

CHAPTER 13

Catalysis of Diels–Alder reactions in water and in hydrogen-bonding environments

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I. INTRODUCTION

One of the main questions in chemical synthesis is the choice of solvent. Apart from the fact that it determines the outcome of a reaction, it also creates one of the main sources of pollution, an aspect which is particularly important in industrial processes. Modern chemistry attempts to reduce sources of environmental hazards caused by organic solvents which are typically used in much larger quantities than the solutes. Leakage and evaporation often lead to direct pollution of the environment. For instance, in 1995 the emission of volatile organic compounds in Germany amounted to about 2.1×10^6 tons¹. Furthermore, halogenated solvents are particularly notorious with respect to their toxic character and limited bio-degradability. For these reasons a lot of research is currently devoted to the development of solvent-free systems² or to the replacement of organic solvents by more environmentally-friendly ones³. Water may be the prime choice for this purpose because of its non-toxic character, its ubiquitous availability and its price.

A. Water – A Unique Substance

Water is a moderately volatile, highly mobile liquid over a large temperature range with many exceptional characteristics. Compared to simpler liquids with fewer solvent–solvent or solvent–solute interactions, water has certain anomalous thermodynamic properties: a temperature of maximum density in the liquid phase over a wide range of pressures, an unusually high surface tension, a minimum in the isothermal compressibility as a function of temperature and a large heat capacity throughout the liquid range⁴. Most of these properties originate from strong hydrogen bonds between the water molecules and the large dipole moment ($\mu = 1.82$ D; 298 K, bulk water). The large dielectric constant ($\epsilon = 78.36$ at 298 K) and its solvation power make water an extremely good solvent for many substances. Most salts as well as many covalently bound polar compounds like methanol, acetic acid or acetone are completely soluble in water. Another property is the ability of water molecules to act as efficient hydrogen-bond donors and acceptors⁵. The tendency for hydrogen bonding also leads to other qualities of water which make it unique amongst solvents. These characteristics are partly due to the small size of the water molecule, which enables water to interact efficiently and multi-molecularly with Lewis bases⁶. The relatively high melting and boiling points of water are quite unusual for a chemical compound of such a small molecular mass. The high boiling point and the high enthalpy of evaporation may be considered as disadvantages for organic reactions because removal of the solvent is difficult. On the other hand, the high affinity of water towards some inorganic salts to build up hydrates (like $\text{MgSO}_4 \cdot n\text{H}_2\text{O}$ or $\text{Na}_2\text{SO}_4 \cdot n\text{H}_2\text{O}$) partially annihilates this alleged disadvantage. Aqueous reaction mixtures can be extracted with smaller amounts of organic solvents than would be needed if the reaction was conducted in a non-aqueous solvent. Again, this leads to high yields and decreased consumption of environmentally dangerous substances. Another advantage of water leading to simplified reaction conditions is that an inert atmosphere is normally not needed.

The amphoteric character of water (i.e., the ability to act either as an acid or as a base) makes water so special. While this renders the use of water as a solvent in acid- or base-sensitive reactions problematic, the possibility to have the solvent as a reactant in acid- or base-initiated reactions is often desirable. These qualities led chemists to re-discover water as a solvent in organic chemistry. Unfortunately, from a chemical point of view, not all transformations are feasible in aqueous solvent systems. Many reagents decompose when brought into contact with water while many others are insoluble. Consequently, it is not surprising that water has not been a very popular solvent in organic chemistry in the past, but this picture is changing rapidly.

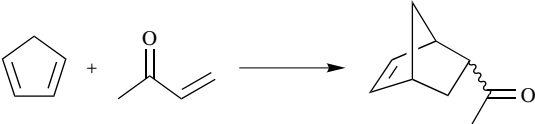
B. Organic Chemistry in Water

Hydrogen-bonding and hydrophobic effects⁷ (we will describe these terms later) are prime factors in commonly observed accelerations of pericyclic reactions in water, with⁸ and without⁹ added co-catalysts. The remarkable efficiency of these catalytic systems with accelerations up to one million-fold¹⁰, increased yields, higher selectivities and their obvious relation with and compatibility to physiological conditions are a clear indication that, for instance, pericyclic reactions are likely also to occur in biosynthesis. Most biochemical processes take place in pure water or in the presence of water, and the diversity of the reactions *in vivo* should prompt chemists to discover the potential of water as the solvent of choice. Biological processes are of exemplary efficiency and biological catalysts, i.e. enzymes, lead to outstanding rate accelerations and very high selectivities. All these biological processes and reactions are carried out in ‘aqueous media’ and chemists are well advised to investigate the potential of organic synthesis in water.

There are a number of chemical transformations which are not only compatible with aqueous media but actually benefit strongly from the unique characteristics of water. These are demonstrated in Tables 1–3¹¹.

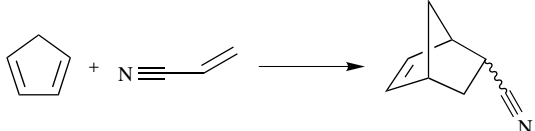
The fact that water often permits, as noted above, a simplified reaction or work-up procedure made ‘Organic Chemistry in Water’ an active field of research^{9,12–14}. This might sound quite surprising due to (a) the limited solubility of non-polar organic molecules in water and (b) the danger of hydrolysis. Nevertheless, many organic reactions can be carried out in water, often with improved results.

TABLE 1. Rate constants for the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone in different solvents

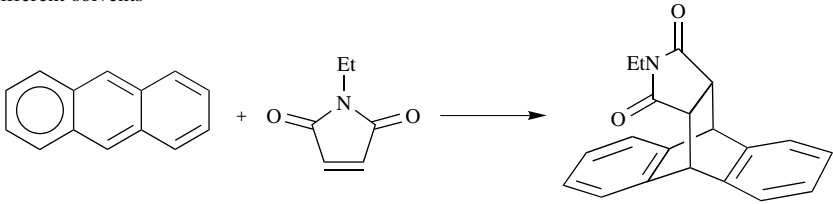


Solvent	$10^5 k(\text{M}^{-1} \text{s}^{-1})$
iso-octane	5.94 ± 0.3
MeOH	75.5
H ₂ O	4400 ± 70

TABLE 2. Rate constants for the Diels–Alder reaction of cyclopentadiene and acrylonitrile in different solvents



Solvent	$10^5 k(\text{M}^{-1} \text{s}^{-1})$
iso-octane	1.9
MeOH	4.0
H ₂ O	59.3

TABLE 3. Rate constants for the Diels–Alder reaction of anthracene and *N*-ethylmaleimide in different solvents


Solvent	$10^5 k(\text{M}^{-1} \text{s}^{-1})$
iso-octane	796 ± 71
1-Butanol	666 ± 23
MeOH	344 ± 25
Acetonitrile	107 ± 8
H ₂ O	22600 ± 700


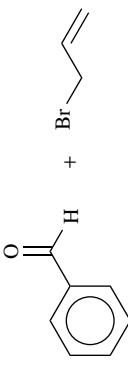
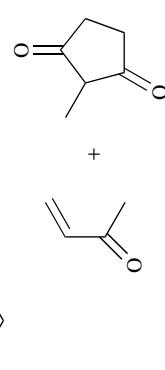
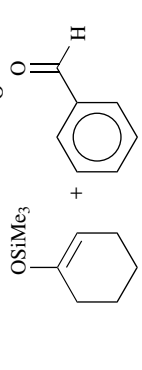
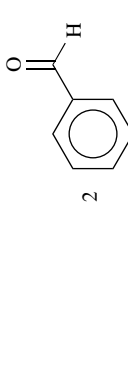
One might suspect that water is disadvantageous for catalytic reactions, because traditional Lewis acid catalysts are expected to be much less effective in the aqueous phase, but we will demonstrate in the following sections that the accelerating effects of Lewis acids and water can be additive. It will be shown that the complexation abilities of water and those of Lewis acids can lead to enhanced reactivities and selectivities, despite their apparent competition.

To date, most standard organic transformations have been carried out in water. Organic peroxide oxidations which convert olefins into epoxides result in improved yields in aqueous media compared with organic solvents (Table 4, entry A)^{15–17}. A large number of metal-catalysed hydrogenations^{18,19} and metal mediated allylations²⁰ in aqueous media have been reported (Table 4, entry B). Both 1,2- and 1,4-nucleophilic additions to carbonyl groups can be conducted in aqueous solutions and have been shown to benefit from such media (Table 4, entry C)^{21–23}. The aldol condensation is another example where a Lewis acid catalyst is often required in organic solvents but where the reaction occurs readily in pure water (Table 4, entry D)^{24–26}. Other nucleophilic transformations like the benzoin condensation (Table 4, entry E)²⁷, the Mannich (Table 4, entry F)²⁸, the Prins (Table 4, entry G)²⁹ and the Wittig–Horner reaction (Table 4, entry H)³⁰ were realized in aqueous media.

Water can also have a beneficial effect on halogenations (Table 4, entry I)^{31,32}, polymerizations³³ and photochemical transformations (Table 4, entry J)^{34,35}. As mentioned before, a large number of organometallic reactions^{18,20} were conducted in water, whereby Lewis acid catalysis is still feasible even in aqueous media³⁶. Notoriously solvent-insensitive reactions such as Claisen rearrangements (Table 4, entry K)^{37–40}, 1,3-dipolar cycloadditions (Table 4, entry L)^{41–44} and Diels–Alder (Table 4, entry M)^{11,44} reactions can be accelerated dramatically in aqueous media. In the case of the Diels–Alder reaction, accelerations in the order of 12,800 were observed simply by changing the solvent from hexane to water⁴⁵.

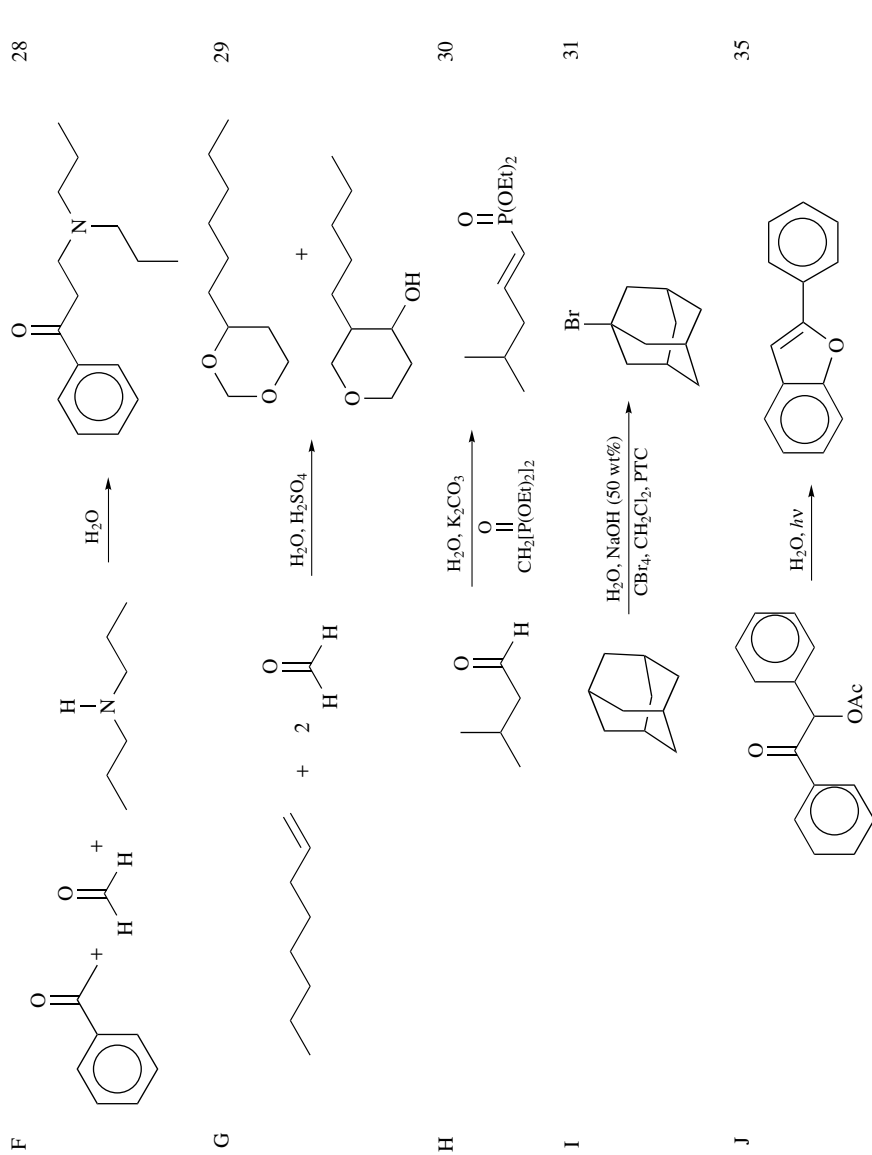
In this chapter we wish to review the collected evidence for the astonishing effects of water on reactivities and selectivities as exemplified by the Diels–Alder reactions of dienes. Examples of Lewis acid and micellar catalysis in aqueous media are also presented. Finally, the newest computational investigations including solvent effects on Diels–Alder reactions are put forward in order to rationalize some of the remarkable observations.

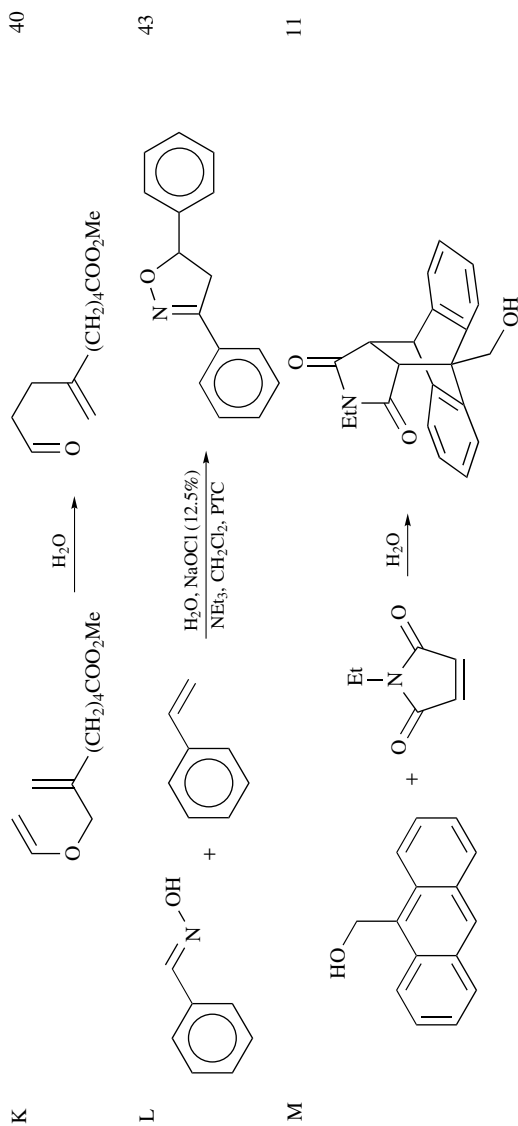
TABLE 4. Examples of organic reactions carried out in water

Entry	Exemplary reaction		Reference
A		$\alpha\text{-(HO}_2\text{C)C}_6\text{H}_4\text{CO}_3\text{H}$ $\text{H}_2\text{O (pH = 12.5)}$	16
B		$\text{H}_2\text{O, indium}$	20
C		H_2O	22
D		$\text{H}_2\text{O (pH = 7)}$	24
E		$\text{H}_2\text{O, CN}^-$	27

(continued overleaf)

TABLE 4. (Continued)





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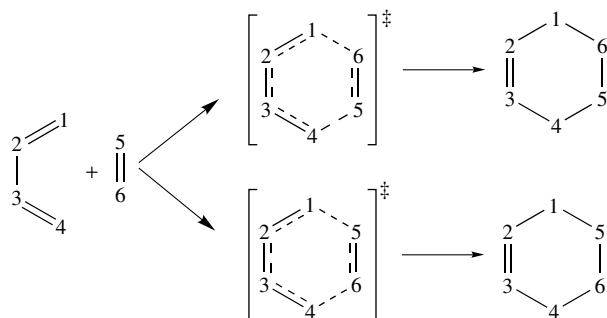
K

L

M

C. The Diels–Alder Reaction

The Diels–Alder reaction is *the* classical method for the synthesis of substituted cyclohexenes. The six-membered ring is typically formed by a [4 + 2]-cycloaddition of a diene and a two- π -electron component which is usually referred to as the dienophile. The Diels–Alder reaction is of outstanding value for the synthetic organic chemist and is the key step in the construction of compounds containing six-membered rings (Scheme 1). Since the reaction is stereospecific in the sense that the conformation of the reacting double bonds is fully retained in the configuration of the product, and because the regioselectivity of the ring closure can be controlled efficiently, the reaction is a formidable tool in synthetic organic chemistry.

