

## A Kinetic Study of 1,3-Dipolar Cycloadditions in Micellar Media

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The kinetics of the 1,3-dipolar cycloadditions (DC) of benzonitrile oxide with a series of *N*-substituted maleimides in micellar media have been investigated. Surfactants studied include anionic sodium dodecyl sulfate, cationic cetyltrimethylammonium bromide, and a series of nonionic alkyl poly(ethylene oxide) surfactants ( $C_xE_y$ ). The kinetic data have been analyzed by using the pseudo-phase model for bimolecular reactions. Much larger micellar accelerations (up to a factor of 17) were observed for these reactions than was previously found for Diels–Alder (DA) reactions (*J. Org. Chem.* **2002**, *67*, 7369–7377). This is explained by the smaller solvent sensitivity of DC reactions, which causes the *micellar* rate constants to be much closer to the value of water ( $k_m/k_w \approx 0.25$ – $0.45$  for DC reactions vs  $0.02$ – $0.05$  for DA reactions). Further evidence is presented, that a water/1-propanol mixture ( $[H_2O]$  ca. 15 M) is a fairly good mimic of the micellar reaction environment for these reactions. Isobaric activation parameters have been determined for the reaction in the micellar phase of  $C_{16}E_{20}$ , using *micellar* rate constants. They correspond well to values obtained for the aforementioned micelle mimic.

## Introduction

1,3-Dipolar cycloadditions (DC) share many features with the more well-known Diels–Alder (DA) reactions. An important difference, when studying medium effects, is that for 1,3-dipolar cycloadditions rate constants sometimes decrease and sometimes increase with solvent polarity, and in some cases are almost completely insensitive to the medium (variations in  $k$  less than a factor of 1.8).<sup>1</sup> In many cases, rate constants are influenced far less by the polarity of the medium than in the case of typical Diels–Alder reactions, and hardly ever exceed 1 order of magnitude over the full range of solvent polarities, i.e., from *n*-hexane to water. It is this latter feature that makes a comparison between DA reactions and DC reactions in micellar media worthwhile.

In previous work,<sup>2</sup> we systematically studied the effects of micelles on a series of Diels–Alder (DA) reactions and concluded that although the rate is enhanced because of concentrating the reactants in a small micellar reaction volume, this effect is counteracted by the micellar rate constant being 20–40 times smaller than the rate constant in water. As a consequence, the net effect on the observed rate constants is remarkably small. The main factor determining these micellar rate constants appears to be a local medium effect. The local medium was mimicked by a water/1-propanol mixture with  $[H_2O]$  ca. 10–15 M. The DC reactions are ideal for further testing this approach. Furthermore, it may shed light on other factors that constitute the micellar rate

constant, but are overshadowed in the case of the DA reactions.

For the present study, we chose DC reactions of benzonitrile oxide (**1**) with a series of *N*-substituted maleimides: ethyl- (**2a**), *n*-butyl- (**2b**), and benzylmaleimide (**2c**) (Scheme 1). Cycloadditions of **1** with substituted maleimides have been reported previously.<sup>3–5</sup> These DC reactions form a nice comparison with typical DA reactions, and in view of the extremely small solvent effects on DC reactions, the effect of concentrating the reactants in a small micellar reaction volume should dominate and substantial accelerations are anticipated.

The (micelle-forming) surfactants studied include cationic cetyltrimethylammonium bromide (CTAB) and anionic sodium dodecyl sulfate (SDS) (Scheme 2). Since many fewer kinetic studies have been carried out with nonionic surfactants, we also included a series of nonionic alkyl poly(ethylene glycol) surfactants, abbreviated as  $C_xE_y$ . In the absence of counterions, surface charges, etc., kinetic rate effects induced by these surfactants may be easier to understand. The analysis of a bimolecular reaction in the presence of these micelles turns out to be more difficult, however.

For the analysis of the influence of surfactant aggregates on reaction kinetics, it is necessary to have insights into the different types of microenvironments that can be offered to substrates inside the aggregate. An important question regarding the nonionic surfactants

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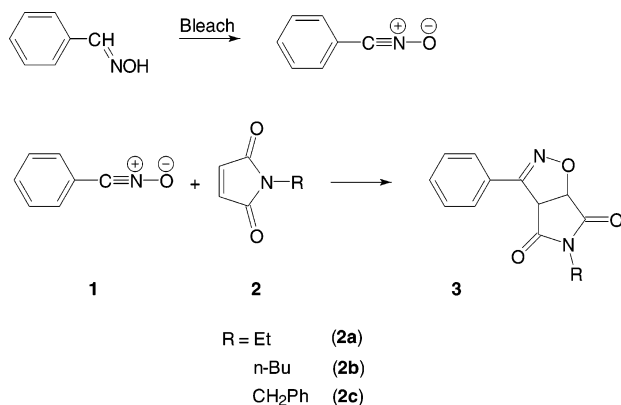
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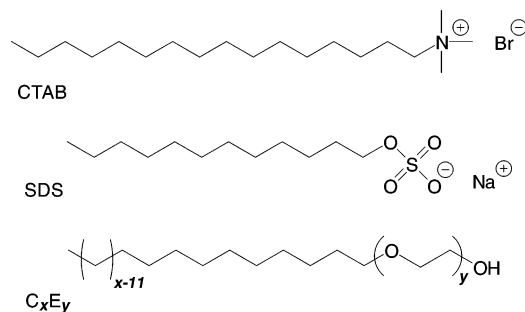
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## SCHEME 1

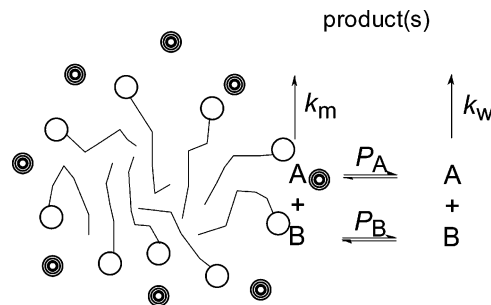


## SCHEME 2



is, whether the hydrophobic and hydrophilic parts of the molecules are predominantly contained in separated phases, or whether an extended intermediate region exists between the core and the outer layer, in which alkyl tails and poly(ethylene glycol) (PEO) headgroups form a mixed phase.

