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Million-Fold Acceleration of a Diels–Alder Reaction due to Combined Lewis Acid and Micellar Catalysis in Water

Sijbren Otto,† Jan B. F. N. Engberts,*‡ and Jan C. T. Kwak†

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Received May 12, 1998

Abstract: The effect of micelles of sodium dodecyl sulfate (SDS), cetyltrimethylammonium bromide (CTAB), dodecyl hexaoxyethylene ether (C12E7), and copper and zinc didecyl sulfate (M(DS)2) on the Diels–Alder reaction of 3-(para-substituted phenyl)-1-(2-pyridyl)-2-propen-1-ones (1a–g, containing neutral, cationic, or anionic substituents, with cyclopentadiene (2) has been studied. In the absence of catalytically active transition-metal ions, micelles invariably retard the reaction. This can be rationalized on the basis of different binding locations of the reaction partners in the micelle. These binding sites have been probed using solubilizate-induced aromatic shifts in the 1H NMR spectrum of the surfactant and paramagnetic counterion-induced relaxation enhancements of the 1H NMR signals of the solubilizate. In contrast to SDS, CTAB, and C12E7, Cu(DS)2 micelles catalyze the Diels–Alder reaction between 1 and 2 with extremely high efficiency, leading to rate enhancements up to $1.8 \times 10^6$ compared to the uncatalyzed reaction in acetonitrile. This results primarily from the essentially complete complexion of 1 to the copper ions at the micellar surface. Analysis of substituent effects and endo/exo ratios of the Diels–Alder adducts indicates that the reaction experiences a waterlike environment.

Introduction

The Diels–Alder reaction is an important tool in synthetic organic chemistry, forming the key step in the preparation of many six-membered rings. Many procedures have been developed to increase the yields and selectivities of Diels–Alder reactions.1 In particular, the discovery that Lewis acids can catalyze these reactions in organic solvents had a large impact on synthetic organic chemistry.2 The mechanism by which Lewis acids influence the rate and selectivity of the Diels–Alder reaction can be readily explained in terms of the frontier molecular orbital (FMO) theory.3 For a normal electron demand Diels–Alder reaction, the rate and selectivity depend on the efficiency of the interaction of the HOMO of the diene with the LUMO of the dienophile. Raising the energy of the diene HOMO and lowering the energy of the dienophile LUMO increases the mutual overlap. Therefore, most dienophiles carry an electron-withdrawing substituent to lower their LUMO energy. Coordination of a Lewis acid to this group leads to a further dramatic enhancement of its electron-withdrawing capacity, thereby magnifying its effect on rate as well as on selectivity.

Since 1980, another important impulse in Diels–Alder chemistry came from the discovery of the special effect of water on the Diels–Alder reaction.4 Accelerations of up to 12 800 times on going from an organic solvent to water have been reported.5 Synthetic applications of the increase in rate and also selectivity by this solvent followed promptly.6 Computer simulations and detailed kinetic studies on the effect of water on a multitude of Diels–Alder reactions have clearly demonstrated that two important properties of this solvent give rise to the dramatic accelerations.5,7 Hydrogen-bonding interactions between water and the activating group of the dienophile accounts for part of the rate enhancement. The mode of action is analogous to Lewis acid catalysis. The remainder of the acceleration can be attributed to enforced hydrophobic interactions.8 The reaction in water is facilitated by the favorable expulsion of water molecules from the hydrophobic hydration shells of the reacting molecules upon approaching the transition state. The relative contributions of hydrogen-bonding and enforced hydrophobic interactions in the aequous acceleration depend on the character of the diene and the dienophile.7b

We have recently reported the first example of a Diels–Alder reaction that benefits from both Lewis acid catalysis and the special effects of water simultaneously, leading to high selectivities and accelerations up to 250 000 times.9 Herein we show...
that even higher rate enhancements of the aqueous Lewis acid-catalyzed Diels–Alder reaction can be achieved through micellar catalysis. Before embarking on a detailed analysis of micelle-catalyzed Diels–Alder reactions, it is appropriate to briefly summarize the basic features of micellar catalysis.

When relatively apolar compounds are introduced in an aqueous micellar solution, dipolar and hydrophobic interactions will cause them to bind to or be taken up by micelles. The solubilization of these compounds is usually treated in terms of the pseudophase model, regarding the bulk water phase as one phase and the micellar pseudophase as another. The affinity of the solubilize for the micelle can then be quantified by a partition coefficient $P$. In this article, we will express $P$ as the ratio of the concentration of the solubilize in the micellar pseudophase divided by the concentration of the solubilize in the aqueous phase.

There has been controversy over the time-averaged location of different solubilizes in or at the micelle. The binding of the aqueous phase.

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**Figure 1.** Kinetic analysis of a bimolecular reaction $A + B \rightarrow C$ according to the pseudophase model.

The present work deals with micellar catalysis of bimolecular and termolecular processes. Following the pioneering work of Berezin, using the pseudophase model, the kinetics of these processes can be accounted for by taking into account the individual partition coefficients of both reaction partners and separate rate constants for reaction in the micellar and in the aqueous phase (Figure 1). Determination of the rate constant in the micellar pseudophase generally requires independent assessment of at least one of the involved partition coefficients. The kinetics of a large number of bimolecular micelle-catalyzed processes have been analyzed in this way. In the majority of cases studied, at least one of the reaction partners is ionic, so that competition in binding with the surfactant counterions has to be taken into account. Romsted et al. have developed the pseudophase ion-exchange model for dealing with these ionic bimolecular reactions. Examples of bimolecular reactions involving two nonionic reactants have been reported. The effect of micelles on the observed rates of all these bimolecular reactions originates from two distinct effects: (a) the medium effect, the reaction partners will experience a different local environment, so that $k_0$ is different from $k_w$; (b) the local concentration effect, the concentrations of both reaction partners in the micellar pseudophase will be different from those in bulk water. One of the most remarkable observations is that, for nearly all nonionic as well as ionic bimolecular processes, the second-order rate constant for reaction in the micellar pseudophase $k_0$ virtually equals the rate constant for reaction in the aqueous phase $k_w$. Hence, the significant accelerations in terms of the observed rates of many bimolecular reaction should be attributed primarily to the increased local concentrations of both reaction partners in the micelle or, more precisely, at the micellar surface.

