Solvent Effects on a Diels−Alder Reaction Involving a Cationic Diene: Consequences of the Absence of Hydrogen-Bond Interactions for Accelerations in Aqueous Media

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In order to study the influence of hydrogen-bond interactions on the accelerations of Diels−Alder reactions in water and highly aqueous mixed solvent systems, second-order rate constants for the Diels−Alder reaction of acridizinium bromide (**1a**) with cyclopentadiene (CP) have been measured in aqueous media and organic solvents. Only modest rate accelerations were found in water-rich media. This is attributed to the absence of hydrogen-bonding groups in the reactants. Comparison with cycloadditions of CP with 9-carbomethoxyacridizinium bromide (**1b**), acrylonitrile (**3**), and methyl vinyl ketone (**4**), which do contain hydrogen-bond acceptors, reveals substantially larger aqueous accelerations. These results demonstrate that hydrogen bonding is a major factor in aqueous accelerations. Also rate constants for the cycloaddition of CP to **1a** in surfactant solutions were determined. Micellar catalysis is observed in SDS solutions, due to binding of both the diene and the dienophile to the anionic micellar surface.

Introduction

Diels−Alder (DA) reactions are concerted, nearly synchronous reactions, and long thought to entail only small solvent effects.[1] However, Rideout and Breslow[2] found that these reactions can be accelerated enormously in water. This interesting discovery set the stage for a large number of studies. At present, many DA reactions are known to be accelerated in highly aqueous media,[3,4] and accelerations up to 8000 have been reported on going from *n*-hexane to water.[4] Also the mechanistically related 1,3-dipolar cycloadditions[5] as well as Claisen rearrangements,[6] aldol condensations,[7] and benzoin condensations[8] benefit from water as the reaction medium.

Many explanations have been proposed to account for these observations, but extensive kinetic studies[4,9,10] indicate two factors to be predominantly responsible. First, "enforced hydrophobic interactions" stem from the usually low affinity of the reactants for water, compared to organic solvents. Since DA reactions are characterized by a negative volume of activation, the hydrophobic surface area of the reactants in water is reduced on going from the initial state to the transition state. Therefore, the Gibbs energy of activation is lowered, and the reaction is accelerated. Secondly, hydrogen bonding between water molecules and hydrogen-bond acceptor groups in the polarizable activated complex also lowers the Gibbs energy of activation. These proposals are strongly supported by computer simulations of Blake and Jorgensen,[11] which suggest that hydrophobic effects contribute a relatively constant factor of about 10 to the rates. The major part of the observed accelerations is therefore in many cases attributed to hydrogen bonding. An interesting DA reaction in this respect is the dimerization of cyclopentadiene, in which hydrogen bonding is excluded, so that the rate acceleration should be attributed to hydrophobic effects. The rate in water has been measured by Breslow *et al.*[12] and by Sangwan and Schneider,[13] but due to the high volatility of cyclopentadiene, measurements are complicated. Computer simulations by Jorgensen *et al.*[11c] reveal that in water the transition state is lowered by 7.6 kJ mol^{-1} (1.8 kcal mol^{-1}) relative to the initial state. However, the experimental problems associated with this reaction make it desirable to study another DA reaction in which hydrogen bonding is largely excluded.

For this purpose, the cationic polar cycloaddition of acridizinium bromide (**1a**) and cyclopentadiene (CP) has been studied (Scheme 1). This reaction was selected because hydrogen-bond donor and acceptor groups are very weak or absent in both the diene and the dienophile. Although the π-electron systems of both the aromatic cation and CP can act as hydrogen-bond acceptors,[14] these interactions are much weaker than conventional hydrogen bonds,[15] and the differences in hydrogen-bond interactions between the initial state and the transition

