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*Published in:*  
Journal of the American Chemical Society

*DOI:*  
[10.1021/ja960318k](https://doi.org/10.1021/ja960318k)

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
1996

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*Citation for published version (APA):*

Otto, S., Bertoncin, F., & Engberts, JBFN. (1996). Lewis acid catalysis of a Diels-Alder reaction in water. *Journal of the American Chemical Society*, 118(33), 7702-7707. <https://doi.org/10.1021/ja960318k>

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## Lewis Acid Catalysis of a Diels–Alder Reaction in Water

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**Abstract:** Here we report the first detailed study of a Diels–Alder (DA) reaction that is catalyzed by Lewis acids in water. The effect of  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$  ions as Lewis acid catalysts on the rate and endo–exo selectivity of the DA reaction between the bidentate dienophiles 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (**1a–e**) and cyclopentadiene (**2**) in water has been studied. Relative to the uncatalyzed reaction in acetonitrile, catalysis by 0.010 M  $\text{Cu}(\text{NO}_3)_2$  in water accelerates the reaction by a factor of 79 300. The kinetics of the catalyzed reaction were analyzed in terms of equilibrium constants for complexation of the Lewis acid with **1a–e** and rate constants for the reaction of the resulting complexes with **2**. The rate enhancement imposed upon the uncatalyzed DA reaction of substrates **1** with **2** by water is much more pronounced than that for the catalyzed reaction. The increase of the endo–exo selectivity induced by water in the uncatalyzed process is completely absent for the Lewis acid catalyzed reaction. The modest solvent and substituent effects observed for the catalyzed reaction indicate that the change in charge separation during the activation process is not larger than the corresponding change for the uncatalyzed reaction.

## Introduction

The Diels–Alder (DA) reaction is of great synthetic value and is often an important step in the (stereoselective) synthesis of six-membered rings. The factors governing the reactivity and selectivity of this cycloaddition reaction have been studied in detail.<sup>1</sup> Generally, the process of bond breaking and bond formation in the DA reaction is considered to be concerted<sup>2</sup> but not necessarily synchronous.<sup>3</sup> In extreme cases the DA reaction can even become a two-step process with a zwitterionic<sup>4</sup> or biradical<sup>5</sup> intermediate.

The concertedness implies that there is only a small change in charge separation on going from the initial state to the activated complex. As a result the rates of many DA reactions remain almost unaffected by the solvent.<sup>1,6</sup> The rate of some DA reactions, however, can be strongly influenced by the medium.<sup>7</sup> This is especially true for aqueous media, where accelerations up to 13 000 times (when compared to organic solvents) can be achieved.<sup>8</sup> This special effect of water has

attained much attention ever since its discovery in 1980.<sup>9</sup> An extensive discussion of the origin of the remarkable acceleration induced by water has already been given in previous papers.<sup>8</sup> Evidence has been presented<sup>8</sup> that there are two effects causing this aqueous rate enhancement: enforced hydrophobic interactions and hydrogen bonding to the activating group of the dienophile. The way one can envisage these two effects to operate will be briefly summarized.

The reaction partners in a typical DA reaction are usually poorly soluble in water. As a result the water molecules surrounding these reagents arrange themselves in hydrophobic hydration shells. The DA reaction *forces* the reaction partners into close contact in the activated complex, leading to a reduction of the molecular surface area exposed to water. This causes the transition state to be less destabilized than the initial state, resulting in a faster reaction in water as compared to nonaqueous solvents.

The second effect involves hydrogen bonding of the water molecules to the activating group in the dienophile (for normal electron-demand DA reactions). The role of this activating group is to withdraw electron density from the double bond, thereby lowering the LUMO energy of the dienophile and facilitating the interaction with the diene HOMO. When a hydrogen bond is formed to such an activating group, its electron withdrawing capacity is enhanced, which results in a further lowering of the LUMO energy, a smaller HOMO–LUMO gap, and thus a faster reaction. The importance of hydrogen bonding is also apparent from ab-initio studies by Jorgensen et al.<sup>10</sup>

Water also influences the selectivity of the DA reaction. Studies of the effects of solvents on the regio-<sup>11</sup> and diastereo-facial<sup>12</sup> selectivity of DA reactions have provided evidence that these parameters are mainly influenced by the hydrogen-bond

<sup>®</sup> Abstract published in *Advance ACS Abstracts*, August 1, 1996.

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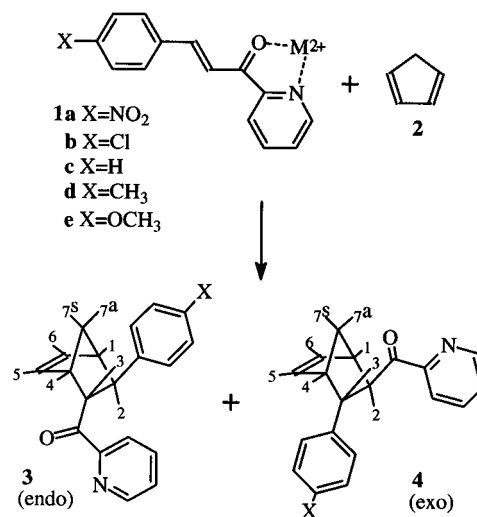
donating ability of the solvent which affects the orbital coefficients of the dienophile. Computer simulations suggest that hydrogen bonds affect the diastereofacial selectivity by influencing the *s*-cis/*s*-trans conformational equilibrium.<sup>13</sup> It has also been suggested that hydrogen bonding, by increasing the orbital coefficients, leads to a tighter transition state in which the asymmetric center already present has more interaction with the stereocenter that is being formed.<sup>14</sup> With regard to the regio- and diastereofacial selectivity, water behaves as anticipated on the basis of its hydrogen-bond donating capability.