Hydration numbers, determined by various methods,<sup>6–9</sup> indicate that the hydrophilic PEO headgroups on average reside in a relatively aqueous environment (35–40 M in water), which makes it unlikely that a large part of the PEO chain is buried in the hydrophobic interior. Studies on inverted micelles, formed by C<sub>x</sub>E<sub>y</sub> in e.g. hexane, further support the idea that the alkyl and PEO parts of the amphiphiles only have a small tendency to “dissolve” each other, and stress the strong tendency of the PEO groups to be hydrated.<sup>10–12</sup> It should also be noted that hexane and PEO form a two-layer system. The amount of water per EO unit seems to increase upon going from the inside to the outside on the micelle,<sup>6,13–15</sup> and there is evidence that in Triton-X-100 micelles a small region exists, where tails and EO units coexist.<sup>16</sup> In summary, many studies support the picture of a



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

**TABLE 1.** Rate Constants in Various Media at 25 °C

	2a		2b		2c	
medium	$k_2$ (M <sup>-1</sup> s <sup>-1</sup> )	$k/k_w$	$k_2$ (M <sup>-1</sup> s <sup>-1</sup> )	$k/k_w$	$k_2$ (M <sup>-1</sup> s <sup>-1</sup> )	$k/k_w$
water	0.35	1	0.55	1	0.73	1
1-propanol	0.30	0.86	0.37	0.67	0.45	0.59
3 M TMAB	0.31	0.89	0.60	1.1		
3 M SMS	0.19	0.56	0.34	0.62		

micelle formed by nonionic surfactants consisting of a hydrophobic core, mainly containing the hydrophobic tails, and a hydrophilic headgroup region, containing most of the (hydrated) PEO groups and also loosely bound “entrapped” water.

The kinetic data presented in this paper have been analyzed in terms of the pseudo-phase model.<sup>17,18</sup> Herein, 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). The observed rate constant is given by the following equation:<sup>18,2</sup>

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

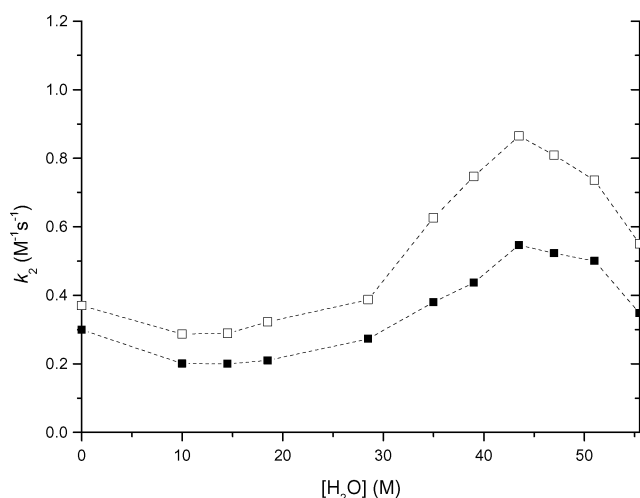
where  $C$  is the concentration of surfactant minus the cmc and  $V$  the partial molar volume of the surfactant.

## Results and Discussion

The rate constants for the reactions of **1** with **2a–c** in water and 1-propanol are listed in Table 1. Obviously, there is only a small difference in rate constants between these solvents. Also in mixtures of water and 1-propanol, no large variation in rate is observed (Figure 2). Interestingly, a maximum in rate constant is observed around [H<sub>2</sub>O] ca. 40 M, corresponding to a mole fraction of water of 0.9. Tetramethylammonium bromide (TMAB) and

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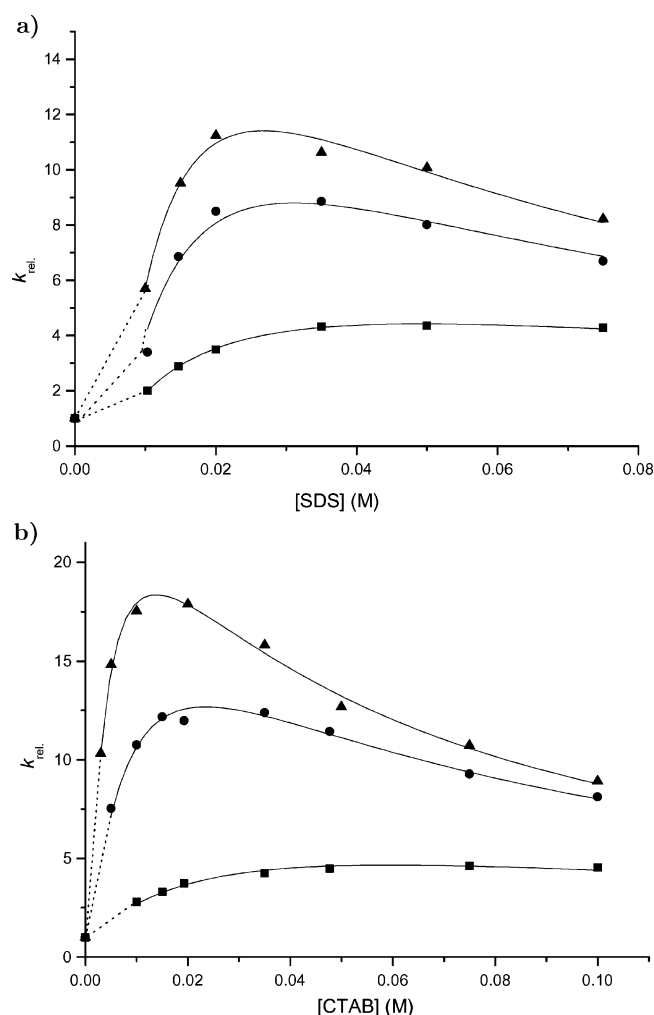
**FIGURE 2.** Rate constants in water/1-propanol mixtures (squares) for the reaction of **1a** with **2a** (closed symbols) and **2b** (open symbols).

sodium methyl sulfate (SMS) are used as mimics of the headgroups of CTAB and SDS, respectively, and rate constants in solutions containing TMAB or SMS are also included in Table 1.

**Micellar Solutions of SDS and CTAB.** Upon addition of surfactants (SDS, CTAB) the observed rate constants of the reactions of **1** with **2a–c** are significantly increased, up to a factor of 17 (**1** + **2c**/CTAB) (Figure 3). This catalytic efficiency strongly contrasts with the DA reactions, where accelerations rarely exceed a factor of 2, especially when only neutral species are involved in the reaction.<sup>2</sup> For **2a**, SDS and CTAB have a nearly equal effect on the rate. For **2b** and **2c**, rate profiles for SDS and CTAB are quite different from each other. The maximum acceleration is largest for the most hydrophobic dipolarophile.

Attempts were made to analyze the data with use of the pseudo-phase model. For SDS, this is straightforward, as partition coefficients for **2a–c** have been determined previously.<sup>2</sup> By using these values, reasonably consistent values for the binding of **1** are obtained (Table 2), taking into account that the errors in the values of  $P_{2a-c}$  are considerable (20%). For CTAB, no binding affinities were known for any of the reactants. Therefore, initially, fits with a range of fixed values for  $P_{2a-c}$  were performed, as to choose the ones that give the same value for  $P_1$ . Unfortunately, this did not lead to well-defined values for the partition coefficients, as a wide range of consistent values exist (boundaries given in Table 2). Nevertheless, the micellar rate constants are fairly well-defined (within ca. 10%). The results are presented in Table 2. Binding of **1** to CTAB could be determined spectroscopically, and a binding constant of  $K_s = 22 \text{ dm}^3 \text{ mol}^{-1}$  was found ( $P_1 = 60$ ). The results of the fits with this value are also presented in Table 2.