There are only a few documented examples of micellar catalysis of Diels–Alder reactions. Jaeger has employed orientational effects in micelles to promote the regioselectivity of a Diels–Alder reaction of a surfactant diene and a surfactant dienophile. Recently, Diego-Castro and Hailes studied the influence of sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) on the endo/exo selectivity of the Diels–Alder reactions of a range of acrylate esters with cyclopentadiene. Kinetic studies by several authors have...

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Million-Fold Acceleration of a Diels–Alder Reaction

In previous studies, we described the Diels–Alder reaction between a class of bidentate dienophiles 3-(para-substituted 2-cation, they react rapidly with organic chemistry.27 The inability of micelles to catalyze Diels–Alder reactions is surprising, since, in view of the nonpolar nature of most dienes and dienophiles, micellar catalysis is anticipated. In the present study, we will shed light on this discrepancy. As far as we know, we report herein the first detailed kinetic study of micellar catalysis of Diels–Alder reactions. It also represents the first in-depth study of Lewis acid catalysis in conjunction with micellar catalysis, a combination that has recently found application in synthetic organic chemistry.27

Results and Discussion

In previous studies, we described the Diels–Alder reaction between a class of bidentate dienophiles 3-(para-substituted phenyl)-1-(2-pyridyl)-2-propen-1-ones 1a–e and cyclopentadiene (2) leading to racemic mixtures of endo as well as exo adducts 3 (Scheme 1).9 Compounds 1 are relatively poor dienophiles, but once coordinated to a Co2+, Ni2+, Cu2+, or Zn2+ cation, they react rapidly with 2 to give cycloadducts 3.28

We describe the influence of micelles of CTAB, SDS, and dodecyl heptaoxyethylene ether (C12E7) as well as copper and zinc didodecyl sulfate (M(DS)2)29 on the rates and selectivities of the uncatalyzed as well as the Lewis acid-catalyzed Diels–Alder reactions of 1 and 2. Particularly the micelles bearing catalytically active transition-metal counterions are interesting, since they are likely to exhibit micellar catalysis and Lewis acid catalysis simultaneously.

Note that the dienophiles can be divided into nonionic (1a–e), anionic (1f), and cationic (1g) species. A comparison of the effects of nonionic (C12E7), anionic (SDS, Cu(DS)2), and cationic (CTAB) micelles on the rates of their reaction with 2 will allow assessment of the importance of electrostatic interactions in micellar catalysis.


(30) For all ionic surfactants, the cmc has been determined under the Diels–Alder reaction conditions, which yielded values 3–14% lower than the cmc’s of the surfactant in water.

(31) To estimate these values, we have used the partition coefficients of 2, which will be derived later in this article.

Table 1. Influence of Micelles of CTAB, SDS, and C12E7 on the Apparent Second-Order Rate Constants (M−1 s−1) for the Diels–Alder Reaction between 1a, 1f, and 1g, respectively, and 2 at 25 °C

<table>
<thead>
<tr>
<th>Medium</th>
<th>1a</th>
<th>1f</th>
<th>1g</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>4.02×10−3</td>
<td>1.74×10−3</td>
<td>2.45×10−3</td>
</tr>
<tr>
<td>SDS</td>
<td>3.65×10−3</td>
<td>1.44×10−3</td>
<td>1.47×10−3</td>
</tr>
<tr>
<td>CTAB</td>
<td>3.61×10−3</td>
<td>2.83×10−4</td>
<td>2.01×10−3</td>
</tr>
<tr>
<td>C12E7</td>
<td>3.35×10−3</td>
<td>1.62×10−3</td>
<td>2.05×10−3</td>
</tr>
</tbody>
</table>

kobs = k_{app} / [2], wherein [2] is the overall concentration of 2.8 1a ≈ 2 × 10−3 M; [2] = 2.0 × 10−3 M. All solutions contain 1.0 × 10−4 M EDTA in order to suppress catalysis by trace amounts of transition metal ions. The concentration of surfactant is 7.8 mM above the cmc of the particular compound under the reaction conditions.

<table>
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<tr>
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<th>1a</th>
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In Table 1, the effect of micelles of SDS, CTAB, and C12E7 on the apparent second-order rate constants (k_{app}) of the Diels–Alder reaction between nonionic 1a, anionic 1f, and cationic 1g, respectively, with 2 is summarized. For all entries, the concentration of surfactant is 7.8 mM above the cmc of the particular amphiphile.30 The rate constants have been obtained by following the decrease of the UV-visible absorbance of 1 by employing spectroscopic techniques. This technique allows the use of low concentrations of 1 (~2 × 10−3 M) so that, on average, there will be no more than one dienophile molecule per micelle. The overall concentration of 2 is 2.0 mM, which ensures that, depending on the aggregation number of the surfactant, the average number of cyclopentadiene molecules per micelle varies between 1 and 3.31 Under these conditions, the effect of micelles on the rate of the Diels–Alder reaction is obviously small and invariably results in a slight inhibition of the reaction. It is striking to observe that the most significant effect occurs for anionic 1f in CTAB solutions and for cationic 1g in SDS solutions. These are the two combinations where one would expect essentially complete binding of the dienophile to the micelle as a result of favorable electrostatic interactions in addition to hydrophobic interactions. Apparently, reaction in the micellar environment is slower than that in the bulk aqueous phase, despite the anticipated increased concentrations of the reactants in the micellar pseudophase. Note that also in the case where electrostatic interactions inhibit binding of the dienophile to the micelle, i.e., 1f in SDS and 1g in CTAB solution, a retardation of the reaction is observed. In these cases, the dienophile most likely will reside primarily in the aqueous phase. Presumably, the retardation will then result from a decrease in the concentration of 2 in this phase due to its partial solubilization by the micelles.

To interpret the data in Table 1 in a quantitative fashion, we have analyzed the kinetics in terms of the pseudophase model (Figure 1). For the limiting cases of essentially complete binding of the dienophile to the micelle as a result of favorable electrostatic interactions in addition to hydrophobic interactions. Apparently, reaction in the micellar environment is slower than that in the bulk aqueous phase, despite the anticipated increased concentrations of the reactants in the micellar pseudophase. Note that also in the case where electrostatic interactions inhibit binding of the dienophile to the micelle, i.e., 1f in SDS and 1g in CTAB solution, a retardation of the reaction is observed. In these cases, the dienophile most likely will reside primarily in the aqueous phase. Presumably, the retardation will then result from a decrease in the concentration of 2 in this phase due to its partial solubilization by the micelles.