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Scheme 1

1a: R=H
1b: R=CO₂CH₃

2a: R=H
2b: R=CO₂CH₃
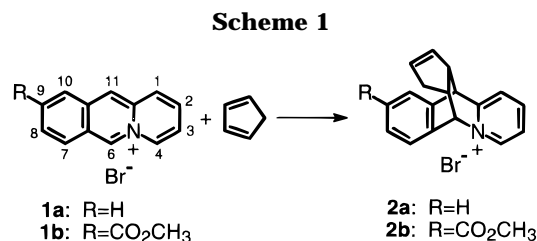
state will be negligible. Therefore, possible water-induced accelerations should be attributed to enforced hydrophobic interactions. Comparison with the reaction of diene **1b** may provide a more complete picture about the role of hydrogen bonding. Water can interact with the ester functionality, which is a hydrogen-bond acceptor group in conjugation with the reaction center and can therefore provide an additional stabilization of the transition state. It is known that for an aromatic system an additional carboxymethyl functionality does not bring about significant changes in hydrophobicity,[16] so hydrophobic effects will not significantly interfere in our comparison of **1a** and **1b**.

The polar cycloaddition of the acridizinium cation was the first cationic polar cycloaddition reported[17] (the classification of this type of reaction as "polar" cycloadditions was introduced to distinguish cycloadditions employing cationic or anionic components from those employing dipolar or uncharged components[18]). During the following decades, Bradsher and co-workers[19–22] made considerable efforts to clear up the mechanism of this type of reaction, which is normally both strongly regio- and stereoselective[19] (for the reaction of the acridizinium cation with CP, only one product is found, whereas four isomers would be possible[20]). First, they proposed a two-step mechanism,[21] mainly because the Hammett ρ-value estimated for 9-substituted acridizinium perchlorates in their reaction with styrene is higher than those expected for a concerted reaction.[21b] Later, this conclusion was withdrawn and formation of weak charge-transfer complexes was proposed under the conditions of their experiments.[22]

Most DA reactions that have been studied in aqueous media proceed with normal electron demand, i.e. the reaction is dominated by HOMO (diene)−LUMO (dienophile) interactions and consequently, electron-withdrawing groups in the dienophile accelerate the reaction. In contrast, the polar cycloaddition of CP to the acridizinium cation is an inverse electron demand DA reaction, i.e. the

Table 1. Second-Order Rate Constants and Gibbs Energies of Activation for the Diels−Alder Reaction of 1a with CP in Organic Solvents and Water (25 °C)

solvent	$10^3 \times k_2$ (dm³ mol⁻¹ s⁻¹)	$\Delta^\ddagger G^\vartheta$ (kJ mol⁻¹)
chloroform	6.63	85.5
dichloromethane	4.56	86.4
acetone	1.78	88.7
acetonitrile	2.39	88.0
methanol	4.11	86.6
ethanol	4.04	86.7
2,2,2-trifluoroethanol	8.84	84.7
water	21.4	82.6

reaction is dominated by HOMO (dienophile)−LUMO (diene) interactions, and electron-donating groups in the dienophile or electron-withdrawing groups in the diene facilitate the reaction. Recently, an inverse electron demand DA reaction has been reported to proceed also very efficiently in water.[23]

This paper presents kinetic data of the DA reaction of **1a** with CP in organic and aqueous solvents and in the presence of surfactant micelles. Not many DA reactions are known to be accelerated in micellar solutions. Recently, a Lewis-acid catalyzed DA reaction has been shown to benefit from micellar solutions as the reaction medium,[24] but in most cases, both for cationic and anionic surfactants, rate inhibition is observed.[25,26] For the acridizinium cation, it is interesting to study rates in aqueous surfactant solutions, because electrostatic interactions between charged surfactant aggregates and the cationic diene may have a crucial effect on the reaction rate.

Results and Discussion

Because formation of weak charge-transfer complexes was proposed in cationic polar cycloadditions,[22] it is important to verify whether this is also the case under the conditions of our experiments. Formation of these complexes may have consequences for the mechanism, but UV experiments (see Experimental Section) strongly suggest that in the range of concentrations used in our experiments, charge transfer complex formation between the acridizinium cation and CP does not occur. Therefore, though not synchronous, the mechanism of this reaction is not different from that of conventional DA reactions.