The partition coefficient of dipolarophile **2a** for CTAB is comparable to that for SDS, but the more hydrophobic compounds **2b** and **2c** clearly have a larger affinity for CTAB than for SDS. The partition coefficient of **1** is smaller for CTAB than for SDS. This is somewhat surprising, as compounds bearing aromatic groups often bind stronger to CTAB than to SDS.<sup>19</sup> One reason could



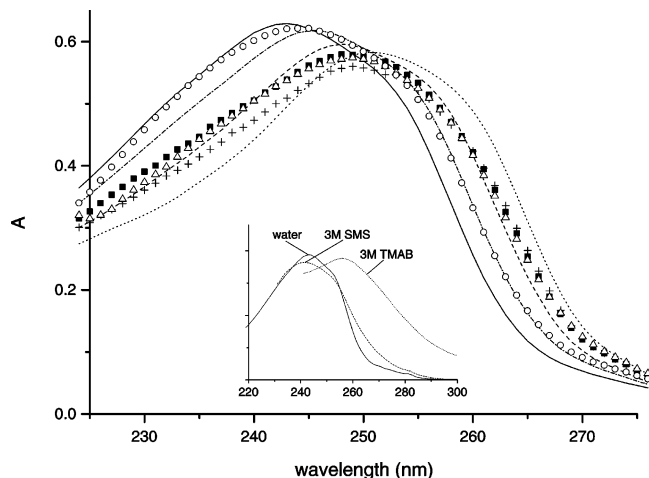
**FIGURE 3.** Relative rate constants ( $k_{\text{rel}} = k_{\text{obs}}/k_w$ ) in solutions of SDS (a) and CTAB (b) at 25 °C for the reaction of **1** with **2a** (■), **2b** (●), and **2c** (▲). The solid lines represent the fits with use of the pseudo-phase model, with the parameters listed in Table 2.

**TABLE 2.** Results from a Kinetic Analysis in Terms of the Pseudo-Phase Model for SDS and CTAB at 25 °C

A	B	$P_A$	$P_B$	$k_m/k_w$
SDS				
<b>2a</b>	<b>1</b>	35 <sup>a</sup>	200	0.23
<b>2b</b>	<b>1</b>	135 <sup>a</sup>	183	0.22
<b>2c</b>	<b>1</b>	263 <sup>a</sup>	144	0.23
CTAB				
<b>2a</b>	<b>1</b>	20–30	73 <sup>b,e</sup>	0.44 <sup>b</sup>
		30 <sup>f</sup>	60	0.42 <sup>f</sup>
<b>2b</b>	<b>1</b>	160–280	64 <sup>c,e</sup>	0.46 <sup>c</sup>
		240 <sup>f</sup>	60	0.46 <sup>f</sup>
<b>2c</b>	<b>1</b>	400–800	74 <sup>d,e</sup>	0.45 <sup>d</sup>
		760 <sup>f</sup>	60	0.49 <sup>f</sup>

<sup>a</sup> Values taken from previous work.<sup>2</sup> <sup>b</sup> Obtained with  $P_{2a} = 25$ . <sup>c</sup> Obtained with  $P_{2b} = 220$ . <sup>d</sup> Obtained with  $P_{2c} = 600$ . <sup>e</sup> Extremes for  $P_1$  are 60–80. <sup>f</sup> Obtained with  $P_1 = 60$ , as determined spectroscopically.

be that **1** interacts more favorably with the anionic headgroups of SDS than with the cationic headgroups of CTAB, because the positive charge of the 1,3-dipole is



**FIGURE 4.** UV spectra of **1** at 25 °C in water (solid line), 1-propanol (dotted line), water/1-propanol mixtures (15 and 40 M of water, dashed and dash-dotted lines, respectively), and 100 mM surfactant solutions of SDS (○), CTAB (△),  $C_{12}E_{23}$  (■), and  $C_{16}E_{20}$  (+). The inset shows spectra in 3 M solutions of SMS and TMAB.

fairly localized on the nitrogen, whereas the negative charge is delocalized over a large part of the molecule. Also, the relatively large dipole moment ( $4 D^1$ ) of **1**—corresponding to a charge distribution best represented by the mesomeric structure depicted in Scheme 1—will fit into anionic micelles naturally, with (anionic) headgroups mainly interacting with the positive charge and (cationic) counterions with the negative charge. In cationic micelles, the dipole will not efficiently “fit” into the micelle (assuming that the aromatic moiety prefers to point inward, interacting with the hydrophobic interior of the micelle). Another possibility is that the micelles of CTAB, containing about 1.5 times as much apolar material on the inside, offer binding locations that are too apolar for the 1,3-dipole to be sufficiently stabilized relative to water.

In Figure 4, UV spectra of **1** are shown in 100 mM solutions<sup>20</sup> of SDS, CTAB,  $C_{12}E_{23}$ , and  $C_{16}E_{20}$ , as well as in water, 1-propanol, and mixtures of water and 1-propanol. The spectra in all surfactant solutions are similar to that in a mixture of water (15 M) and 1-propanol, except for SDS, where the spectrum resembles a much more aqueous/polar environment. In SDS micelles, the dipole of **1** apparently still experiences a polar environment. For the nonionic surfactants and especially CTAB, binding locations for **1** are less polar, and necessarily interact less favorably with the dipole, leading to a smaller overall binding affinity. The inset of Figure 4 shows spectra of **1** in 3 M solutions of SMS and TMAB. SMS has no appreciable effect on the spectrum. TMAB, on the other hand, has a significant effect, consistent with a cation- $\pi$  interaction between the tetramethylammonium ions and the aromatic moiety of **1**.<sup>21</sup> As the absorption band of **1** in CTAB is only slightly shifted, and

identical with those in  $C_{12}E_{23}$ ,  $C_{16}E_{20}$ , and water (15 M)/1-propanol, but very different from that in 3 M TMAB, cation- $\pi$  interactions between the headgroups of CTAB and **1** seem to be weak or absent. At concentrations of CTAB just above the cmc, a small, additional absorption band is visible, probably indicating that at these concentrations cation- $\pi$  interactions do occur. Nevertheless, these interactions are weak, as the absorption band has disappeared at concentrations of CTAB above ca. 50 mM.

The micellar rate constants (Table 2) are larger for CTAB than for SDS, although the difference is only a factor of 2. This may correspond to salt effects, induced by the surfactant headgroups. In concentrated solutions of SMS and TMAB (Table 1) the relative rate constants are 0.56 and 0.89, respectively (for **2a**), and the difference is comparable to the difference in micellar rate constants. For this explanation to hold, the reaction has to take place mainly in the outermost part of the micelle. However, previous kinetic and NMR data<sup>2</sup> support the view that the reaction takes place mainly in a slightly aqueous environment, corresponding to the region in the micelle close to the first few methylene moieties of the surfactant tails. Alternatively, the aforementioned good “fit” of **1** in SDS micelles leads to relatively strong binding, and therefore to additional stabilization of the dipolar initial state. As the dipole largely disappears during the activation process of the DC reaction, the transition state will be less stabilized, and a net decrease of the rate constant results.