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\[
\frac{[2]}{k_{obs}} = \frac{V_{mol,S}}{k_m} + \frac{V_w}{P_z V_{mol,S}} + \frac{cmc V_{mol,S}}{k_m}
\]

Herein [2] is the total number of moles of 2 present in the reaction mixture, divided by the total reaction volume V\text{r} _{obs}
is the observed pseudo-first-order rate constant; $V_{\text{mol,S}}$ is an estimate of the molar volume of micellized surfactant $S$; $k_m$ is the second-order rate constant in the micellar pseudophase (see Figure 1); $V_a$ is the volume of the aqueous phase; and $P_2$ and $k_m$ can be obtained. We have used estimates for the molar volume of micellized CTAB and SDS of 0.25 and 0.37 M$^{-1}$, respectively, and assumed $V_a/V_1 = 1$, which is reasonable in view of the low concentrations of surfactant used. Figure 2 shows the dependence of the apparent rate constants ($k_{\text{app}}$) on the concentration of surfactant for the Diels–Alder reactions of 1f and 1g with 2 in, respectively, the CTAB and SDS micellar pseudophase at 25 °C.

Figure 2. Apparent second-order rate constant, $k_{\text{app}} = k_{\text{obs}}/[2]_0$, versus the concentration of surfactant for the Diels–Alder reaction of 1f with 2 in CTAB solution (●) and of 1g with 2 in SDS solution (■) at 25 °C. The inset shows the treatment of these data using eq 1. From slopes and intercepts, $P_2$ and $k_m$ can be calculated (see Table 2).

Table 2. Analysis Using the Pseudophase Modela

<table>
<thead>
<tr>
<th>surfactant</th>
<th>dienophile</th>
<th>$k_m$ (M$^{-1}$ s$^{-1}$) (±10%)</th>
<th>$P_2$ (±10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTAB</td>
<td>1f</td>
<td>5.9 × 10$^{-6}$</td>
<td>68</td>
</tr>
<tr>
<td>SDS</td>
<td>1g</td>
<td>3.1 × 10$^{-5}$</td>
<td>61</td>
</tr>
</tbody>
</table>

a Partition coefficients for 2 over CTAB or SDS micelles and water and second-order rate constants for the Diels–Alder reaction of 1f and 1g with 2 in, respectively, the CTAB and SDS micellar pseudophase at 25 °C.

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a Partition coefficients for 2 over CTAB or SDS micelles and water and second-order rate constants for the Diels–Alder reaction of 1f and 1g with 2 in, respectively, the CTAB and SDS micellar pseudophase at 25 °C.

Effects of Micelles on the Rate and Selectivity of the Lewis Acid-Catalyzed Diels–Alder Reaction. In the previous section it was demonstrated that, in the absence of Lewis acid catalysts, micelles inhibit the Diels–Alder reaction between 1 and 2, irrespective of the charge of the dienophile and the micelle. Since this Diels–Alder reaction can be catalyzed by transition-metal ions, we have also studied the effect of micelles on this process. The complexion behavior of 1 with transition-metal ions has been studied using UV–visible spectroscopy. Figure 3 shows the spectra of nonionic 1c as well as the anionic and cationic counterparts 1f and 1g in water and in surfactant solutions containing copper(I1) ions. The shifts of the absorption bands primarily reflect the extent of coordination of the dienophile to the copper ions. Binding to micelles has a negligible influence on the spectrum. Addition of C12E7 to a 10 mM Cu(NO3)$_2$ solution containing the dienophiles 1f and 1g leaves the absorption spectra essentially unchanged. Apparently 1f and 1g have little affinity for C12E7 micelles. A similar picture emerges for cationic 1g, which resides preferably in the aqueous phase rather than binding to cationic CTAB micelles. In contrast, 1c has some affinity for C12E7 and CTAB micelles, resulting in a decreased coordination to the copper ions in the presence of these surfactants. Interestingly, all three dienophiles, even anionic 1f, bind more efficiently to the copper ions in the presence of Cu(DS)$_2$ micelles than in aqueous solution containing twice the overall concentration of copper ions. This is in line with literature observations$^{37}$ that revealed an increased interaction between transition-metal ions and chelating organic molecules in the presence of anionic surfactant. The enhanced binding predicts a catalytic potential for these solutions and prompted us to investigate the influence of the different types of micelles on the rate of the copper ion-catalyzed reaction. Table 2 summarizes the results, which are in perfect agreement with the conclusions drawn from the complexion studies. In all surfactant solutions, 2 is expected to prefer the nonpolar micellar environment over the bulk aqueous phase. Consequently, those surfactant/dienophile combinations where the dienophile resides primarily in the aqueous phase show inhibition. This is the case for 1f and 1g in C12E7 solution and for 1g in CTAB solution. On the other hand, when diene, dienophile, and copper ion simultaneously bind to the micelle, as is the case for Cu(DS)$_2$ solutions with all three dienophiles, efficient micellar catalysis is observed. An intermediate situ-

Table 3. Endo/Exo Product Ratios for the Diels–Alder Reaction of 1c with 2 in Surfactant Solutions Compared to Water and Organic Solvents

<table>
<thead>
<tr>
<th>medium</th>
<th>% endo/% exo (±2%)</th>
<th>medium</th>
<th>% endo/% exo (±2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mM CTAB</td>
<td>86/14 (±2%)</td>
<td>water</td>
<td>84/16$^a$</td>
</tr>
<tr>
<td>100 mM SDS</td>
<td>88/12 (±2%)</td>
<td>ethanol</td>
<td>77/23$^a$</td>
</tr>
<tr>
<td>100 mM C12E7</td>
<td>85/15 (±2%)</td>
<td>acetonitrile</td>
<td>67/33$^a$</td>
</tr>
</tbody>
</table>

$^a$ Data taken from ref 9b.

(32) Inevitably, the estimate of a molar volume of the micellized surfactant that is available for solubilization is somewhat arbitrary.


concentration of Cu(DS)\(_2\). For all three dienophiles, the counteractive influences. First, at higher surfactant concentration exists for 1c in CTAB solution. Now the dienophile binds to the micelle and is shielded from the copper ions that apparently prefer to reside in the aqueous phase. This results in an overall retardation, despite the possible locally increased concentration of 2 in the micelle.

