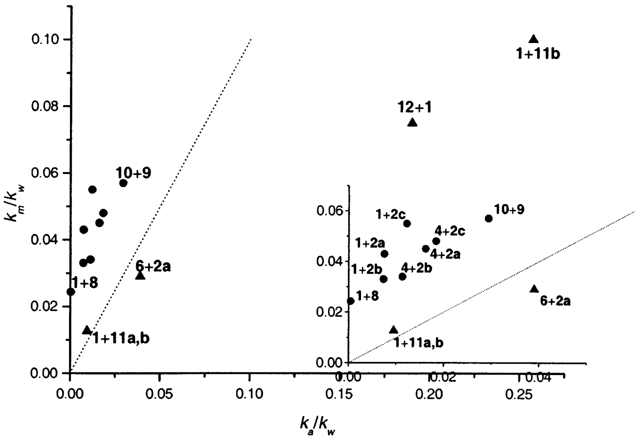


FIGURE 8. Relative rate constants in ethanol or propanol (k_a/k_w) versus relative rate constants in the micellar phase (k_m/k_w) for a range of Diels–Alder reactions. The upper triangles (▲) correspond with reactions involving an ionic substrate. They form a distinct group, for which the micellar rate 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.

TABLE 3. A Comparison between the Micellar Rate Constants and the Rate Constants in Water and Organic Solvents

diene	dieno-phile	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]	0.026[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 the rate constant in acetonitrile. [b] k_a is the rate constant in 1-propanol or ethanol. [c] k_m is the micellar rate constant. All values were fitted by using a cmc for SDS of 0.007 M and a molar volume of 0.25 L/mol. [d] Reference 32. [e] Value from fit of the data given in ref 18, using a value for $P_1 = 70$; resulting in $P_8 = 330$. [f] Reference 32. [g] Value for **11a**. [h] Value for **11b**. [i] Reference 42. [j] Cu^{2+}-catalyzed reaction. [k] Reference 44. [l] Value from fit of the data given in ref 44, assuming complete binding of **12** thus neglecting the reaction in the aqueous phase (eq 7); resulting in $P_1 = 65$. [m] Reference 42. [n] Value from fit of the data given in ref 42, using a value for $P_{10} = 250$ (this value gave the best fit, also, compared to **1**, **10** has one extra CH_2 unit, which, in general, gives a 3–4 times higher binding constant to SDS,[23] which is in agreement with this value; resulting in $P_9 = 93$). It is clear that no strong correlation exists between these rate constants.

reactions.[31] The reactions include those studied in this paper as well as previously studied reactions. In Table 3 and Scheme 3, details of the reactions are given, as well as of the analysis. It is clear that no strong correlation exists between these rate constants.

One observation to be made is the generally lower values of k_m/k_w for reactions in which one of the reactants is (positively) charged (indicated in Figure 8 with upper triangles). For most of them the micellar rate constant is actually lower than that for ethanol. Further experiments are needed here, as only ad hoc explanations can be invoked at this stage. Possibly the ionic species remain in a relatively small region at the micellar surface, strongly held in place by ionic interactions—as opposed to the neutral substrates that may be situated in a larger part of the micelle (but not so much at the surface). Here, differences in binding location may become important and affect the activation process for the cycloaddition reaction (Figure 6). What is not apparent from Figure 8, but can be judged from the data in Table 3, is that the relative rates in alcohol vary much more widely than the micellar rate constants, also when only taking into account neutral substrates. Especially the reaction between **1** and **8**, which for a Diels–Alder reaction is extremely sensitive toward changes in solvent, is 2500 times slower in alcohol than in water, but only 40 times slower in the micellar phase. Nevertheless, as mentioned above, micellar rate constants all correspond well to rate constants in *mixtures* of alcohol and water at similar concentrations of water, also for the reaction of **1** and **8**. This points to a complicated dependence of the rate of Diels–Alder reactions in mixtures containing only small amounts of water (up to a few moles/liter), which we will not address here. It also makes clear that the Diels–Alder reactions do not take place in the fully apolar core of the micelle, as in that case the variation in k_m/k_w would have been much larger and the values would have resembled the (much smaller) rate constants in propanol much more closely.

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 becoming limited. We did not find evidence for a difference in average binding location being 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 is not fully adequate to explain these (low) rates, and other micellar effects also must play a role (vide supra).