It is striking that the micellar rate constants for the DC reactions are *much larger* than any micellar rate constant found for a Diels-Alder reaction. This is a direct consequence of the smaller solvent sensitivities of these 1,3-dipolar cycloadditions (Figure 2), and explains why these reactions are much more accelerated than the Diels-Alder reactions studied previously. The micellar reaction environment is comparable to either a concentrated salt solution or, more likely for these reactions, an alcohol/water mixture. In any case, the micellar rate constant will be lower than the rate constant in water. This will be further discussed in the Comparison with Micelle Mimics section.

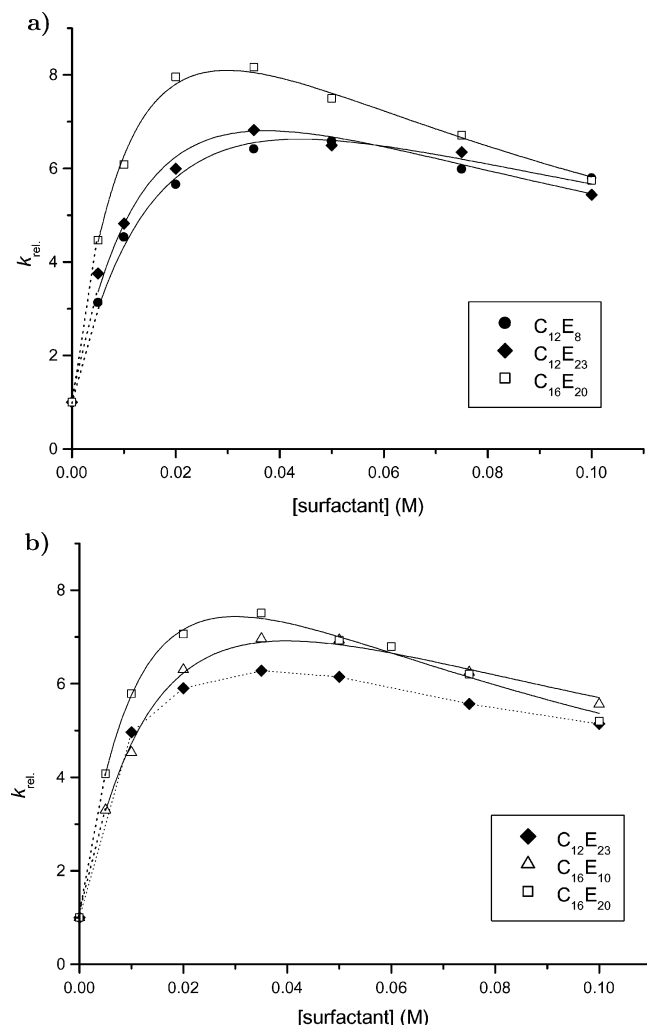
**Micellar Solutions of Alkyl Poly(ethylene glycol) Surfactants.** Rate constants have also been determined in solutions of the nonionic surfactants  $C_{12}E_8$ ,  $C_{12}E_{23}$  (Brij 35),  $C_{16}E_{10}$  (Brij 56), and  $C_{16}E_{20}$  (Brij 58).  $C_{12}E_8$  and  $C_{16}E_{10}$  have comparable headgroups, as have  $C_{12}E_{23}$  and  $C_{12}E_{20}$ , which makes it possible to study the effect of variation in both tail length and headgroup size. Because  $C_{16}E_{10}$  has a Krafft temperature of about 33 °C,<sup>22</sup> measurements were also performed at 35 °C. Results for both 25 and 35 °C are presented in Figure 5. Despite the differences in both tail length and headgroup size, the observed rate constants are affected largely in the same way by these surfactants. There are small, but noticeable differences, however. For  $C_{12}E_8$  and  $C_{12}E_{23}$ , the maximum acceleration is about 25% less than that for SDS. The shape of the curves in Figure 5 suggests that smaller binding affinities of one or both of the substrates are mainly responsible for the smaller rate enhancements induced

(20) Under these conditions, about 70–80% of the substrate is bound to micelles, based on the partition coefficients as described in the text. For  $C_{16}E_{20}$  and CTAB, spectra were also recorded at 200 mM of surfactant, but this does not lead to appreciable changes in the spectra.

(21)  $E_T(30)$  values in both concentrated solutions of SMS and TMAB are only marginally different from the value in water.<sup>46</sup>

(22) It is interesting to note that this surfactant appears to have both a Krafft temperature and a cloud point, and clear solutions are solely formed in a temperature range of about 33–60 °C.





**FIGURE 5.** Relative rate constants ( $k_{rel} = k_{obs}/k_w$ ) for the reaction of **1** with **2b** in surfactant solutions of  $C_xE_y$  at (a) 25 and (b) 35 °C. Solid lines represent fits with the pseudo-phase model.

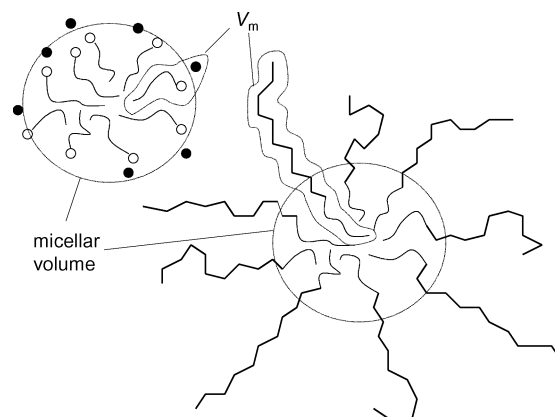
**TABLE 3. Results from Fits with Use of the Pseudo-Phase Model for Nonionic Surfactants for the Reaction of 1 with 2b**

surfactant	$T$ (°C)	$K_{s,1}$ (M <sup>-1</sup> )	$P_1$	$P_{2b}$	$k_m/k_w$
$C_{12}E_8$	25	21	73 <sup>a</sup>	76 <sup>a</sup>	0.34 <sup>a</sup>
$C_{12}E_{23}$	25	29	101 <sup>a</sup>	76 <sup>a</sup>	0.30 <sup>a</sup>
$C_{16}E_{10}$	35	27	77 <sup>b</sup>	59 <sup>b</sup>	0.39 <sup>b</sup>
$C_{16}E_{20}$	15	37.5	107 <sup>b</sup>	74 <sup>b</sup>	0.39 <sup>b</sup>
$C_{16}E_{20}$	25	37	106 <sup>b</sup>	78 <sup>b</sup>	0.34 <sup>b</sup>
$C_{16}E_{20}$	35	36.5	104 <sup>b</sup>	77 <sup>b</sup>	0.32 <sup>b</sup>

<sup>a</sup> Calculated with  $V_m = 0.286$ . <sup>b</sup> Calculated with  $V_m = 0.35$ .

by these surfactants. But without an analysis in terms of the pseudo-phase model, no definite conclusions can be drawn.