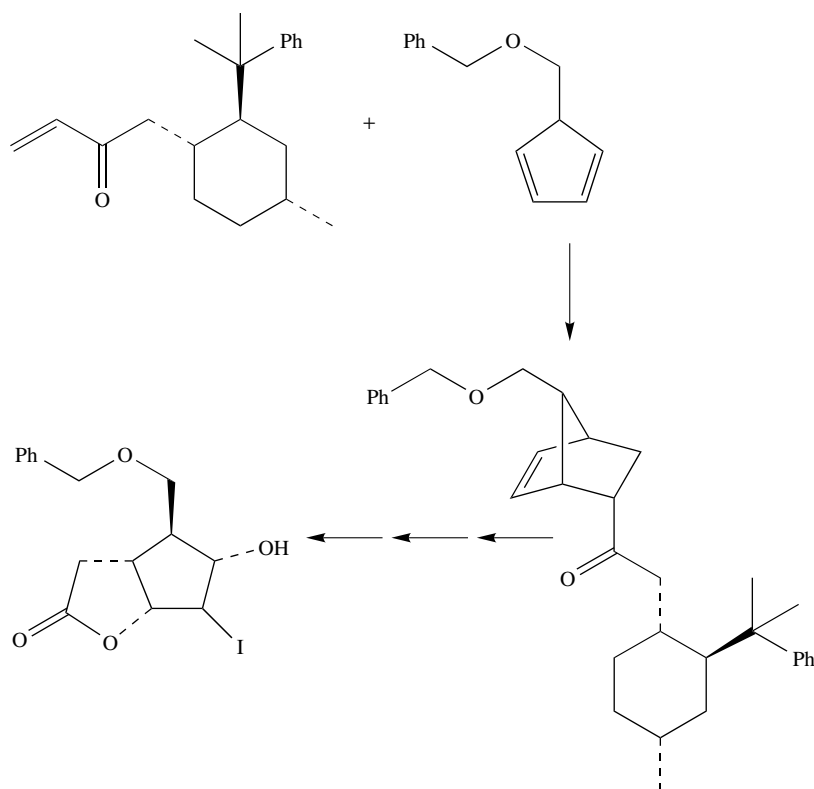


SCHEME 1. Schematic representation of the Diels–Alder reaction. The two possible ring closures together with the two transition states and the resulting regioisomers are presented. The versatility of the reaction is illustrated by the fact that heteroatoms are allowed at any of the positions 1–6 (hetero-Diels–Alder reaction)

The first example of a Diels–Alder reaction, the dimerization of tetrachlorocyclopentadienone, was observed in 1892⁴⁶, and was further investigated in the next 20 years^{47–49}, but it took nearly 30 years until its importance was recognized by chemists in the 1920s. In 1928 the famous paper on the detailed description of synthetic and theoretical aspects of this reaction was published by Otto Diels and Kurt Alder⁵⁰, two German chemists. For their ground-breaking work, they ultimately were awarded the Nobel Prize in 1950.

Since the Diels–Alder reaction is both experimentally and theoretically well characterized, we now have a thorough understanding of this important transformation. This allowed one to influence rates and selectivities of this cycloaddition. An illustrative example is the selective synthesis of a key prostaglandine precursor⁵¹ (Scheme 2) in which all stereochemical information derives from the starting materials. Although the general mechanism of Diels–Alder reactions is well understood, it is still uncertain if these reactions occur in biosynthesis. An instructive example is represented by the total synthesis of optically active plagiospirolides **1** and **2** (Scheme 3)⁵². These syntheses were considered to be biomimetic and are indications that Diels–Alder reactions may also occur *in vivo*.

Although there are many natural products **1–4** (Scheme 3 and 4)^{52,53} which may formally derive from [4 + 2]-cycloadditions, and although the Diels–Alder (DA) reaction is of great value and is irreplaceable for synthetic chemists, there is no definitive proof for Diels–Alder reactions occurring in biosynthesis⁵⁴. At the same time cell-free extracts, for instance, from the fungus *aletermaria solani*, accelerate Diels–Alder reactions by a factor of 4.1 and reverse the normally observed *endo*-selectivity⁵⁵. Still, there is no

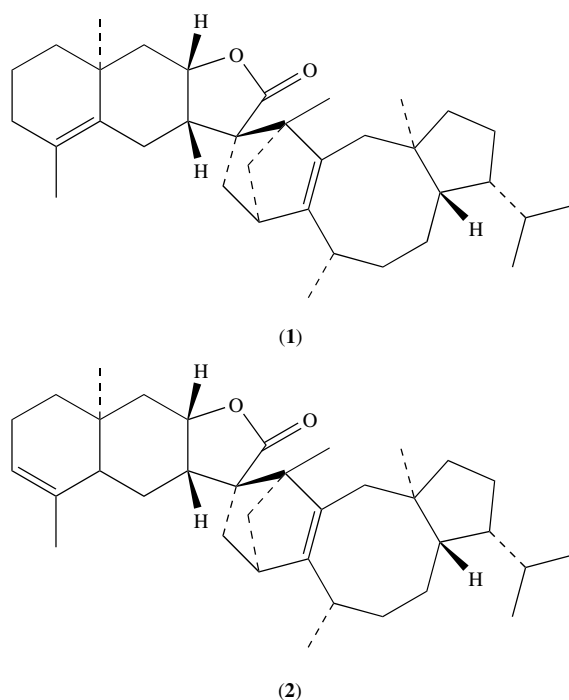


SCHEME 2. The stereoselective Diels–Alder reaction leading to an important iodolactone prostaglandin precursor

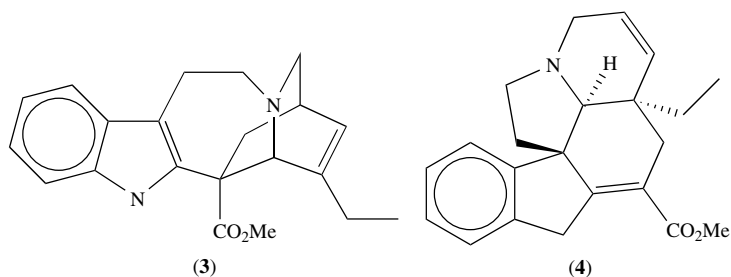
specific ‘Diels–Alder-ase’ enzyme which would, by analogy to commonly carried out DA reactions, catalyse these transformations at ambient temperatures⁵⁶.

The controversy on the existence of *in vivo* Diels–Alder reactions cannot be put to rest here, but the numerous examples of natural products containing cyclohexene groups and the catalytic effectivity of ‘biological’ surroundings support the idea of *in vivo* Diels–Alder reactions. Apart from cell-free extracts, RNA-based mixtures of metals also show catalytic activity and it was demonstrated that this catalyst system can be quite effective as an artificial Diels–Alder-ase⁵⁷. We will show that water, the prime solvent of biosynthesis, also catalyses [4 + 2]-cycloadditions. Considering that biosyntheses are often of exceptional selectivity, it is clear that understanding biomimetic transformations in water as the solvent is an important goal of modern chemistry. The possibilities offered by and the reasons for Diels–Alder catalysis in water will be the main topic of this chapter.

We will present mechanistic aspects of the Diels–Alder reaction, its selectivity and reactivity in order to explain solvent effects on the one hand, and the effects of Lewis acids on the other. Other catalytic systems like micelles will also be addressed. Some of the explanations may seem trivial or are well-known but, as we will use these in later sections, a clear terminology is desirable.



SCHEME 3. Plagiospirolides **1** and **2**, synthesized by Diels–Alder reactions. The natural compounds are suggested to be formed via *in vivo* cycloaddition processes



SCHEME 4. Catharanthine **3** and tabersonine **4**, natural compounds containing a cyclohexene moiety. These may derive from *in vivo* Diels–Alder reactions⁵³

The reactivity and selectivity of the Diels–Alder reaction can be understood in terms of Frontier Molecular Orbital (FMO) theory which evolved during studies of the role of orbital symmetry in pericyclic reactions by Woodward and Hoffmann⁵⁸ and, independently, by Fukui⁵⁹. FMO theory explains the driving force of a reaction between two compounds by the efficiency with which the molecular orbitals of the two partners overlap. This orbital interaction is maximized when their energy separation is small. FMO theory further states that the two most important interacting orbitals are the Highest Occupied

Molecular Orbital (HOMO) of one component and the Lowest Unoccupied Molecular Orbital (LUMO) of the other. Within the scope of FMO theory, the reactivity of two reaction partners towards each other is described quantitatively by the Klopman–Salem–Fukui relationship (equation 1)^{60–62}:

$$\Delta E = - \sum_{ab} (q_a + q_b) \beta_{ab} S_{ab} + \sum_{k < l} \frac{Q_k Q_l}{\varepsilon R_{kl}} + \sum_r \sum_s^{occ. unocc.} - \sum_s \sum_r^{occ. unocc.} 2 \frac{\left(\sum_{ab} c_{ra} c_{sb} \beta_{ab} \right)^2}{E_r - E_s} \quad (1)$$

where q_a and q_b are electron densities at the atomic orbitals a and b , β and S are the resonance and overlap integral, Q_k and Q_l are the total charges of atoms k and l , ε is the dielectric constant, R_{kl} is the distance between atoms k and l , c_{ra} is the coefficient of atomic orbital a in the molecular orbital r , r and s are the indices of the two interacting molecules and E_r is the energy of the molecular orbital r .

The three terms of this equation simply represent the different energetic aspects of two approaching molecules leading to a reaction. The first part determines the first-order closed-shell repulsion, i.e. the interaction of the occupied orbitals of one reaction partner with those of the other. In general, this first sum is larger than the others but its value is nearly constant for different reaction paths. Hence, the first term is nearly unspecific and does not explain the observed selectivities. Within the scope of FMO theory the first part of the Klopman–Salem–Fukui equation is generally neglected because the theory attempts to explain changes in the reaction rates and selectivities.

The second term determines the electrostatic interactions of the two reacting partners. This part is important in reactions of ions and other charged species, but in the scope of FMO theory this term is usually disregarded. Hence, this limits the general applicability of FMO theory; in reactions of highly charged molecules it may lead to wrong conclusions. In reactions of uncharged molecules with low polarity, neglect of the second term of the Klopman–Salem–Fukui equation is an acceptable approximation.

The interactions of the occupied orbitals of one reactant with the unoccupied orbitals of the other are described by the third term of the Klopman–Salem–Fukui equation. This part is dominant and the most important for uncharged reaction partners. Taking into account that the denominator is minimized in case of a small energy gap between the interacting orbitals, it is clear that the most important interaction is the HOMO–LUMO overlap. With respect to the Diels–Alder reaction, one has to distinguish between two possibilities depending on which HOMO–LUMO pair is under consideration. The reaction can be controlled by the interaction of the HOMO of the electron-rich diene and the LUMO of the electron-poor dienophile (normal electron demand) or by the interaction of the LUMO of an electron-poor diene and the HOMO of an electron-rich dienophile (inverse electron demand; cf Figure 1).

In the case of normal electron demand Diels–Alder reactions, the HOMO–LUMO gap can be diminished by either raising the energy of the HOMO of the diene by introducing electron-donating groups or by lowering the energy of the dienophile LUMO through electron-withdrawing groups. The opposite applies to inverse electron demand Diels–Alder reactions⁶³.

While the reactivity is determined by the HOMO–LUMO energy separation, the selectivity is dominated by the orbital coefficients⁶⁴. As a consequence, the kinetically controlled regioselectivity of the Diels–Alder ring closure, and thus the formation of the two new σ -bonds (between atoms 1,6 and 4,5 or between atoms 1,5 and 4,6 in Scheme 1), is determined by the FMO coefficients at the terminal carbon atoms of the diene and the dienophile. The FMO predictions boil down to the fact that the formation of σ -bonds between carbon atoms with similar orbital coefficients is preferred. The magnitudes of these coefficients

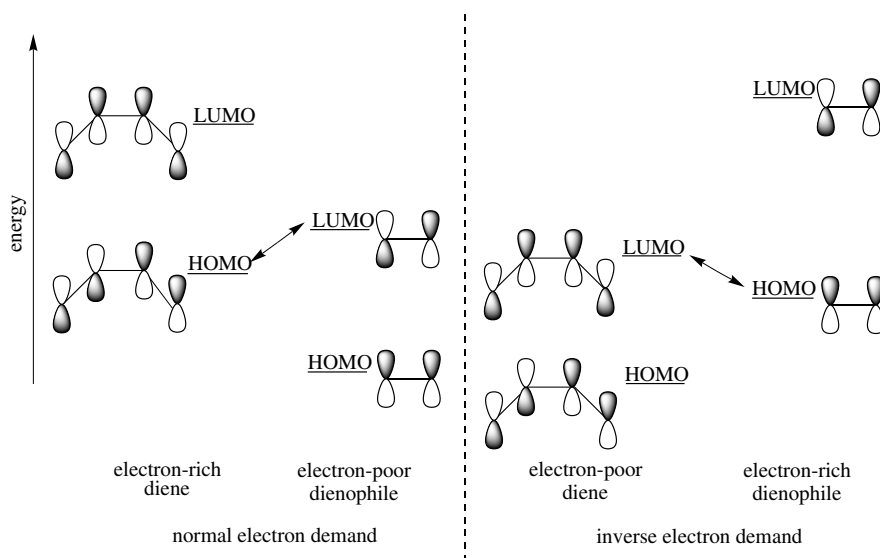


FIGURE 1. The HOMO/LUMO interactions in Diels–Alder reactions with normal and inverse electron demand

can be qualitatively evaluated using resonance theory^{65–68}, or by high-level quantum chemical computations.

Besides the regioselectivity described in the previous paragraph, there is another type of selectivity arising when substituted dienes and dienophiles form cyclohexene derivatives. While the above-mentioned selectivity determines the ring closure, there are still two different products possible, namely the *endo*- and *exo*-forms, depending on the way the dienophile attacks the diene (Figure 2). The *endo/exo* ratio is kinetically controlled; under normal conditions the *endo*-product is preferred. This preference was studied extensively and is now explained in terms of secondary orbital interactions (Figure 2)⁶⁹. The Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone is an example for a normal electron demand Diels–Alder reaction in which the selectivity is controlled by the diene HOMO and the dienophile LUMO interaction. Considering that only the geometry of the *endo*-transition structure allows for effective secondary orbital interactions, the selectivity of Diels–Alder reactions for the *endo*-product becomes clear. Hence, only the *endo*-transition structure is energetically stabilized and the reaction forming the *endo*-product is accelerated.

The reasons for the *endo*-selectivity of Diels–Alder reactions are only useful for the reactions of dienophiles bearing substituents with lone pairs; without a Lewis basic site no secondary orbital interactions are possible. But even in reactions of pure hydrocarbons the *endo*-selectivity is observed, requiring alternative explanations. For example, the *endo*-preference of the reactions of cyclopropene with substituted butadienes have been rationalized on the basis of a ‘special type’ of secondary orbital interactions⁷⁰. Apart from secondary orbital interactions which are probably the most important reason for the selectivities of Diels–Alder reactions, recent literature also advocates other interpretations.