Very promising catalytic results were obtained for the Cu(DS)\(_2\) solutions. We have analyzed this system in some detail. Figure 4 shows the dependence of the rate of the Diels–Alder reaction between 1c, 1f, and 1g, respectively, with 2 on the concentration of Cu(DS)\(_2\). For all three dienophiles, the apparent second-order rate constant for their reaction with 2 increases dramatically when the concentration of Cu(DS)\(_2\) reaches the cmc (1.11 mM). Beyond the cmc, the behavior of the rate at increasing surfactant concentration is subject to two counteractive influences. First, at higher surfactant concentration, a larger fraction of dienophile will be bound to the micelle, where it reacts faster than in bulk water, resulting in an increase in the rate of the reaction. Second, at the same time, the concentration of diene bound to the micelle will drop with increasing number of micelles, resulting in a decrease of the apparent second-order rate constant. At higher surfactant concentrations, the dienophile will be nearly completely bound to the micelles and the dilution effect will dominate the behavior. Together, these two effects result in the appearance of a rate maximum at a specific concentration of surfactant that is typical for micelle-catalyzed bimolecular reactions. Together, these two effects result in the appearance of a rate maximum at a specific concentration of surfactant that is typical for micelle-catalyzed bimolecular reactions. The position of the maximum depends primarily on the micelle–water partition coefficient of the dienophile. For instance, cationic 1g reacts fastest close to the cmc, because of its very high affinity for the anionic Cu(DS)\(_2\) micelles. Formation of a complex with a copper cation will only increase the affinity for the micelles. As a result, 1g will be almost completely bound to the micelles, even at very low concentrations of Cu(DS)\(_2\). By contrast, the reaction of 1f still benefits from an increasing surfactant concentration at 10 mM Cu(DS)\(_2\). In fact, it is surprising that the Diels–Alder reaction of this anionic compound is catalyzed at all by an anionic surfactant. Probably it is the copper complex of 1f, being overall cationic, that binds to the micelle. Not surprisingly, the neutral 1c shows intermediate behavior.

Interestingly, at very low concentrations of micellized Cu(DS)\(_2\), the rate of the reaction of 1a with 2 was observed to be zero order in 1a and dependent only on the concentration of Cu(DS)\(_2\) and 2. This is similar to the turnover and saturation kinetics exhibited by enzymes. The acceleration, relative to the reaction in organic media in the absence of catalyst, also approaches enzyme-like magnitudes: compared to the reaction in acetonitrile, Cu(DS)\(_2\) micelles accelerate the Diels–Alder reaction between 1a and 2 by a factor of 1 800 000. This uncommonly high catalytic efficiency shows how a combination of a beneficial aqueous solvent effect, Lewis acid catalysis, and micellar catalysis can lead to extremely large accelerations.

The essentially complete binding of 1g to the Cu(DS)\(_2\) micelles allows treatment of the kinetic data shown in Figure 4 using the pseudophase model. Since it is likely that 1g binds in the Stern region (vide infra), complete binding to the copper ions can be assumed. Using eq 1, the Cu(DS)\(_2\)–water distribution coefficient of 2 can now be obtained as well as the second-order rate constant for the reaction in the micellar pseudophase

![Figure 3](image3.png)

Figure 3. UV spectra of 1c, 1f, and 1g in water (a) compared to those in solutions containing 10 mM Cu(NO\(_3\))\(_2\) (b), 5 mM Cu(DS)\(_2\) (c), 10 mM CTAB plus 10 mM Cu(NO\(_3\))\(_2\) (d), and 10 mM C\(_{12}\)E\(_7\) plus 10 mM Cu(NO\(_3\))\(_2\) (e).

![Figure 4](image4.png)

Figure 4. Apparent second-order rate constant (k\(_{app}\)) versus the concentration of Cu(DS)\(_2\) for the Diels–Alder reaction of 1c (□), 1f (●) and 1g (▲) with 2 at 25 °C. The inset shows the treatment of the data for the reaction of 1g according to the pseudophase model.

Table 4. Influence of Micelles of Cu(DS)\(_2\), CTAB, and C\(_{12}\)E\(_7\) on the Apparent Second-Order Rate Constants (M\(^{-1}\) s\(^{-1}\)) for the Copper(II)-Catalyzed Diels–Alder Reaction between 1c, 1f, and 1g, Respectively, and 2 at 25 °C\(^{a}\)

<table>
<thead>
<tr>
<th>medium</th>
<th>1c</th>
<th>1f</th>
<th>1g</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mM Cu(NO(_3))(_2)</td>
<td>1.11</td>
<td>1.38</td>
<td>2.13</td>
</tr>
<tr>
<td>5 mM Cu(DS)(_2)</td>
<td>5.95</td>
<td>5.50</td>
<td>15.3</td>
</tr>
<tr>
<td>CTAB(^{+}) + 10 mM Cu(NO(_3))(_2)</td>
<td>0.401</td>
<td>0.150</td>
<td>1.84</td>
</tr>
<tr>
<td>C(_{12})E(_7)(^{+}) + 10 mM Cu(NO(_3))(_2)</td>
<td>0.630</td>
<td>1.08</td>
<td>1.71</td>
</tr>
</tbody>
</table>

\(^{a}\)[1] \(\approx 2 \times 10^{-3}\) M; [2] = 1.0 \times 10^{-3}\) M. The concentration of surfactant is 7.8 mM above the cmc of the particular compound under reaction conditions.
## Table 5. Hammett $\rho$-Values for the Copper(II)-Catalyzed Diels−Alder Reaction between 1a−e and 2 in Different Media

<table>
<thead>
<tr>
<th>medium</th>
<th>$\rho$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mM Cu(DS)$_2$</td>
<td>0.86</td>
</tr>
<tr>
<td>10 mM Cu(NO$_3$)$_2$ in acetonitrile</td>
<td>0.96$^b$</td>
</tr>
<tr>
<td>10 mM Cu(DS)$_2$ in ethanol</td>
<td>1.00$^b$</td>
</tr>
<tr>
<td>10 mM Cu(NO$_3$)$_2$ in water$^*$</td>
<td>0.82$^b$</td>
</tr>
</tbody>
</table>

$^a$ Ionic strength 2.00 M (KNO$_3$). $^b$ Data taken from ref 9b.