With respect to the endo–exo selectivity, water is an outstanding solvent for the DA reaction since endo–exo ratios are almost invariably higher in water than in organic solvents.<sup>15</sup>

The general preference for endo product is often rationalized in terms of secondary orbital interactions.<sup>16,17</sup> For explaining the special effect of water on the endo–exo selectivity three factors appear to be important. First of all water is a polar solvent and polar solvents are known to favor the more polar endo activated complex.<sup>18</sup> Furthermore, the charge transfer resulting from secondary orbital overlap in the endo activated complex is more favored in polar media.<sup>15b</sup> Secondly, the endo activated complex is usually the most compact with the smallest surface area in contact with water and is thus favored over the exo activated complex. This is underlined by the correlation of endo–exo ratios with the *S*<sub>p</sub> parameter.<sup>15c,19</sup> Finally, hydrogen bonding to the activating group is of importance as is shown by linear free energy relationships in which the hydrogen-bond donating capacity of the solvent (quantified by the  $\alpha$ -parameter) contributes to a significant extent.<sup>11,20</sup> Since a good hydrogen-bond donating solvent is often also a structured solvent, we note that an intrinsic correlation between the *S*<sub>p</sub> and  $\alpha$ -parameter can exist.<sup>12d</sup>

Rates and selectivities of DA reactions can also benefit markedly from the use of Lewis acids as catalysts in *organic* solvents.<sup>21</sup> The mechanism by which Lewis acids affect the DA reaction is analogous to the effects of hydrogen bonding as delineated above.<sup>14,17a</sup> In the present study we address the question whether the beneficial effects of water and Lewis acids on the rate and endo–exo selectivity of the DA reaction can be combined. Two important questions arise immediately. Is the Lewis acid catalyzed reaction still accelerated by water? Secondly, what is the effect of water on the selectivity of the catalyzed reaction? In order to provide answers to these questions, the first step was to design a diene/dienophile pair which is subject to Lewis acid catalysis *in water*. This was by

## Scheme 1



no means trivial, since most Lewis acids used for the catalysis of DA reactions in organic solvents are decomposed in water. Although some examples of water–tolerant Lewis acids that retain their activity when a small amount of water is present in the solution have been reported,<sup>22</sup> Lewis acid catalysis of DA reactions in pure water was (to our knowledge) unprecedented at the time we started our study. There are examples in the literature of other organic reactions that are catalyzed by Lewis acids in water. As early as 1951 it was shown that simple transition metal ions catalyze the decarboxylation of dimethyl-oxaloacetic acid.<sup>23</sup> There are also many studies on the metal-ion catalyzed hydrolysis of esters, amides, and phosphates.<sup>24</sup> However, it should be noted that in these hydrolysis reactions the metal ion does not only act as a Lewis acid, but also coordinates the hydroxide nucleophile. In all cases the substrates contain two sites for interaction with the metal ion. Coordination of a monodentate substrate to a Lewis acid in water is apparently not feasible. Displacement of a water molecule from the coordination sphere of the Lewis acid by the substrate is not likely to lead to a significant gain in Gibbs energy since water is an appreciable Lewis base and present in a large excess. We therefore restricted our search for a Lewis acid catalyzed DA reaction in water to potentially bidentate dienophiles. 3-Phenyl-1-(2-pyridyl)-2-propen-1-one, **1** (Scheme 1), which offers apart from a carbonyl oxygen also a pyridyl nitrogen atom to the Lewis acid, turned out to be very successful.<sup>25</sup> Herein we present the first detailed study of Lewis acid catalysis of a DA reaction in water.

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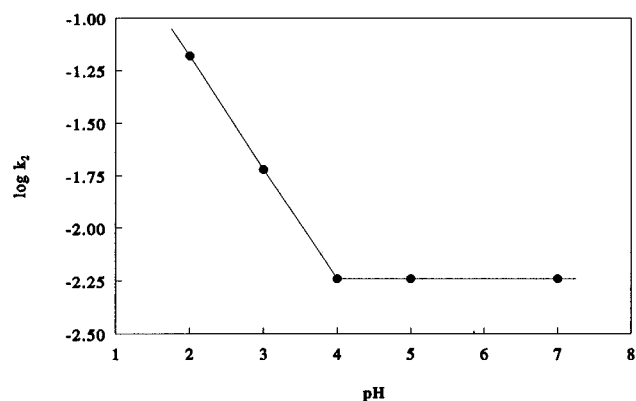
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**Table 1.** Second-Order Rate Constants  $k_2$  for the Uncatalyzed DA Reaction of **1a** with **2** in Different Solvents at 25 °C

solvent	$k_2$ ( $M^{-1} s^{-1}$ )	$k_{rel}$
acetonitrile	$1.40 \times 10^{-5}$	1
ethanol	$3.83 \times 10^{-5}$	2.7
water	$4.02 \times 10^{-3}$	287
2,2,2-trifluoroethanol	$6.75 \times 10^{-3}$	482

