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Substituent Effects on an Inverse Electron Demand Hetero Diels−Alder Reaction in Aqueous Solution and Organic Solvents: Cycloaddition of Substituted Styrenes to Di(2-pyridyl)-1,2,4,5-tetrazine

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The kinetics of the Diels−Alder reactions of di(2-pyridyl)-1,2,4,5-tetrazine (**1**) with substituted styrenes **2** was investigated in aqueous media and in organic solvents. The second-order rate constants of this reaction increase dramatically in water-rich media. A decrease in pH accelerates the aqueous Diels−Alder reaction even more. The Hammett ρ-values and also the electronic demand η-values of the reaction are solvent sensitive. In protic solvents the dipolar character of the activated complex is increased, but simultaneously hydrogen-bond interactions stabilize the activated complex. These effects are most pronounced in 2,2,2-trifluoroethanol, which shows that the aqueous accelerations cannot be solely attributed to solvent-induced changes of the reaction mechanism.

Introduction

Organic reactions in aqueous media continue to fascinate chemists. The Diels−Alder reaction is a surprising example of a common organic reaction that benefits from an aqueous reaction medium. Although some of the first Diels−Alder reactions were performed in aqueous solution[1] and the use of water as a solvent for an industrial Diels−Alder reaction was mentioned in a U.S. patent[2] over 50 years ago, the aqueous Diels−Alder reaction first started to attract attention after Rideout and Breslow had reported unusual accelerations of these cycloadditions in water.[3] Since then, many other Diels−Alder reactions have been performed in aqueous solutions.[4]

In nonaqueous media, solvent effects on Diels−Alder reactions are rather small. The polarity, the cohesive energy density, and especially the hydrogen-bond donating capacity of the solvent have all been invoked as relevant properties for explaining the kinetic medium effects.[5] However the rate constant of the cycloaddition increases dramatically in highly aqueous media, and these large accelerations cannot be completely accounted for by these solvent properties. Detailed kinetic studies[6,7] suggest that the accelerations in aqueous solution are due to two factors. First, hydrogen bonds provide a stabilizing interaction between water and the activated complex, thereby reducing the Gibbs energy of activation. This process resembles Lewis acid catalysis. Second, "enforced hydrophobic interactions" enhance the reaction rate. During the activation process the hydrophobic surface area of the reactants is reduced, which provides an additional driving force for the reaction. This also explains the observed high [endo]/[exo] ratio of products for aqueous cycloadditions in which cyclopentadiene acts as a diene. Computer simulations have confirmed that the accelerations of aqueous Diels−Alder reactions are due to these two factors.[8]

Current research activities in this field are focused on extending the application of aqueous media for cycloadditions. Hetero Diels−Alder reactions have been performed in aqueous solution,[4,9] and recently Lewis acid catalysis of Diels−Alder reactions in water has been reported.[10] Also, the mechanistically related 1,3-dipolar cycloadditions have been shown to proceed efficiently in aqueous solutions.[11]

In order to develop a more detailed understanding of the origins of the aqueous acceleration of Diels−Alder reactions and to explore the scope and limitations of water as a solvent for cycloadditions, the hetero Diels−Alder reaction of di(2-pyridyl)-1,2,4,5-tetrazine **1** with substituted styrenes **2** in aqueous media has been investigated (Scheme 1). This reaction was selected for study because it enabled (i) a comparison of the kinetics of an inverse electron-demand hetero Diels−Alder reac-

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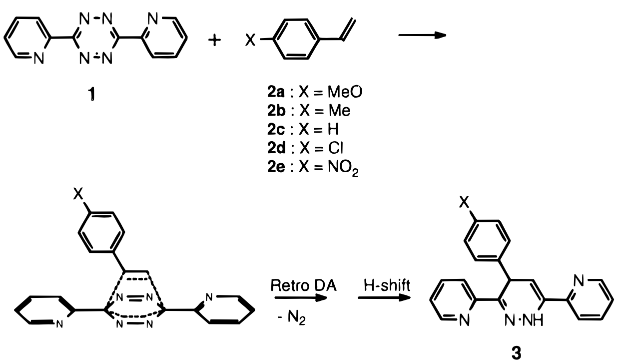
Scheme 1



tion in aqueous solutions with previously studied homo Diels−Alder reactions and (ii) a facile determination of solvent effects on the Hammett ρ-parameters of a Diels−Alder reaction, in order to signal possible changes in the polarity of the activated complex.