(see inset in Figure 4). Unfortunately no literature data exist for the molar volume of micellized Cu(DS)$_2$ that is required for the kinetic analysis. We have used an estimate of 0.50 M$^{-1}$, twice as large as the number that we have used previously for micellized SDS.$^{39}$ Calculations using this value yield a partition coefficient for 2 of 96 and a micellar second-order rate constant of 0.21 M$^{-1}$ s$^{-1}$. This partition coefficient is higher than the corresponding values for SDS and CTAB micelles given in Table 2. This is in agreement with literature data, that indicate Cu(DS)$_2$ micelles are able to solubilize 1.5 times as much benzene as SDS micelles.$^{29b}$ Most likely this is a result of the higher counterion binding of Cu(DS)$_2$ micelles (89 versus 60%), which reduces the headgroup repulsion and allows a tighter packing of the headgroups resulting in decreased water penetration and an increased nonpolar character of the micellar binding sites compared to SDS. Comparing the value of the micellar second-order rate constant of 0.21 M$^{-1}$ s$^{-1}$ with the rate constants for the reaction in acetonitrile (0.472 M$^{-1}$ s$^{-1}$) and ethanol (0.309 M$^{-1}$ s$^{-1}$) again suggests an apolar reaction medium for the Diels−Alder reaction. This is hard to reconcile with the ionic character of two of the three reaction partners involved. To obtain more insight into the local environment of the catalyzed reaction, we have investigated the influence of substituents on the rate constants for this process in micellar solution and compared it to the corresponding effect in different aqueous and organic solvents. Plots of the logarithms of the rate constants versus the Hammett $\sigma$-values show good linear dependences for all media. The resulting $\rho$-values are shown in Table 5. The $\rho$-value in Cu(DS)$_2$ solution resembles that in aqueous solution more than those in organic solvents. Therefore, it appears that the outcome of the analysis using the pseudophase model is not in agreement with experimental observations. Apparently, one (or more) of the assumptions of the pseudophase model is not valid for the system studied here. In particular, the treatment of the micellar pseudophase as a homogeneous “solution” might not be warranted. Therefore, we contend that diene and dienophile, on average, reside in different parts of the micelle, thereby impeding the reaction. This would also explain the absence of a large catalytic effect in cases where diene and dienophile bind efficiently to the micelle. To check this hypothesis, we have probed the binding location of diene and dienophile using $^1$H NMR techniques.

**Binding Locations of Diene and Dienophile and Their Implications.** NMR methods have been regularly employed in the study of micellar solutions.$^{40}$ The most frequently encountered technique to probe the binding location of aromatic compounds in micelles makes use of changes in the chemical shifts in the $^1$H NMR spectrum of the surfactant that are induced by the aromatic ring of the solubilizate.$^{11a,41}$ Such studies with a large number of aromatic compounds have revealed that for CTAB the largest shift occurs for the alkyl chain protons near the surfactant headgroup, whereas in SDS nearly all proton signals are shifted significantly, but with the most pronounced shifts for the protons around the center of the chain. This has been interpreted in terms of a deeper penetration of aromatic compounds in SDS micelles relative to CTAB micelles.$^{41b,4e}$

We have determined the aromatic shifts that are induced by 1c, 1f, and 1g in the $^1$H NMR spectra of SDS, CTAB, and Zn(DS)$_2$. The latter is used as a model system for Cu(DS)$_2$, which is paramagnetic. The cme’s and counterion binding of Cu(DS)$_2$ and Zn(DS)$_2$ are very similar,$^{29a}$ and Zn(II) ions have been reported to be also capable of coordinating to I, albeit somewhat less efficiently that copper ions.$^{9b}$ Figure 5 shows the results of the chemical shift measurements. For the purpose of comparison the data for chalcone (4) have been added. This compound has almost no tendency to coordinate to transition-metal ions in aqueous solutions.$^{9b}$ In Figure 5 and throughout the rest of this study, N stands for the protons at the three headgroup methyl moieties of CTAB; $\alpha$ and $\beta$ stand for the methylene protons at the $\alpha$ and $\beta$ positions relative to the headgroup. $\omega$ represents the terminal methyl group protons and $n$ the protons between the $\beta$- and $\omega$-positions. Figure 5 shows the corresponding values for SDS and CTAB micelles. The concentration of the solubilizate is 2.0 M, 5.0, or 8 mM. N stands for the protons at the three headgroup methyl moieties of CTAB; $\alpha$ and $\beta$ stand for the methylene protons at the $\alpha$ and $\beta$ positions relative to the headgroup. $\omega$ represents the terminal methyl group protons and $n$ the protons between the $\beta$- and $\omega$-positions.

From the data in Figure 5, a number of conclusions can be drawn. (1) The shifts induced by 1c on the NMR signals of SDS and CTAB show the characteristics usually observed for benzene derivatives.$^{11a,41}$ (2) Introduction of an ionic group into the dienophile (compare panel e of Figure 5 with (h) and

![Figure 5. Aromatic solubilizate-induced changes in the chemical shift of the proton NMR signals of micellized surfactant. (a−f) show the effect of 4 and 1c on the proton resonances of Zn(DS)$_2$ (25 mM), SDS (50 mM), and CTAB (50 mM). (g) and (h) show the corresponding effect of 1g on Zn(DS)$_2$ (25 mM) and SDS (50 mM), respectively. (i) depicts the effect of 1f on the CTAB (50 mM) resonances. The concentrations of the solubilize were 2.0 (●), 5.0 (▴) or 8 (■) mM.](image)

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(39) The number for the molar volume of micellized Cu(DS)$_2$ is probably too large. Using a smaller number will result in a larger value for $P_2$ and a decrease of $k_0$ which will even further justify the conclusions drawn from these numbers.

