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Specific acid catalysis and Lewis acid catalysis of Diels–Alder reactions in aqueous media

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ABSTRACT: A comparative study of specific acid catalysis and Lewis acid catalysis of Diels–Alder reactions between dienophiles (**1**, **4** and **6**) and cyclopentadiene (**2**) in water and mixed aqueous media is reported. The reactions were performed in water with copper(II) nitrate as the Lewis acid catalyst whereas hydrochloric acid was employed for specific acid catalysis. At equimolar amounts of copper(II) nitrate and hydrochloric acid (0.01 M, for example) and under the same reaction conditions, the reaction rate for **1a** with **2** is about 40 times faster with copper catalysis than with specific acid catalysis. Moreover, at 32 °C and 0.01 M HCl, the reaction of **1b** with **2** is about 21 times faster than the same uncatalyzed reaction in pure water under the same reaction conditions. The inverse solvent kinetic isotope effect shows that these Diels–Alder reactions undergo specific acid catalysis. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: Diels–Alder; catalysis; specific acid catalysis; Lewis acid catalysis; kinetics

INTRODUCTION

The Diels–Alder reaction is a stereospecific [4 + 2] cycloaddition of a dienophile and a conjugated diene to form a six-membered ring. It is one of the most important and fundamental stereoselective reactions in the synthesis of six-membered ring compounds, including natural products. The reaction is thermally reversible and the reverse process is referred to as the retro-Diels–Alder reaction. A critical survey of reactivity, selectivity and mechanistic aspects of this reaction in various organic solvents has been reported.[1] After a long, heated debate on the mechanism of Diels–Alder reactions, there is now a consensus that bond breaking and bond making in Diels–Alder cycloaddition is predominantly concerted[2,3] although not necessarily synchronous.[4,5] The reaction being concerted implies that Diels–Alder reactions undergo only a small charge separation on going from the initial state to the activated complex. This means that the rates of Diels–Alder reactions are not strongly influenced by the nature of the solvent employed for the reaction. Interestingly, however, there is a substantial rate acceleration when Diels–Alder reactions are performed in water.[6,7] It is interesting that Diels–Alder reactions were also performed in water by Diels and Alder themselves[8] and other workers.[9] The breakthrough came, however, with a paper by Rideout and Breslow in 1980.[10] In their study, they observed that the Diels–Alder reaction of cyclopentadiene with methyl vinyl ketone in water is about 700 times faster than the same reaction in isooctane.[10] Today, many organic reactions that are traditionally performed in organic solvents have successfully been performed in water or aqueous systems.[11] Diels–Alder reactions in water benefit not only from the increase in reaction rates but also from the increased *endo*/*exo* selectivity.[12–15]

Although Diels–Alder reactions can proceed without the need for catalysts, the reactions are sometimes slow and need to be accelerated by physical methods such as high pressure, high temperature or ultrasound irradition. However, the acceleration of the reactions through catalysis is more attractive as it avoids high temperature and pressure. The most effective catalysts for Diels–Alder reactions are Lewis acids. Lewis acid-catalysed Diels–Alder reactions were first reported in the 1960s by Yates and Eaton.[16] Lewis acids catalyse Diels–Alder reactions by coordinating to the activating group of the dienophile (for normal electron demand Diels–Alder reactions) and in this way lower the $LUMO_{dienophile}$–$HOMO_{diene}$ energy gap, accelerating the reaction. Even if Lewis acid catalysis proceeds at room temperature with an excellent yield and turnover numbers, these reactions are faced with the problem of the excess amounts of Lewis acids employed. Normally, an excess of up to 2 molar Lewis acid catalysts is required to activate a carbonyl group-containing dienophile. In larger scale production, this

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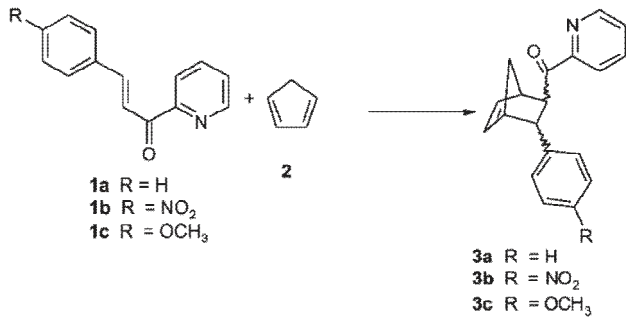
excess Lewis acid poses an environmental problem. The problem may be overcome by the use of solid protic acids[17] and surfactant-assisted Brønsted acids.[18]