In 1959 it was shown that a substituted tetrazine can participate as a diene in a [4 + 2] cycloaddition,[12] and at present a large number of these cycloadditions are known.[13] The rate-determining addition of the dienophile is followed by a rapid retro Diels−Alder reaction, which leads to the final product, a dihydropyridazine **3**.[14] According to frontier molecular orbital theory these reactions are characterized by a dominating HOMO-(dienophile)−LUMO(diene) interaction, and consequently electron-donating substituents in the dienophile accelerate the reaction. Several studies have demonstrated that this is also the case for Diels−Alder reactions in which a tetrazine acts as a diene.[12−14] The reaction between styrene and 3,6-diphenyl-1,2,4,5-tetrazine has been studied in a limited number of organic solvents,[15] and the reaction showed a typical Diels−Alder solvent effect, *i.e.*, k_2(formamide)/k_2(toluene) = 2.4.

This particular reaction offers possibilities for a detailed study of the substituent effect of this Diels−Alder reaction in various solvents. Traditionally, both solvent and substituent effects are important tools to distinguish between the different possible activated complexes in cycloadditions. Thus, [2 + 2]-cycloadditions, which proceed via zwitterionic intermediates, have large Hammett ρ-values and are very solvent-sensitive, whereas both homo and hetero Diels−Alder reactions exhibit small ρ-values and are modestly affected by a change of solvent.[15] This is generally considered to be strong evidence for a concerted mechanism without a significant charge buildup. However, a water-induced charge buildup during the activation process could provide a logical explanation for the unusual accelerations in these media, since polar solvents (like water) are expected to stabilize such an activated complex. In this study the nature of the activated complex is probed by analyzing substituent effects, *i.e.*, by determining Hammett ρ-values in a series of organic and aqueous solvents.

Results and Discussion

Figure 1 shows second-order rate constants for the cycloaddition of styrene to di(2-pyridyl)-1,2,4,5-tetrazine in water−alcohol mixtures. The kinetics of this reaction in these solutions agree nicely with previous kinetic data for the Diels−Alder reaction between cyclopentadiene and alkyl vinyl ketones or substituted naphthoquinones.[7a] Initially, the rate constants increase gradually with increasing mole fraction of water. However, the cycloaddition is dramatically accelerated in water-rich media. For the different alcoholic cosolvents this sudden acceleration is observed at different mole fractions of alcohol in the order MeOH > EtOH > 1-PrOH reflecting the different hydrophobicities of the alcohols. On a synthetic scale, the use of highly aqueous media facilitates workup procedures since the product of the cycloaddition precipitates immediately. Unfortunately, this prevents kinetic measurements in highly aqueous solutions. However, preliminary results of kinetic studies using cyclopentadiene and 2,3-dihydrofuran as dienophile (instead of styrene) have shown that the rate constant of these Diels−Alder reactions in water containing 5 mol % ethanol or 1-propanol is similar to the rate constant in pure water.[16]

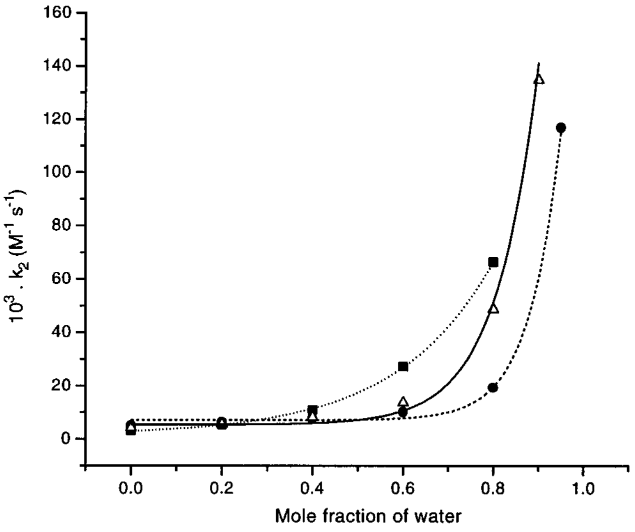


Figure 1. Second-order rate constants for the reaction of **1** with **2c** in water/alcohol mixtures: (■) MeOH, (△) EtOH, (●) 1-PrOH.