Conclusion

We have shown that despite the relatively low micellar rate constants, Diels–Alder reactions nevertheless can be accellerated by adding surfactant, depending on the binding properties of the substrates to the micelles.

We did not find evidence for differences in average binding location being responsible for the low micellar rate constants. Combinations of dienes and dienophiles with different binding characteristics all lead to micellar rate constants that are substantially lower than the respective aqueous rate constants, but higher than those in, for instance, 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

---

[31] For most Diels–Alder reactions, rate constants in 1-propanol and ethanol are equal within 15%.

a polar environment, which, however, is not sufficiently aqueous ([H_2O] ≈ 10−15 M) as to attain aqueous rates.

Experimental Section

(a) Materials. Cyclopentadiene was prepared from its dimer immediately before use. Demineralized water was distilled twice in a quartz distillation setup. *n*-Butyl maleimide has been synthesized previously.[32] Sorbyl alcohol (2,4-hexadien-1-ol, **4**) has been prepared by using a literature procedure.[33] All other chemicals were obtained from commercial suppliers and were of the highest purity available, unless indicated otherwise.

(b) Sorbyltrimethylammonium Bromide (2,4-Hexadienyltrimethylammonium Bromide, 6). The first step involves a modified literature procedure;[34] for the second step the procedure for preparing allyltrimethylammonium bromide[35] has been adapted.

A 7.6-g sample 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 1 h the mixture was poured onto ice−water and extracted with ether. The etheral 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 mmHg). H NMR indicated this liquid 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 2 days in the absense 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). Mp 135−137 °C. Anal. Calcd: C 49.1, H 8.24, N 6.36. Found: C 48.9, H 8.35, N 6.45.

(c) Product Analysis. For compounds **3a** and **3b**, see ref 32. Compound **3c**[36] has been prepared analogously. Mainly the endo product is formed.[32]

2-Alkyl-4-(hydroxymethyl)-7-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-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 and the etheral layers were washed with brine, dried (magnesium sulfate), and evaporated; the remainder (oils that after some time solidified) was analyzed 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-1*H*-isoindole-1,3(2*H*)-dione (5a).[37] H NMR ($CDCl_3$): δ 5.77 (dt,[37] J = 9, 3 Hz, 1H), 5.66 (dt,[37] 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 (br, 1H), 2.43 (br, 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-1*H*-isoindole-1,3(2*H*)-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 (br, 1H), 2.42 (br, 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-1*H*-isoindole-1,3(2*H*)-dione (5c).[38] H NMR ($CDCl_3$): 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 (br, 1H), 2.37 (br, 1H), 1.41 (d, J = 8 Hz, 3H).

2-Alkyl-7-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-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 analyzed 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-1*H*-isoindol-4-yl-*N*,*N*,*N*-trimethylmethanaminium Bromide (7a). ^{1}H NMR (CD_3OD): 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 (br, 1H), 2.52 (br/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-hexahydro1*H*-isoindol-4-yl-*N*,*N*,*N*-trimethylmethanaminium Bromide (7b). ^{1}H NMR (CD_3OD): 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 (br, 1H), 2.55 (br/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-1*H*-isoindol-4-yl-*N*,*N*,*N*-trimethylmethanaminium Bromide (7c). ^{1}H NMR (CD_3OD): 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 (br, 2H), 2.55 (br/m, 1H), 1.27 (d, J = 7 Hz, 3H).

(d) Kinetic Measurements. Kinetic measurements were performed with UV−vis spectroscopy (Perkin-Elmer λ2, λ5 or λ12 spectrophotometer) at 25.0 °C. All reactions were followed at 298 nm (dissappearance 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 μL) of a concentrated stock solution in acetonitrile (water in the case of **6**). The rates of the faster reactions were followed for at least 4 half-lives and pseudo-first-order rate constants were obtained by using a fitting program. The rate constants of the slower reactions were obtained by using initial rate kinetics. Typical conditions were the following: [diene] = 1−5 mM, [dienophile] = 0.05−0.1 mM. For the slower reactions possible competition of the hydrolysis of the maleimides[39] was excluded by measur-

---

[32] Meijer, A.; Otto, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8989−8944.

[33] Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 2548−2549.