Binding constants of **1** to the nonionics have been determined spectroscopically (Table 3). The probe binds stronger to micelles of these nonionic surfactants than to those of CTAB. Binding is about 25% stronger to  $C_{16}E_{20}$  than to  $C_{12}E_{23}$  (25 °C), in line with the longer hydrocarbon tails of  $C_{16}E_{20}$ . The same trend is observed for  $C_{12}E_8$  and  $C_{16}E_{10}$ . **1** binds less efficiently to  $C_{16}E_{10}$  than to  $C_{16}E_{20}$ , or to  $C_{12}E_8$  than to  $C_{12}E_{23}$ .



**FIGURE 6.** Left: For many ionic surfactants the molar volume results in a reasonable estimate of the micellar volume. Right: For the nonionic surfactants, with the large PEO headgroups, the molar volume results in a poor estimate of the micellar volume.

To use the binding constants for the analysis of the kinetic data, they have to be converted into partition coefficients, for which estimates of the total micellar volume in solution are needed.<sup>23</sup> Often, as in the case of SDS or CTAB, the molar volume of the (micellized) surfactant is used, according to  $V_{micelle} = n_s \cdot V_m$ , with  $V_{micelle}$  the total volume of the micellar (pseudo-)phase,  $n_s$  the number of moles of micellized surfactant, and  $V_m$  the molar volume of the surfactant.<sup>24</sup> Then, the partition coefficient is given by:<sup>19</sup>

$$P_1 = \frac{[1]_{m,local}}{[1]_{w,local}} = \frac{n_{1,m} V_{water}}{n_{1,w} V_{micelle}} = \frac{n_{1,m} V_{water}}{n_{1,w} [S] V_m V_{tot}} \approx \frac{[1]_m}{[1]_w [S] V_m} = K_s / V_m \quad (2)$$

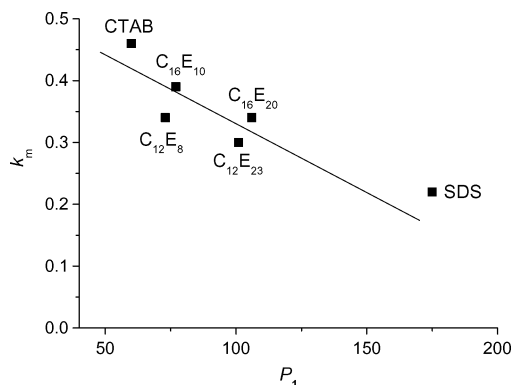
where  $V_{water}$  and  $V_{tot}$  are the total volumes of the aqueous phase and of the total solution, respectively. It was discussed above that the best representation of a micelle, formed by these surfactants, is a hydrophobic core, mainly consisting of alkyl tails, and an extended, aqueous headgroup region (Figure 6). The tendency of organic substrates to bind into the headgroup region may be estimated from the solubility of organic substrates in water/PEO mixtures, which is at best only slightly higher, compared to pure water.<sup>25,26</sup> For example, partition coefficients between the hydration layer of PEO and bulk water of several  $\alpha$ -amino acids have been determined.<sup>25</sup> For phenylalanine, it hardly exceeds 1, and even for the large, very hydrophobic tryptophan, it reaches a value of only 3 (for hydrophilic  $\alpha$ -amino acids, values are

(23) This is necessary to determine second-order micellar rate constants, which are directly comparable to the aqueous rate constants. For this purpose, the *local* concentrations of the reactants have to be known. This is taken into account in the partition coefficients that are defined as  $P_A = [A]_{m,local} / [A]_{w,local}$ .

(24) The exact micellar reaction volume will in almost all cases differ somewhat from  $V_{micelle}$ , as the reactants may be taken up only into a certain area of the micelle. Within the model, these differences are contained in  $k_m$ . In extreme cases, like binding of hydrophilic ions to the surface, alternative models, like the PPIE model,<sup>47</sup> can be used.

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**FIGURE 7.** Micellar rate constants for the reaction of **1** with **2b** plotted against the partition coefficient of **1**.

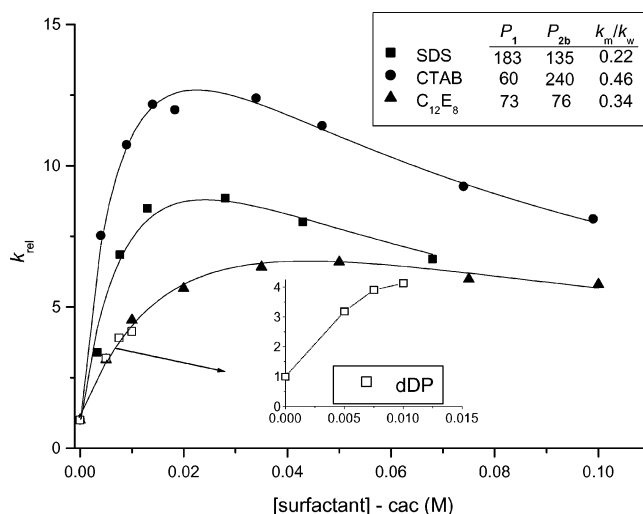
smaller than 1). It is therefore not likely that significant partitioning of organic substrates into the headgroup region of nonionic micelles will occur.

Therefore, an estimate of the micellar volume cannot be based directly on the molar volume of the surfactant. Instead, reasonable estimates of this volume were made, by using the contribution of the  $C_xE_2$  part of the nonionic surfactants to the molar volume.<sup>27</sup> These values are comparable to those of ionic surfactants with equal tail lengths ( $C_{12}E_2$ ,  $0.286 \text{ dm}^3 \text{ mol}^{-1}$ ; SDS,  $0.25 \text{ dm}^3 \text{ mol}^{-1}$ ;  $C_{16}E_2$ ,  $0.35 \text{ dm}^3 \text{ mol}^{-1}$ ; CTAB,  $0.363 \text{ dm}^3 \text{ mol}^{-1}$ ).

The results of the fits with use of these numbers in combination with the binding constants for **1** are presented in Table 3. Although the binding constant of **1** is smaller for  $C_{12}E_8$  compared to  $C_{16}E_{10}$ , or for  $C_{12}E_{23}$  compared to  $C_{16}E_{20}$ , the differences in molar volumes result in partition coefficients that are equal for the two groups of surfactants with comparable headgroups (the larger alkyl tails provide a larger apolar phase, and this effect is captured by the larger molar volume). The micellar rate constant is about 13% larger for  $C_{16}E_{20}$ , which largely accounts for the difference in the maximum  $k_{\text{obs}}$  (20%), and also for  $C_{16}E_{10}$ , the micellar rate constant is larger than that for  $C_{12}E_8$  (values for  $C_{16}E_{10}$  are at  $35^\circ\text{C}$  rather than  $25^\circ\text{C}$ , but  $K_{s,1}$  or  $P_1$  for  $C_{16}E_{20}$  are nearly constant, and  $k_m/k_w$  would be even smaller for  $C_{12}E_8$  at  $35^\circ\text{C}$ , when following the same trend as for  $C_{16}E_{20}$ ).