The extent of the hydrophobic acceleration becomes apparent when the rate constants for the reaction in a wide range of solvents are examined (Table 1). Compared to 1,4-dioxane, the reaction turns out to be 13 times faster in ethylene glycol, but in water/*t*-BuOH (mole fraction of water, $X_\mathrm{w} = 0.95$) it is nearly 130 times faster. Also, this Diels−Alder reaction is promoted by protic solvents, indicating that hydrogen bonding is an important factor. But the large difference in the rate constant between water/*t*-BuOH and 2,2,2-trifluoroethanol is quite remarkable as fluorinated alcohols can induce accelerations comparable to those observed in water.[6] As mentioned previously, the rate constants for Diels−Alder reactions roughly correlate with the solvent polarity or the acceptor number (AN) of the solvent. In Figures 2 and 3 the Gibbs energies of activation of the reaction are plotted against the $E_\mathrm{T}(30)$ values and the AN parameters of the solvent, respectively. The scatter observed in these plots indicates that the kinetic solvent effect is not dominated by one of these parameters. This is also apparent when the kinetic data are analyzed using the KOMPH2 equation of Gajewski.[5c]

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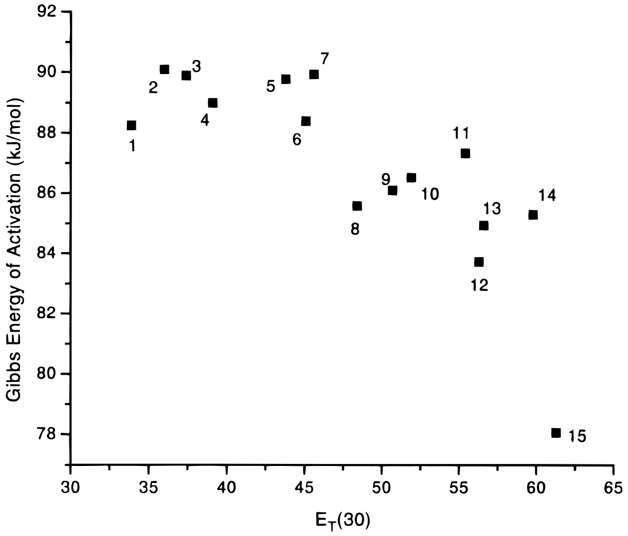

Figure 2. Gibbs energy of activation for the reaction of **1** with **2c** in (1) toluene, (2) dioxane, (3) THF, (4) $CHCl_3$, (5) DMF, (6) DMSO, (7) CH_3CN, (8) 2-PrOH, (9) 1-PrOH, (10) EtOH, (11) MeOH, (12) glycol, (13) formamide, (14) TFE, and (15) H_2O/*t*-BuOH (X_w = 0.95) vs. the $E_T(30)$-value of the solvent.

Table 1. Solvent Parameters and Second-Order Rate Constants for the Diels–Alder Reaction of 1 with 2c in Different Solvents at 25 °C

solvent	10^3k_2 (M^{-1} s^{-1})	$E_T(30)^a$	AN^a
toluene	2.15	33.9	
dioxane	1.02	36.0	10.8
THF	1.11	37.4	8.0
$CHCl_3$	1.60	39.1	23.1
DMF	1.16	43.8	16.0
DMSO	2.03	45.1	19.3
CH_3CN	1.09	45.6	18.9
2-PrOH	6.29	48.4	33.6
1-PrOH	5.10	50.7	37.3
EtOH	4.31	51.9	37.9
MeOH	3.10	55.4	41.5
ethylene glycol	13.3	56.3	
formamide	8.18	56.6	39.8
TFE	7.08	59.8	53.3
H_2O/*t*-BuOH (X_w = 0.95)	131	61.3	54.8^b

[a] See ref 5b. [b] AN of pure water.