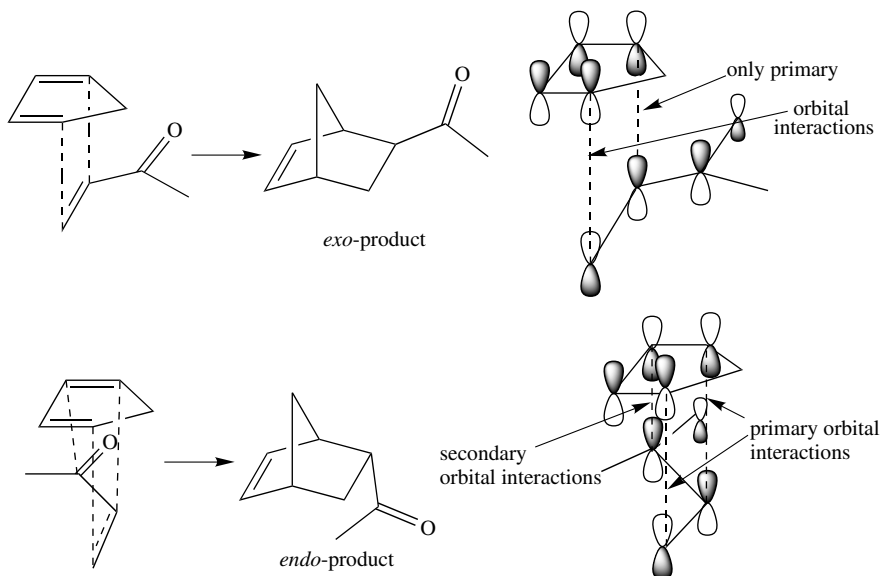


FIGURE 2. The Diels–Alder reaction of cyclopentadiene with methyl vinyl ketone. The selectivity leading to the *endo*-product (*endo*-selectivity of Diels–Alder reactions) is rationalized by secondary orbital interactions in the *endo*-transition state

For instance, steric effects are frequently suggested to be important in determining the selectivity, especially in the reactions of α -substituted dienophiles and in reactions forming the unexpected *exo*-product with high selectivity (Scheme 5)^{71,72}. London dispersion interactions have also been considered, and it has been argued that these interactions can sometimes override secondary orbital interactions^{73–75}.

While many observations are well understood, e.g. those dealing with the reaction rate or with the selectivity, there are some factors which cannot be generalized. Many transformations of particular reactants or under unusual reaction conditions led to unexpected results. There are often singular explanations for such reactions but no overall concept. For instance, computations on Diels–Alder transition structures and thermodynamics of retro-Diels–Alder reactions confirmed that the activation volume of these [4 + 2]-cycloadditions is negative⁸⁰. This result, pointing to the compact character of the transition structure, is used to explain the dependence of reactivity and selectivity on internal as well as external pressure^{81–83}. These effects are only observed at relatively high external pressures (Table 5).

Another example is the influence of ultrasonic sound treatment. In chlorinated or brominated solvents it leads to extreme rate accelerations and higher selectivities (Table 6)⁸⁴. This observation was explained by the formation of hydrogen halide from the sonolysis of the solvent molecules, followed by protonation of the dienophiles and ordinary acid catalysis. Nevertheless, although there are quite a few aspects of the Diels–Alder reaction which are not totally understood, the general mechanisms leading to selectivities and catalysis are clear.

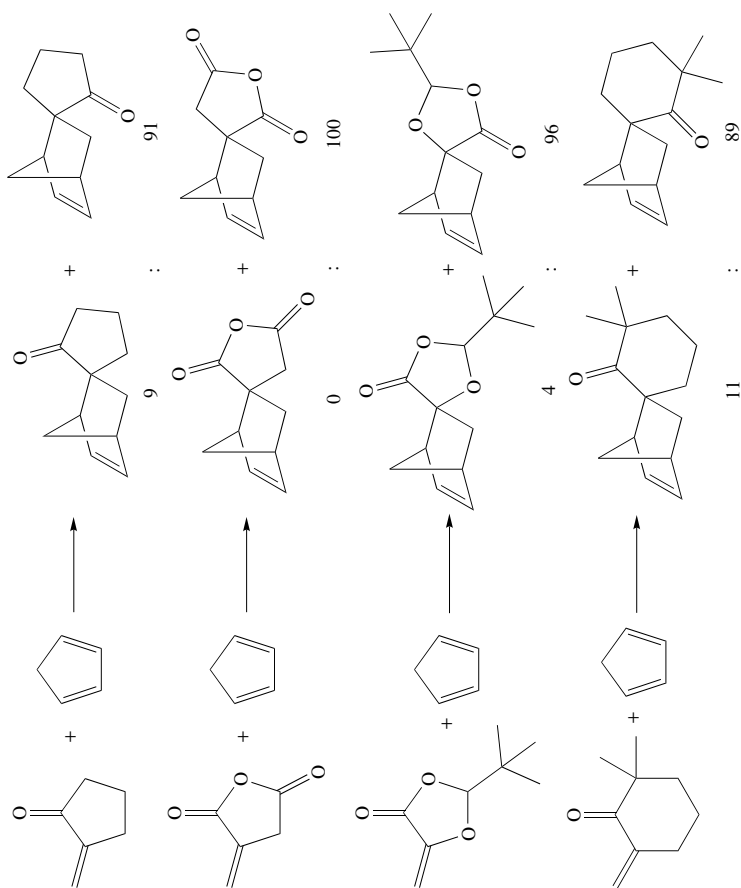
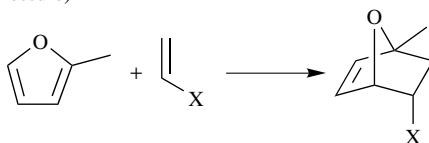

 SCHEME 5. High *exo*-selectivities in the Diels–Alder reaction of α -substituted dienophiles with cyclopentadiene.^{76–79}

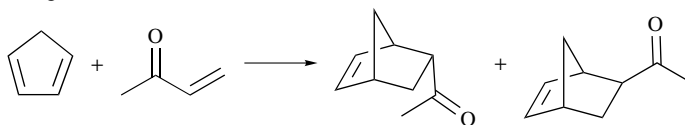
TABLE 5. External pressure dependence on the reaction of 2-methylfuran with several dienophiles⁸² (these reactions do not proceed at atmospheric pressure)



Entry	X	Medium	Ratio ^a
1	COCH ₃	water	3.4
		CH ₂ Cl ₂	4.6
2	COOCH ₃	water	3.2
		CH ₂ Cl ₂	5.0
3	CN	water	3.1
		CH ₂ Cl ₂	5.3

^aReactivity ratio at 3000 vs 1100 bar, respectively.

TABLE 6. Influence of ultrasonic irradiation on the yield and *[endo]/[exo]* product ratio of the reaction of cyclopentadiene with methyl vinyl ketone in various organic solvents⁸⁴



Solvent	Yield (%) ^a		<i>[endo]/[exo]</i> ratio ^a	
))))))))
CH ₃ OH	17 ± 1	17 ± 2	11.5 ± 0.5	11.5 ± 0.5
C ₆ H ₅ CH ₃	3 ± 1	3 ± 1	5.0 ± 0.3	4.9 ± 0.3
CHCl ₃	7 ± 1	15 ± 2	7.2 ± 0.4	12.7 ± 0.5
CH ₂ Cl ₂	4 ± 1	18 ± 2	6.7 ± 0.3	15.5 ± 0.5
CH ₂ Br ₂	7 ± 1	58 ± 3	6.5 ± 0.3	19.5 ± 0.6

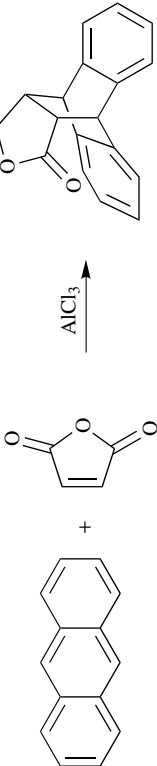
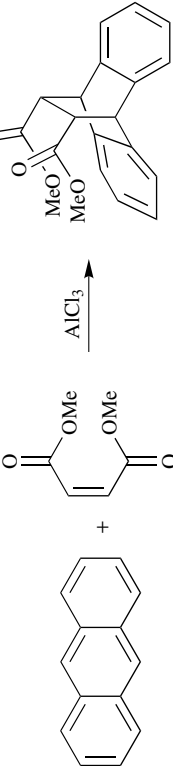
^aAfter 1 h at 10 °C.

II. ASPECTS OF CATALYSIS

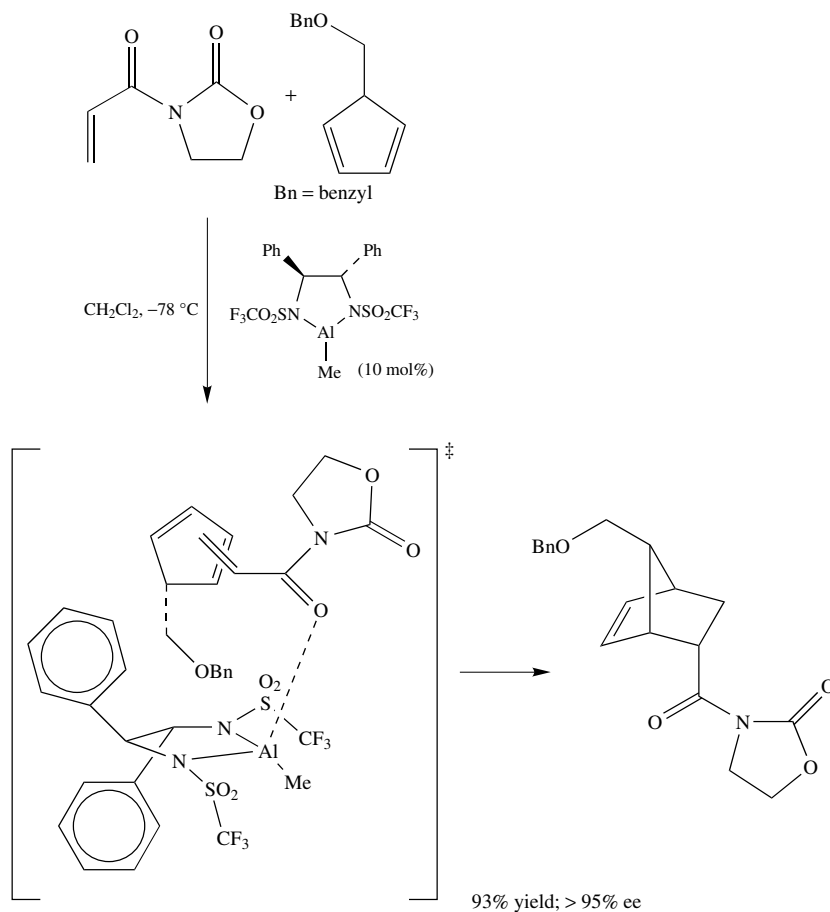
A. Lewis Acids

Uncatalysed Diels–Alder reactions usually have to be carried out at relatively high temperatures (normally around 100 °C)⁷³, often leading to undesired side reactions and retro-Diels–Alder reactions which are entropically favoured. The Diels–Alder reaction became applicable to sensitive substrates only after it was realized that Lewis acids (e.g. Al₂Cl₆) are catalytically active⁵⁶. As a consequence, Diels–Alder reactions can now be carried out at temperatures down to –100 °C⁸⁵. The use of Lewis acid catalysts made the [4 + 2]-cycloaddition applicable to the enantioselective synthesis of many natural compounds^{51,86}. Nowadays, Lewis acid catalysis is the most effective way to accelerate and to stereochemically control Diels–Alder reactions. Rate accelerations of ten-thousand to a million-fold were observed (Table 7, entries A and B).

TABLE 7. Effects of Lewis acid catalysis on the rate of some Diels–Alder reactions

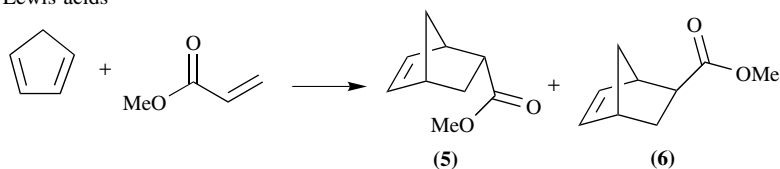
Entry	Reaction	Observation
A		<p>Catalysed reaction completed after 1.5 min. From an extrapolation of the rate curve it was estimated that 4800 h would be required for 95% yield in the uncatalysed reaction</p>
B		<p>Catalysed reaction (CH₂Cl₂, rt) completed after 5 min. In the absence of catalyst the reaction took 3 days (95%) in refluxing dioxane</p>

Lewis acid catalysis is not limited to cases in which increased yields or enhanced selectivities are desired. Lewis acids offer also the possibility to induce chiral information leading to enantioselective product formation. The *enantioselective induction* by chiral Lewis acids found widespread application in organic synthesis, especially in the synthesis of natural products with many chiral centres. An enantioselective Diels–Alder reaction is the key step in the synthesis of an iodolactone prostaglandine precursor (Scheme 6).⁸⁸



SCHEME 6. Enantioselective Diels–Alder reaction induced by a chiral aluminium-containing Lewis acid⁸⁸

Furthermore, regioselectivities⁸⁹ as well as the diastereofacial selectivities^{90,91} may be increased in the presence of Lewis acids (Table 8). For instance, $\text{AlCl}_3 \cdot \text{OEt}_2$ improves the *endo*-selectivity of the reaction of cyclopentadiene and methyl acrylate from 82% to 98%.⁸⁷ The astonishing rate accelerations, the improved yields and higher selectivities make the Lewis acid catalysed Diels–Alder reaction one of the most important organic reactions.

TABLE 8. Rate and selectivity enhancements of Diels–Alder reactions by addition of Lewis acids^{56,87}

Entry	Catalyst	Yield (%)	5	6
1	—	22–51	82	18
2	BF ₃ · OEt ₂	66	97	3
3	AlCl ₃ · OEt ₂	79–91	98	2
4	SnCl ₄	67–79	95	5
5	TiCl ₄	80	95	5

Lewis acid catalysis enormously enriches the scope of Diels–Alder reactions, but it is limited to reagents containing Lewis basic sites, i.e. functional groups with lone pairs such as carbonyl, amino, ether or nitro close to the reaction centre. As we have seen in the discussion about the FMO aspects of Lewis acids, the major reason for catalysis is the reduction of the HOMO–LUMO gap. In case of Diels–Alder reactions with normal electron demand, it follows that the coordination of the Lewis acid lowers the LUMO energy of the dienophile. Such interactions are only possible if there is a spatial proximity or an electronic conjugation between the coordinated Lewis basic site and the reaction centre. Fortunately, in nearly every Diels–Alder reaction one of the reagents, mostly the dienophile, meets this requirement.

The Lewis acid activation mechanism can be understood within the scope of FMO theory. Upon coordination to a lone pair at the Lewis basic centre of the dienophile (in the case of a Diels–Alder reaction with normal electron demand), the electron-withdrawing effect of the catalytically active Lewis acids leads to a change of the electron density on the Lewis basic atom and, in turn, of the entire conjugated system. It might be surprising, but the complexation by an electron-withdrawing group does not necessarily lead to a decrease of electron density at the Lewis acidic centre. For instance, while the charge on the carbonyl oxygen of acrolein is calculated to be $-0.52 e$, the charge on this atom after protonation is $-0.62 e$. In the case of the acrolein–trifluoroborane complex the charge amounts to $-0.59 e$ ⁹². On the other hand, of course, the charge at the reacting carbon–carbon double bond is increased, or rather the atoms become more positive. This change in charge goes hand in hand with a lowering of the orbital energies. The decrease of the HOMO–LUMO energies causes the increased rate of accelerations in Diels–Alder reactions.