**Figure 1.** pH dependence of the rate of the DA reaction between **1a** and **2** in water at 25 °C.**Table 2.** Second-Order Rate Constants  $k_2$  for the  $Cu^{2+}$ -Ion Catalyzed Reaction of **1c** with **2** in Different Solvents at 25 °C

solvent	$[Cu^{2+}]$ (mM)	$k_2$ ( $M^{-1} s^{-1}$ )
acetonitrile	10	0.472
ethanol	10	0.309
water	10	1.11
2,2,2-trifluoroethanol	0.10	3.22

## Results and Discussion

The dienophiles **1a–e** are readily prepared<sup>32</sup> from an aldol condensation between (substituted) benzaldehyde and 2-acetylpyridine. The compounds are poor dienophiles and, as far as we know, no DA reactions have been reported previously. Herein we describe an extensive study of the DA reaction of **1** with **2** putting particular emphasis on rates and selectivity by systematic variation of the solvent, the substituent X, and the Lewis acid.

### Effect of Solvent on the Rate of the Uncatalyzed Reaction.

Rates of the DA reaction of **1a** with **2** in water and three organic solvents are shown in Table 1. The solvents were chosen to cover as broad a range in solvent properties as possible. In fact hexane was initially also among them, but unfortunately the rate of the reaction in this solvent is extremely low. It is clear that the DA reaction is accelerated markedly by water. Striking is the observation that the reaction is fastest in 2,2,2-trifluoroethanol (TFE). This might well be a result of the high Brønsted acidity of this solvent. Indirect evidence comes from the pH-dependence of the rate of the reaction in water (Figure 1). Protonation of the pyridyl nitrogen obviously accelerates the reaction.

**Solvent and Substituent Effects on the  $Cu^{2+}$ -Catalyzed Reaction.** The rate of the uncatalyzed reaction is in all four solvents rather slow. (The half-life at  $[2] = 1.00$  mM is at least 28 h). We find that complexation of  $Cu^{2+}$  ion to **1a–e** dramatically increases the rate of the DA reaction between these compounds and **2**. Table 2 shows the rate constants for the  $Cu^{2+}$ -catalyzed DA reaction between **1c** and **2** in different solvents. It is obvious that the relatively large solvent effect of water observed in the uncatalyzed reaction (Table 1) is strongly diminished for the catalyzed reaction. This can be

**Table 3.** Solvent Effect on the Hammett  $\rho$ -Values for the DA Reaction of **1** with **2** Catalyzed by  $Cu(NO_3)_2$  at 25 °C

solvent	$[Cu^{2+}]$ (mM)	$\rho$	r
acetonitrile	10	0.96	0.997
ethanol <sup>a</sup>	10	1.00	0.999
water	10	0.69	0.997
2,2,2-trifluoroethanol	0.10	0.90	0.990

<sup>a</sup> For unknown reasons the point for **1a** in the Hammett plot for ethanol strongly deviates from the otherwise good correlation. The data for **1a** in ethanol have therefore not been used in the calculation of  $\rho$ . Instead a new compound **1** with  $X = CO_2CH_3$  was used in the correlation.

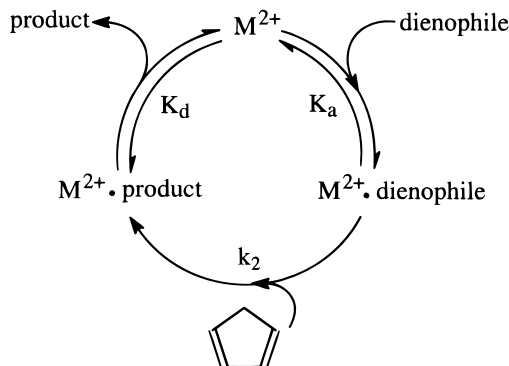
rationalized as follows. For the Lewis acid catalyzed reactions the hydrogen bonding part of the acceleration will be largely taken over by the Lewis acid, so it is likely that only the hydrophobic effect will remain. This contribution will not be unaffected by the Lewis acid either, since the catalyst will partly destroy the hydrophobic hydration shell of the activated complex and of the dienophile in the initial state. This will result in a much smaller aqueous solvent effect on the catalyzed reaction. The highest catalytic activity is observed in TFE. One might envisage this to be a result of the poor interaction between TFE and the copper(II) cation, so that the cation will retain a large part of its Lewis acidity. In the other solvents the interaction between their electron-rich heteroatoms and the cation is likely to be stronger, thus diminishing the efficiency of the Lewis acid catalysis. The observation that  $Cu(NO_3)_2$  is only poorly soluble in TFE and much better in the other solvents used is in accord with this reasoning.