Table 1 shows second-order rate constants for the cycloaddition of CP to **1a** in organic solvents. Solvent effects are modest, as usual for concerted DA reactions. It has been observed that DA reactions may show an increase in rate of the reaction in trifluoroethanol,[9,10] which is a strong hydrogen-bond-donating solvent (comparable to water). However, due to the absence of hydrogen-bond acceptor groups, the rate in this solvent does not differ much from that in other organic solvents. In water, the reaction rate is increased (by a factor of 5 compared to ethanol), but this is only a modest effect, when compared to accelerations that have been found for DA reactions that do benefit from hydrogen bonding.[2−4,9,10,23] In water, the Gibbs energy of activation is lowered by 4.1 kJ mol⁻¹ compared to ethanol and by 6.1 kJ mol⁻¹ compared to acetone, the solvent in which the

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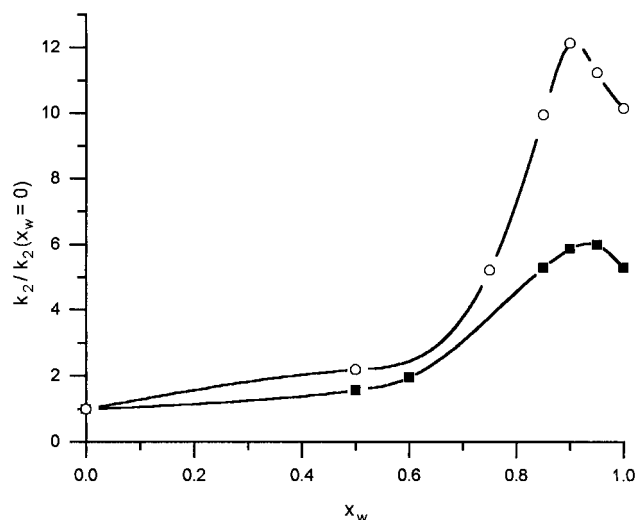(22) Bradsher, C. K.; Carlson, G. L. B.; Porter, N. A.; Westerman, I. J.; Wallis, T. G. *J. Org. Chem.* **1978**, *43*, 822.

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Figure 1. Aqueous accelerations for the cycloadditions of **1a** and **1b** with CP in water−ethanol mixtures as a function of the mole fraction of water (25 °C). The rate in ethanol is taken as reference. (■) **1a**; (○) **1b**.

Table 2. Second-Order Rate Constants for the Diels−Alder Reaction of 1a with CP in Water/Cosolvent Mixtures (25 °C)

cosolvent	mol %	$10^3 \times k_2$ (dm³ mol⁻¹ s⁻¹)
none		21.4
EtOH	5	24.2
t-BuOH	1	23.4
	2	25.0
	2.5	25.5
	3	23.3
N-CHP[a]	0.5	24.3
	1	23.4
	2	16.3

[a] N-CHP = 1-*N*-cyclohexyl-2-pyrrolidinone.

Scheme 2

reaction proceeds slowest. This is in good agreement with the stabilization of the transition state relative to the initial state by 7.6 kJ mol⁻¹, calculated by Jorgensen *et al.* for the dimerization of cyclopentadiene in water.[11c] This value may be considered as the difference in Gibbs energy of activation in water relative to the gas phase, in which the reaction is not influenced by any solvent at all. It is known that for this dimerization, the Gibbs energy of activation is not much lower in organic solvents than in the gas phase.[1c] Because of the absence of hydrogen-bond interactions, this reduction of the Gibbs energy in water is solely attributed to hydrophobic effects. Due to solubility problems, it was impossible to examine the DA reaction of **1a** in more apolar solvents like hexane, ether, or carbon tetrachloride.

Ion pairing effects may also have an influence on the reaction rate, since the bromide ion will be closer to the acridizinium cation in apolar organic solvents than in water. However, this probably results in a slight rate decrease in organic solvents, compared to water, because both sterically and electronically, the bromide anion will hinder the reaction more in organic solvents than in water. Therefore, these effects do not interfere with the purpose of our study.