Table 2 summarizes the rate constants and the Hammett ρ-values of the Diels–Alder reactions of the substituted styrenes with the tetrazine in toluene, tetrahydrofuran (THF), acetonitrile, 1-PrOH, 2,2,2-trifluoroethanol (TFE), and water/*t*-BuOH (X_w = 0.95). Interestingly, in the various solvents different σ-parameters are required in order to obtain linear Hammett-type correlations. For the aprotic solvents the use of σ^+-values gives satisfactory results, whereas σ-values provide a good fit for TFE and the aqueous solution (examples are given in Figures 4 and 5). For 1-PrOH neither σ nor σ^+ give acceptable correlations. However, using a Yukawa–Tsuno *r*-parameter of 0.45, a ρ-value of −0.99 is obtained.

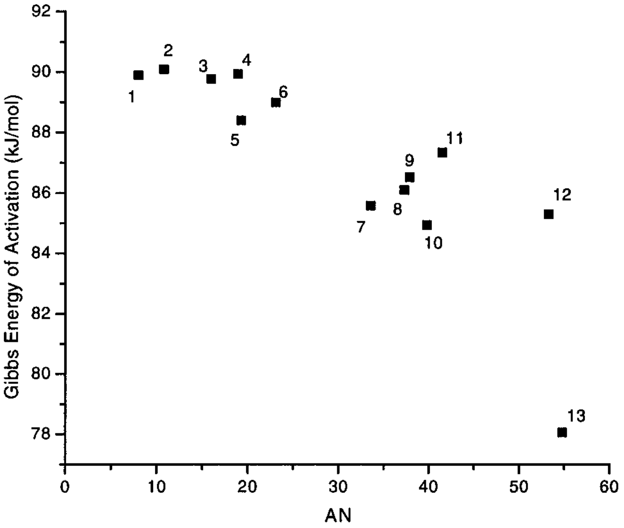

Figure 3. Gibbs energy of activation for the reaction of **1** with **2c** in (1) THF, (2) dioxane, (3) DMF, (4) CH_3CN, (5) DMSO, (6) $CHCl_3$, (7) 2-PrOH, (8) 1-PrOH, (9) EtOH, (10) formamide, (11) MeOH, (12) TFE, and (13) H_2O/*t*-BuOH (X_w = 0.95) vs. the AN of the solvent.

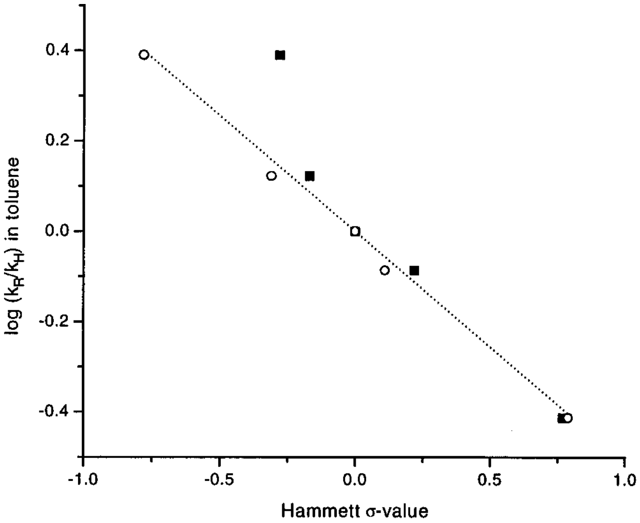

Figure 4. Hammett plot for the reaction of **1** with **2a–e** in toluene: (○) σ^+-values, (■) σ-values.

Contrary to the results of Otto *et al.*,[6] Hammett ρ-values increase with increasing reaction rates. The ρ-values of this reaction in aprotic solvents are comparable to those previously reported for Diels–Alder reactions with substituted tetrazines in different solvents and at different temperatures.[15] Of course, a comparison and interpretation of ρ-values that have been calculated using different types of substituent constants requires caution, but the data still justify the conclusion that the charge buildup during the activation process is modest. But clearly the solvents have a distinct effect on the activated