It is interesting to examine the influence of substituents on the Lewis acid catalyzed DA reaction, since there are indications for a relatively large charge separation in the activated complex of the catalyzed reaction compared to the uncatalyzed one in organic solvents.<sup>17a</sup> This might induce a larger effect of substituents on the rate of the catalyzed reaction. Therefore, we have measured the rate of the  $Cu^{2+}$ -catalyzed DA reaction between **1a–e** and **2** in four solvents, resulting in excellent Hammett correlations with  $\sigma^+$  (Table 3). The fact that good correlations are observed with  $\sigma^+$  rather than with  $\sigma$  is indicative of a strong interaction of the substituent through direct resonance with a positive charge in the reacting system. However, the  $\rho$ -values do not exceed unity and are not significantly different from those values reported in the literature for the uncatalyzed reaction.<sup>1</sup> The tempting conclusion that the charge separation in the activated complex of the catalyzed reactions is also not significantly different from that in the uncatalyzed reaction is, however, not valid. Since it is reasonable to assume that the initial state of the catalyzed reaction (the dienophile/Lewis acid complex) is more polarized than the initial state of the uncatalyzed reaction, it is not justified to make a direct comparison between the activated complexes of the rate-limiting step for the uncatalyzed and catalyzed reactions just on the basis of  $\rho$ -values. Among the different solvents water occupies a special position with a relatively small  $\rho$ -value (Table 3). This is anticipated, since water is the solvent with the strongest interactions with the partial charges of the reacting system and the substituents. Substituent effects are usually larger in solvents that only weakly interact with these partial charges<sup>26</sup> and, hence, have maximal values in vacuum.<sup>27</sup> It is important to note here that we have no detailed knowledge about the exact structure of the catalytically active species in the organic solvents.

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## Scheme 2



**Table 4.** Second-Order Rate Constants ( $k_{\text{obs}}$ ) for the Catalyzed DA Reaction between **1c** and **2**, Equilibrium Constants for Complexation of **1c** to Different Lewis Acids ( $K_a$ ), and Second-Order Rate Constants for the Reaction of These Complexes with **2** ( $k_2$ ) in Water at 2 M Ionic Strength at 25 °C

Lewis acid	$k_{\text{obs}}$ ( $\text{M}^{-1} \text{s}^{-1}$ ) <sup>a</sup>	$K_a$ ( $\text{M}^{-1}$ )	$k_2$ ( $\text{M}^{-1} \text{s}^{-1}$ )
$\text{Co}^{2+}$	$4.53 \times 10^{-2}$	$1.17 \times 10^2$	$8.40 \times 10^{-2}$
$\text{Ni}^{2+}$	$8.26 \times 10^{-2}$	$6.86 \times 10^2$	$9.46 \times 10^{-2}$
$\text{Cu}^{2+}$	2.36	$1.16 \times 10^3$	2.56
$\text{Zn}^{2+}$	$4.29 \times 10^{-2}$	$7.28 \times 10^1$	$1.18 \times 10^{-1}$

<sup>a</sup> For  $[\text{M}^{2+}] = 10 \text{ mM}$ .

**Variation of the Catalyst.** We contend that Lewis acids affect the rate of a DA reaction in water by the mechanism depicted in Scheme 2. The first step in the cycle comprises rapid and reversible coordination of the Lewis acid to the dienophile, leading to a complex in which the dienophile is activated for reaction with the diene. After the irreversible DA reaction the product has to dissociate from the Lewis acid in order to make the catalyst available for another cycle. The overall rate of the reaction is determined by  $K_a$ ,  $k_2$ , and  $K_d$ . In our kinetic runs we always used a large excess of catalyst. Under these conditions  $K_d$  will not influence the observed rate of the DA reaction. Kinetic studies by UV–vis spectroscopy require a low concentration of the dienophile ( $\sim 10^{-5} \text{ M}$ ). The use of only a catalytic amount of Lewis acid will seriously hamper complexation of the dienophile because of the very low concentrations of *both* reaction partners under these conditions. The contributions of  $K_a$  and  $k_2$  to the observed overall rate constant have been determined by measuring  $k_{\text{obs}}$  and  $K_a$  separately (Experimental Section). The data obtained in this way are in excellent agreement with the results of the Line-weaver–Burke analysis of the rate constants at different catalyst concentrations. The results for  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Zn}^{2+}$  catalysis of the reaction of **1c** with **2** in water at constant ionic strength (2.00 M  $\text{KNO}_3$ ) are shown in Table 4.  $\text{Cu}^{2+}$  is the best catalyst with respect to both complexation and rate of reaction with **2**. The trend observed in rate and equilibrium constants follows the empirical Irving–Williams order<sup>28</sup>  $\text{Co}^{2+} < \text{Ni}^{2+} < \text{Cu}^{2+} > \text{Zn}^{2+}$ . This order is usually observed for equilibrium constants of binding processes and catalytic activities of these metal ions.<sup>28</sup> A quantitative correlation between rate and equilibrium constants for the different metal ions is absent. The observed rate enhancements are a result of catalysis by the metal ions and are clearly not a result of protonation of the pyridyl group, since the pH's of all solutions were within the region where the rate constant is independent of the pH (Figure 1). Catalysis by the four transition-metal ions was also compared with respect to their sensitivity toward substituents in the dienophile. To this end the equilibrium constants for

**Table 5.** Hammett  $\rho$ -Values for Complexation of **1a–e** to Different Lewis Acids and for the DA Reaction of **1a–e** with **2** Catalyzed by Different Lewis Acids in Water at 2.00 M Ionic Strength at 25 °C