Figure 1 shows rates of cycloaddition of CP to **1a** over the whole mole fraction range in ethanol−water mixtures. Introduction of a hydrogen-bond-accepting group leads to an enhanced aqueous acceleration, as the cycloaddition of CP to **1b** demonstrates. However, ester functionalities are relatively weak hydrogen-bond-acceptor groups, and the conjugated π-system of the acridizinium cation is large. Therefore, the effect of hydrogen bonding at the reaction center and, consequently, the additional stabilization of the transition state will be rather limited, but the difference in reactivity of **1a** and **1b** is consistent with the notion that hydrogen-bond interactions are important for aqueous accelerations.[9−11]
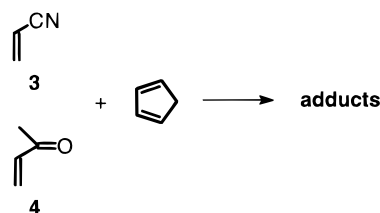
Figure 1 shows that the largest rate accelerations are obtained when a small amount of ethanol is added to the water. This rate effect is also observed upon addition of small amounts of *t*-BuOH or 1-*N*-cyclohexyl-2-pyrrolidinone (N-CHP), which are more hydrophobic cosolvents.[25,27] The rate constants for these mixtures are listed in Table 2.

This additional rate increase was also observed by Blokzijl *et al.*[10a] and is considered to be quite normal, although it does not emerge for every DA reaction. Blokzijl[25] attributes this acceleration to an increase of the hydrophobic effect. Due to hydration of the hydrophobic cosolvent by water, less water is available for the formation of a complete hydrophobic hydration sphere[4] of the reactants. Consequently, an additional driving force for reaction is created. Also the existence of microheterogeneities in the mixtures may offer an explanation, but it is difficult to distinguish between these effects. Although even observed for EtOH, which is, in fact, only weakly hydrophobic, the increase in rate should be more pronounced when the cosolvent is more hydrophobic, like *t*-BuOH and N-CHP. However, this is not observed. Both for *t*-BuOH and N-CHP, the additional increase is comparable to that of EtOH. This is particularly striking in the case of N-CHP, which is much more hydrophobic than EtOH. However, N-CHP shows characteristics of a nonionic surfactant, and its tendency to aggregate[27,28] in water may be responsible for this observation. On the other hand, although the rate itself does not clearly depend on cosolvent hydrophobicity in this case, the mole fraction of cosolvent for which the rate constant is largest does. As shown in Table 2, this mole fraction is lower for the more hydrophobic cosolvents. In view of these results, it seems somewhat curious that Breslow *et al.*[12] attribute every increase in rate for DA reactions in aqueous solvents to a decrease in solubility of the reactants. Obviously, this explanation does not account for an increase in rate on addition of small amounts of hydrophobic cosolvents, since the solubility of the relatively hydrophobic reactants will increase in these media, compared to pure water.

Another question to be addressed is the hydrophobicity of the acridizinium cation. Because hydrogen-bond interactions are absent in the cycloaddition of CP to **1a**, any observed rate enhancement in water is attributed to hydrophobic effects. However, the cationic substrate is probably rather weakly hydrophobic, and it is therefore