(40) Chachaty, C. Prog. NMR Spectrosc. 1987, 19, 183.
(f) with (i)) causes this compound to bind more closely to the headgroups of the micelles. (3) Chelation of the dienophile to a zinc(II) ion has little effect on its location in the micelle (compare (a) with (d)). (4) The presence of the pyridine nitrogen atom influences the binding location only to a minor extent (compare (b) with (e) and (c) with (f)). Surprisingly, the shifts observed in the $^1$H NMR spectrum of Zn(DS)$_2$ as caused by 1g seem to point toward a relatively deep penetration of this compound into the micelle. This is extremely unlikely. 1g, when bound to Zn(DS)$_2$ micelles, will coordinate to a Zn(II) ion. The resulting complex will now have three positive charges: two of the zinc ion at one end of the complex and one of the trimethylammonium group at the other end. It is hard to imagine that this hydrophilic complex will penetrate into the nonpolar core of the micelle. The observed shifts indicate a proximity of aromatic groups and, strictly, do not provide direct information about the location where this encounter takes place. Still, we suggest that we may draw at least one solid conclusion from the data in Figure 5: on average, the dienophile is not in the core of the micelle.

In a second attempt to obtain more insight into the binding location of the dienophile and now also of the diene, we have used the paramagnetic relaxation technique to study protons of the surfactant and the aromatic rings of 1g. A likely explanation for this behavior is bending of the alkyl chain of the surfactant toward the aromatic parts of the dienophile. This demonstrates that an interpretation of shift data solely in terms of depth of penetration into the micelle is hazardous. The observed shifts of surfactant protons merely indicate a proximity of aromatic groups and, strictly, do not provide direct information about the location where this encounter takes place. Still, we suggest that we may draw at least one solid conclusion from the data in Figure 5: on average, the dienophile is not in the core of the micelle.

We have used the paramagnetic relaxation technique to study the binding locations of 1c, 1f, or 1g and 2 in CTAB, SDS or Zn(DS)$_2$ solutions by employing [Cu(EDTA)]$^{2-}$, Cu$^{+}$ (for 2), or Dy$^{3+}$ (for 1) as paramagnetic species. Figure 6 shows the values of $r_p$ relative to $r_p$ of the surfactant $\alpha$-methylene protons for 1c and 1f in CTAB solution. To provide a frame of reference, the relative paramagnetic relaxation rates of the CTAB protons are also shown. The latter show a clear decrease upon going from the headgroup toward the end of the hydrocarbon chain. The values for both dienophiles are of a magnitude somewhere between those of the $\beta$ and the $n$ methylene protons of CTAB. Consequently, on average they are somewhat further away from the paramagnetic ions than the $\beta$-protons but not as far as the $n$ protons.

The introduction of an ionic group (compare 1f with 1c) results in a modest decrease of the average distance to the paramagnetic ion. Presumably, two counteracting effects are operative. The presence of a charged group might well result in a shift of the average binding location toward the outer regions of the micelle, resulting in an increased influence of the paramagnetic ion on the rate of relaxation. On the other hand, the electrostatic repulsion between the charged substituent and the paramagnetic counterion will result in a decrease of the effect of this ion on the relaxation rate. Analogous studies on 1c and 1g in SDS and Zn(DS)$_2$ led to essentially the same conclusions and are not shown here.

Figure 7 visualizes the effect of paramagnetic ions on the relaxation rate of 2 in CTAB, SDS, and Zn(DS)$_2$ solutions. 2 is molecularly dispersed up to concentrations of 0.04 M. (Blokzijl, W. Ph.D. Thesis, Groningen, 1991, p 136.) The concentrations of 2 used were well below this limit.
In this case, the relative value of \( r_\text{p} \) is invariably smaller than the corresponding effect on the \( \omega \)-methyl protons of the surfactant. This clearly demonstrates that diene 2, in contrast to the dienophiles, is located in the interior of the micelle and does spend little time at the surface.

Careful analysis of the influence of the character of the solubilizate on the relaxation data of the surfactant led to another interesting observation. Table 6 summarises these data. The first row represents the relative \( r_\text{p} \) values of the different surfactant protons in the absence of any solubilizate. The second and third rows show the corresponding effects in the presence of 8 mM 1c, 1f, or 1g. The introduction of these compounds into a micellar solution does not lead to a significant perturbation of the alkyl chains of the micelle since the relative paramagnetic relaxation rates are similar to those for the pure surfactant.

Yet, when 2 is added to the solutions of SDS and Zn(DS)\(_2\), significant increases in the relative paramagnetic relaxation rates of the \( \beta \)-, the \( n \), and the \( \omega \)-protons are observed. Apparently, the nonpolar solute bound in the interior of these micelles pushes the alkyl chains of the individual surfactant molecules toward the surface. Curiously, this effect is completely absent for CTAB. This might be a result of the increased length of the alkyl chain of this surfactant compared to the two anionics, ensuring an increased tolerance toward incorporation of a solubilizate.

In summary, the NMR studies indicate different average binding locations for diene and dienophile. The diene resides preferentially in the interior of the micelle, which is not surprising in view of its nonpolar character. The dienophiles, on the other hand, are located more toward the surface of the aggregates. This behavior has important implications for the rationalization of the kinetic data. Clearly, when the Diels–Alder reactants are not homogeneously distributed over the micellar pseudophase, analysis according to the pseudophase model will provide erroneous results. It will predict a secondary order rate constant in the micellar pseudophase that is too low. However, the partition coefficients that are produced using this model are still correct, considering that they represent the ratio of the average concentrations of solubilizate in the micellar phase and in the aqueous phase. Another consequence of the above analysis is that the surprising inefficiency of micellar aggregates to catalyze Diels–Alder reactions in the absence of Lewis acids can now be rationalized. Obviously, micelles are able to bind diene and dienophile efficiently but at different locations in the micelle. The reactions seem to take place at the surface of the micelle in a rather aqueous environment, where the concentration of diene is low. Therefore, inhibition most likely results from a local concentration effect rather than from a kinetic medium effect.

The only micellar system that shows efficient catalytic behavior is Cu(DS)\(_2\). These micelles concentrate both diene and copper ion at their surface, thereby promoting complexation of these compounds. Note that, at concentrations slightly higher than the cmc of Cu(DS)\(_2\), already very efficient coordination of the dienophile to copper can take place, which, in the absence of the surfactant, requires copper ion concentrations that are orders of magnitude higher.

Interestingly, the apparent rate constants obtained for the reaction between 1 with 2 in the presence of Cu(DS)\(_2\) exceed those obtained in the case of complete binding of 1 to copper(II) ions in water. Apparently, the local concentration of 2 at the surface of the Cu(DS)\(_2\) micelles is high enough to allow this rate enhancement. In contrast, at the surface of the SDS and CTAB, the concentration of 2 is lower as a result of the reduced partition coefficients of 2 for these micelles as compared to Cu(DS)\(_2\).