Table 2. Second-Order Rate Constants (×10^3) for the Diels–Alder Reaction of 1 and 2a–e in Different Solvents at 25 °C

	dienophile						
solvent	**2a**	**2b**	**2c**	**2d**	**2e**	ρ-value	subst constant
toluene	5.26	2.85	2.15	1.76	0.83	−0.51 (0.02)	σ_p^+
THF	2.83	1.60	1.11	0.91	0.53	−0.56 (0.02)	σ_p^+
CH_3CN	3.20	1.67	1.09	0.79	0.41	−0.58 (0.04)	σ_p^+
1-PrOH	17.2	8.33	5.10	3.01	0.86	−0.99^a	*a*
TFE	24.5	14.6	7.08	3.40	0.41	−1.64 (0.06)	σ_p
H_2O/*t*-BuOH (X_w = 0.95)	406	218	131	69.1	13.7	−1.32 (0.07)	σ_p

[a] A Yukawa–Tsuno *r*-parameter of 0.45 gives the best results.

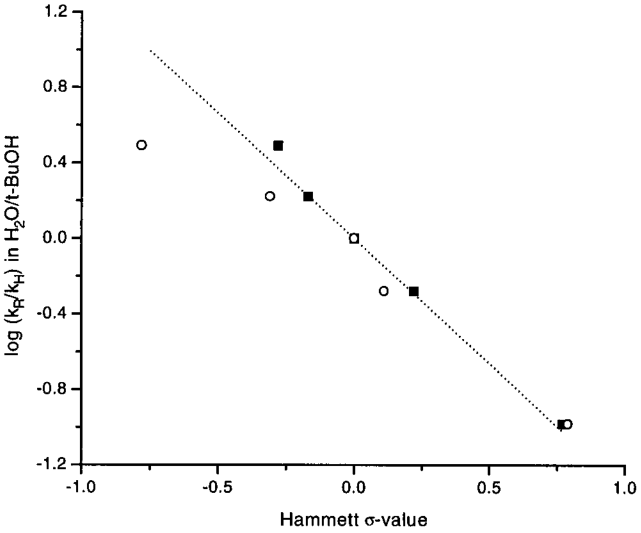

Figure 5. Hammett plot for the reaction of **1** with **2a**−**e** in H_2O/*t*-BuOH ($X_w = 0.95$); (○) σ^+-values, (■) σ-values.

Table 3. Values of σ_l, σ_d, σ_e, and σ_{50}[a]

substituent	σ_l	σ_d	σ_e	σ_{50}
MeO	0.30	−0.55	−0.064	−0.25
Me	−0.01	−0.14	−0.030	−0.15
H	0	0	0	0
Cl	0.47	−0.28	−0.011	0.19
NO_2	0.67	0.18	−0.077	0.85

[a] See text.

complex, since it obviously becomes more dipolar in the protic solvents, the effect of TFE being the most pronounced.

The observation that in aprotic and protic solvents different σ-parameters are required for a linear Hammett-type correlation is puzzling. In the literature many ρ-values for Diels−Alder reactions have been reported, and usually either σ^+-[17] or σ^--values[18] are used, although sometimes σ-values are satisfactory. The correlation with σ^+- or σ^--values indicates a direct resonance interaction between the substituent and the small partial charge in the activated complex. Apparently, such an interaction is primarily manifested in the aprotic solvents. In TFE and water/*t*-BuOH, σ-values are sufficient for linear correlations, possibly because the solvent-activated complex interaction has become dominant, thereby reducing the direct resonance interaction with the styrene substituents. This agrees nicely with previous kinetic results and vapor pressure measurements,[6] which indicate a strong stabilization of the activated complex in these media.

The hypothesis that protic solvents considerably stabilize the activated complex is supported by a more sophisticated approach[19,20] that enables determination of the electronic demand parameter (η) of this reaction in all the solvents investigated. Simultaneously, this method circumvents the problem of the different types of substituent constants.