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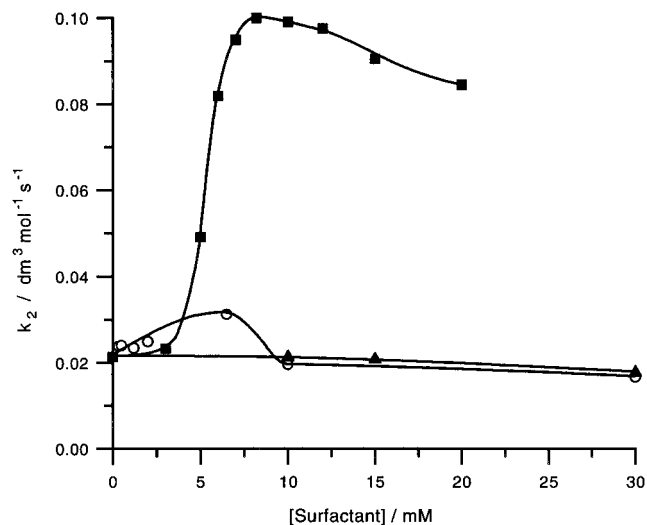(28) Apperloo, J. J.; Engberts, J. B. F. N. To be published.
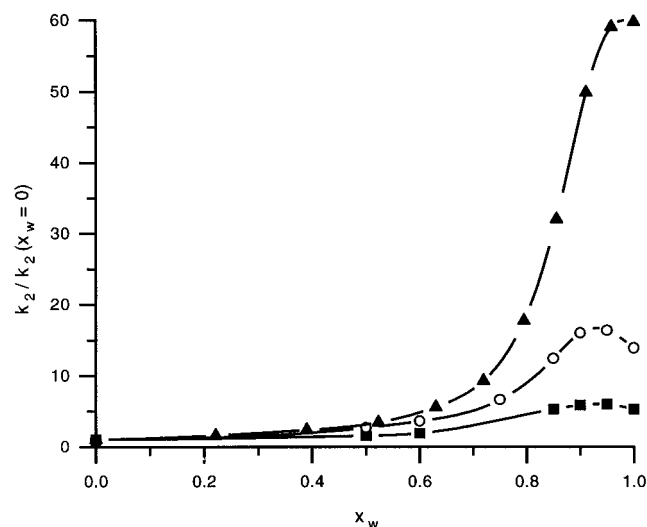
Figure 2. Aqueous accelerations for the cycloadditions of **1a**, **3**, and **4** (data from ref 10a, supplementary material) with CP in water−ethanol mixtures as a function of the mole fraction of water (25 °C). The rate in ethanol is taken as reference. (■) **1a**; (○) **3**; (▲) **4**.

Figure 3. Second-order rate constants for the reaction of **1a** with CP in aqueous surfactant solutions (25 °C). (■) SDS; (○) Triton X-100; (▲) 1-*N*-dodecyl-4-methylpyridinium bromide.

of interest to compare the observed rate enhancements with those of other substrates of limited hydrophobicity. Accordingly, the results for the DA reaction of CP with **1a** are compared with rates for cycloaddition of acrylonitrile (**3**) and methyl vinyl ketone[10a] (**4**) with CP (Scheme 2). Acrylonitrile is a hydrogen-bond acceptor and is even less hydrophobic than acridine hydrochloride, as indicated by the Hansch *P*-parameter.[29] The hydrophobicity of acridine hydrochloride is very similar to that of acridizinium bromide. Also the cycloaddition of methyl vinyl ketone has been examined, because the carbonyl group is a better hydrogen-bond acceptor than the cyano group,[30] and consequently larger accelerations are expected.

In Figure 2, relative accelerations for the DA reactions of **1a**, **3**, and **4**[10a] with CP in mixtures of ethanol and water are compared. Although CP serves as a dienophile in our present study and as diene in the other reactions, in all cases it acts as the electron-rich species. Hydrogen-bond interactions can only affect the reactivity of the electron-poor **1b**, **3**, and **4**; therefore, a comparison of these reactions will reveal the water-induced stabilization of the polarizable transition state.

Cycloaddition of **3** to CP is indeed accelerated more effectively than that of **1a**, showing that even cycloadditions of reactants which are only weakly hydrophobic can be accelerated considerably. However, cycloaddition of **4** to CP is accelerated much more, supporting the notion that there is a direct relationship between hydrogen-bonding capacity and the magnitude of the aqueous acceleration effect.

Finally, the effect of micelles on the cycloaddition of CP to **1a** has been studied. When anionic surfactants are used, electrostatic interactions between negatively charged surfactant aggregates and the cationic diene are likely to lead to micellar catalysis. For this purpose, the common anionic surfactant sodium dodecyl sulfate (SDS) has been used, which has a critical micelle concentration (CMC) of 8.2 mM in water. To provide a more complete picture, also solutions of the cationic surfactant 1-*N*-

dodecyl-4-methylpyridinium bromide (CMC 9.7 mM) and the nonionic surfactant Triton X-100 (CMC approximately 0.25 mM) have been examined.