The results described in this article may well provide a rationale for the surprising inability of micelles to catalyze Diels–Alder reactions as is apparent from the literature. In view of the structures of most dienes and dienophiles, differences in the preferred location of binding of the reaction partners are expected, which will diminish the rate of their reaction.

Conclusions

The Diels–Alder reaction of 3-(para-substituted phenyl)-1-(2-pyridyl)-2-propan-1-ones 1a–g, containing neutral, cationic, or anionic substituents, and cyclopentadiene (2) in the absence of Lewis acids is retarded by micelles of CTAB, SDS, and C\(_12\)E\(_\text{5}\). In the situation where the dienophile does not bind to the micelle, the reaction is inhibited because uptake of 2 in the micelles lowers its concentration in the aqueous phase. However, retardations are most pronounced when there is essentially complete binding of the dienophile to the micelle. In this case, the reaction still experiences a waterlike environment. We contend that the retardation mainly results from a significant difference in the binding locations of 1 and 2, with the dienophiles preferring the outer regions of the micelle and the diene residing in the interior. Evidence comes from solubilize-induced aromatic shifts in the \(^1\)H NMR spectra of the surfactants as well as from paramagnetic ion-induced relaxation enhancements of the \(^1\)H NMR signals of the solubilizate. The latter experiments also show that 2, in contrast to 1, perturbs the micelles of SDS and Cu(DS)\(_2\). Under conditions of inhomogeneous distribution of 1 and 2 over the micelle, kinetic analysis using the pseudophase model, which is so successful for many other micelle-catalyzed processes, leads to erroneous estimates of the second-order rate constant in the micellar pseudophase.

Micelles of Cu(DS)\(_2\) induce rate enhancements up to a factor \(1.8 \times 10^6\) compared to the uncatalyzed reaction in acetonitrile. These enzyme-like accelerations result from efficient complexation of the dienophile to the catalytically active copper ions, both species being concentrated at the micellar surface. Moreover, the higher affinity of 2 for Cu(DS)\(_2\) compared to SDS and CTAB micelles (\(P_2 = 96\) versus 61 and 68, respectively) will diminish the inhibitory effect due to spatial separation of 1 and 2 as observed for SDS and CTAB.

Experimental Section

Materials. trans-Chalcone (4) (mp 57.1–57.7 °C) was obtained from Aldrich and crystallized from ethanol. Cyclopentadiene (2) was prepared from its dimer (Merck-Schuchardt) immediately before use. Dimineralized water was distilled twice in a quartz distillation unit. Cu(NO\(_3\))\(_2\)·3H\(_2\)O (Merck), KNO\(_3\) (Merck), CTAB (Merck), SDS (BDH

| Table 6. Effect of the Solubilizate on the Paramagnetic Ion-Induced Spin–Lattice Relaxation Rates (\( r_\text{p} \)) of the Protons of CTAB (C), SDS (S), and Zn(DS)\(_2\) (Z), Normalized to \( r_\text{p} \) of the Surfactant \( \alpha\)-CH\(_3\). \( ^a \) |
|-------------|---|---|---|---|---|---|---|---|---|
| solubilizate | N  | α  | β  | n  | ω  |
| 1c          | C  | 100 | 100 | 100 | 64 | 37 | 48 | 13 | 11 | 14 | 9 | 7 | 9 |
| If or Ig    | C  | 166 | 100 | 100 | 68 | 50 | 11 | 15 | 6 | 8 |
| 2           | C  | 181 | 100 | 100 | 69 | 36 | 44 | 12 | 17 | 13 | 7 | 9 | 9 |
|             | Z  | 152 | 100 | 100 | 71 | 62 | 65 | 13 | 27 | 25 | 8 | 22 | 19 |

\( ^a \) For a definition of \( \alpha \), \( \beta \), \( n \), and \( \omega \), see Figure 5. \( ^a \) The solutions contained 25 mM Zn(DS)\(_2\), 50 mM CTAB or SDS, 3 mM 2 and 8 mM 1c, If, or Ig and 0 or 0.4 mM [Cu(EDTA)]\(^2+\) for CTAB solutions, and 0 or 0.2 mM Cu\(^{2+}\) (with 2 as solubilize) or Dy\(^{3+}\) (with 1 as solubilize) for SDS and Zn(DS)\(_2\) solutions. \( ^c \) If was used in CTAB solutions, whereas Ig was used in SDS and Zn(DS)\(_2\) solutions.
Scheme 2

![Scheme 2](image)

Chemicals. C_{12}E_{5} (Nikko) and ethylenediaminetetraacetic acid tetrasodium salt trihydrate (EDTA, Aldrich) were of the highest purity available. Cu(DS)_{2} and Zn(DS)_{2} were prepared following literature procedures,\(^{26}\) and were crystallized from water. Compounds 1a-e were prepared by an aldol condensation of the corresponding substituted aldehyde with 2-acylpyridine as has been described previously.\(^{46}\) H NMR shift and relaxation time measurements were performed in D_{2}O (99.9\% D, Aldrich). Stock solutions of 1c and 4 used in the NMR experiments were prepared in methanol-d_{4} (99.8\% D, CIL).

If and Ig were prepared as outlined in Scheme 2. Yields were not optimized. p-(Bromomethyl)benzaldehyde was prepared by reaction of p-(bromomethyl)benzonitrile (Acros) with diisobutylaluminum hydride following a literature procedure.\(^{45}\)

**Sodium (p-Oxomethylphenyl)methyl Sulfonate.** A suspension of 3.90 g (19.6 mmol) of p-(bromomethyl)benzaldehyde and 4.00 g (31.7 mmol) of sodium sulfite in 40 mL of water was refluxed for 2 h, after which a clear solution was obtained. The reaction mixture was cooled in an ice bath, resulting in precipitation of some sodium sulfite. After filtration, the solvent was evaporated. Ethanol was added to the remaining solid, and the suspension was refluxed for 10 min. After filtering the hot solution, the filtrate was allowed to cool slowly to \(-18^\circ C\) whereupon sodium (p-oxomethylphenyl)methyl sulfonate separated as colorless crystals. The extraction procedure was repeated two more times, affording 2.29 g (10.3 mmol, 53\%) of the desired product: H NMR (200 MHz, D_{2}O) \(\delta (ppm) 4.10\ (s, 2H), 7.44\ (d, 2H), 7.76\ (d, 2H), 9.75\ (s, 1H).