The effects of Lewis acids on the stereoselectivities can also be understood in terms of orbital interactions. The variation in charge at the respective basic centre gives rise to a change in the magnitude of the orbital coefficients of the entire interacting molecular orbital. These effects are visualized by the HOMO and LUMO representations of the Lewis acid–base complex of acrolein and trifluoroborane (Figure 3), and in an even more extreme case by the HOMO and LUMO representations of one of the simplest dienophile–Lewis acid complexes: protonated acrolein^{92,93}.

The change in electron distribution caused by the Lewis acid involves the entire conjugated system. Firstly, the decrease in HOMO and LUMO energies leads to a more efficient

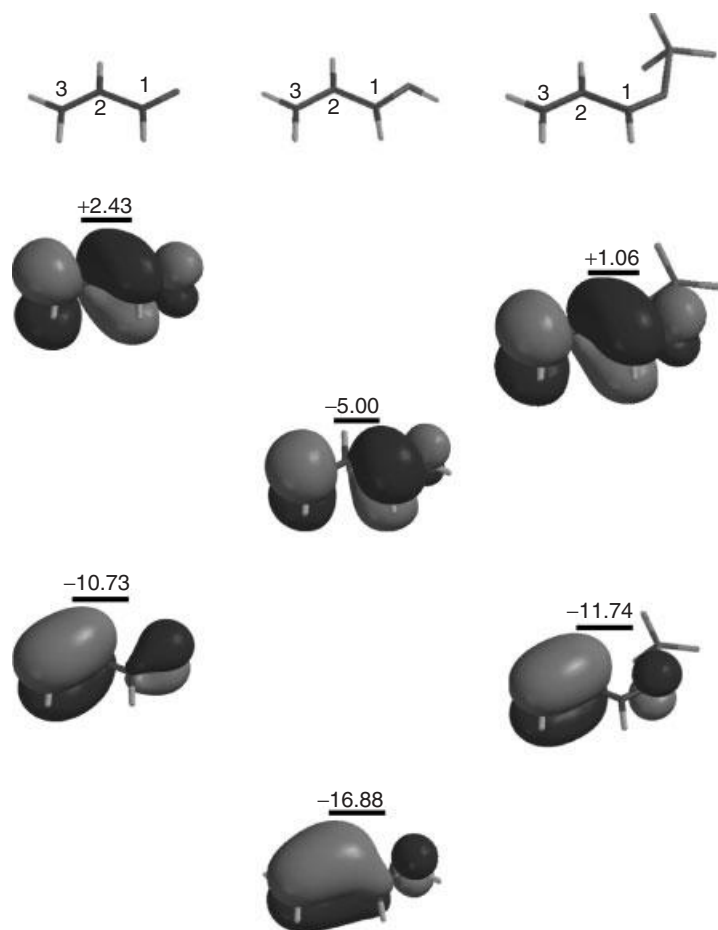
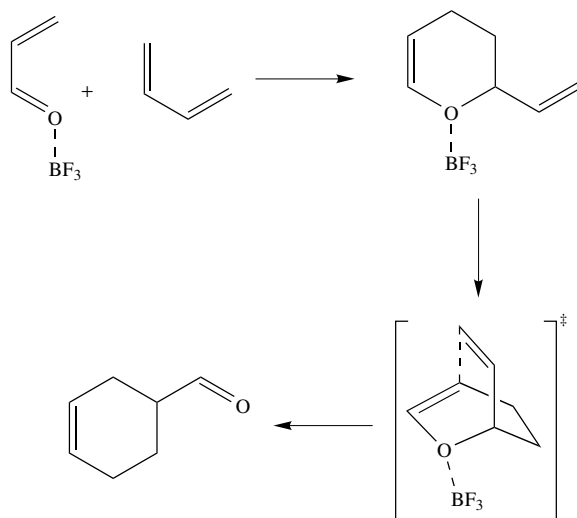


FIGURE 3. Frontier molecular orbital energies (eV) and representations of the coefficients of acrolein, protonated acrolein and the acrolein–trifluoroborane complex¹⁰¹. Geometry optimizations were performed at the AM1^{102,103} level of theory; orbital energies and electronic distributions were determined at HF/3-21G^{104–107}

orbital overlap between the reactants and thus to a rate acceleration. Secondly, the higher polarization at the alkene moiety, reflected in the increased difference of the orbital coefficients at carbons 1 and 2, gives rise to enlarged regioselectivities observed in Lewis acids catalysed Diels–Alder reactions. Thirdly, the increase of the orbital coefficient at the carbonyl carbon 1, in connection with stronger secondary orbital interactions, results in higher *endo/exo* selectivities. The FMO theory serves well to explain the effects of Lewis acids on the reactivities^{94–97} and on the stereoselectivities, but there are also other rationalizations. For example, a more compact transition state for the catalysed reaction⁹³ and conformational changes in the complexed dienophile^{98–100} are used as arguments for the increased diastereofacial stereoselectivity.

In the Lewis acid catalysed reactions of α,β -unsaturated carbonyl compounds with dienes, sometimes the products of a [2 + 4]-cycloaddition, where the carbonyl compounds function as heterodienes, were isolated. It was proposed that the intermediate of the [2 + 4]-cycloaddition is formed first in this case, followed by a Cope rearrangement which leads to the 'normal' Diels–Alder product (Scheme 7).



SCHEME 7. Postulated alternative mechanism of a Lewis acid catalysed Diels–Alder reaction¹⁰⁸, the so-called Butadiene + Acrolein Paradigm¹⁰⁹

Further investigations of this unexpected behaviour showed a complex dependence on the steric demand of the dienophile as well as on the nature of the Lewis acid¹¹⁰. Large substituted dienophiles lead to [2 + 4]-cycloaddition, whereas dienophiles with less steric demand follow the normal path of the Diels–Alder reaction. While $\text{BF}_3 \cdot \text{OEt}_2$ gives the usual Diels–Alder products, Al_2Cl_6 reacts rather unselectively, while BBr_3 leads to hetero-Diels–Alder products. These findings initiated several studies on the stereoselectivities of Lewis acid catalysed Diels–Alder reactions of small α,β -unsaturated carbonyl compounds with butadiene or cyclopentadiene. Since the selectivities of kinetically controlled reactions are directly related to the transition state energies, computations on the transition structures of several Diels–Alder reactions were carried out. These *ab initio* computations supported the experimental findings that both large and electron-demanding substituents favour [2 + 4]-cycloaddition^{110–112}. The cycloaddition of a diene and a sterically demanding dienophile mostly leads to the hetero-Diels–Alder product.

During investigations into the dependence on the Lewis acid it was noted that in the case of Al_2Cl_6 the activation energies of the hetero and homonuclear Diels–Alder reactions are rather similar. On the other hand, it was found that for the $\text{BF}_3 \cdot \text{OEt}_2$ catalysed reaction the [4 + 2]-, and for the BBr_3 catalysed reaction the [2 + 4]-transition structure, is energetically favourable. In cases where the normal Diels–Alder products were obtained, calculations [HF/3-21G geometry optimizations in connection with MP3/6-31G(d) single-point energies] showed that the [2 + 4]-cycloaddition can be followed by a Cope rearrangement leading to the 'normal' Diels–Alder adduct¹⁰⁸. The computations

suggest that sometimes the Cope rearrangement does not occur and that it should be possible to isolate the [2 + 4] adduct¹⁰⁸. In a similar way the hetero-Diels–Alder reactions of azadienes¹¹³, sulphur dioxide¹¹⁴ and nitrosoethylene¹¹⁵ were investigated in great detail¹¹⁶. These examples demonstrate the far-reaching power of computational chemistry methods in elucidating reaction mechanisms.

The Diels–Alder reaction of enantiomerically pure chiral acrylic esters with cyclopentadiene leads to a pair of diastereomers. Their ratio depends strongly on the choice and amount of Lewis acid catalyst (Scheme 8)¹¹⁷. While titanium tetrachloride leads preferentially to the (2*R*)-diastereomer with high selectivity, ethyl aluminium dichloride gives the (2*S*)-diastereomer in only 56% de.

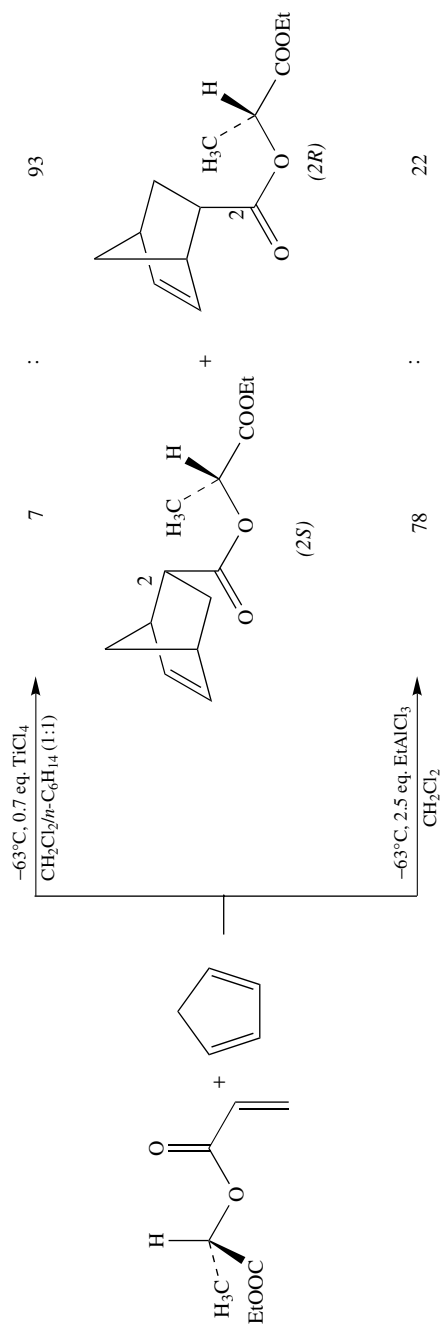
The dependence of the diastereomeric ratio on the choice of Lewis acid can be understood when considering the geometry of the Lewis acid complex. In the case of the titanium tetrachloride catalysed reaction, the interaction of the ester and the catalyst is strongly supported by the first crystal structure observed of the Lewis acid with a chiral dienophile (Figure 4)¹¹⁸.

The activation of various reactions by Lewis acids is now an everyday practice in synthetic organic chemistry. In contrast, solvent effects on Lewis acid catalysed Diels–Alder reactions have received much less attention. A change in the solvent can affect the association step leading to the transition structure. *Ab initio* calculations on the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone in aqueous media showed that there is a complex of the reactants which also involves one water molecule¹¹⁹. In an extreme case solvents can even impede catalysis¹²⁰. The use of inert solvents such as dichloromethane and chloroform for synthetic applications of Lewis acid catalysed Diels–Alder reactions is thus well justified. General solvent effects, in particular those of water, will be discussed in the following section.

B. Solvent Effects on Diels–Alder Reactions

Solvent effects on the reactivities and selectivities of organic reactions are intricate combinations of non-covalent interactions. Generally, these are separated into hydrogen bonding, hydrophobic interactions and electrostatic effects. In a typical approach, a property of a reaction, such as its rate or selectivity, is measured in a number of different solvents. This procedure allows the comparison of solvent properties and their effects on reaction rates as well as selectivities, and other observable parameters. Correlating the characteristics of a particular reaction with one or more solvent parameters reveals which non-covalent interactions are important. The major drawback is, however, that solvent parameters are often not independent. Here also, theoretical models and computer simulations provided valuable additional insights¹²¹. Both methods, the experimental dissection of the solvent effects and the computational models, have been applied successfully to Diels–Alder reactions. In the following we will attempt to generalize the results of these studies. We will discuss separately the interactions which lead to rate accelerations and increased selectivities.

At first glance the Diels–Alder reaction represents an organic transformation which is relatively insensitive to solvent effects (Table 9). For the dimerization of cyclopentadiene, the second-order rate constants in a broad range of organic solvents are quite similar⁵. The data of Table 9 refer to the special case of a Diels–Alder reaction between two pure hydrocarbons. Usually, Diels–Alder reactions only proceed at an appreciable rate when either the diene or the dienophile is activated by electron-donating or electron-withdrawing



SCHEME 8. Stereodichotomy of the Lewis acid catalysed Diels-Alder reactions of a chiral acrylic ester and cyclopentadiene

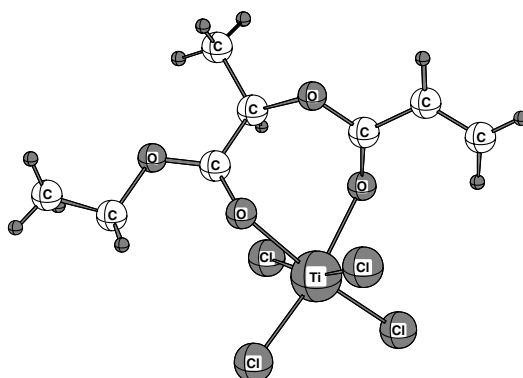


FIGURE 4. The crystal structure of the Lewis acid complex of a chiral dienophile with titanium tetrachloride¹¹⁸

substituents which mostly contain heteroatoms. These can interact efficiently with the solvent, resulting in an amplification of the solvent effect on the reaction.

There are numerous attempts to correlate solvent parameters with the reaction rate of Diels–Alder reactions¹²². Examples are the Brownstein Polarity Parameter S^{123} , the Solvophobicity Parameter $Sp^{124,125}$ the $D-\pi$ parameter (based on the solvent effect on the reaction of tetracyanoethylene and diazodiphenylmethane with benzene as the reference solvent)¹²⁶ or the Acceptor Number $AN^{127,128}$ (a parameter which describes the ability of a solvent to act as an electron pair acceptor)¹²⁹. These examples included either reactions that were next to insensitive to solvent effects (like that in Table 9) or reactions in which the reactants mainly interact with the electron pair on the donor atom of the solvent¹³⁰.

These results led to a separation of the observed Diels–Alder reactivities into three categories: (a) increase of the rate constants on increasing the Lewis acid character of the solvent as quantified by the AN parameter; this behaviour reflects the interactions between the LUMO of the solvent and the HOMO of the reactants and is similar to Lewis acid catalysis (*vide supra*); (b) reaction retardation by electron donation, as quantified by the $D-\pi$ parameter; the $HOMO_{\text{solvent}}-LUMO_{\text{reactant}}$ interactions are held responsible for this effect, representing an ‘anti-Lewis acid’ interaction which increases the HOMO–LUMO gap and hence hampers the reaction; (c) the Diels–Alder reactions show very small solvent effects and are relatively insensitive to specific reactant–solvent interactions, and

TABLE 9. Second-order rate constants k for the dimerization of cyclopentadiene in the gas phase and in several solvents at 25°C⁵

Solvent/state	$k \text{ M}^{-1} \text{ s}^{-1}$
Gas phase	6.9×10^{-7}
Neat	5.6×10^{-7}
CCl_4	7.9×10^{-7}
PhNO_2	13×10^{-7}
EtOH	19×10^{-7}

the dimerization of cyclopentadiene is a typical example (Table 9). To our knowledge, pure water or mixtures of water with other solvents were not examined¹³¹.

In studies on Diels–Alder reactions of type (a) in which only organic solvents were used, the rate constants correlate well with the solvent hydrogen-bond donating capacity α ¹⁰⁶. For the methyl acrylate/cyclopentadiene reaction, $\log k$, the logarithm of the rate constant in a number of solvents, correlates linearly with α . In mixtures of water with acetone or 1,4-dioxane, $\log k$ gave a linear correlation with the solvophobicity parameter Sp ¹³². In studies including mixtures of water and several organic solvents, an empirical combination of Sp and the E_T^N [a normalized E_T (30) parameter] scale⁵ allowed the calculation of rate constants leading to excellent agreement with observed rate constants^{133,134}. The rates of Diels–Alder reactions in highly viscous media were correlated with solvent density and were ascribed to internal pressure effects^{135,136}. These empirical correlations can only be generalized within narrow bounds. It should be noted that analysis of the interplay between a specific organic reaction and the physical properties of the solvents is not easy. Even the effects of apparently simple solvent systems like a 5 M solution of lithium perchlorate in diethyl ether lead to controversy^{137–139}. Diels–Alder reactions in such media are accelerated and rationalizations from internal pressure effects^{138,140} to Lewis acid catalysis by the lithium cation had been advanced^{137,139}. It was suggested that only if Diels–Alder reactions are not sensitive to Lewis acid catalysis, internal pressure and similarly weak effects can explain the very modest accelerations¹⁴¹. If there are several catalytic effects, Lewis acid catalysis is most effective. Combining Lewis acid catalysis with the use of water as a solvent seems therefore a worthwhile undertaking. The results available to date will be presented in the following.