Lewis acid	complexation		rate constants	
	$\rho$	r	$\rho$	r
$\text{Co}^{2+}$	-0.19	0.981	0.72	0.999
$\text{Ni}^{2+}$	-0.44	0.999	0.94	0.999
$\text{Cu}^{2+}$	-0.51	0.997	0.85	0.999
$\text{Zn}^{2+}$	-0.42	0.991	0.84	0.998

complexation of **1a–e** to the four different transition-metal ions were determined. Good to excellent Hammett plots were obtained using  $\sigma^+$  substituent constants.<sup>29</sup> As anticipated the data in Table 5 show that the complexation is characterized by negative  $\rho$ -values, indicating that the binding process is favored by electron donating substituents. The order of the  $\rho$ -values for complexation of the different Lewis acids again follows the Irving–Williams series.

The effect of substituents on the rate of the reaction catalyzed by different metal ions has also been studied. Correlation with  $\sigma^+$  resulted in perfectly linear Hammett plots. Now the  $\rho$ -values for the four Lewis acids do not follow the Irving–Williams order. Note that the substituents have opposing effects on complexation, which is favored by electron donating substituents, and reactivity, which is increased by electron withdrawing substituents. The effect on the reactivity is clearly more pronounced than the effect on the complexation equilibrium.

So far we have compared the four transition-metal ions with respect to their effect on (1) the equilibrium constant for complexation to **1c**, (2) the rate constant of the DA reaction of the complexes with **2**, and (3) the substituent effect on processes 1 and 2. We have tried to correlate these data with some physical parameters of the respective metal ions. The second ionization potential of the metal should, in principle, reflect its Lewis acidity. Furthermore the values for  $k_2$  might be strongly influenced by the Lewis acidity of the metal. A quantitative correlation between these two parameters is, however, not observed. Alternatively, the acidity of the hexaquo metal cation can be taken as a measure of Lewis acidity but this parameter did not exhibit a quantitative correlation with the above data either.

**Endo–Exo Selectivity.** The reaction between **1** and **2** yields four products: two enantiomeric endo products and two enantiomeric exo products. We have examined the effect of the solvent, the Lewis acid, and the substituents on the endo–exo selectivity.

The endo and the exo isomer (Scheme 1) give rise to two different NMR spectra with several peaks that are well separated. From the integration of those signals the endo–exo ratio can be determined. Measurement of the endo–exo ratio by GC was not successful, most likely because the adducts are subject to a retro-DA reaction at elevated temperatures. Assignment of the signals to the different isomers was based on COSY and NOESY spectra. Interpretation of the spectra starts with the identification of the long-range coupling between  $\text{H7}^s$  and  $\text{H2}$ , characteristic for norbornene systems.<sup>30</sup> The chemical shifts of the other protons can now easily be deduced. The discrimination between endo and exo adduct is subsequently based upon the following considerations. A NOE signal between  $\text{H3}$  and a proton on the phenyl ring and a long-range coupling between  $\text{H2}$  and a proton of the phenyl ring are both characteristic for

(29) Literature examples of good Hammett correlations of stability constants are rare: May, W.R.; Jones, M.M. *J. Inorg. Nucl. Chem.* **1962**, *24*, 511.

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**Table 6.** Solvent Effect on the Endo–Exo Selectivity (% endo – % exo) of the Uncatalyzed and Cu<sup>2+</sup>-Ion Catalyzed DA Reaction between **1c** and **2** at 25 °C

solvent	uncatalyzed	10 mM Cu <sup>2+</sup>
acetonitrile	67–33	94–6
ethanol	77–23	96–4
water	84–16	93–7
2,2,2-trifluoroethanol	87–13	

**Table 7.** Effect of Different Catalysts on the Selectivity of the DA Reaction between **1c** and **2** in Water at 25 °C

catalyst	% endo – % exo
10 mM Co(NO <sub>3</sub> ) <sub>2</sub>	87–13
10 mM Ni(NO <sub>3</sub> ) <sub>2</sub>	86–14
10 mM Cu(NO <sub>3</sub> ) <sub>2</sub>	93–7
10 mM Zn(NO <sub>3</sub> ) <sub>2</sub>	86–14
10 mM HCl	94–6

**Table 8.** Substituent Effect on the Selectivity of the Cu<sup>2+</sup>-Catalyzed Reaction of **1** and **2** in Water at 25 °C

dienophile	% endo – % exo
1a	88–12 <sup>a</sup>
1b	92–8 <sup>a</sup>
1c	93–7
1d	93–7
1e	93–7

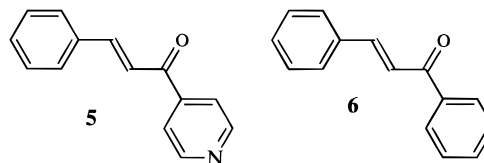
<sup>a</sup> The dienophile was not completely dissolved.

the endo isomer. Furthermore, the downfield shift of H3 is larger in the exo isomer, where it experiences the influence of the nearby carbonylpyridyl group, than in the endo adduct, where H3 is situated next to the phenyl group. Comparison of the NMR data with literature data reported for the DA adducts of cyclopentadiene and substituted cinnamic acids<sup>30</sup> further supports the assignments.