The electrical effects in the substituted styrene can be represented by the LDR equation

$$Q_X = L\sigma_{lX} + D\sigma_{dX} + R\sigma_{eX} + h \tag{1}$$

where σ_l is the localized (field) electrical effect parameter, σ_d is the intrinsic delocalized (resonance) electrical effect parameter, and σ_e is the electronic demand sensitivity parameter. *L*, *D*, *R*, and *h* are coefficients determined statistically. The observed electrical effect is then characterized by three quantities: (i) its magnitude, represented by *L*, the coefficient of the localized electrical effect; (ii) its composition, given by quantity P_D, where *D* is the coefficient of the delocalized electrical effect,

$$P_D = \frac{100D}{L + D} \tag{2}$$

and (iii) its sensitivity to electronic demand, given by the quantity η:

$$\eta = \frac{R}{D} \tag{3}$$

The LDR equation cannot be successfully applied to a data set with less than seven members. It is possible, however, to study data sets with only five members by making use of the CR equation

$$Q_X = C\sigma_{ldX} + R\sigma_{eX} + h \tag{4}$$

where σ_{ld} represents a mixture of the two parameters σ_l and σ_d:

$$\sigma_{ldX} = l\sigma_{lX} + d\sigma_{dX} \tag{5}$$

The ratio of these two parameters is given by:

$$P_D = \frac{100d}{l + d} \tag{6}$$

Thus, by holding P_D constant, the CR equation is obtained from the LDR equation. In the case of the 4-substituted styrenes it is reasonable to assume that P_D is 50, as is the case for most 4-substituted benzene systems.[19] The composite substituent constants required in this case are simply the sum of the σ_l- and σ_d-values; they are designated σ_{50} constants. The advantage in the use of the CR equation is that there is no *a priori* choice of substituent constant required, the same substituents being used for all data sets. In the CR-equation the parameter η, which describes the electronic demand of the reaction, is defined as

$$\eta = \frac{R}{C} \tag{7}$$

The substituent parameters are presented in Table 3, and the results of the correlations with the CR equation are given in Table 4. The results are highly significant for all but the toluene data set, for which they are significant.

The electronic demand, η, is very useful in mechanistic studies. In the case of the Hammett equation ρ reflects the sensitivity of the reaction to electrical effects, and the major effect on ρ is the change of charge on the

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Table 4. Correlation of the Kinetic Data with the CR Equation and Electronic Demand Parameter (η) for the Different Solvents[a]

solvent	C	R	h	$100R^2$	η
toluene	−0.725 (0.069)	−2.85 (0.906)	0.324 (0.0391)	98.24	3.93 (1.19)
THF	−0.680 (0.0423)	−3.51 (0.555)	0.0363 (0.0240)	99.23	5.16 (0.751)
CH_3CN	−0.840 (0.0446)	−4.07 (0.586)	0.0146 (0.0253)	99.44	4.84 (0.648)
1-PrOH	−1.21 (0.0544)	−3.68 (0.714)	0.676 (0.0309)	99.61	3.05 (0.576)
TFE	−1.65 (0.0223)	−2.25 (0.292)	0.839 (0.0126)	99.97	1.36 (0.176)
H_2O/*t*-BuOH ($X_w = 0.95$)	−1.35 (0.0558)	−2.62 (0.732)	2.081 (0.0316)	99.69	1.94 (0.536)

[a] Standard errors in brackets.

Table 5. Second-Order Rate Constants for the Diels−Alder Reaction of 1 with 2a in Water/*t*-BuOH ($X_w = 0.95$) at 25 °C

pH	k_2 ($M^{-1}\ s^{-1}$)
7	0.13
3	0.17
2	0.23
1	0.40
0.1 M LiCl	0.13

reacting atom(s) during the activation process. The electronic demand, η, reflects the need for stabilization of the transition state by the resonance effect of the substituent. It responds to any electronic deficiency or excess whether or not it is a result of a charge. The positive sign shows that the rate is accelerated by delocalized (resonance) effect donors. The values of η in toluene and the dipolar aprotic solvents THF and acetonitrile are very large. They show a transition state in which the substituent is strongly electron donating. The protic solvents have smaller values of η. Hydrogen bonding of protic solvent molecules to the lone pairs of the tetrazine should decrease the electron density and therefore accelerate the reaction. If this results in a transition state further along the reaction coordinate with more bonding between the reactants, then the electron demand should be lowered as there is less need to stabilize the transition state. Both the C- and the η-values for the hydrogen bonding solvents follow the order expected for the acidity of the hydroxy compound, 1-PrOH < water/*t*-BuOH < TFE.