**1f.** A solution of 75 mL of ethanol and 3.75 mL of a 10\% solution of sodium hydroxide in water was cooled to 0 \(^\circ C\), and 2.13 g (9.57 mmol) of sodium (p-oxomethylphenyl)methyl sulfonate and 1.28 g (10.6 mmol) of 2-acylpyridine were added. The solution was stirred for 16 h at 0 \(^\circ C\), and filtered affording 2.47 g (7.66 mmol, 89\%) of crude 1f. Crystallization from methanol yielded 1.08 g (35\%) of the desired product: mp 220 \(^\circ C\) (dec), H NMR (200 MHz, D_{2}O) \(\delta (ppm) 4.50\ (s, 2H), 7.42\ (d, 2H), 7.55\ (m, 1H), 7.58\ (d, 2H), 7.61\ (m, 2H), 7.81 (d, 1H). Anal. Calcd for C_{15}H_{12}NO_{4}SNa: C, 55.4; H, 3.74; N, 4.19; S, 9.41; Na, 6.97.

3-(p-(Bromomethyl)phenyl)-1-(2-pyridyl)-2-propen-1-one. A solution of 10 g of sodium hydroxide in 1000 mL of water was cooled to 0–5 \(^\circ C\). 2-Acetylpyridine (5.95 g, 49.2 mmol) and a solution of 7.25 g (36.4 mmol) of p-(bromomethyl)benzaldehyde dissolved in a minimal amount of ethanol were added. The resulting suspension was stirred for 48 h at 0–5 \(^\circ C\). The product was filtered and washed extensively with water until the smell of the 2-acylpyridine had disappeared. After drying at 50 \(^\circ C\) under vacuum, 10.5 g (34.8 mmol, 96\%) of 3-(p-(bromomethyl)phenyl)-1-(2-pyridyl)-2-propen-1-one was obtained: H NMR (200 MHz, CDCl_{3}) \(\delta (ppm) 4.50\ (s, 2H), 7.42\ (d, 2H), 7.44\ (m, 1H), 7.70\ (d, 2H), 7.85\ (m, 1H), 7.91\ (d, 1H), 8.20\ (d, 1H), 8.31\ (d, 1H), 8.75\ (d, 1H).

1g. 3-(p-(Bromomethyl)phenyl)-1-(2-pyridyl)-2-propen-1-one (5.00 g, (16.6 mmol) was suspended in 350 mL of anhydrous ether under a nitrogen atmosphere. A 20-mL aliquot of a 4.2 M solution of trimethylamine in ethanol (Fluka) was added. The reaction mixture was stirred for 24 h at room temperature under a nitrogen atmosphere. Evaporation of the solvents and excess of trimethylamine afforded crude 1g in quantitative yield. The very hygroscopic product was crystallized from dry 1-propanol. Removal of this solvent from the crystals is not possible by conventional methods. However, dissolving the product in water, filtration, and subsequent freeze-drying afforded 3.10 g (8.59 mmol, 52\%) of 1g: mp 212.5 \(^\circ C\) (dec); H NMR (200 MHz, CDCl_{3}) \(\delta (ppm) 3.44\ (s, 9H), 5.16\ (s, 2H), 7.50\ (m, 1H), 7.75\ (s, 4H), 7.84\ (d, 1H), 7.85\ (m, 1H), 8.01\ (d, 1H), 8.31\ (d, 1H), 8.72\ (d, 1H). Anal. Calcd for C_{15}H_{13}BrN_{2}O: C, 60.0; H, 5.88; Br, 21.92; N, 7.78. Found: C, 59.8; H, 5.97; Br, 21.77; N, 7.58.

**Endo/Exo Ratios.** Endo/exo ratios of the micelle-catalyzed reactions were determined by adding 0.25 mmol of 1c and 0.5 mmol of 2 to a solution of 5 mmol of surfactant and 0.005 mmol of EDTA in 50 mL of water in carefully sealed 50-mL flasks. The solutions were stirred for 7 days at 26 \(^\circ C\) and subsequently freeze-dried. The SDS- and CTAB-containing reaction mixtures were stirred with 100 mL of ether. After filtration and evaporation of the ether, crude 3c was obtained as an oil.\(^{47}\) The endo/exo ratios were determined using H NMR as described previously.\(^{46}\) Extraction of the Diels–Alder adducts from the freeze-dried reaction mixture containing C_{12}E_{5} was performed by stirring with 50 mL of pentane. Cooling the solution to \(-18^\circ C\) resulted in precipitation of the surfactant. Filtration and evaporation of the solvent afforded the adduct mixture.

**Kinetic Measurements.** All kinetic measurements were performed using UV–visible spectroscopy (Perkin-Elmer A2, A5, or J212 spectrophotometers) monitoring the decrease of the absorption of the dienophile at 25 ± 0.1 \(^\circ C\). Two methods were used to determine the reported second-order rate constants. The rate constants of the fast reactions (half-lives not more than a few hours) were determined by following the reaction for 4–5 half-lifetimes. The rate constants for the slower reactions and the reactions with cyclopentadiene in aqueous solutions with half-lifes of more than 15 min were determined using initial rate kinetics. Using the former method, the kinetic data were reproducible within 3\%, whereas the data obtained using the initial rate technique were reproducible within 5\%. Both methods have been described previously.\(^{46}\)

**NMR Measurements.** Routine spectra were taken on a Varian VXR 200- or 300-MHz spectrometer. The aromatic shift measurements and the paramagnetic relaxation measurements were performed on a Bruker AC 250-MHz spectrometer. Proton chemical shifts were determined relative to the signal of HOD (4.63 ppm). Paramagnetic relaxation times were determined using the inversion–recovery pulse sequence.\(^{42}\) The variable delay times between the 180\(^\circ\) and the 90\(^\circ\) pulse were chosen so that they cover the relaxation process during the time span of minimally 5 times \(\tau_{I}\). The 10–16 different delay times were in a random order to minimize systematic errors that might result from fluctuations of the strength of the magnetic field during the experiment. The delay time between subsequent pulse sequences was at least 5 times \(\tau_{I}\). The \(\tau_{I}\) values were calculated using a least-squares fitting procedure available on the Varian software.

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