The effects of the solvent on the endo–exo selectivity of the uncatalyzed and Cu<sup>2+</sup>-catalyzed reaction are shown in Table 6. For the uncatalyzed reaction the endo isomer is preferred over the exo isomer. This tendency becomes even more pronounced in more polar solvents, which is in good agreement with previous studies of the solvent effect on the selectivity of DA reactions.<sup>15</sup> For the Cu<sup>2+</sup>-catalyzed reaction the differences between the selectivities in the four solvents are much smaller. Obviously, water does not induce a higher selectivity in this case and there appears to be no indication for an enforced hydrophobic effect favoring the endo-activated complex. Presumably this is caused by the disturbing influence of the metal cation on the hydrophobic hydration shells of the reacting system.

Table 7 shows the endo–exo selectivities for the DA reaction between **1c** and **2** catalyzed by protons and four different metal ions in water. Copper is clearly the most selective metal-ion catalyst. Interestingly, proton catalysis also leads to high selectivities. This is a strong indication that selectivity in this DA reaction does not result from steric interactions. Table 8 shows the effect of substituents on the endo–exo ratio. Under homogeneous conditions there is hardly any substituent effect on the selectivity. Consequently the substituents must have equal effects on the Gibbs energies of the endo and the exo activated complex.

In summary, we have examined the effects of a number of important parameters for the catalyzed DA reaction between **1** and **2** representing the first example of Lewis acid catalysis of a DA reaction in water. Crucial for the success of Lewis acid catalysis of this reaction is the bidentate character of **1**. The structurally related compounds **5** and **6** (Chart 1), lacking the

**Chart 1**

capability of forming a chelate with the Lewis acid, react with **2** in the presence of catalyst at rates at least three orders of magnitude lower than those for **1**. The scope of Lewis acid catalysis of DA reactions in water appears to be limited to bidentate reactants. Whether and how this restriction can be circumvented is currently under investigation. Furthermore, a study of Lewis acid catalyzed DA reactions in the presence of micelles is in progress.<sup>31</sup>

## Conclusions

The DA reaction between **1** and **2** can be accelerated dramatically by Lewis acid catalysis combined with the beneficial aqueous solvent effect. The catalytic efficiency of the Lewis acids studied followed the empirical Irving–Williams order: Co<sup>2+</sup> < Ni<sup>2+</sup> < Cu<sup>2+</sup> >> Zn<sup>2+</sup>. The rate enhancing effect of water on the catalyzed reaction is less pronounced than the corresponding effect on the uncatalyzed reaction between **1** and **2**. In general, the solvent effect on the catalyzed reaction is remarkably modest and the substituent effects observed are similar to those normally obtained for uncatalyzed DA reactions. This implies that the changes in charge separation during the activation process of the catalyzed reaction are not significantly larger than the corresponding changes for the uncatalyzed reaction. The endo–exo selectivity of the catalyzed DA reaction is also only moderately sensitive to the solvent and to substituents in the dienophile. Water does not induce an enhanced endo-selectivity for this reaction.

## Experimental Section

**Materials.** *trans*-Chalcone (**6**) (mp 57.1–57.7 °C) was obtained from Aldrich and recrystallized from ethanol. Cyclopentadiene was prepared from its dimer (Merck-Schuchardt) immediately before use. Dimineralized water was distilled twice in a quartz distillation unit. Ethanol (Merck) was of the highest purity available. Acetonitrile (Janssen) was run over basic aluminium oxide prior to use. 2,2,2-Trifluoroethanol (Acros) was purified by distillation (bp 79 °C). Co(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O, Zn(NO<sub>3</sub>)<sub>2</sub>·4H<sub>2</sub>O, and KNO<sub>3</sub> were of the highest purity available. Compounds **1a–e** and **5** were prepared by an aldol condensation of the corresponding substituted benzaldehyde with 2- or 4-acetylpyridine, following either of two modified literature procedures.<sup>32</sup>

**1a and 1b.** To a stirred solution of 0.5 ml of 10% aqueous sodium hydroxide and 8.25 mmol of the appropriate aldehyde in 10 mL of ethanol was added dropwise over 2–3 h 8.25 mmol of 2-acetylpyridine. The temperature was kept at 0 °C. After being stirred for another 2 h the reaction mixture was filtered, yielding almost pure solid **1a** (7.26 mmol, 88%) or **1b** (7.76 mmol, 94 %). After crystallization from ethanol the melting points were recorded and the compounds were characterized by <sup>1</sup>H NMR. **1a**: mp 158.2–158.5 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.55 (m, 1H), 7.86 (d, 2H), 7.91 (m, 2H), 8.22 (m, 1H), 8.27 (d, 2H), 8.45 (d, 1H), 8.77 (d, 2H). **1b**: mp 102.2–102.5 °C; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.39 (d, 2H), 7.50 (m, 1H), 7.67 (d, 2H), 7.88 (m, 2H), 8.19 (m, 1H), 8.29 (d, 1H), 8.75 (m, 1H).

**1c, 1d, 1e, and 5.** Seventeen millimoles of the appropriate acetylpyridine and 16.5 mmol of the appropriate benzaldehyde were introduced in 100 mL of water at temperatures below 5 °C. The mixture

(31) In the presence of copper dodecylsulfate micelles rate enhancements in the order of 10<sup>6</sup> can be achieved.