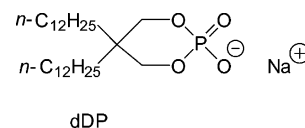
It is interesting to note that an inverse correlation between  $k_m$  and  $P_1$  (Figure 7) exists. This shows, as suggested already, that the better the binding to the micelle, the more the reactants are stabilized. For SDS, we already discussed that the 1,3-dipole may be in a relatively polar environment, and stabilized by favorable polar/ionic interactions. In CTAB, the opposite may be true: forced into a relatively apolar environment, the substrate will be more reactive. Destabilization resulting from unfavorable polar/ionic interactions in this case probably also accelerates the reaction. The nonionics are an intermediate case. Although ionic interactions are absent, the 1,3-dipole will probably still have a preference for being oriented with the dipole in a polar region and the phenyl moiety in a less polar environment. One can imagine that in smaller aggregates, with more water penetration, this type of binding is easier to accomplish.

(27) From ref 35. Calculated from group contributions to molar volume of micellized surfactant.



**FIGURE 8.** A comparison between different classes of surfactants for the reaction of **1** with **2b**. Open symbols are rate constants in vesicular solutions of dDP.

### SCHEME 3



In this respect, a comparison with a vesicle-forming surfactant would also be of interest, as the morphology of the vesicular aggregate will significantly differ from a micellar structure, especially in the sense of being more ordered and possessing a much larger hydrophobic part. Rate constants were determined for DC reactions in vesicular solutions of the sodium salt of 5,5-di-*n*-dodecyl-2-hydroxy-1,3,2-dioxaphosphorinane-2-one (dDP)<sup>28</sup> (Scheme 3 and Figure 8). Vesicles, formed by this phosphate by tip sonication, are stable for several days and have a main phase transition temperature of  $8^\circ\text{C}$ <sup>28</sup> and an average size of 32 nm,<sup>29</sup> and the solutions have low turbidity, which minimizes interference with monitoring the reaction at 273 nm. Although at slightly higher concentrations of dDP perhaps the rate may be higher,<sup>30</sup> the reaction rates are unexpectedly low, considering that vesicles are expected to bind apolar substrates better than micelles. Apparently, this is not the case for **1** and **2b**. Therefore, the binding constants of these substrates are only in part determined by hydrophobic interactions. Assuming that the 1,3-dipole is destabilized in an apolar environment, binding of **1** will be optimal to an aggregate that mainly offers hydrophobic binding locations that allow the 1,3-dipole to remain in a polar environment.

In Figure 8, a comparison between SDS, CTAB, and  $C_{12}E_8$  is presented for the reaction of **1** with **2b**. It nicely shows that the order in  $k_{\text{obs,max}}$  does not follow the order in  $k_m$ , as  $k_{\text{obs,max}}$  is also determined by the partition coefficients. Apart from variation in  $P_1$ , which was already discussed, also  $P_{2b}$  varies significantly among the different surfactants. These differences are not readily

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(30) At these higher concentrations, the increased turbidity prohibited the acquisition of reliable rate constants.

understood, but indicate that although hydrophobic interactions are the primary driving force for binding (recall that  $P_{2a} < P_{2b} < P_{2c}$ ); the binding strength is affected by other types of interactions as well.

**Comparison with Micelle Mimics.** Previously, attempts were made to mimic the micellar reaction environment with either a concentrated salt solution or a water/1-propanol mixture. It was found that for most Diels–Alder reactions, the micellar reaction site resembles a water/1-propanol mixture with  $[H_2O]$  ca. 15 M. The reactions of **1** with **2a–c** form a nice comparison with those reactions, because of their small sensitivity to changes in medium. As a result, other (small) effects that micelles may have on the rate, like an imperfect match in binding sites of the reactants, will show up more clearly. Moreover, the second-order rate constant is nearly constant in water/1-propanol mixtures with a concentration of water between 10 and 30 M, allowing a critical test of the comparison between micelles and these mixtures.

Rate constants, predicted from a water/1-propanol mixture ( $[H_2O] = 15$  M), are in reasonable agreement with the micellar rate constants found for CTAB. For SDS, values of the micellar rate constants are lower by a factor of 2.5, whereas those for the nonionic surfactants are lower by a factor of 1.5. Though this is a significant effect, it is nevertheless small<sup>31</sup> and the present data do not provide clear clues as to explain such a small additional retardation in the micellar phase (in addition to a mere “medium effect”). As suggested above, “asymmetric solvation” of **1** could account for a small additional stabilization, enough to explain the difference in catalytic efficiency. One may therefore conclude that a mixture of water and propanol is a satisfactory mimic of the reaction sites of these cycloadditions in a micelle.

**Isobaric Activation Parameters.** Isobaric activation parameters ( $\Delta^\ddagger G^\ominus$ ,  $\Delta^\ddagger H^\ominus$ , and  $\Delta^\ddagger S^\ominus$ ) can provide additional information about the changes in reactivity upon variation of the reaction medium.  $\Delta^\ddagger H^\ominus$  and  $\Delta^\ddagger S^\ominus$  generally vary much more widely than  $\Delta^\ddagger G^\ominus$  does, because  $\Delta^\ddagger H^\ominus$  and  $\Delta^\ddagger S^\ominus$  are usually compensating in nature.<sup>32,33</sup> Especially in aqueous mixtures,  $\Delta^\ddagger H^\ominus$  and  $\Delta^\ddagger S^\ominus$  are known to greatly depend on composition, and indeed, DA reactions do not form an exception.<sup>34</sup> As rate constants do not vary much for these 1,3-dipolar cycloadditions, obscuring a comparison of  $k_m$  with rate constants in micelle mimics, we instead made an attempt to make a similar comparison using activation parameters.

For  $C_{16}E_{20}$ , binding constants and rate profiles were determined at 15, 25, and 35 °C. Although nonionic aggregates tend to increase in size upon raising the temperature,<sup>35</sup> for  $C_{16}E_{20}$  in this temperature range no significant changes in morphology are expected. The binding constant of **1** to  $C_{16}E_{20}$  is almost independent of the temperature. From the analysis it turns out that this

is also the case for **2b**. This is not unexpected, as cmc values only weakly depend on the temperature.<sup>35</sup> However, the micellar rate constant, relative to that in water, does change significantly.

For several processes, activation parameters have been obtained for the micellar phase.<sup>36–41</sup> Usually, *observed rate constants* in a micellar solution at different temperatures were used to that end. These numbers, of course, include the temperature dependence not only of the kinetics in the micellar phase (as described by  $k_m(T)$ ), but also of the partition coefficients. Activation parameters, obtained in this way, therefore do not represent the characteristics of the activation process in the micellar phase.<sup>42</sup> In a few cases, a more complete analysis has been presented. García-Río et al.<sup>36</sup> determined activation parameters from second-order micellar rate constants that were calculated from observed rate constants at a fixed concentration of surfactant using the PPIE model. Assumptions about the temperature dependence of the other parameters (including binding constants) had to be made. Khan et al.<sup>37</sup> determined rate profiles for the methanolysis of phenyl salicylate in the presence of CTAB at different temperatures and calculated activation parameters using pseudo-first-order micellar rate constants.