Brønsted acid catalysis of Diels–Alder reactions was reported[19] almost two decades before Lewis acid catalysis was performed by Yates and Eaton.[16] Wassermann and co-workers reported the reaction rates of Brønsted acid-catalyzed Diels–Alder reactions of cyclopentadiene with several dienophiles in both polar and nonpolar organic solvents.[19,20] Their studies established that general acid catalysis operated in these typical Diels–Alder cycloaddition reactions.[20] It is unfortunate, however, that their studies did not use water as a reaction medium because at that time water was not considered an important solvent for organic reactions. Since then, no further interest in the Brønsted acid catalysis of Diels–Alder reactions was reported until the mid-1990s when specific acid catalysis of Diels–Alder reactions was performed in water.[14,21] To our knowledge, no comparative studies between Brønsted acid catalysis and Lewis acid catalysis of Diels–Alder reactions in water have been reported. The present study provides such a comparison.

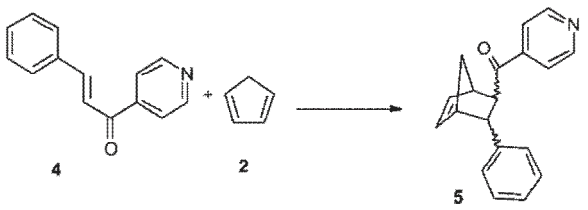
RESULTS AND DISCUSSION

Specific acid catalysis of Diels–Alder reactions of azachalcone dienophiles (1, 4) with cyclopentadiene (2)

Specific acid catalysis of the Diels–Alder reactions of azachalcone dienophiles (**1**, **4**) with cyclopentadiene (**2**) was performed at 32 °C in dilute hydrochloric acid at different pH (Schemes 1 and 2). These cycloadditions are known to be efficiently catalyzed by Lewis acid catalysts in aqueous media.[14,21] In both proton and Lewis acid catalysis, **1b** is more reactive than dienophiles **1a**, **1c** and **4**. The reactivity difference is anticipated for normal electron demand Diels–Alder reactions on the basis of the frontier molecular orbital (FMO) theory regarding substituent effects.[1] The presence of an electron-donating group in the dienophile **1c** slows the reaction rates. In fact, the Diels–Alder reaction of **1c** with **2** was too slow to establish reliable reaction kinetics. On the other hand, the



Scheme 1



Scheme 2

reactions of **1a** and **1b** with **2** at 32 °C gave reliable second-order rate constants (Table 1). Figure 1 shows a full reaction profile of the Diels–Alder reaction of dienophile **1b** with cyclopentadiene **2** in dilute hydrochloric acid at 32 °C. The profile levels off at relatively high acid concentration, indicating that the dienophile becomes completely protonated. The protonation lowers the LUMO of the dienophile, causing a decrease in the energy gap of the frontier molecular orbital and therefore enhancing the reaction rate with an increase in the acid strength.

Tables 1 and 2 give a comparison of the reaction rates of the catalyzed and the uncatalyzed Diels–Alder reactions in water under similar reaction conditions. At 0.01 M

Table 1. Second-order rate constants for Brønsted acid (0.01 M HCl)-catalyzed (k_H) and uncatalyzed (k_w) Diels–Alder reactions in doubly distilled water at 32 °C

Reaction	k_H ($M^{-1}s^{-1}$) in 0.01 M HCl	k_w ($M^{-1}s^{-1}$)	k_H/k_w
1a+**2**	0.042	0.0049	9
1b+**2**	0.14	0.0065	21
4+**2**	0.024	0.0041	6