(32) (a) Engler, C.; Engler, A. *Chem. Ber.* **1902**, *35*, 4061. (b) Marvel, C.S.; Coleman, L.E., Jr.; Scott, G.P. *J. Org. Chem.* **1955**, *20*, 4061.

was shaken thoroughly in order to obtain a finely dispersed emulsion. Ten milliliters of a 10% sodium hydroxide solution was added. The mixture was again shaken and left overnight undisturbed at 4 °C. The solution should not be stirred since this results in a phase separation and lower yields. The product separated as an oil that solidified upon shaking. Filtration and washing with water gives the almost pure product in satisfactory yields: **1c**, 95%; **1d**, 84%; **1e**, 96%; **5**, 76%. After crystallization from ethanol the melting points were recorded and the compounds were characterized by <sup>1</sup>H NMR. **1c**: mp 74.5–75.3 °C, <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.46 (m, 4H), 7.74 (m, 2H), 7.86 (m, 1H), 7.95 (d, 1H), 8.20 (m, 1H), 8.32 (d, 1H), 8.75 (m, 1H). **1d**: mp 84.8–85.3 °C, <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.40 (s, 3H), 7.23 (d, 2H), 7.49 (m, 1H), 7.64 (d, 2H), 7.87 (m, 1H), 7.93 (d, 1H), 8.19 (m, 1H), 8.27 (d, 1H), 8.74 (m, 1H). **1e**: mp 84.6–85.2 °C, <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 3.85 (s, 3H), 6.93 (d, 2H), 7.47 (m, 1H), 7.69 (d, 2H), 7.86 (m, 1H), 7.92 (d, 1H), 8.19 (d, 1H), 8.19 (m, 1H), 8.73 (m, 1H). **5**: mp 89.0–89.2 °C, <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.44 (d, 1H), 7.45 (m, 3H), 7.65 (m, 2H), 7.77 (m, 2H), 7.85 (d, 1H), 8.84 (m, 2H).

**Kinetic Measurements.** All kinetic measurements were performed using UV–vis spectroscopy (Perkin Elmer λ2, 5 or 12) monitoring the disappearance of the absorption of the dienophile at 25 ± 0.1 °C. Two methods were used to determine the reported second-order rate constants. The rates of the faster reactions (half-lives not more than a few hours) were determined following procedures described earlier.<sup>3a</sup> The rate constants of the slower reactions in organic solvents and the reactions with cyclopentadiene in water with half-lives of more than 15 minutes were determined using initial rate kinetics.<sup>33</sup> Using a known excess of cyclopentadiene, the following expression was used to calculate the second-order rate constants:

$$k_2 = d[A_{\text{dienophile}}]/dt \cdot ((\epsilon_{\text{dienophile}} - \epsilon_{\text{product}}) \cdot [\text{dienophile}]_0 \cdot [\text{cyclopentadiene}]_0)^{-1}$$

Where  $d[A_{\text{dienophile}}]/dt$  is the slope of the plot of the absorption of the dienophile vs time during the first 5% of the reaction. The extinction coefficients of the dienophile and the product were determined separately under the same conditions as used in the kinetic runs. This method has been successfully tested by comparing the results with rate constants obtained by traditional pseudo-first-order kinetics. Typical concentrations were  $[\text{dienophile}] = 1 \times 10^{-5}$  M,  $[\text{cyclopentadiene}] = 1 \times 10^{-3}$  M, and  $[\text{catalyst}] = 1 \times 10^{-2}$  M. All rate constants were measured at least three times. Those obtained by the traditional method were reproducible to within 3%, whereas the initial rate method gave a reproducibility of 5%.

**Equilibrium Constants.** Measurements were performed employing a Perkin Elmer λ2, 5 or 12 UV–vis, spectrophotometer at 25 ± 0.1 °C. Equilibrium constants were determined by measuring the extinction coefficient at a suitable wavelength of the partially complexed dienophile ( $\epsilon_{\text{obs}}$ ) as a function of the concentration of metal ion. The following expression can be derived:<sup>34</sup>

$$[M^{2+}]/(\epsilon_{\text{dienophile}} - \epsilon_{\text{obs}}) = K_a/(\epsilon_{\text{dienophile}} - \epsilon_{\text{complex}}) + [M^{2+}]/(\epsilon_{\text{dienophile}} - \epsilon_{\text{complex}})$$

After determining the extinction coefficient of the uncomplexed dienophile ( $\epsilon_{\text{dienophile}}$ ),  $[M^{2+}]/(\epsilon_{\text{dienophile}} - \epsilon_{\text{obs}})$  was plotted versus  $[M^{2+}]$  yielding a straight line. The equilibrium constant now equals the ratio intercept/slope of this line. Very accurate measurements of the extinction coefficients are a prerequisite for obtaining reliable equilibrium constants. Crucial in this respect were the choice of the wavelength and the choice of the appropriate metal-ion concentrations. The most accurate results were obtained at the wavelength of maximal

difference between the extinction coefficients of uncomplexed and complexed dienophile. The metal-ion concentrations were chosen so as to cover the largest possible change in  $\epsilon_{\text{obs}}$  with the smallest possible change in  $[M^{2+}]$ . Solutions of different  $[M^{2+}]$  with total ionic strength of 2.00 M were prepared. KNO<sub>3</sub> was used as the background electrolyte. Extinction coefficients were determined by filling the cuvet with an accurately known volume of this solution and measuring the absorption after injection of 3–10 μL of a stock solution of the dienophile in 1-propanol. Typical concentration ranges were  $[\text{dienophile}] = (6 \times 10^{-6})$ – $(2 \times 10^{-5})$  M and  $[M^{2+}] = (5 \times 10^{-3})$ – $(2 \times 10^{-5})$  M.