The Hammett ρ-values demonstrate that the solvents affect the dipolar character of the activated complex. Solvents also influence the electronic demand of this reaction, as indicated by the η-parameter. Both parameters explain the observed acceleration of the reaction by protic solvents: these solvents both induce an increased charge separation in the activated complex and stabilize it through hydrogen-bond interactions. Accordingly, one would expect TFE to accelerate the reaction most, yet the kinetic data show that the reaction is by far the fastest in the highly aqueous medium. This observation can be reconciled with the operation of enforced hydrophobic interactions.[6,7] Another interesting aspect worth mentioning is the fact that protic solvents do not always accelerate this reaction. For example, the cycloaddition of **2e** to **1** is the slowest in TFE. However, the highly aqueous medium always has a favorable effect on the cycloaddition; the enforced hydrophobic interactions seem rather insensitive to the nature of the substituents.

The data in Table 5 show that the second-order rate constants for the cycloaddition in water/*t*-BuOH are increased in acidic solutions. At pH = 1 and 2 some hydrolysis of the tetrazine is observed as well, but the cycloaddition is much faster. The rate constant is not affected by addition of LiCl; therefore, the increased ionic strength cannot account for the acceleration in acidic media. Since the tetrazine ring itself is not basic,[21] the acid-induced acceleration is most likely due to protonation of the pyridine nitrogen atoms. This acceleration can be viewed as a simple kind of Lewis acid catalysis.

In conclusion, we have shown that solvent effects on the kinetics of hetero Diels−Alder reactions in highly aqueous solutions are very similar to those for homo Diels−Alder reactions. Change of solvent affects the charge separation in the activated complex, but this is not the dominant cause for the large "aqueous acceleration" of the cycloaddition. In aprotic solvents, the activated complex is mainly stabilized by the substituents in the aromatic ring of the styrene, whereas interactions of the activated complex with the solvent become more important in protic solvents.

Experimental Section

Materials. Di(2-pyridyl)-1,2,4,5-tetrazine[22] and *p*-nitrostyrene[23] were synthesized according to literature procedures. The other styrenes were purchased from Aldrich and distilled before use. All solvents used were of the highest purity available. Water was distilled twice in a quartz distillation unit.

Kinetic Measurements. Second-order rate constants were determined by vis spectroscopy (Perkin-Elmer Lambda 2 or 5 spectrophotometer) in a thermostated quartz UV cell (1 cm) at 530 nm and 25 °C (±0.1 °C). The reported rate constants are the average of at least three kinetic runs and were reproducable to within 2%. In all cases an excess of the (substituted) styrene was used. Starting concentrations of the (substituted) styrenes were 2×10^{-3}−5×10^{-2} mol L^{-1} and for the tetrazine about 1×10^{-4} mol L^{-1}. Visual inspection of the solutions in the cuvettes indicated that all the reaction media were homogeneous.

Product Analysis. The cycloaddition was also performed on a preparative scale in aqueous solutions. In a mixture of 36 mL of water and 29 mL of ethanol (this corresponds to a mole fraction of water of 0.8) 0.05 mol of the styrene and 50 mg (0.21 mmol) di(2-pyridyl)-1,2,4,5-tetrazine were dissolved and the solution was left at room temperature. After 6 h the purple color of the tetrazine had turned to pale yellow and a cream-colored solid precipitated. The solid was filtered, washed with cold water, and dried: mp 196 °C; ^1H NMR ($CDCl_3$) δ 5.56 (d, 1H), 5.82 (dd, 1H), 7.15−7.29 (m, 5H), 7.42 (m, 2H), 7.64−7.70 (m, 3H), 8.11 (d, 1H), 8.56 (t, 2H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 36.7, 98.9, 118.8, 120.9, 122.4, 122.8, 126.4, 127.9, 128.4, 128.5, 135.7, 136.0, 136.3, 141.9, 143.9, 148.2, 150.3, 155.0. Anal. Calcd for $C_{20}H_{16}N_2$: C, 76.9; H, 5.16; N, 17.94. Found: C, 76.75; H, 5.22; N, 18.03.

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