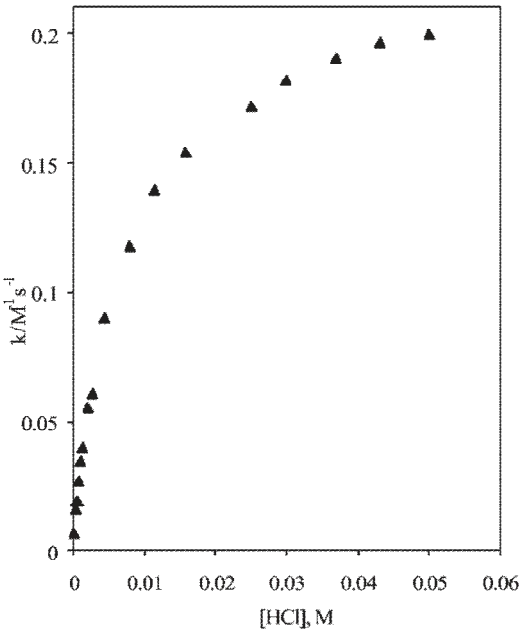


Figure 1. A specific acid-catalyzed Diels–Alder reaction profile for **1b** with **2** at 32 °C

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Table 2. Second-order rate constants (k_H) for Diels–Alder reaction of **1b** with cyclopentadiene (**2**) at different acid strengths at 25 °C

[HCl] (M)	k_H ($M^{-1}s^{-1}$)	k_H/k_w
0	0.004	1
0.003	0.038	9.5
0.005	0.049	12
0.010	0.067	18
0.016	0.086	22
0.021	0.096	24
0.043	0.11	28

HCl and 32 °C, for instance, the catalyzed reaction of **1b** with **2** is about 21 times faster than the uncatalyzed reaction. Table 2 gives a comparison of the uncatalyzed reaction with specific acid catalysis at 25 °C. When compared with previous reported results on the uncatalyzed reaction of **1b** with **2** performed in acetonitrile at 25 °C ($k = 1.4 \times 10^{-5}\,M^{-1}s^{-1}$)[22] and that performed in 0.043 M HCl ($k = 0.11\,M^{-1}s^{-1}$) at 25 °C, the reaction is accelerated about 8000-fold.

Comparison of specific acid and Lewis acid catalysis of Diels–Alder reactions of azachalcones (1, 4) with cyclopentadiene (2)

The Diels–Alder reactions of dienophiles **1** and **4** with cyclopentadiene (**2**) were performed in aqueous solutions of copper(II) nitrate and hydrochloric acid at 32 °C for comparison (Table 3). Equimolar amounts of copper(II) ions and dilute hydrochloric acid were employed and the reactions were performed under similar reaction conditions. Although it is an unfair comparison because copper(II) Lewis acid binds in a bidentate fashion[15] whereas the proton binds monodentate, it gives some insights into the different catalytic efficiencies. It is clear from Fig. 2 that the reaction profile reaches a plateau at higher copper(II) concentrations as observed for specific acid catalysis in the preceding section. The observed levelling off of the reaction profile is indicative of full binding of the copper(II) catalyst to the dienophile.

Table 3 shows the corresponding second-order rate constants for the reaction of dienophiles **1** and **4** with cyclopentadiene (**2**). It is apparent from the reaction rates of reaction **1a** with **2** that copper(II) catalysis is about 40

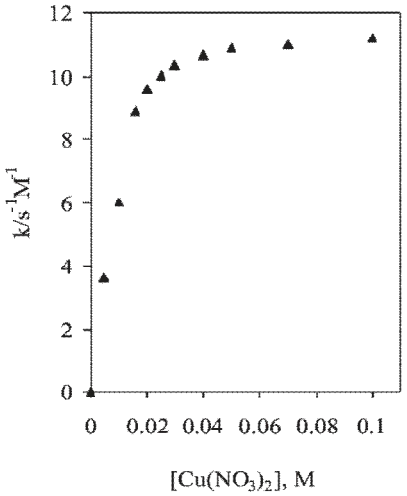


Figure 2. Copper(II) nitrate catalysis of the Diels–Alder reaction of **1b** with **2** at 32 °C at an ionic strength of 2 M (KNO_3)

times faster than proton catalysis. Likewise, copper(II) catalysis is about 50 times faster than proton catalysis for the reaction of **1b** with **2**. In contrast, copper(II) catalysis for the reaction of **4** with cyclopentadiene **2** does not occur except for a possible salt effect. It is obvious that copper catalysis only takes place for the dienophiles that contain two centers for interaction with the metal ion. This crucial role of the bidentate character of Lewis acid catalysts for Diels–Alder reactions in water has been stressed previously.[14,22] In the present study, we established that specific acid catalysis of these Diels–Alder reactions does not depend on the bidentate nature of the dienophile.