Solvents and additives can influence Diels–Alder reactions through a multitude of different interactions, of which the contributions to the overall rate depend uniquely on the particular solvent–diene–dienophile combination. Attempts to build a general picture are limited to the most extensively studied type (a) Diels–Alder reactions. These Diels–Alder reactions are dominated by hydrogen-bonding and solvophobic interactions. This observation predicts a very special role of water as a solvent for type (a) Diels–Alder reactions.

The influence of the solvent on the regioselectivity is perfectly described by FMO theory¹⁴². As mentioned above, the regioselectivity is determined by orbital coefficients on the terminal carbons of the diene and dienophile which, in turn, are determined by the electronic substituent effects. These can be modified by electron donation or electron withdrawal by the solvent or additives like Lewis acids.

Changing the electron distribution through the solvent can be achieved efficiently by hydrogen bonding. This has become apparent from multiparameter analyses of the solvent effects on the regioselectivities, which revealed a dominant contribution of the hydrogen-bond donating character of the solvent¹⁴³. Apart from that, solvent effects on the *endo/exo* ratio of Diels–Alder reactions were interpreted in terms of different polarities of the individual Lewis acid–base complexes involved¹⁴⁴. In general, the *endo*-transition structure is of higher polarity than the *exo*-transition structure because the dipole moments in the *endo*-complex of the diene and dienophile are aligned, whereas in the latter they are pointing in opposite directions (Figure 5).

This explains the experimentally confirmed predictions that polar solvents attenuate the *endo*-preference, while non-polar solvents increase the *endo*-selectivity of Diels–Alder reactions. The strong correlation between the polarity of the solvent and the *endo/exo* ratios in the Diels–Alder reaction led to the empirical polarity scale $\Omega = \log(\textit{endo/exo})$ using the reaction of cyclopentadiene with methyl acrylate as the standard¹⁴⁴. The importance of solvent polarity has also been discerned on the basis of experimental¹⁴² and theoretical investigations¹⁴⁵. Dependence on the polarizability was also noted¹⁴⁶.

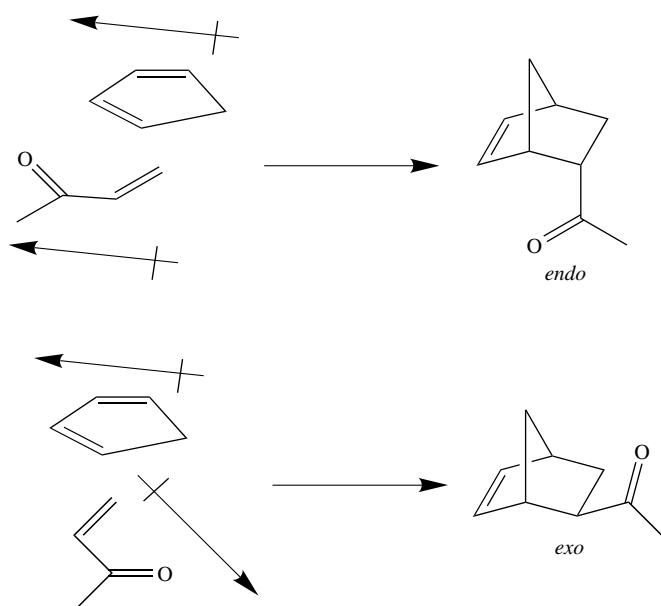


FIGURE 5. The different transition structure polarities, as indicated by the dipole arrows, of the Diels–Alder reaction

In summary, the interactions responsible for the typical solvent effects on Diels–Alder reactions are comparable to those of Lewis acids. The rate acceleration, the increase of regioselectivity and the higher *endo/exo* selectivity on changing the solvent may be explained by the FMO theory.

C. Hydrogen Bonding

1. Water

The classical description of a hydrogen bond begins with a pair of closed-shell molecules, both in their electronic ground state¹⁴⁷. The interactions between a molecule AH containing a positively polarized hydrogen atom and another molecule containing a negatively polarized heteroatom X with at least one electron lone pair, mostly oxygen, nitrogen or fluorine, are summarized as *hydrogen bonding*. AH and X are not necessarily different molecules; intermolecular and intramolecular hydrogen bonds are also possible. Although in most cases AH and X are uncharged, one of the most important contributions to hydrogen bonding is electrostatics. The lone pair of the acceptor atom is 'pulled' towards the bridging proton to form a non-covalent bond. The strength of these hydrogen bonds reaches from 2 kcal mol⁻¹ up to 15 kcal mol⁻¹ for strongly hydrogen-bonded complexes like the ammonia–hydrogen fluoride complex¹⁴⁸. The water dimer, which lies in between, will be used to describe the various components leading to hydrogen bonding. With the help of the Morokuma–Kitaura schemes^{149,150} it is possible, at least approximately¹⁵¹, to separate the different interactions (Table 10). This energy separation shows that the electrostatic interaction E_{ES} between the monomers is the most important. The other terms, the exchange energy E_{EX} , the stabilization by polarization E_{PL} and the charge transfer

TABLE 10. Morokuma–Kitaura component analysis of the SCF interaction energy of the water dimer^d

Morokuma–Kitaura component	Energy
E_{ES}	-7.5
E_{EX}	4.3
E_{PL}	-0.5
E_{CT}	-1.8
E_{MIX}	-0.1
ΔE	-5.6

^dAll values in kcal mol⁻¹¹⁵⁰.

energy E_{CT} , are normally less important. All remaining effects are collected in the last ‘mixing’ term, E_{MIX} .

The component analysis demonstrates the importance of the electrostatic attraction for the stability of the water dimer, but it also emphasizes the significance of other interactions. In hydrogen-bonded complexes of molecules which are more easily polarizable than water, the polarization and the charge transfer energies may constitute a larger fraction of the total complexation energy. Hydrogen bonding is intimately involved in the structures and properties of water in its various phases, and of molecules in aqueous solution. In addition to the traditional role of the hydrogen bond as a structural element in large molecules such as proteins and nucleic acids¹⁵², a cooperative array of such bonds appears to be vital to the function of many enzymes¹⁵³. There are some indications that hydrogen bonds play an even more important role in biological electron transfer across long distances than much stronger covalent bonds¹⁵⁴. The principles of hydrogen-bond formation have been taken as a means to design new materials capable of self-assembly into well-ordered crystal structures¹⁵⁵, for molecular recognition of organic molecules¹⁵⁶ and for organic analogs of zeolites with supramolecular cavities and continuous channels¹⁵⁷. Hydrogen bonding opens an avenue to stereocontrol of certain reactions¹⁵⁸ and for understanding the structures of monolayers¹⁵⁹. The most obvious effects of hydrogen bonding are the anomalous thermodynamic properties of water, which mostly derive directly from the unique molecular structure of liquid water and ice (Figure 6). Strong hydrogen bonds between the water molecules produce relatively stable clusters even in the liquid state. These lead to the high heat capacity, the large enthalpies of evaporation and solidification and the high surface tension of water. The water–water interactions can be influenced by solutes as well as by suspended agents. This can lead to the unique solvent effects observed in organic transformations carried out in water or aqueous solutions.

Studies of such solvent effects on type (a) Diels–Alder reactions revealed that the reactivity was primarily determined by two solvent parameters: hydrogen-bond donating capacity and solvophobicity¹⁶¹. The interactions of water with the activating group of the dienophile in normal electron demand Diels–Alder reactions via hydrogen bonding strongly influence the reaction rate^{45,162}. The correlation with the hydrogen-bond donating capacity strongly suggests that in water, a hydrogen-bond donating solvent *par excellence*, the Diels–Alder reaction benefits not only from hydrophobic but also from hydrogen-bonding interactions. Several computations, including *ab initio* calculations and Monte Carlo simulations, as well as NMR studies showed that water is able to build up strong hydrogen bonds to Lewis-basic functional groups of organic compounds^{119,121,163}.

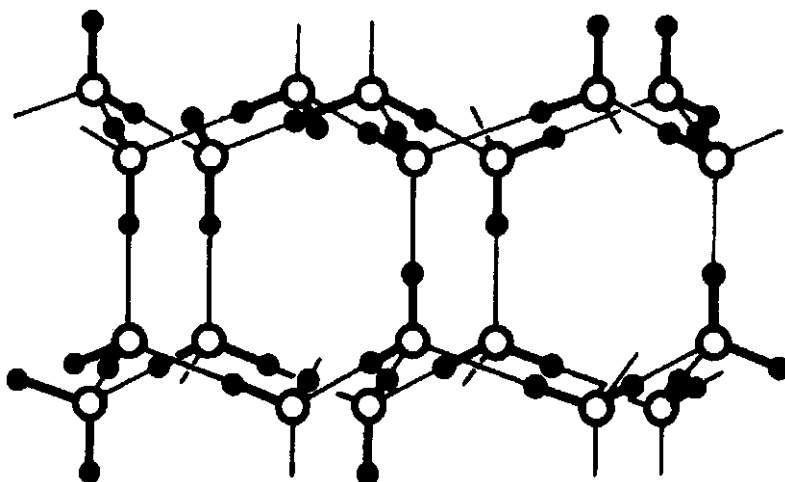


FIGURE 6. The crystal structure of water, dominated by hydrogen bonds¹⁶⁰

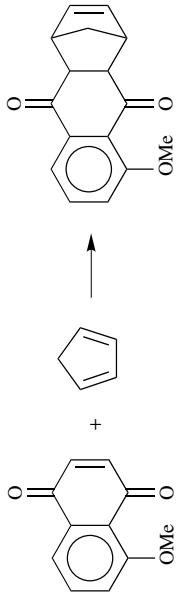
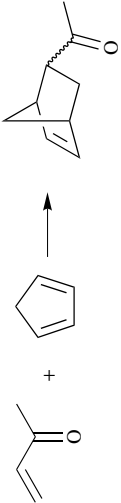
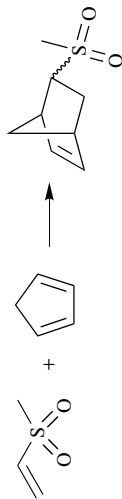
The interactions of hydrogen-bond donors and carbonyl groups are of particular interest, as these interactions often lead to effective H-bonding^{164,165}. Furthermore, the small size of the water molecules allows efficient interaction with hydrogen-bond acceptors by forming more hydrogen bonds than in the case of larger protic organic solvents. This notion is supported by detailed kinetic studies on a number of carefully selected Diels–Alder reactions which showed that hydrogen bonds strengthen the electron-withdrawing capacity of the carbonyl functionality and thereby decrease the HOMO–LUMO gap between diene and dienophile.

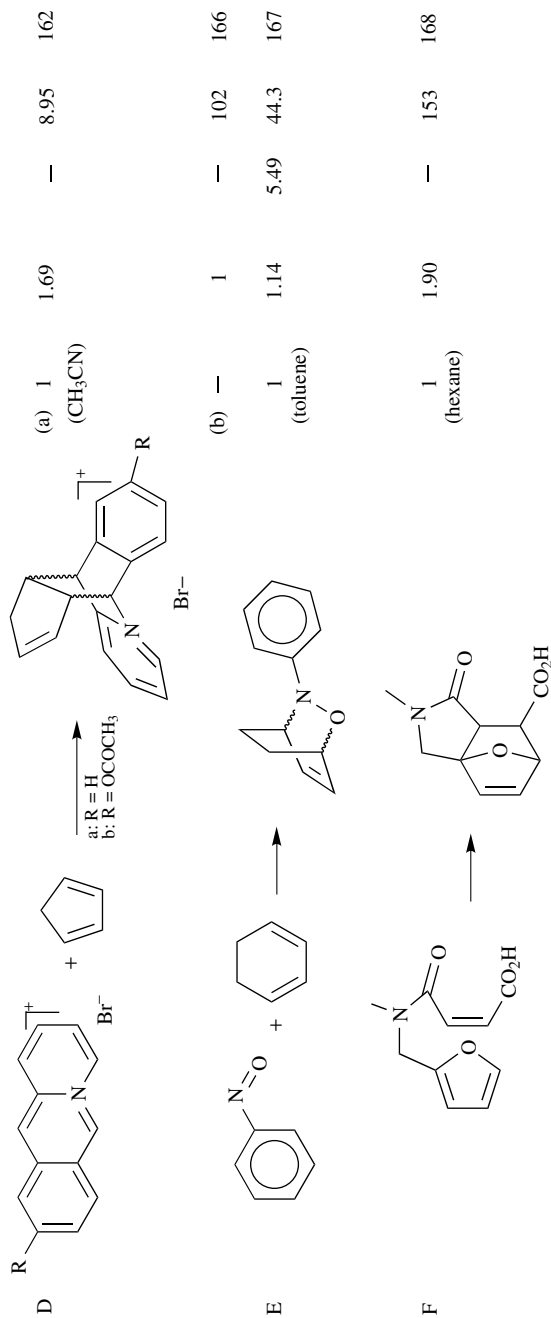
By comparison of the reaction of cyclopentadiene with a carbonyl (Table 11, entry B) and a sulphonyl-containing substrate (Table 11, entry C), the effects of hydrogen bonding on the reaction rates were examined. The presence of the sulphur atom results in less effective hydrogen bonding and, in turn, in a smaller rate acceleration. The lower sensitivity of the sulphonyl compound in comparison with the carbonyl compound is demonstrated by a much less pronounced water-induced acceleration. Further proof for the importance of hydrogen-bonding interactions comes from the observation that the strong hydrogen-bond donor HFP also leads to impressive rate enhancements (Table 11, entries A, C, D, F)¹⁶⁹ and that in case of weak hydrogen-bond acceptors the rate accelerations in water are somewhat smaller (Table 11, entry E)¹⁶⁶.

2. Hydrogen-bonding additives

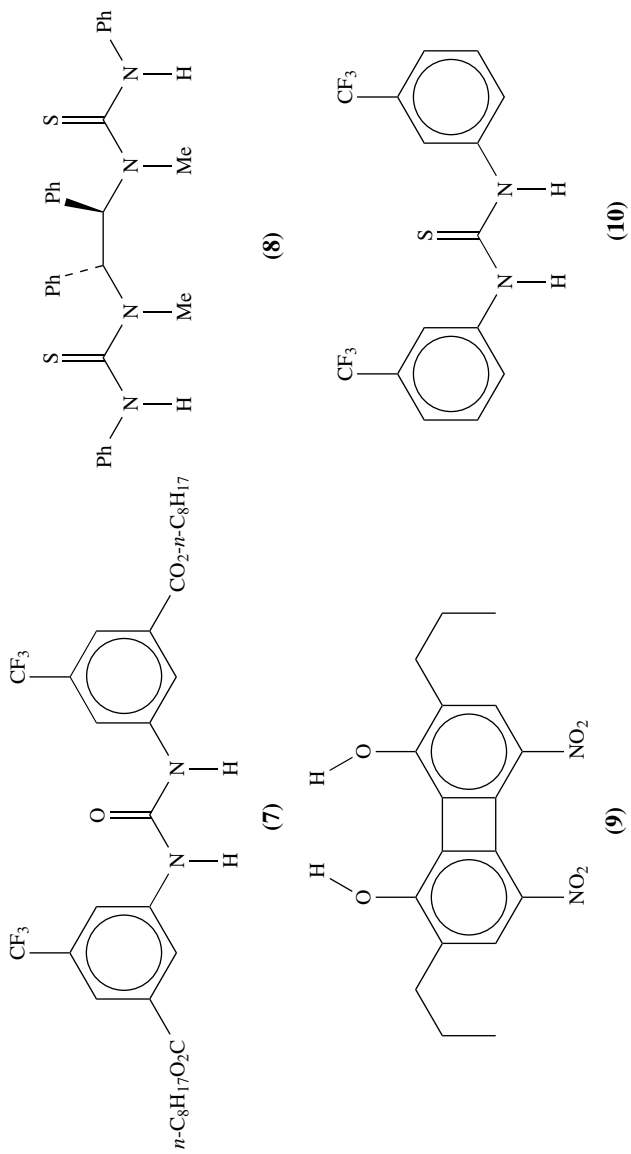
In an extension of these conclusions hydrogen-bonding additives can be of particularly great value in non-hydrogen-bonding solvents. Specific catalysts (Scheme 9, **7–10**) are hydrogen-bond donors, which lead to rate accelerations and selectivity enhancements¹⁷⁰. Only very few examples of non-aqueous hydrogen-bond donors in organic synthesis are known, but they open new avenues for developing such catalytic systems, perhaps to ultimately replace sometimes harmful Lewis acids.