[34] Mori, K. *Tetrahedron* **1974**, *30*, 3807−3810.

[35] Menger, F. M.; Venkataram, U. V. *J. Am. Chem. Soc.* **1986**, *108*, 2980−2984.

[36] Yasuda, M.; Saito, S.; Arakawa, Y.; Yoshifuji, S. *Chem. Pharm. Bull.* **1995**, *43*, 1318−1324.

[37] Tarasow, T. M.; Tarasow, S. L.; Tu, C.; Kellogg, E.; Eaton, B. E. *J. Am. Chem. Soc.* **1999**, *121*, 3614−3617.

[38] Brettle, R.; Cummings, D. P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2385−2392.

[39] Matsui, S.; Aida, H. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1277−1280.

ing under slightly acidic conditions (pH 3−3.5). Rate constants were generally reproducible to within 3%.

(e) NMR Measurements. Paramagnetic relaxation times were determined by using an inversion−recovery pulse sequence. The T_1 values were calculated by using a least-squares fitting procedure available on the Varian software. Solutions contained 50 mM SDS, 5 mM either **4** or **6**, and 0 or 0.2 mM $CuCl_2$. 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 with 100 mM SDS rather than 50 mM yielded the same, corrected values.

(f) Kinetic Analysis with the Pseudophase Model. The details of the pseudophase model have been described in detail[10,40] and will be summarized here. The micellar solution is assumed to consist of an aqueous (w) and a micellar (m) phase. Then it is assumed that a definite distribution of the reagents over the two phases does exist (Figure 1) and the partitioning is described by the partition coefficients:

$$P_A = [A]_m/[A]_w \tag{1}$$

$$P_B = [B]_m/[B]_w \tag{2}$$

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

$$v = k_{app}[A]_t[B]_t = v_m CV + v_w(1 - CV) = k_m[A]_m[B]_m CV + k_w[A]_w[B]_w(1 - CV) \tag{3}$$

where C is the concentration of surfactant minus the cmc and V the molar volume of the surfactant. Combination of eqs 1−3 together with

$$[A]_t = [A]_m CV + [A]_w(1 - CV) \tag{4}$$

$$[B]_t = [B]_m CV + [B]_w(1 - CV) \tag{5}$$

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

$$k_{app} = \frac{k_m P_A P_B CV + k_w(1 - CV)}{(1 + (P_A - 1)CV)(1 + (P_B - 1)CV)} \tag{6}$$

In deriving eq 6, it is assumed that the reagents do not affect the properties, in particular the cmc, of the surfactant. This assumtion 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. We found that 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 complete already at these low surfactant concentrations. We circumvented this problem by only taking into account data with concentrations of SDS higher than 10 mM, such that [**6**]/[SDS] < 0.3. (This also applies to the reaction between **12** and **1**.)

Fits were performed with Microcal Origin 6.0[41] using the Levenberg−Marquardt algoritm. Data were fitted to eq 6. For V_{SDS}, a value of 0.25 $dm^3\ mol^{-1}$ was used.[23] 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 $P_{dienophile}$ 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 1, with the corresponding values for $P_{dienophile}$ and k_m/k_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_6 (10^4−10^5), leads to eq 7

$$k_{app} = \frac{k_m P_A}{1 + (P_A - 1)CV} \tag{7}$$

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

Acknowledgment. Dr. Ron Hulst is gratefully acknowledged for his help in performing the NMR relaxation experiments. The National Research School Combination Catalysis is acknowledged for financial support.

Supporting Information Available: Proton NMR spectra for compounds **5b** and **7a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0260802

---

[40] Martinek, K.; Yatsimirski, A. K.; Levashov, A. V.; Berezin, I. V. In *Micellization, Solubilisation, and Microemulsions*; Mittal, K. L., Ed.; Plenum Press: New York, 1977; Vol. 2, pp 489−507.

[41] Microcal Software, Inc., One Roadhouse Plaza, Northhampton, MA 01060, USA. http://www.originlab.com.

[42] Wijnen, J. W.; Engberts, J. B. F. N. *Liebigs Ann. Recl.* **1997**, 1085−1088.

[43] Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798−6806.

[44] Wijnen, J. W. Cycloadditions in Aqueous Media. Ph.D. Thesis, University of Groningen, 1997.