The advantage of the bidentate character for specific acid Diels–Alder catalysis is clear when dienophiles **1a** and **4** are compared. The reaction of the bidentate dienophile **1a** with **2** is much faster than that of dienophile **4** with **2** under similar reaction conditions (Tables 3 and 4). The reasons for this reactivity difference may be due to hydrogen-bonding and electronic effects. It is realistic to consider that the proton attached at the pyridyl nitrogen of **1a** will undergo intramolecular hydrogen bonding with the oxygen of the carbonyl carbon. This hydrogen-bonding interaction may lower the LUMO energy of **1a**, enhancing its reactivity. In contrast, the proton attached at the pyridyl nitrogen of the dienophile **4**

Table 3. Second-order rate constants of Lewis acid [0.015 M $Cu(NO_3)_2$] catalysis compared with Brønsted acid (0.015 M HCl) catalysis of Diels–Alder reactions in water at 32 °C

Reaction	k_{Cu} ($M^{-1}s^{-1}$) in 0.015 M $Cu(NO_3)_2$	k_H ($M^{-1}s^{-1}$) 0.015 M HCl	k_{Cu}/k_H
1a + **2**	1.87	0.050	37
1b + **2**	8.5	0.159	53
4 + **2**	0.007	0.028	0.25

Table 4. Second-order rate constants of Lewis acid [0.015 M $Cu(NO_3)_2$] catalyzed reactions relative to uncatalyzed reactions in doubly distilled water at 32 °C

Reaction	k_{Cu} ($M^{-1}s^{-1}$) in 0.015 M $Cu(NO_3)_2$	k_w, ($M^{-1}s^{-1}$)	k_{Cu}/k_w
1a + **2**	1.87	0.0049	382
1b + **2**	8.5	0.0065	1260
4 + **2**	0.007	0.0041	1.6

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is at too remote a distance from the carbonyl oxygen for intramolecular hydrogen bonding. This makes dienophile **4** less reactive than dienophile **1a** under similar reaction conditions. In addition to hydrogen bonding, an intramolecular electrostatic interaction between the positive charge on the pyridyl nitrogen and the lone pair of the oxygen of the carbonyl carbon is expected to cause this reactivity difference. The electrostatic interaction is more likely to occur when the pyridyl group is in close proximity (*ortho*-position) than when it is more remote (*para*-position). The electrostatic interaction will lead to electron density withdrawal from the double bond of the dienophile **1a**. The electron withdrawal makes **1a** relatively more electrophilic and hence more reactive than **4** for these Diels–Alder reactions.

Determination of the pK_a of the dienophile

The basicity of the dienophile was established by determining the pK_a for *N*-protonation of **1b** by UV–visible spectrophotometry at 32 °C. The difference between the extinction coefficients of the unprotonated and protonated dienophiles at different acid concentrations was obtained at the wavelength of maximum difference. The azachalcone derivative **1b**, gave a pK_a of 2.55 for *N*-protonation, which is in good agreement with the literature value for the structurally similar 2-phenylacetylpyridine, which has a pK_a of 2.30 for *N*-protonation.[23] Reliable data were only possible in the pH range 4.4–1.4 and there was a clear deviation from the isosbestic point at pH < 1 or > 4.4, suggesting that there are other possible chemical processes taking place.