TABLE 11. Relative rate constants of selected Diels-Alder reactions in water compared with organic solvents of different hydrogen-bond donor capacities

Entry	Reaction	Aprotic	EtOH	HFP ^a	H ₂ O	Reference
A		I (hexane)	28.0	4320	12800	45
B		I (CH ₃ CN)	4.79	100	290	45
C		I (CH ₃ CN)	2.49	22.6	71.0	45 162

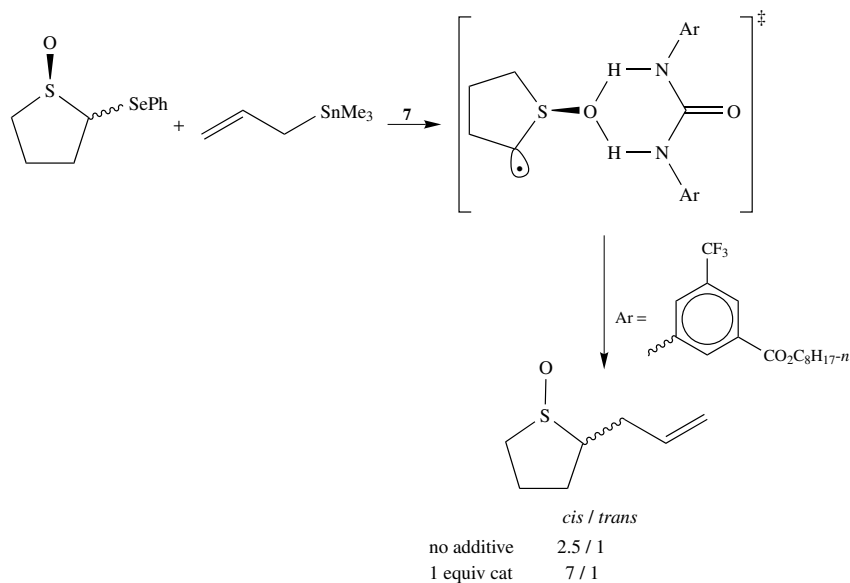


^a1,1,1,3,3,3-Hexafluoro-2-propanol.



SCHEME 9. Catalytically active hydrogen-bond donors

Hydrogen-bond donors have the ability to enhance the selectivities and rates of organic reactions. Examples of catalytic active hydrogen-bond donor additives are urea derivatives, thiourea derivatives (Scheme 10, Tables 12 and 13) as well as diols (Table 14). The urea derivative **7** (Scheme 9) increases the stereoselectivity in radical allylation reactions of several sulphoxides (Scheme 10)¹⁷¹. The modest increase in selectivity was comparable to the effects exerted by protic solvents (such as CF₃CH₂OH) or traditional Lewis acids like ZnBr₂¹⁷². It was mentioned that the major component of the catalytic effect may be the steric shielding of one face of the intermediate radical by the complex-bound urea derivative.

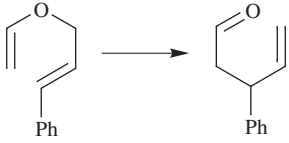
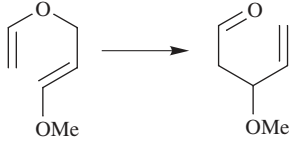


SCHEME 10. Catalysis of a radical allylation by the urea derivative **7**^{171,172}. The enhanced *cis/trans*-selectivity is caused by the steric shielding in the transition structure

TABLE 12. The asymmetric reduction of prochiral ketones under catalysis of chiral urea derivative **8**¹⁷³ (in all reactions 5% catalyst was used)

Reaction	Time	Yield(%)	ee(%)
	3 h	85	87 (S)
	9 h	98	87 (S)
	3 h	30	94 (S)
	17 h	92	94 (S)

TABLE 13. Acceleration of Claisen rearrangements by substituted diphenylurea **7**.¹⁷⁴

Reaction	equiv cat	k_{rel}^a
	none	1
	0.2	1.7
	0.5	3.1
	1.0	4.2
	none	1
	0.1	2.7
	1.0	22.4

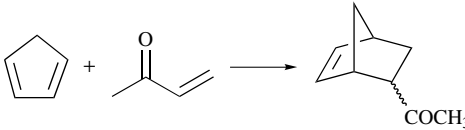
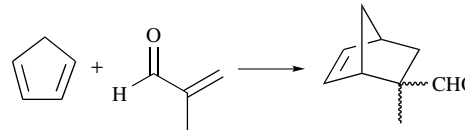
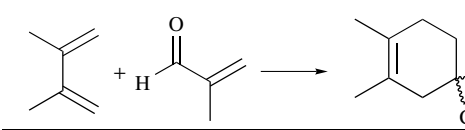
^aRelative first-order rate constants compared with the uncatalysed reaction.

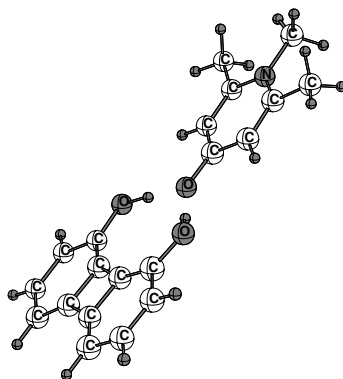
Apart from enhanced stereoselectivities, rate accelerations by hydrogen-bonding interactions were also observed. Examples of noticeable rate accelerations are Claisen rearrangements catalysed by a substituted diphenylurea **7** (Scheme 9, Table 13)¹⁷⁴. Apart from changing the *cis/trans* ratio (Scheme 10), stereoselective induction by chiral hydrogen-bond donors is also possible. A chiral thiourea catalyst **8** (Scheme 9) for the asymmetric reduction of prochiral ketones and aldehydes yields up to 87% enantiomeric excess (with an overall yield of 98% after 9 h; Table 12). In this reaction a direct coordination of the hydrogen-bond donor to the Lewis-basic carbonyl group of the prochiral ketones is, however, rather unlikely, as the ruthenium centre of the reactant is much more Lewis-acidic. A complex of urea catalyst and metal centre sounds more reasonable. An important advantage of the urea catalyst in comparison with other compounds like the diol **9** (Scheme 9) is that the chemistry of nitrogen-containing organic compounds offers wider possibilities, and the search as well as evaluation of new kinds of chiral ligands is still a topical issue¹⁷³.

The strong dependence of the reaction rate on the catalyst concentration relative to control experiments in which the amino-hydrogen atoms of **7** were substituted by methyl groups demonstrate that hydrogen bonding represents the major interaction responsible for the observed accelerations. Diels–Alder reactions are also accelerated by hydrogen-bond *donors*. It was shown that a biphenylenediol **9** is able to catalyse [4 + 2]-cycloadditions of cyclopentadiene, 2,3-dimethylbutadiene and other simple dienes with various α,β -unsaturated carbonyl compounds (Table 14)¹⁷⁵.

There are very few examples of crystal structures exhibiting chelate-like dihydrogen bonds, in which the hydrogen bond donors and acceptors are different molecules¹⁷⁶. The geometry of the initial complex between the biphenylenediol and the carbonyl compounds leading to Diels–Alder catalysis is suggested by an X-ray structure of a hydrogen-bonded adduct of the catalyst and a trimethyl pyranone (Figure 7)^{177,178}. This structure was used as a binding motive for the transition structure of the catalysed reaction.

TABLE 14. Some Diels–Alder reactions catalysed by the biphenylenediol catalyst (cat) **9**¹⁷⁵

Reaction	Conditions	Product formation (%)	
		without cat	with cat
	23 °C, 10 min	3	90
	55 °C, 2 h	16	97
	55 °C, 48 h	5	60

FIGURE 7. Crystal structure of the bidendate hydrogen-bonded complex of 1,2,6-trimethyl-4-pyridone and 1,8-biphenylenediol¹⁷⁷

Most hydrogen-bond-containing crystal structures are homomolecular, i.e. both the hydrogen-bond accepting and donating functionality exist in the same molecule. Examples of such co-crystals are urea and thiourea derivatives as well as non-cyclic imides^{156,179,180}.

The effectivity of ureas and thioureas as catalysts and the possibility to catalyse Diels–Alder reactions leads to the assumption that thioureas also should be active catalysts for the [4 + 2]-cycloaddition. A thiourea should be a more active nitrogen-containing

catalyst for the Diels–Alder reaction than a urea derivative. The higher acidity of the thiourea (urea: $pK_a = 26.9$, thiourea: $pK_a = 21.0$)¹⁸¹ most likely leads to more stable hydrogen-bonded complexes. The *m*-trifluorotolyl group is an ideal substituent because it increases the acidity and, in turn, the hydrogen-bond donor activity of the N–H bonds. Further advantages of a *m*-trifluorotolyl-substituted thiourea are, in comparison with the respective urea derivative, the better solubility and the cheap and safe preparation. Finally, the sulphur atom is a much weaker hydrogen-bond acceptor, which leads to less self-association of the catalyst and to a higher concentration of free catalyst. Hence, the substituted diphenylurea **10** offers the possibility to catalyse the Diels–Alder reaction by a nitrogen-containing organic compound. As expected, the thiourea **10** is catalytically active in Diels–Alder reactions, even in solvents which are donors themselves. The results of this investigation are summarized in Table 15¹⁸².

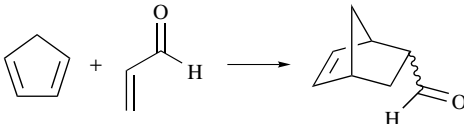
As expected, the reaction is fastest in water due to its hydrogen-bonding ability and high dielectric constant. Addition of 1 mol% of the thiourea catalyst **10** increases the yields after 1 h in cyclohexane and chloroform by about 60%; a 40 mol% catalyst doubles the yield. A sizeable catalytic effect of the *m*-trifluoromethyl-substituted thiourea was also found in water. Explanations for the surprising fact that this hydrogen-bond donor is catalytically active even in a highly competitive solvent such as water will be given in Section III.D.3.

In the previous part we showed that hydrogen bonding may lead to rate accelerations and increased selectivities. The effects of pure hydrogen bonding of suitable additives is most evident in non-polar solvents, because of the competition of H-bond accepting solvents and the reactants. Water exhibits some other solvent effects derived from its special properties, as discussed below.

D. Hydrophobicity

Apart from hydrogen bonding, the unique position of water amongst solvents derives from an intriguing phenomenon observed in this solvent: hydrophobicity⁷. This rather complex property is governed by the limited ability of water to dissolve non-polar molecules and is considered to be important in the folding of proteins, enzyme–substrate interactions, the formation of biological membranes, the aggregation of amphiphilic molecules into supramolecular structures (e.g. micelles and vesicles), in molecular recognition phenomena¹⁸³ and surface forces¹⁸⁴. The interactions appearing with the introduction of a non-polar solute into water can be reduced to two distinct processes: *hydrophobic*

TABLE 15. Dependence of the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone on the solvent and the catalyst concentration using thiourea **10**

Reaction	Solvent	Mol% cat	Conversion ^a
	cyclohexane	none	18
	cyclohexane	1	30
	chloroform	none	31
	chloroform	1	52
	chloroform	40	65
	water	none	74
	water	1	85

^aAfter one hour, in %.

hydration and *hydrophobic interaction*, which are often summarized as *hydrophobicity*. This term should not detract from the fact that the overall interactions between water and a hydrophobic substance are *attractive*.

The *hydrophobic hydration* denotes the way in which non-polar solutes affect the organization of the water molecules in their immediate vicinity. Investigations on the transfer of non-polar molecules from the gas phase into a solvent showed that the temperature dependence of the thermodynamic data (ΔH_t° , ΔG_t° , ΔS_t°) of this process are characteristic for a particular solvent¹⁸⁴. This pattern indicates that the enthalpy and entropy changes upon solvation of small non-polar compounds (from hydrogen to cyclohexane) in aqueous media are dominated by the properties of water. This led to the concept that to a first approximation the effects of solvation depend only on the nature of the solvent¹⁸⁵. Classical studies on this topic state that the water molecules around a non-polar solute show increased quasi-solid structuring^{186–188}. Already in the early days of these studies the importance of hydrophobic effects in protein folding was stressed¹⁸⁹.

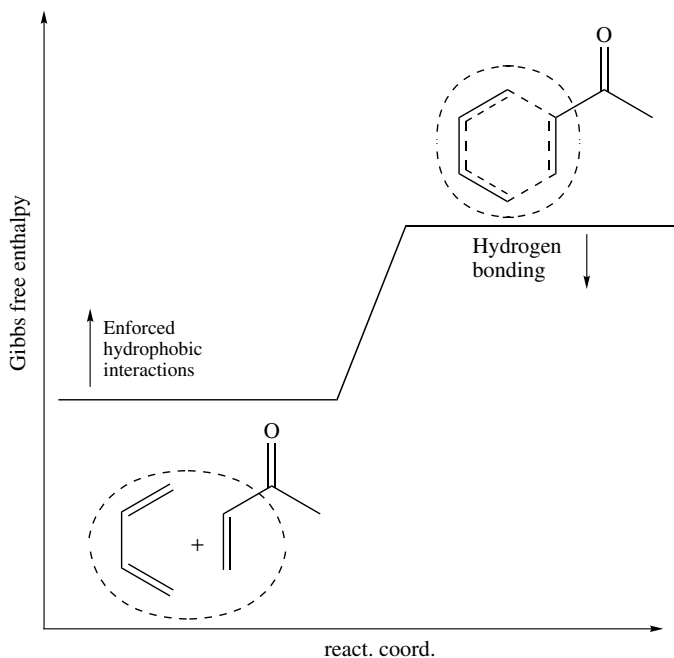
With more detailed information from computer simulations, on the hydrophobic hydration shells the ideas about hydrophobic hydration gradually changed. It became apparent that the hydrogen bonds in the hydrophobic hydration shell are not¹⁹⁰, or only to a minor extent¹⁹¹, stronger than in normal water. These results are confirmed experimentally through neutron scattering^{192–194} and X-ray studies (EXAFS)¹⁹⁵. These studies revealed that the water molecules in the hydrophobic hydration shell remain essentially fully hydrogen-bonded. For each water molecule in contact with the non-polar solute one O–H bond is oriented parallel to the non-polar surface; the other bonds point into bulk water.

In summary, it is evident that water is able to accommodate non-polar solutes without sacrificing a significant number of its hydrogen bonds. Hence, the water molecules in the first solvation shell are engaged in hydrogen bonds with their neighbours, leading to a tangential orientation with respect to the non-polar surface. Due to this arrangement, the water molecules around a non-polar solute suffer an entropic penalty, which is most likely a consequence of the reduction of the number of hydrogen bonds.