In the present study, we determined *second-order micellar rate constants* from rate profiles at different temperatures by using the pseudo-phase model and using the binding constants of **1** determined at these temperatures. An Eyring plot, using the micellar rate constants obtained from the fits, yields a linear relationship (Figure 9), and the activation parameters are presented in Table 4,<sup>43</sup> together with values in water, 1-propanol, and several aqueous mixtures. The values for  $C_{16}E_{20}$  micelles closely resemble those for a 15 M water/1-propanol mixture, in line with expectations about the character of the micellar reaction environment. Moreover, they resemble values in water, 1-propanol, or aqueous solutions of PEO much less, and therefore support the use of a 15 M water/1-propanol mixture as a reasonable micelle-mimic for these reactions.

## Conclusions

In micellar solutions, much larger accelerations (up to a factor of 17) are observed for 1,3-dipolar cycloadditions, as compared to Diels–Alder reactions, of which observed

(31) Compare this to the micellar rate constants for Diels–Alder reactions, which are 20–40 times lower than the rate constants in water.<sup>2</sup>

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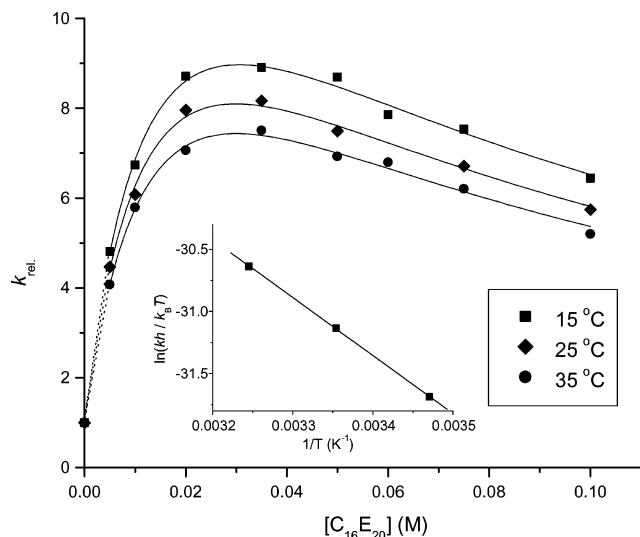
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(42) For first-order reactions, if binding constants do not heavily depend on  $T$ , and plateau values of  $k_{obs}$  at sufficiently high concentration of surfactant are used, activation parameters may be determined from  $k_{obs}(T)$  directly. ( $k_{obs}$  approaches  $k_m$  for first-order reactions at high concentrations of surfactant, i.e., as binding of the probe to the micelles is complete.)

(43) Although the values of  $k_m$  are not precise, due to the estimated values for  $V_m$ ,  $V_m$  is not expected to vary significantly between 15 and 35 °C. Then, for this series, the uncertainty due to  $V_m$  will not affect the value of  $\Delta^\ddagger H$ , but  $\Delta^\ddagger S$  will be less precise.





**FIGURE 9.** Relative rate constants ( $k_{\text{obs}}/k_w$ ) for the reaction of **1** with **2b** in surfactant solutions of  $\text{C}_{16}\text{E}_{20}$  at different temperatures. Solid lines represent fits using the pseudo-phase model. The inset shows the Eyring plot, constructed using the micellar rate constants obtained from the fits.

**TABLE 4.** Activation Parameters for the Reaction of **1** with **2b** in Different Media at 25 °C

medium	$\Delta^\ddagger G^\ominus$ <sup>a</sup> (kJ mol <sup>-1</sup> )	$\Delta^\ddagger H^\ominus$ <sup>b</sup> (kJ mol <sup>-1</sup> )	$-T\Delta^\ddagger S^\ominus$ <sup>b</sup> (kJ mol <sup>-1</sup> )
1-propanol	75.2	40.5	34.8
water (15 M)/1-propanol	76.1	38.5	37.6
water (27 M)/1-propanol	75.3	38.5	36.8
water (39 M)/1-propanol	73.7	33.8	40.0
water	74.6	48.0	26.6
PEG1000 (48 M water)	73.4	47.3	26.2
PEG1000 (41 M water)	72.6	37.5	35.1
$\text{C}_{16}\text{E}_{20}$	77.1	38.7	38.4

<sup>a</sup> Error <0.1 kJ mol<sup>-1</sup>. <sup>b</sup> Error 1 kJ mol<sup>-1</sup>, except for PEG1000 (1.5 kJ mol<sup>-1</sup>).

rates typically are only weakly influenced by the presence of micelles. However, the rate constants of 1,3-dipolar cycloadditions vary much less with changes in medium than is the case for Diels–Alder reactions. In line with this, we find that the 1,3-dipolar cycloadditions of benzonitrile oxide with *N*-alkylmaleimides have only slightly reduced rate constants for the reaction in the micellar phase, with respect to water, whereas typical Diels–Alder reactions have much smaller relative micellar rate constants ( $k_m/k_w \approx 0.25$ – $0.45$  and  $0.02$ – $0.05$ , respectively).

Although various studies of kinetics of bimolecular processes in the presence of nonionic micelles have been made, in most cases it involves a hydrolysis reaction. Invariably, pseudo-first-order micellar rate constants were determined.<sup>44</sup> We are not aware of a previous study in which a detailed analysis has been made (in terms of the pseudo-phase model, discussing second-order micellar rate constants) of a bimolecular reaction of two organic substrates, catalyzed by nonionic micelles.

(44) A few recent examples are given in refs 41, 48, 49, and 50. A modified pseudo-phase model, yielding pseudo-first-order micellar rate constants, has been applied to kinetics of a bimolecular process in the presence of  $\text{C}_{12}\text{E}_{23}$ .<sup>51,52</sup> Second-order micellar rate constants for a nonionic micelle have been reported in a brief communication: Dougherty, S. J.; Berg, J. C. *J. Colloid Interface Sci.* **1974**, *49*, 135–138.

The present study provides further support for the notion that reaction sites of (neutral) Diels–Alder reactions or 1,3-dipolar cycloadditions in the micelle are mimicked reasonably well by a water/1-propanol mixture, with  $[\text{H}_2\text{O}]$  ca. 15 M. Because rate constants do not vary substantially in a wide concentration range around 15 M, a comparison of  $k_m$  with rate constants in these mixtures does not provide detailed information about the exact nature of the reaction environment in the micellar phase. Instead, it provides information about the question insofar as the micellar reaction environment is satisfactorily mimicked by these mixtures. We found differences in  $k_m$  by a factor of 2 for different types of surfactants (SDS, CTAB,  $\text{C}_{12}\text{E}_8$ ), and  $k_m$  deviated from the rate constants in these water/1-propanol mixtures up to a factor of 2.5. These are small differences, compared to a factor of 20–40 difference between  $k_m$  and  $k_w$  for Diels–Alder reactions, which was captured well by this micellar mimic. It suggests that the local medium in the micelle can be readily understood as a mixture of its components, like headgroups, tails, and water, but also that small differences in rate constants (by about a factor of 2) may be caused by other effects, including a (small) mismatch in binding sites for the two reactants.