Elucidation of the mechanism of specific acid-catalyzed Diels–Alder reactions

In order to obtain information about the nature of the acid-catalyzed Diels–Alder reactions, the kinetic deuterium isotope effect (KDIE) was measured. Data are summarized in Table 5 and Figure 3. The inverse primary KDIE is consistent with specific acid catalysis, involving

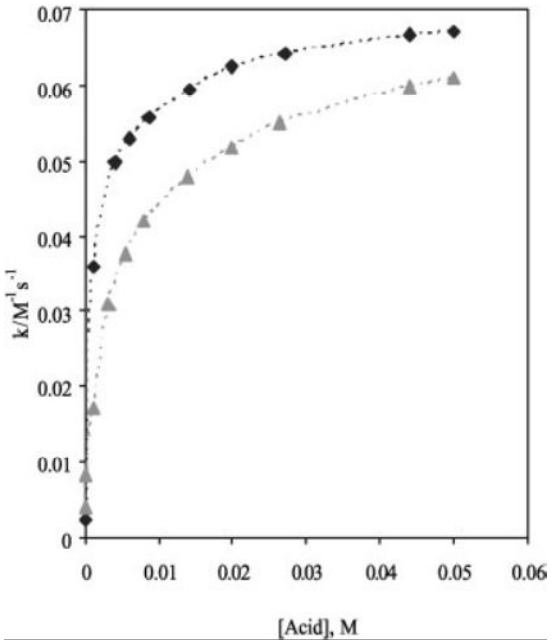


Figure 3. A reaction profile of the reaction of dienophile **1a** with cyclopentadiene **2** in DCl (◆) and HCl (▲) at 32 °C to establish k_H/k_D

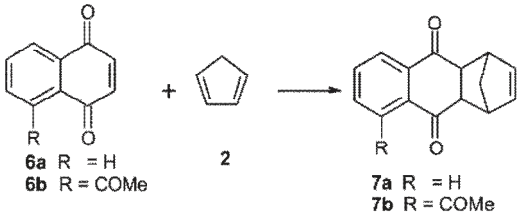
reversible protonation of the substrate followed by the rate-determining cycloaddition step. As expected, the KDIEs approach a value of unity under conditions of complete protonation of the dienophile.

The observations indicate that the mechanism of the specific acid catalysis of these Diels–Alder reactions in water is similar to that of Lewis acid catalysis.[14,22] This means that the first catalytic step of a specific acid-catalysed Diels–Alder reaction is a rapid but reversible pre-equilibrium protonation of the dienophile. The protonated dienophile is more electrophilic and thus activated for the reaction with the electron-rich diene. The product then dissociates to a pure product, leaving the specific acid available for another catalytic reaction cycle. At very high acid concentrations, the reaction rates were irreproducible and this could possibly be due to other processes such as Michael addition of water to the dienophile that may take place at low pH.

Table 5. Solvent kinetic isotope effect (KIE) for reactions of **1a** and **1b** with **2** at different deuterium chloride and hydrochloric acid concentrations

Reaction	$[D_3O^+]$ (M)	k_D ($M^{-1}s^{-1}$)	$[H_3O^+]$ (M)	k_H ($M^{-1}s^{-1}$)	k_H/k_D
1a + **2**	0.014	0.059	0.014	0.048	0.81
1a + **2**	0.019	0.062	0.020	0.052	0.84
1a + **2**	0.027	0.064	0.027	0.055	0.86
1a + **2**	0.050	0.068	0.050	0.061	0.90
1b + **2**	0.001	0.048	0.001	0.035	0.73
1b + **2**	0.004	0.135	0.0038	0.090	0.68
1b + **2**	0.008	0.169	0.0079	0.118	0.70
1b + **2**	0.010	0.170	0.0099	0.140	0.82
1b + **2**	0.05	0.195	0.043	0.197	1.01

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Scheme 3

Specific acid catalysis of the Diels–Alder reaction of napthoquinones (6) with cyclopentadiene (2)

The Diels–Alder reactions of naphthoquinones (**6**) with **2** (Scheme 3) were performed in dilute hydrochloric acid in the pH range 1–6. The concept is that an electrostatic interaction between the hydronium ion and the activated complex might lead to a stabilization of the activated complex. This stabilization could be similar to that involving hydrogen bonding to the activated complex in water and protic solvents as they both lower the LUMO (dienophile)–HOMO (diene) energy gap. However, the second-order rate constants did not show any acid catalysis on these reactions. The reaction of **6a** with **2**, for instance, gave second-order rate constants of 7.8 and 7.5 $M^{-1}s^{-1}$ for the reaction performed at pH 2 and 6, respectively. Similarly, the second-order rate constants for the reaction of **6b** with **2** were also constant, giving rates of 13.8 $M^{-1}s^{-1}$ for the reactions performed at both pH 2 and 6. The use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) and 2,2,2-trifluoroethanol (TFE) solvents for the Diels–Alder reaction of **6b** with **2** also showed no detectable acid catalysis. The second-order rate constants recorded in HFP and TFE solvents were 3.41 and 1.01 $M^{-1}s^{-1}$, respectively.