The *hydrophobic interaction* describes the tendency of non-polar molecules or parts thereof to agglomerate in aqueous media⁷. In the traditional view, hydrophobic interactions are assumed to originate from the release of water molecules from the hydrophobic hydration shells when non-polar solutes approach each other. Although the concepts about the structure of the hydrophobic hydration shell are constantly modified, this view is essentially unaltered. Nevertheless, one has to consider that the reorganization of water molecules around a non-polar solute is essential to solvation, i.e. if the water did not have to be reorganized and be forced to form a hydrophobic hydration shell, hydrogen bonds would have to be sacrificed upon dissolving the solute, so that the solubility of non-polar compounds in water would be even smaller. It follows that the formation of a hydrophobic hydration shell opposes the aggregation of the solute. Hence, hydrophobic interactions are entropy driven. The only difference between aggregation under hydrophobic interaction control and a normal phase separation is the fact that the separation process is arrested in an intermediate stage because efficient interactions between the polar headgroups of the detergent and the surrounding water molecules prevent the aggregates from forming still larger structures¹⁹⁶.

Hydrophobic interactions appear when a non-polar compound is transported into aqueous media. They include the following steps: separating the non-polar molecule from its non-polar surrounding, filling up this empty space in the non-polar medium with water, cavity formation accounting for the interactions between water and the non-polar molecules, and reorganizing the water molecules around the non-polar solute.

In summary, the effects of water which lead to rate accelerations of Diels–Alder reactions can be explained by a combination of hydrophobic interactions and hydrogen bonding. Firstly, the enforced hydrophobic interactions lead to an increase in the Gibbs free enthalpy of the starting material. Secondly, hydrogen bonding leads to a stabilization of the transition structure. These two effects are the most important reasons for the observed rate accelerations of Diels–Alder reactions in water and aqueous solutions (Scheme 11). The big difference between water and ordinary organic solvents is the molecular origin of the hydrophobic interaction which is entropy driven in pure water at room temperature and results primarily from the strong water–water interactions.



SCHEME 11. The reasons for the acceleration of Diels–Alder reactions in water

In 1948 the effects of water on the reactivity of a Diels–Alder reaction were examined for the first time. A change in the *endo/exo* selectivity in the reaction of furan and maleic acid (Table 16, entry A) was noticed¹⁹⁷. Twenty-five years later the first rate acceleration in a [4 + 2]-cycloaddition was reported (Table 16, entry B)¹⁹⁸. Still, it was not until the work of Breslow that it became common knowledge that water was a unique medium for Diels–Alder reactions¹¹.

Further investigations showed that these accelerations in water are a general phenomenon; Table 11 contains another selection from the multitude of Diels–Alder reactions in aqueous media. Note that the rate enhancements induced by water can amount to a factor of 12,800 compared to organic solvents (Table 11, entry A). A detailed study on solvent effects in an exemplary Diels–Alder reaction is presented in Table 17¹⁶². It was demonstrated that the solvent enhancements depend on the dienophile and, more strongly, on the solvent.

TABLE 16. Historical experiments concerning the observed rate accelerations and selectivities of Diels-Alder reactions in different solvents

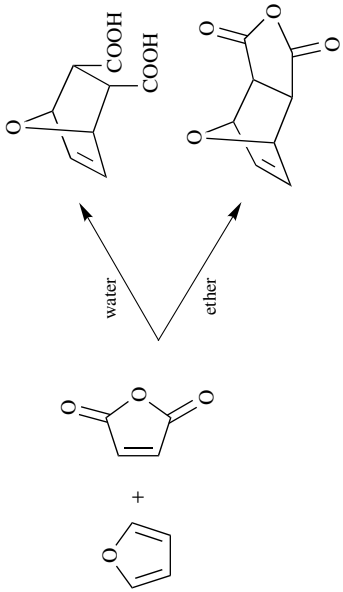
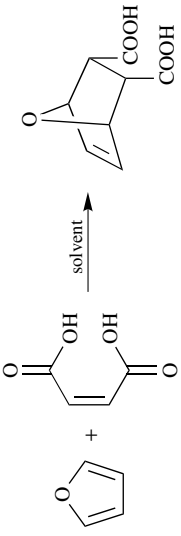
Entry	Reaction	Reference
A		197
B		<p>yields after 5 days (rt)</p> <p>D₂O: 55%</p> <p>CD₃OD: 33%</p> <p>DMSO-d₆: 10%</p>

TABLE 17. Second-order rate constants $10^3 k_2 (\text{M}^{-1} \text{s}^{-1})$ for the Diels–Alder reaction of **11a–e** with cyclopentadiene in different solvents at 25°C ¹⁶²

(11)(a) R = NO₂
 (b) R = COCH₃
 (c) R = H
 (d) R = CH₃
 (e) R = OCH₃

Solvent	11a	11b	11c	11d	11e
<i>n</i> -Hexane	21.2	5.37	1.08	0.509	0.435
Acetonitrile	92.2	21.6	6.28	5.35	3.90
Ethanol	158	45.0	10.0	12.2	
1-Propanol	228		19.6		
2-Propanol		64.9		13.2	14.8
TFE ^a	3520	867	438	291	326
HFP ^b	13100	3080	1690	988	1880
Water	25000	8870	4950	3690	5560

^a1,1,1-Trifluoroethanol.^b1,1,1,3,3,3-Hexafluoro-2-propanol.

These rate accelerations were explained in terms of hydrophobicity¹¹. The influences of a solute on the internal structure of the solvent are summarized in the terms ‘chaotropic’ and ‘anti-chaotropic’. Chaotropic agents are compounds (mostly salts) which destroy the ordered structure of liquid water by forming hydrogen bonds; anti-chaotropic agents are compounds which stabilize the ordered structure of water¹⁹⁹. By demonstrating that cycloadditions can further be accelerated by adding ‘anti-chaotropic’ salts such as lithium chloride (‘chaotropic’ salts like guanidinium chloride lead to retardation)^{200,201}, it was shown that it must be hydrophobic effects which cause these changes in reactivity¹².

There are numerous alternative explanations for the observed Diels–Alder reactions in water. It was suggested that catalysis with amphiphilic compounds may be due to micellar catalysis^{202–205}. This notion inspired some authors to raise aggregation phenomena as general explanations for the aqueous acceleration of Diels–Alder reactions^{206–208}. Other studies suggest that ‘hydrophobic packing’^{200,201,209} and ‘aggregation’¹² induce pre-association of the reactants. Although it is likely that the lifetime of such encounter complexes of non-polar molecules in water exceeds that in organic solvents, this pre-association is unlikely to be strong enough to be held responsible for the observed rate effects; this is supported by kinetic measurements for an intramolecular Diels–Alder reaction (Table 11, entry F). Despite the fact that the diene and the dienophile are already associated, water is still capable of accelerating the reaction by a factor of 153 compared with *n*-hexane¹⁶⁸.

Other authors have repeatedly invoked the ‘internal pressure’ of water as an explanation for the rate enhancement of Diels–Alder reactions in water^{138,210,211}. These studies were inspired by the large effects of external pressure on the rates of cycloadditions^{80,212,213}. However, the internal pressure $p_i = (\delta E / \delta V)_T$ ^{214,215} of water is very low (due to the open and relatively flexible hydrogen-bond network of water, a small change in volume of the solvent does not require much energy)⁵ and does not seem to offer a good explanation for the effect of water on Diels–Alder reactions. The cohesive energy density $ced = (\Delta H_{vap} - RT) / V_M$ of water is another term used to explain solvent effects in

Diels–Alder reactions. This term describes how much energy is needed for evaporation of the solvent per unit of volume^{168,216} and represents a measure of the internal water–water interactions. In contrast to the internal pressure, the *ced* of water is extremely high due to the large number of hydrogen bonds per unit volume. Since solvation and cavity formation lead to the rupture of solvent–solvent interactions, the *ced* essentially quantifies solvophobicity and hydrophobicity, and has been used successfully for describing solvent effects on Diels–Alder reactions²¹⁷. These studies stress the importance of hydrophobic interactions. The significance of these and the relative unimportance of internal pressure is further supported by the observation that Diels–Alder reactions in water are less accelerated by pressure than those in organic solvents, which is in line with the notion that pressure diminishes hydrophobic interactions.

III. REACTIONS IN WATER

A. Reactivity

The reasons for the observed rate accelerations of Diels–Alder reactions in aqueous media were elucidated mainly by quantum chemical methods. In one of the first studies, the energy lowering of the transition structure by water complexation was revealed by Monte Carlo simulations¹¹⁹. Going down from the transition structure to the reactants as well as to the product, the minimum energy reaction path (MERP) of the Diels–Alder reaction of methyl vinyl ketone with cyclopentadiene in the gas phase was determined by means of *ab initio* computations. The resulting structures along the MERP were then ‘solvated’ employing three solvents (water, methanol and propane)¹⁶³. Two main conclusions followed from this study. Firstly, the change in the total dipole moment along the MERP is significant; the dipole moments for methyl vinyl ketone, the transition structure and the product are 3.06, 3.44 and 2.98 D, respectively. As a consequence, the transition structure interacts more strongly with the solvents than the reactants or the product. Secondly, this finding is also supported by the computed relative energy changes. The predicted stabilization of the transition structure in water relative to propane of 4.2 kcal mol⁻¹ compares well with the observed rate data, which gave a 3.8 kcal mol⁻¹ lowering of the Gibbs free enthalpy of activation in water relative to *iso*-octane¹¹. The difference in Gibbs enthalpy of solvation of the initial state and the product amounted to 1.1 kcal mol⁻¹ in favour of the product. This estimate is in excellent agreement with the difference in Gibbs enthalpy, derived from experiments, of the transfer from the gas phase to water between initial and product state for the Diels–Alder reaction of ethene with butadiene ($\Delta\Delta G_t = 1.5$ kcal mol⁻¹) and with isoprene ($\Delta\Delta G_t = 1.3$ kcal mol⁻¹)¹¹⁹. Further analysis showed that, although the number of hydrogen bonds to the carbonyl oxygen remains around 2–2.5 during the reaction, the strength of each bond is 1–2 kcal mol⁻¹ greater at the transition structure. This reflects the sensitivity of hydrogen bonding to small charge variations²¹⁸. The main consequence is that the aqueous acceleration of the Diels–Alder reaction of cyclopentadiene and methyl vinyl ketone contains a significant non-hydrophobic component which derives from enhanced polarization of the transition structure due to stronger hydrogen bonds at the carbonyl oxygen.

Analogous studies on the dimerization of cyclopentadiene in water revealed a stabilization of the transition structure relative to the initial structure as a result of a difference in solvation of 1.7 kcal mol⁻¹¹¹⁹. Unfortunately, at least to our knowledge, reliable experimental data for this process are not available. Recently, in a similar approach²¹⁹, the Gibbs enthalpies of hydration of the Diels–Alder reaction of cyclopentadiene with isoprene and methyl vinyl ketone were determined. Surprisingly, it was observed that water stabilized the transition structure of the cyclopentadiene + isoprene reaction more than that of the

cyclopentadiene + methyl vinyl ketone reaction (4.6 vs 3.5 kcal mol⁻¹) relative to the initial state. This trend opposes the experimental data collected in Table 11, which seem to indicate that the aqueous acceleration diminishes when the hydrogen-bonding interactions become less effective. The authors attributed the transition structure stabilization in the non-hydrogen bonding case to hydrophobic effects. However, these calculations suggest that the magnitude of the hydrophobic effect on Diels–Alder reactions in aqueous solution depends on the nature of the diene and the dienophile.

B. Effects on Selectivity

Three years after the first notion of the large effects of water on the rate of the Diels–Alder reactions¹¹, the same authors demonstrated that the *endo/exo* selectivity is also increased in water⁴⁴. Studying the influence of salting-in and salting-out agents²²⁰, the authors pinpointed hydrophobic effects as the most important contributors to the enhanced *endo/exo* selectivities²⁰⁹ because hydrophobic effects are assumed to stabilize the more compact *endo*-transition structure more than the *exo*-transition structure. This difference in compactness of both structures is evident from the well-known smaller activation volume of the *endo*-cycloaddition (*vide supra*)²¹². Additionally, the high polarity of water significantly enhances the *endo/exo* selectivity²¹⁰.

Likewise, in the reactions of amphiphile-like reactants in aqueous solutions one finds an increased preference for the *endo*-adduct. This was attributed to ‘orientational effects’ within the micelles that are presumed to be present in the reaction mixtures²⁰². Although the existence of some type of aggregates cannot be excluded under these conditions, other studies have clearly demonstrated that micelle formation is not the reason for the improved selectivities²²¹. In contrast, it was shown that micellar aggregates tend to diminish the preference for the *endo*-adduct⁴⁴. Studies dealing with solvent effects on the *endo/exo* selectivity of Diels–Alder reactions revealed the importance of hydrogen bonding in addition to the already mentioned solvophobic interactions and polarity effects. These findings are supported by computer simulations²²² and by the analogy to Lewis acid catalysis which is known to enhance the *endo/exo* ratio dramatically (*vide supra*).

In conclusion, the special influence of water on the *endo/exo* selectivity stems from the fact that all effects favouring the *endo*-adduct are combined in this solvent: (1) strong hydrogen bonding, (2) polarity and (3) hydrophobicity. Water also increases the diastereofacial^{143,161,223} and the regioselectivity^{223,224} of Diels–Alder reactions. Mechanistic investigations on the reaction between cyclopentadiene and methyl acrylate emphasized the importance of hydrogen-bond donor characteristics and polarity^{143,161,225}.

C. Additives

In the last paragraphs we presented evidence for the rate accelerations of Diels–Alder reactions in pure water. In the following we will discuss further rate accelerations and stereoselectivity enhancements by additives¹¹. Chaotropic salts or salting-out agents lower the solubility of non-polar compounds in water mainly by preventing solute cavity formation. Anti-chaotropic or salting-in agents are involved in direct solvation of the solute^{226,227}. The resulting increased solubility leads to decreased hydrophobic interactions¹². In general, salt effects on Diels–Alder reactions correlate strongly with the size of the anion of the salt²²⁸. The origins of the rate accelerations caused by salt effects were investigated for the reaction of *cis*-dicyanoethene with cyclopentadiene under lithium chloride catalysis²²⁹. It was found that the modest decrease in Gibbs enthalpy of activation results from a dramatic decrease in the activation enthalpy that is almost completely

compensated by an increase in the activation entropy. This trend can be ascribed to the reduced ability of aqueous lithium chloride solutions to form hydrophobic hydration shells. Consequently, hydrophobic interactions become larger and enthalpy driven.

The addition of alcohols, especially in small amounts, also changes the reaction rates^{162,216}. It was suggested that the alcohol molecules disturb the hydrophobic hydration shell leading to enhanced hydrophobic interactions¹⁶⁸. At higher co-solvent concentrations direct alcohol–reagent contacts are suggested to occur and the rate constant decreases sharply until the value found for the pure alcohol is reached¹⁶⁸. The increased hydrophobic interactions are supported by a good correlation between the solubility of the reagents in alcohol–water mixtures and the rate constant. From this relation the change in solvent-accessible surface between the initial state and the activated complex in the dimerization of cyclopentadiene and in the reaction of 9-(hydroxymethyl)anthracene with *N*-methylmaleimide in alcohol–water mixtures was estimated²³⁰. It was concluded that solvation effects on hydrophobic surfaces in the transition structures are similar to those of normal molecules, at least in these reactions. Besides these additives, the effects of salt solutions in ethanol²⁰⁸ and of the addition of sugars on aqueous Diels–Alder reactions²³¹ were also the topics of several investigations.

While widespread investigations on rate accelerations in Diels–Alder reactions by additives were highly successful, the effect of these additives on the selectivities of [4 + 2]-cycloadditions in water has not received much attention. Scattered reports on this aspect point to an increase in *endo/exo* selectivity by additives, due to an increase in the hydrophobic interactions²⁰⁹.

In a Lewis acid catalysed Diels–Alder reaction, the first step is coordination of the catalyst to a Lewis basic site of one of the reactants, e.g. to the carbonyl oxygen of the dienophile. The most common solvents for these protocols are inert non-polar liquids such as dichloromethane or benzene. Protic solvents, and water in particular, are avoided because of their strong interactions with the catalyst. Other catalysed organic reactions, such as hydroformylations, on the other hand are not problematic and they are carried out industrially in water. This apparent paradox results from the difference in hardness of the reactants and the catalyst.