In Figure 3, the second-order rate constants are plotted as a function of the surfactant concentration. As anticipated, the reaction is catalyzed by micelles of SDS, in agreement with the assumption that acridizinium cations are electrostatically bound to the micellar surface. CP will also bind to the micelle through hydrophobic interactions. The increased local concentration of the reactants in the Stern layer of the micelle therefore accelerates the cycloaddition. At higher SDS concentrations the rate constants drop again, because the reactants are "diluted" over an increased number of micelles. Evidence for this binding of the diene to the micellar surface is given by VIS-spectroscopy. In micellar SDS solutions, the visible spectrum of **1a** is slightly red shifted. This is not observed for the cationic or the nonionic surfactant. An increase in rate already occurs before the CMC of SDS in water is reached, suggesting that either the acridizinium cation or CP lowers the CMC. This has been tested by conductivity measurements, maintaining conditions comparable to those of the kinetic experiments. In the presence of **1a**, no effect on the CMC was observed, but the presence of CP lowered the CMC by approximately 0.6 mM.

Micelles of cationic surfactants have hardly any effect on the reaction rate. Obviously, the cationic diene does not bind to the positively charged micelles. In micellar solutions of the nonionic surfactant, initially a slight rate increase is observed, probably due to the same effects that play a role upon the addition of small quantities of hydrophobic cosolvents (see Table 2).

In conclusion, we have shown that a DA reaction in which hydrogen-bonding groups are absent in both reactants is not prone to large accelerations in highly aqueous media. When a hydrogen-bond acceptor is attached to the diene, the reaction is further accelerated, indicating that hydrogen bonding is an important factor in aqueous accelerations. DA reactions with a cationic reactant are catalyzed by micelles of the anionic surfactant SDS. This catalysis is caused by electrostatic interactions of the cationic reactant with the micellar surface and by hydrophobic effects.

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Experimental Section

Materials. Acridizinium (benzo[*b*]quinolinium) bromide was synthesized as the monohydrate according to a literature procedure.[31] 9-Carbomethoxyacridizinium bromide was synthesized from α-bromo-*p*-toluic acid according to the same procedure, with quaternization during two weeks and cyclization during 24 h. The obtained 9-carboxyacridizinium bromide was esterified according to a known procedure.[32] Acrylonitrile was purchased from Aldrich and distilled before use. Cyclopentadiene was prepared from its dimer immediately before use. All solvents used were of the highest purity available. Water was distilled twice in a quartz distillation unit. Sodium dodecyl sulfate and Triton X-100 were purchased from BDH Chemicals. 1-*N*-dodecyl-4-methylpyridinium bromide was synthesized according to a literature procedure.[33]

Kinetic Measurements. Second-order rate constants were determined by UV/vis spectroscopy (Perkin Elmer Lambda 2 or 5 spectrophotometer) in a thermostated quartz UV cell (1 cm) at 25.0 ± 0.1 °C. The cycloaddition of CP to **1a** and **1b** was followed by monitoring the disappearance of the absorption at the long wavelength maximum in the visible spectrum. The reported rate constants are the average of at least three kinetic runs. An excess of CP was used. In the case of **1a**, all rate constants in organic solvents and aqueous ethanol with mole fractions of water up to 0.60 were determined by normal pseudo-first-order kinetics and were reproducible to within 2%. Starting concentrations of CP were between 20 and 70 mM. All rate constants in aqueous solvents, except those mentioned above, were determined by initial rate kinetics as described by Scheiner *et al.*[34] and were reproducible to within 4%. For initial rate measurements, stock solutions of CP (20 μL in 3.5 mL solvent; starting concentration approximately 1.6 mM) were used, which were prepared by injecting 60 μL of CP in 2 g of 1-propanol. Fresh stock solutions were prepared before every measurement. Starting concentrations of **1a** were $2-3.10^{-5}$ M. In the case of **1b**, all rate constants were determined by normal pseudo-first-order kinetics and were reproducible to within 2%. Concentrations of CP were $3-6$ mM in water and 40 mM in organic solvents. For the cycloaddition of **3** to CP, the disappearance of the absorption of CP at 240 nm was monitored maintaining pseudo-first order conditions. Excess of **3** was used; concentrations were 1.6 M in EtOH and 0.4 M in water.