It is perhaps surprising to observe that no acid catalysis is detected in these Diels–Alder reactions. This is contrary to our hypothesis and to previous studies that have shown general acid catalysis in some Diels–Alder reactions in organic solvents.[20] However, since our reactions are performed in water, the influence of the specific acid may not be noticed owing to the strong influence of hydrogen bonding with water and enforced hydrophobic interaction in Diels–Alder reactions in water. No attempt was made to establish copper catalysis of these Diels–Alder reactions but previous studies for the reaction of **6a** with **2** in aqueous $CuCl_2$ showed a slight enhancement of the rate constant, probably due to salt effects.[24]

Acid-catalysed Diels–Alder reactions in mixed aqueous solutions

The reaction of **1b** with **2** was performed in ethanol–water mixtures (mole fraction of water, $X_{H_2O} = 0.8$) at different 'pH'. The reaction rates were evaluated by initial rate kinetics and compared with the rates of these reactions performed in dilute hydrochloric acid. It is interesting (Table 6) that the reaction rates are inhibited by an average factor of ~10. Assuming that at this ethanol mole fraction the contribution of enforced hydrophobic interaction to the aqueous rate acceleration has vanished, it is noteworthy that the factor of 10 is in the region of the theoretical value predicted to be contributed by hydrophobic effects for Diels–Alder reactions carried out in water.[25] This may indeed be indicative of the hydrophobic influence on the specific acid-catalysed Diels–Alder reaction in water. The results suggest that the hydrophobic contribution to the specific acid-catalyzed Diels–Alder reaction is more or less of the same magnitude as in pure water.

Table 6. Rate constants for the proton-catalyzed Diels–Alder reaction of **1b** with **2** in ethanol–water mixtures ($X_{H_2O} = 0.8$) and in dilute hydrohloric acid

EtOH-H_2O ('pH')	k_{EtOH-H_2O}, ($M^{-1}s^{-1}$)	Dil. HCl (pH)	k_H ($M^{-1}s^{-1}$)	k_H/k_{EtOH-H_2O}
1.49	0.032	1.52	0.18	5.63
2.16	0.0094	2.1	0.118	12.55
2.42	0.0063	2.41	0.09	14.30
3.0	0.0037	3.0	0.035	9.50
3.21	0.0029	3.2	0.027	9.31

CONCLUSION

A comparative study between Lewis acid and specific acid catalysis for Diels–Alder reactions in aqueous media has been carried out. Dienophiles with basic sites were reacted with cyclopentadiene in aqueous copper(II) nitrate or dilute hydrochloric acid. The kinetic investigations of these reactions established that the two types of catalysts have similar reaction mechanisms. Bidentate reactants are required for Lewis acid catalysts but are not a necessity for specific acid catalysis to take place. However, a beneficial effect of a bidentate over a monodentate reactant was also noted for specific acid catalysis. A comparison between copper(II) Lewis acid catalysis and specific acid catalysis showed the copper(II) catalyst to be more efficient. For example, at equimolar amounts of copper(II) and HCl (0.01 M) catalysts, the reaction rate for the Diels–Alder reaction of **1a** with **2** is about 40 times faster for copper catalysis than for the specific acid catalysis. At 32 °C and 0.01 M HCl, the Diels–Alder reaction of **1b** with **2** is 21 times faster than in pure water under the same reaction conditions.