As rate constants in water/1-propanol mixtures were not very indicative of the nature of the binding/reaction sites, we also determined thermodynamic activation parameters for one of the reactions in the micellar phase formed from  $\text{C}_{16}\text{E}_{20}$ . They agreed very well with those obtained for a 15 M water/1-propanol mixture.

The present results show that a combination of kinetic data for cycloaddition reactions in mixed aqueous solution and in micellar media contributes to a better understanding of medium effects on these synthetically important reactions.

## Experimental Section

**Materials.** *N*-*n*-Butylmaleimide (**2b**)<sup>45</sup> and 5,5-di-*n*-dodecyl-2-hydroxy-1,3,2-dioxaphosphorinane-2-one (ddp)<sup>28</sup> were synthesized previously. All other materials were obtained from commercial suppliers, and were of the highest purity available. Solvents were either analytical grade or distilled.

**5-Ethyl-3-phenyl-3aH-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*)-6a*H*)-dione (**3a**).** The reaction of **1** with **2a** was performed on a synthetic scale. *N*-Ethylmaleimide (0.24 g, 2 mmol) and benzaldoxime (0.24 g, 2 mmol) were dissolved in 10 mL of a 1:1 mixture of water and ethanol. About 20 mL of household bleach was added under vigorous stirring. The mixture became warm and precipitation followed. The mixture was decanted, and the residue was crystallized from ether, yielding white needles. <sup>1</sup>H NMR ( $\text{CDCl}_3$ )  $\delta$  7.95 (m, 2H), 7.42 (m, 3H), 5.46 (d,

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$J = 9.5$  Hz, 1H), 4.75 (d,  $J = 9.5$  Hz, 1H), 3.55 (q,  $J = 6.9$  Hz, 2H), 1.13 (t,  $J = 6.9$  Hz, 3H).

**Kinetic Measurements.** For all kinetic experiments, we applied the following procedure. The preparation of **1** was performed in a test tube by dissolving benzaldoxime in a bleach/1-propanol mixture and shaking this tube for a few seconds. After the addition of sodium chloride a two-phase system emerged, and 0.5–1  $\mu$ L of the organic layer was transferred to a quartz cuvette, which contained the reaction mixture with the dipolarophile. Kinetic measurements were performed with use of UV–vis spectroscopy (Perkin-Elmer  $\lambda 5$  or  $\lambda 12$  spectrophotometer). The dipolarophile was used in excess, and reactions were monitored at 273 nm. Overlay spectra show isosbestic points, indicating a single transformation to the cycloaddition product. The reactions were followed for at least 4 half-lives and pseudo-first-order rate constants were obtained by using a fitting program. Typical conditions were the following: [dipolarophile] = 1–10 mM, [1,3-dipole] = ca. 0.025–0.05 mM; for the (aqueous) surfactant solutions, the concentration of dipolarophile was about 0.25–1.0 mM. Rate constants were determined at least three times and were reproducible to within 3%. Rate constants for **1** + **2b** in solutions of C<sub>16</sub>E<sub>20</sub> were determined 10 times. Activation parameters were calculated from 5 rate constants in the temperature range of 20–40 °C.

**Determination of Binding Constants.** UV spectra were recorded on a Perkin-Elmer  $\lambda 5$  spectrophotometer. For the determination of the binding constants of **1** to CTAB, C<sub>12</sub>E<sub>8</sub>, C<sub>12</sub>E<sub>23</sub>, C<sub>16</sub>E<sub>10</sub>, and C<sub>16</sub>E<sub>20</sub>, spectra were recorded at different concentrations of surfactant (10–100 mM). Absorptions at both 240 and 262 nm (C<sub>12</sub>E<sub>23</sub> and C<sub>16</sub>E<sub>20</sub>) and at 242 nm (CTAB) were used for the calculations. For the nonionic surfactants, isosbestic points were observed in the overlay plot of these spectra; for CTAB, an additional, small absorption band appeared around 280 nm at low [CTAB], which disappeared again at higher [CTAB]; however, the absorptions around 242 nm appeared indicative of the binding process. The absorbance (at a particular wavelength) of **1** in a surfactant mixture is described by:<sup>19</sup>

$$A = A_w \frac{[\mathbf{1}]_w}{[\mathbf{1}]_t} + A_m \frac{[\mathbf{1}]_m}{[\mathbf{1}]_t} \quad (3)$$

with  $A_w$  and  $A_m$  the absorbance of **1** in the water phase (w) and micellar phase (m), respectively, and  $[\mathbf{1}]_x$  the analytical concentrations in the respective phases ( $x = w, m, t$ ); t refers to the total system. Together with  $[\mathbf{1}]_t = [\mathbf{1}]_w + [\mathbf{1}]_m$  this rearranges to:

$$\frac{[\mathbf{1}]_m}{[\mathbf{1}]_t} = \frac{A_w - A}{A_w - A_m} \quad (4)$$

The binding constant  $K_s$  is given by:<sup>19</sup>

$$K_s = \frac{[\mathbf{1}]_m}{[\mathbf{1}]_w[S]} \quad (5)$$

with [S] the concentration of surfactant. Equations 4 and 5 and  $[\mathbf{1}]_t = [\mathbf{1}]_w + [\mathbf{1}]_m$  give:

$$\left(1 - \frac{A_w - A}{A_w - A_m}\right) K_s = \frac{A_w - A}{A_w - A_m} \frac{1}{[S]} \quad (6)$$

which can be rewritten as:

$$\frac{[S]}{A_w - A} = \frac{1}{(A_w - A_m)K_s} + \frac{[S]}{(A_w - A_m)} \quad (7)$$

Hence, a plot of  $[S]/(A_w - A)$  vs [S] yields a straight line, and the slope divided by the intercept gives  $K_s$ . Binding constants were reproducible to within 5–10%.

**Analysis with Use of the Pseudo-Phase Model.** The analysis with the pseudo-phase model has been described previously.<sup>2</sup> The molar volumes used were 0.25 and 0.363 dm<sup>3</sup> mol<sup>−1</sup> for SDS and CTAB, respectively,<sup>19</sup> 0.286 dm<sup>3</sup> mol<sup>−1</sup> for C<sub>12</sub>E<sub>8</sub>, and 0.35 dm<sup>3</sup> mol<sup>−1</sup> for C<sub>16</sub>E<sub>8</sub>, as described in the text. CMC's are 7 and 1 mM for SDS and CTAB, respectively, under the reaction conditions. For the nonionic surfactants, the low values for the CMC's ( $\leq 0.1$  mM), as compared to the concentration range of interest ( $\approx 5$ –100 mM), could safely be neglected.

**Acknowledgment.** Markus Johnssen and Jaap E. Klijn are acknowledged for useful discussions. The National Research School Combination Catalysis is acknowledged for financial support.

**Supporting Information Available:** Proton NMR spectrum for compound **3a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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