Charge-Transfer Complex Formation.[35] The possible formation of charge-transfer complexes (both for **1a** and **1b**) was studied by VIS-spectroscopy using two methods.[22] The first method involved observation of the spectrum between 350 and 500 nm. Changes upon addition of CP would be proof for the formation of these complexes, but no change was observed.

The second method involved comparison of the second-order rate constants for high concentrations of CP with those for low concentrations. If charge-transfer complexes are formed, the rate constants would be lower at higher concentrations. However, no differences in rate constants were observed. These findings are consistent with the conclusion that no charge-transfer complexes are formed.

Conductivity Measurements. Conductivity measurements were performed using a Wayne-Kerr Autobalance Universal Bridge B642 fitted with a Philips electrode PW 95121/01. The solution in the cell was thermostated at 25 °C and stirred magnetically. For the determination of the CMC of sodium dodecyl sulfate in the presence of acridizinium bromide or CP, the concentrations were approximately the same as those in the kinetic experiments. In the case of CP, the reported lowering of the CMC is the measured CMC of SDS in the presence of a CP/1-PrOH stock solution, subtracted by the measured CMC of SDS in the presence of 1-PrOH without CP.

Characterization of Adduct 2a. A 1 mmol amount of **1a** was dissolved in 40 mL of ethanol and in a mixture of 20 mL of ethanol and 20 mL of water (this corresponds to a mole fraction of water of 0.8). To these mixtures was added 1 g (15 mmol) of CP, and the solutions were stirred at room temperature until the yellow color disappeared. After removing the solvent and the excess of CP, the solid was dissolved in methanol and crystallized from ethyl acetate/ether to yield a cream-colored microcrystalline solid. Only one single product was found by NMR, as indicated in the literature.[20] ^{1}H-NMR (DMSO-d_6) δ 9.3 (d, 1H), 8.6 (t, 1H), 8.3 (d, 1H), 8.0 (t, 1H), 7.6 (d, 1H), 7.3 (m, 3H), 6.5 (m, 1H), 5.3 (m, 3H), 3.4 (m, 1H), 3.2 (m, 1H), 2.4 (m, 1H), 1.8 (d, 1H). ^{13}C-NMR (DMSO-d_6) δ 34.2 (CH$_2$), 39.8 (CH), 45.4 (CH), 49.9 (CH), 68.6 (CH), 124.9 (CH), 125.2 (CH), 125.9 (CH), 126.4 (CH), 126.9 (CH), 128.8 (CH), 129.8 (CH), 132.4 (C), 132.8 (CH), 136.6 (C), 142.7 (CH), 145.9 (CH), 155.6 (C).

Characterization of Adduct 2b. A 80 mg (0.25 mmol) amount of **1b** was dissolved in 20 mL of ethanol and in a mixture of 10 mL of methanol and 15 mL of water (this corresponds to a mole fraction of water of 0.8). To these mixtures was added 1 g (15 mmol) of CP, and the solutions were stirred at room temperature until the yellow color disappeared. The solvent and the excess of CP were removed, and the cream-colored solid was dried. Again, both mixtures yielded the same compound. ^{1}H-NMR (CD$_3$OD) δ 9.2 (d, 1H), 8.5 (t, 1H), 8.2 (d, 1H), 8.0 (m, 3H), 7.7 (d, 1H), 6.4 (d, 1H), 5.4 (m, 3H), 3.9 (s, 3H), 3.6 (m, 1H), 3.3 (m, 1H), 2.6 (m, 1H), 2.0 (d, 1H).

Note Added in Proof. The absence of ion-pairing effects has been confirmed experimentally by determing the second-order rate constants for the addition of CP to the nitrate salt of **1a**. The nitrate anion is known to coordinate less strongly to cations than the bromide anion, but in water, ethanol, chloroform, and acetonitrile the kinetic data are identical to those for **1a**.

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