EXPERIMENTAL

Materials

4-Acetylpyridine (Aldrich), 2-acetylpyridine (Aldrich), benzaldehyde (Aldrich), $Cu(NO_3)_2 \cdot 3H_2O$ (Merck),

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KNO_3 (Merck), hydrochloric acid (Merck), deuterium chloride (Aldrich), $CDCl_3$ (Aldrich), acetonitrile (Aldrich) and deuterium oxide (Aldrich) were of the highest purity available. Cyclopentadiene was cracked from its dimer (Merck) immediately before use. Dimineralized water was doubly distilled in a quartz distillation unit. Ethanol, 1,1,1,3,3,3-hexafluoro-2-propanol and 2,2,2-trifluoroethanol solvents were of the highest purity available. The solvents were used as received. Dienophiles **1a** and **4** were prepared by aldol condensation of 2- and 4-acetylpyridine with the corresponding substituted benzaldehyde using documented procedures.[14,22] Dienophile **1b** was purified from a stock sample prepared in our group.[22] Similarly, the dienophile was purified from a stock sample pre-prepared in our group.[24]

1a and 4. To 100 ml of water cooled to 5 °C, 16.5 mmol of the appropriate benzaldehyde and 17 mmol of the appropriate acetylpyridine were introduced. The mixture was thoroughly shaken to obtain a finely dispersed emulsion. This was followed by the addition of 10 ml of 10% NaOH. The mixture was once again shaken and left undisturbed overnight at 4 °C. The product, which was oil-like, solidified upon shaking and was filtered and washed with water giving good yields: **1a**, 93%; **4**, 77%. The products were crystallized from ethanol giving pure products with melting-points for **1a**, 74.8–75.5 °C (lit.[22] 74.5–75.3 °C, lit.[26] 74 °C) and for **4**, of 89.5–90.0 °C (lit.[22] 89.0–89.2 °C, lit.[27] 87–88 °C). The ^{1}H NMR spectra of the products were checked and were consistent with the previously reported results.[14]

Kinetic measurements

Kinetic measurements were performed using UV-visible spectrophotometry (Perkin-Elmer λ2, λ5 or λ12 spectrothotometer) by monitoring the disappearance of the absorption of the dienophile at an appropriate wavelength. For reactions involving specific acid catalysis, solutions of hydrochloric acid were prepared by diluting concentrated hydrochloric acid with doubly distilled water. The concentrations of the dilute hydrochloric acid were double checked by using a pH meter. The solutions were then used to perform the specific acid-catalyzed Diels–Alder reactions. The dienophile was introduced into a 1 cm pathlength quartz cuvette containing 3.5 ml of solution. After equilibration, 10–25 µl of a concentrated stock solution of cyclopentadiene in acetonitrile were added. The rates of the faster reactions were monitored for at least four half-lives and the pseudo-first-order rate constants were obtained using a fitting program. The rates of slower reactions were determined using initial rate kinetics. Typical concentrations employed were $[\text{diene}] = 1 \times 10^{-3}$–$2 \times 10^{-3}$ M and $[\text{dienophile}] = 1 \times 10^{-5}$ M. The rate constants were measured at least three times and the reported rate constants are an average of three runs. The rate constants determined by the pseudo-first-order method were reproducible to within 3% and the initial rate method gave a reproducibility of 5%.

Equilibrium constant measurements

The determination of the pK_a for **1b** was performed by employing a Perkin-Elmer λ5 or λ12 spectrophotometer at 32 °C. The equilibrium constant was obtained by measuring the extinction coefficient of the partially protonated dienophile (ε_{obs}) as function of the acid concentration. After the determination of the extinction coefficient differences of the unprotonated dienophile and that of the partially protonated dienophile at the maximum wavelength, the following expression was employed for data analysis:[28]

$$[H_3O^+]/(\varepsilon_{\text{dienophile}} - \varepsilon_{obs}) = K/(\varepsilon_{\text{dienophile}} - \varepsilon_{\text{protonated}}) + [H_3O^+]/(\varepsilon_{\text{dienophile}} - \varepsilon_{\text{protonated}})$$

A plot of $[H_3O^+]/(\varepsilon_{\text{dienophile}} - \varepsilon_{obs})$ against $[H_3O^+]$ yielded a straight line for which the ratio of its intercept to the slope gives the equilibrium constant. To obtain accurate results, it is necessary to follow the difference between the extinction coefficient of protonated and unprotonated dienophile at the maximum wavelength.