**Product Analysis.** Endo–exo product mixtures were isolated using the following procedure. A solution of cyclopentadiene (concentration  $2 \times 10^{-3}$  M in water and 0.4 M in organic solvents) and the dienophile (concentration 1–5 mM) in the appropriate solvent, eventually containing a 0.01 M concentration of catalyst, was stirred at 25 °C until the UV-absorption of the dienophile had disappeared. The reaction mixture (diluted with water in the case of the organic solvents) was extracted with ether. The ether layer was washed with water and dried over sodium sulfate. After the evaporation of the ether the adducts were obtained in quantitative yields and almost invariably as oils. Only the reaction of **1c** and **2** in water with 10 mM HCl gave a white precipitate. The product mixtures were analyzed with respect to their endo–exo ratio by <sup>1</sup>H NMR. By repeating the extraction-drying procedure it was checked that the work-up procedure did not influence to endo–exo ratio of the isolated product mixture.

We have been able to purify only the products of **1a** and **1c** by crystallization from 1-propanol and ethanol, respectively. The purified products were still a mixture of endo and exo isomers. Elemental analyses of these compounds are given below. The DA adducts of **1b**, **1d**, and **1e** were characterized by comparison of their NMR spectra with those of **1a** and **1c**. We will report here only the NMR data for the endo isomer, since the signals of the minor (7–12%) exo isomer partly coincide with the larger signals of the endo isomer and no attempts were made to separate the two. **3a**: Anal. Calcd for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 71.22; H, 5.04; N, 8.75. Found C, 70.82; H, 4.93; N, 8.66. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.65 (dd, 1H), 1.99 (d, 1H), 3.11 (d, 1H), 3.52 (d, 1H), 3.59 (s, 1H), 4.46 (dd, 1H), 5.85 (dd, 1H), 6.47 (dd, 1H), 7.21 (m, 3H), 8.0 (m, 5H), 8.6 (d, 1H). **3b**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.61 (dd, 1H), 2.00 (d, 1H), 3.04 (d, 1H), 3.40 (dd, 1H), 3.54 (s, 1H), 4.45 (dd, 1H), 5.82 (dd, 1H), 6.47 (dd, 1H), 7.21 (m, 5H), 7.45 (m, 1H), 7.82 (m, 1H), 7.99 (d, 1H), 8.66 (d, 1H). **3c**: Anal. Calcd for C<sub>19</sub>H<sub>17</sub>NO: C, 82.87; H, 6.23; N, 5.09. Found: C, 82.28; H, 6.24; N, 5.21. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.61 (dd, 1H), 2.05 (d, 1H), 3.07 (d, 1H), 3.43 (dd, 1H), 3.53 (s, 1H), 4.51 (dd, 1H), 5.81 (dd, 1H), 6.47 (dd, 1H), 7.21 (m, 5H), 7.41 (m, 1H), 7.80 (m, 1H), 7.99 (m, 1H), 8.65 (m, 1H). **3d**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.60 (dd, 1H), 2.07 (d, 1H), 3.06 (d, 1H), 3.42 (d, 1H), 3.54 (s, 1H), 4.53 (dd, 1H), 5.83 (dd, 1H), 6.49 (dd, 1H), 7.09 (d, 2H), 7.22 (d, 2H), 7.43 (m, 1H), 7.80 (m, 1H), 8.00 (d, 1H), 8.67 (d, 1H). **3e**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.59 (dd, 1H), 2.05 (d, 1H), 3.02 (d, 1H), 3.39 (d, 1H), 3.52 (s, 1H), 4.49 (dd, 1H), 5.81 (dd, 1H), 6.48 (dd, 1H), 6.82 (d, 2H), 7.23 (d, 2H), 7.43 (m, 1H), 7.79 (m, 1H), 7.99 (d, 1H), 8.67 (d, 1H).

**Supporting Information Available:** A listing of second-order rate constants of the Cu<sup>2+</sup>-catalyzed reaction of **1a**, **1b**, **1d**, and **1e** with **2** in acetonitrile, ethanol, water and 2,2,2-trifluoroethanol as well as second-order rate constants and equilibrium constants for the Co<sup>2+</sup>-, Ni<sup>2+</sup>-, Cu<sup>2+</sup>-, and Zn<sup>2+</sup>-catalyzed reaction of **1a**, **1b**, **1d**, and **1e** with **2** in water at 2.00 M ionic strength (1 page). See any current masthead page for ordering information and Internet access instructions.

**Acknowledgment.** We gratefully acknowledge financial support from the Research School “Netherlands Institute for Catalysis Research”.

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