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REFERENCES

1. (a) Sauer J, Sustmann R. *Angew. Chem., Int. Ed. Engl.* 1980; **19**: 779; (b) Oppolzer W. In *Intermolecular Diels–Alder Reactions*, vol. 5, Trost BM (ed). Pergamon Press: Oxford, 1991; 315.
2. Houk KN, Li Y, Evanseck D. *Angew. Chem., Int. Ed. Engl.* 1992; **31**: 682.
3. Storer JW, Raimondi L, Houk KN. *J. Am. Chem. Soc.* 1994; **116**: 9675.
4. Leach AG, Houk KN. *Chem. Commun.* 2002, 1243.
5. Gajewski JJ, Peterson KB, Kagel JR. *J. Am. Chem. Soc.* 1987; **109**: 5545.
6. Blokzijl W, Blandamer MJ, Engberts JBFN. *J. Am. Chem. Soc.* 1991; **113**: 4241.
7. Otto S, Blokzijl W, Engberts JBFN. *J. Org. Chem.* 1994; **59**: 5372.
8. Diels O, Alder K. *Liebigs Ann. Chem.* 1931; **490**: 243.
9. Woodward WB, Baer H. *J. Am. Chem. Soc.*, 1948; **70**: 1161; Hopff H, Rautesnstrauch CW. US Patent 2 262 002, 1939; *Chem. Abstr.* 1942; **36**: 10469; Eggelte TA, de Koning H, Huisman HO. *Tetrahedron* 1973; **29**: 2491.
10. Rideout DC, Breslow R. *J. Am. Chem. Soc.* 1980; **102**: 7816.

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11. Li CJ, Chang TH. *Organic Reactions in Aqueous Media*. Wiley: New York, 1997; Grieco PA (ed). *Organic Synthesis in Water*. Blackie: London, 1998; for a special issue on organic reactions in aqueous media, see *Adv. Synth. Catal.* 2002; **344**: 219; for a thematic issue on water, see: *Chem. Rev.* 2002; **102**: 2625.
12. Breslow R, Maitra U, Rideout DC. *Tetrahedron Lett.* 1983; **24**: 1901.
13. Breslow R, Maitra U. *Tetrahedron Lett.* 1984; **25**: 1239.
14. Otto S, Bertoncin F, Engberts JBFN. *J. Am. Chem. Soc.* 1996; **118**: 7702.
15. (a) Otto S, Engberts JBFN. *J. Am. Chem. Soc.* 1999; **121**: 6798; (b) for a review, see Fringuelli F, Piermatti O, Pizzo F, Vaccaro L. *Eur. J. Org. Chem.* 2001; 439.
16. Yates P, Eaton P. *J. Am. Chem. Soc.* 1960; **82**: 4436.
17. Olah GA, Meidar D, Fung AP. *Synthesis*, 1979; 270.
18. Manabe K, Mori Y, Wakabayashi T, Nagayama S, Kobayashi S. *J. Am. Chem. Soc.* 2000; **122**: 7202.
19. (a) Wassermann A. *J. Chem. Soc.* 1942; **618**: 623; (b) Wassermann A. *J. Chem. Soc.* 1946; 1089.
20. Rubin W, Steiner H, Wassermann A. *J. Chem. Soc.* 1949; 3046.
21. Otto S, Engberts JBFN. *Tetrahedron Lett.* 1995; **36**: 2645.
22. Otto S. PhD Thesis, University of Groningen, 1998.
23. McCann GM, More O'Ferrall RA, Walsh SM. *J. Chem. Soc. Perkin Trans.* 1997; **2**: 2761.
24. Wijnen JW. PhD Thesis, University of Groningen, 1997.
25. Blake JF, Jørgensen WL. *J. Am. Chem. Soc.* 1991; **113**: 7430.
26. Tsukerman SV, Nikitchenko VM, Bugai AI, Lavrushin VF. *Khim. Svoistva Reakt. Org. Soedin.* 1969; **53**; *Chem. Abstr.* 1970; **73**: 45276t.
27. Durinda J, Szucs L, Krasnec L, Heger J, Springer V, Kolena J, Keleti J. *Acta Fac. Pharm. Bohemoslov* 1966; **12**: 89; *Chem. Abstr.* 1968; **68**: 114494y.
28. Hartley FR, Burgess C, Alcock R. *Solution Equilibria*. Wiley: New York, 1980.

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