According to the hard and soft acids and bases (HSAB) principle, developed by Pearson in 1963^{232,233}, Lewis acids and Lewis bases are divided into two groups: hard and soft. Pearson correlated the hardness of acids and bases with their polarizability, whereby soft acids and bases are large and easily polarizable, and *vice versa*. A selected list of Lewis acids ordered according to their hardness in aqueous solution is presented in Table 18. The HSAB principle predicts strong association of ‘like’ partners. Hard acid–soft base complexes mainly result from electrostatic interactions, while soft acid–soft base complexes are dominated by covalent interactions.

The described difference between hard–hard and soft–soft interactions is also supported by thermodynamic analysis. In water, hard–hard interactions are usually endothermic and occur only as a result of a gain in entropy, originating from a liberation of water molecules from the hydration shells of the Lewis acid and the ligand. In contrast, soft–soft interactions are mainly enthalpic in origin and are characterized by a negative change in entropy²³⁴.

Several alternative attempts were made to quantify Lewis-type interactions^{235,236}. Following the HSAB principle, the applicability of a one-parameter Lewis acidity scale will inevitably be restricted to a narrow range of structurally related Lewis bases; addition of parameters results in more general relationships^{237–239}. The quantitative prediction of the gas-phase stabilities of Lewis acid–Lewis base complexes is still difficult. Hence the interpretation, not to mention the prediction, of solvent effects on Lewis acid–Lewis base interactions is often speculative.

TABLE 18. Classification of the hardness in aqueous solution of some selected Lewis acids according to the HSAB principle²³²

Hard	Borderline	Soft
H ⁺	Fe ²⁺	Cu ⁺
Fe ³⁺	Ni ²⁺	Hg ⁺
Co ³⁺	Cu ²⁺	Cd ⁺
Al ³⁺	Zn ²⁺	
La ³⁺		

The most effective Lewis acid catalysts for Diels–Alder reactions are ‘hard’ cations. Not surprisingly, they coordinate to hard nuclei of the reacting system, typically to oxygen atoms. Consequently, ‘hard’ solvents such as water are likely to affect these interactions significantly. Solvents are able to affect Lewis acid–Lewis base equilibria through a number of non-covalent interactions. First, the solvent can act itself as a Lewis base by coordinating to the catalyst. Aprotic and non-polar solvents coordinate relatively weakly to catalysts, whereas polar solvents exhibit much stronger interactions. Water with its high polarity, its large chemical hardness and its effective hydrogen-bonding activity is, as a bulk liquid, one of the strongest Lewis basic solvents. The interactions between catalysts and solvents have to be disrupted before the Diels–Alder reactants can coordinate to the added Lewis acid²⁴⁰. Furthermore, steric interactions between the coordinated reactant and solvent molecules are important in determining the stability of the complex²⁴¹. Consequently, catalysis by Lewis acids in strongly coordinating solvents is likely to be less effective.

The second important solvent effect on Lewis acid–Lewis base equilibria concerns the interactions with the Lewis base. Since water is also a good electron-pair acceptor¹²⁹, Lewis-type interactions are competitive. This often seriously hampers the efficiency of Lewis acid catalysis in water. Thirdly, the intermolecular association of a solvent affects the Lewis acid–base equilibrium²⁴². Upon complexation, one or more solvent molecules that were initially coordinated to the Lewis acid or the Lewis base are liberated into the bulk liquid phase, which is an entropically favourable process. This effect is more pronounced in aprotic than in protic solvents which usually have higher cohesive energy densities. The unfavourable entropy changes in protic solvents are somewhat counterbalanced by the formation of new hydrogen bonds in the bulk liquid.

Finally, the solvent also interacts with Lewis acid and Lewis base sites that are not directly involved in mutual coordination, thereby altering the electronic properties of the complex. For example, delocalization of charges onto the surrounding solvent molecules causes ions in solution to be softer than in gas phase²⁴¹. Again, water is particularly effective in this respect because it can act as an efficient electron-pair acceptor and donor.

In summary, water appears as an extremely unsuitable solvent for coordination of hard Lewis acids to hard Lewis bases, as it strongly solvates both species and hinders their interaction. Hence, catalysis of Diels–Alder reactions in water is expected to be difficult due to the relative inefficiency of the interactions between the Diels–Alder reactants and the Lewis acid catalyst. On the other hand, the high stereoselectivities and yields observed in biosyntheses, with water as *the* solvent, indicate that these rationalizations cannot entirely be true. As a matter of fact, we will demonstrate in the following that Lewis acid catalysis in water is not only possible, but also allows for effective as well as environmentally friendly reaction conditions.

The appreciable rate effects in water are generally overpowered by the large accelerations found for Lewis acid catalysis in normal electron demand Diels–Alder

reactions^{120,199,243}. In analogy to the hydrogen-bonding effect, Lewis acids can decrease the HOMO–LUMO gap between the diene and the dienophile and thereby increase the reaction rate. Taking into consideration the effects of water and Lewis acids on the Diels–Alder reaction, one may ask what would be the result of a combination of these two effects. If they are additive, will huge accelerations follow? How does water affect the Lewis acid catalysis and what is the influence of the Lewis acid on the enforced hydrophobic interactions and hydrogen bonding? These and related questions are addressed below.

D. Catalysis

1. General aspects

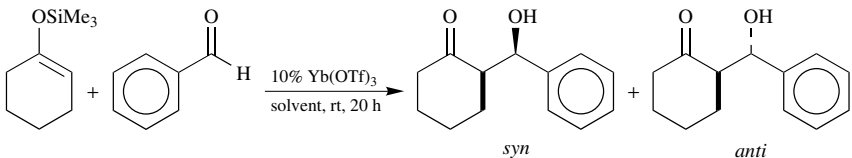
The demand for environmentally friendly chemistry and its widespread applicability have made water an increasingly popular solvent for organic transformations¹³. Mixtures of water and other solvents such as tetrahydrofuran are now commonly employed for a number of organic transformations²⁴⁴. For instance, the Lewis acid catalysed aldol reaction of silyl enol ethers, commonly known as the Mukaiyama aldol reaction, which was firstly reported in the early seventies, can be carried out in such media²⁴⁵. With titanium tetrachloride as the catalyst this reaction proceeds regioselectively in high yields, but the reaction has to be carried out strictly under non-aqueous conditions in order to prevent decomposition of the catalyst and hydrolysis of the silyl enol ethers. In the absence of the catalyst it was observed that water had a beneficial influence on this process (Table 4, entry D)²⁵. Nevertheless, the yields in the uncatalysed version were still unsatisfactory. Improved results were obtained with water-tolerant Lewis acids. The first reported example for Lewis acid catalysis in aqueous media is the hydroxymethylation of silyl enol ethers with commercial formaldehyde solution using lanthanide triflates²⁴⁶. In the meantime, the influence of several lanthanide triflates in cross-aldol reactions of various aldehydes was examined^{247–249}. The reactions were most effectively carried out in 1 : 9 mixtures of water and tetrahydrofuran with 5–10% Yb(OTf)₃, which can be re-used after completion of the reaction (Table 19, entry A). Although the realization of this reaction is quite simple, the choice of the solvent is crucial (Table 20).

While the yields are rather poor in pure organic solvents, the reaction is best carried out in an organic solvent containing 10–20% water. Higher percentages of water decrease again the yields of aldol products which was attributed to the competitive hydrolysis of the silyl enol ether. Besides the catalysis of the Mukaiyama aldol reaction by lanthanide triflates, allylation reactions also benefit from the presence of water. The synthesis of homoallylic alcohols via a Lewis acid catalysed reaction of organometallic reagents with a carbonyl compound in organic media has been reported many times (Table 19, entry B)²⁵⁰. This reaction can also be carried out in aqueous mixtures of tetrahydrofuran, ethanol or acetonitrile catalysed by Sc(OTf)₃ and Yb(OTf)₃²⁵¹. The catalysts in these reactions can be recovered without loss of activity²⁴⁸.

Furthermore, the use of a Lewis acid promoter leads to increased stereoselectivities (Table 19, entry C)^{252,254}. Compared to the aprotic reaction, where allyl silane was used instead of allyl bromide and indium chloride, an almost complete reversal of the diastereoselectivity was found. It was demonstrated recently that the Lewis acid catalysed allylation reaction can be carried out efficiently without any organic solvent in saturated ammonium chloride solution²⁵⁵. Finally, Lewis acid catalysed Mannich reactions can be carried out conveniently in mixtures of organic solvents and water. However, the exact role of the Lewis acid catalyst has not been clarified (Table 19, entry D)²⁵³. The same reaction can be carried out in pure water with catalysis by indium trichloride²⁵⁶.

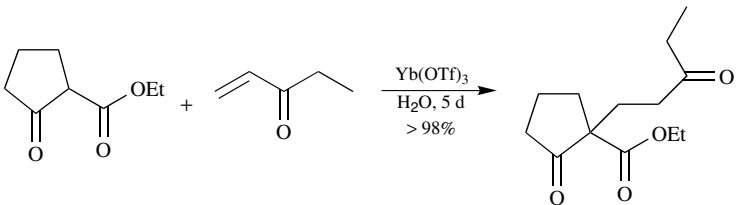
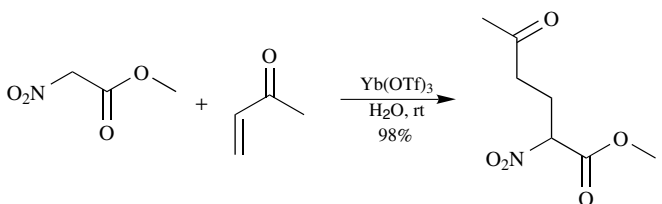
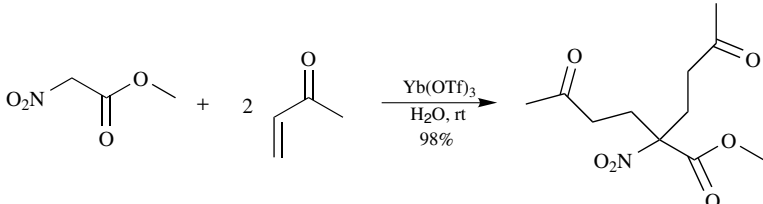
TABLE 19. Lewis acid catalysed organic transformations in aqueous media

Entry	Reaction	Reference
A	<p> <chem>ClCC=O + OSiMe3C=CC1=CC=CC=C1 >> CC(=O)C(O)CC1=CC=CC=C1.Cl</chem> 10% Yb(OTf)₃ / THF / H₂O (9:1) / 95 % </p>	247
B	<p> <chem>O=C(CCC1=CC=CC=C1) + C=CCOC(C)C >> OCC(CCC1=CC=CC=C1)CCOC(C)C</chem> 10% Yb(OTf)₃ / H₂O / EtOH / toluene (1:7:4) / 89 % - 96 % </p>	248
C	<p> <chem>O=C1CCCCC1 + BrC=C(C)C(F)(F)F >> OCC1(C)CCCCC1C=C(C)C(F)(F)F</chem> Sn, InCl₃ / 23 °C, H₂O, 15 h / <i>anti</i>: 100 % / yield: 95 % </p>	252
D	<p> <chem>O=C1=CC=CC=C1 + ClC1=CC=C(N)C=C1 >> CC(O)C(NC1=CC=C(Cl)C=C1)C2=CC=CC=C2</chem> 10% Yb(OTf)₃ / THF / H₂O (9:1) </p>	253

TABLE 20. Effects of solvent on cross-aldol reactions²⁴⁹


Solvent	Yield(%)	[<i>syn</i>]/[<i>anti</i>]
CH ₂ Cl ₂	10	—
THF	10	—
CH ₂ CN	5	—
DMF	56	73/27
H ₂ O–THF (1 : 4)	91	73/27

TABLE 21. Lewis acid catalysed reactions in pure water

Entry	Reaction	Reference
A		257
B		258
		

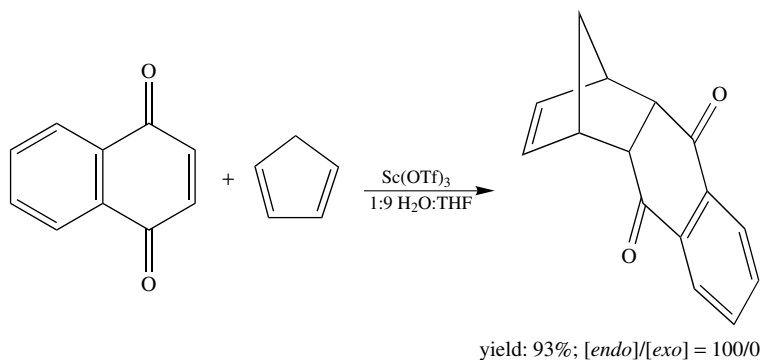
There are only few examples of organic reactions catalysed effectively by Lewis acids which can be carried out in pure water without any organic co-solvent. While water can be used successfully for the uncatalysed Michael addition of 1,3-diketones (Table 4, entry D)²², the corresponding reaction of β -ketoesters does not give satisfactory results. On the other hand, the Yb(OTf)₃ catalysed Michael reaction of various β -ketoesters (Table 21, entry A)²⁵⁷ and α -nitroesters (Table 21, entry B)²⁵⁸ takes place.

Besides these, the metal-ion catalysed hydrolyses of carboxylate esters^{259–262}, phosphate esters^{263–268}, amides^{262,269–273} and nitriles^{274–277} in water were studied extensively. Although the exact mechanism of these reactions is not clear, it was noted that the most important role of the catalyst is coordination of a hydroxide ion which acts as the nucleophile²⁷⁷. Furthermore, the activation of the substrate through coordination to the Lewis acidic metal centre also plays a role in the catalysis but it depends strongly on the substrate; for monodentate reagents, this interaction is not very efficient^{278,279}.

In summary, only a limited number of mechanistic studies of Lewis acid catalysed reactions in water have been published. Most of these studies make use of a lanthanide ion whose coordination to a carbonyl group is assumed. It was noted that in aqueous solutions donor groups containing neutral oxygen or nitrogen atoms generally bind *only* when they are included in multidentate ligands with at least one or two other groups with negatively charged oxygens²⁸⁰. Hence, instead of direct Lewis acid catalysis, the beneficial effect might well be indirect. Solutions of Lewis acids in water are modestly acidic, which indicates the simultaneous presence of lanthanide-ion coordinated hydroxide ions as well as hydronium ions. Clearly, detailed mechanistic studies are required to identify the mechanisms of Lewis acid catalysis in aqueous solutions.

2. Diels–Alder reactions

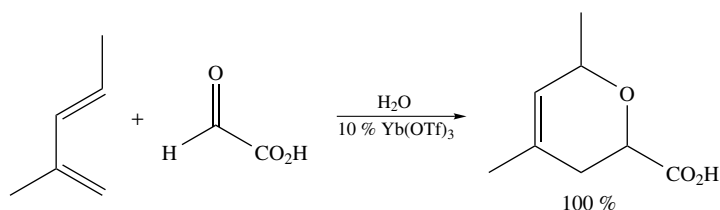
In the preceding paragraphs the advantages of water in uncatalysed Diels–Alder reactions were outlined. An important question is whether these advantages can be transferred to Lewis acid catalysed reactions as well. Since the majority of Diels–Alder reactants are likely to have a negligible tendency to interact with Lewis acid catalysts in water, this issue was addressed only recently. The first step was the development of water-tolerant catalytic systems for [4 + 2]-cycloadditions, and there are now a few examples of Lewis acid catalysed Diels–Alder reactions that not only tolerate the presence of small amounts of water^{281–284} but even benefit from it²⁸⁵. An example of a Lewis acid catalysed Diels–Alder reaction carried out in water:THF mixture is presented in Scheme 12²⁸⁶.



SCHEME 12. A water-tolerant Lewis acid catalysed Diels–Alder reaction²⁸⁶

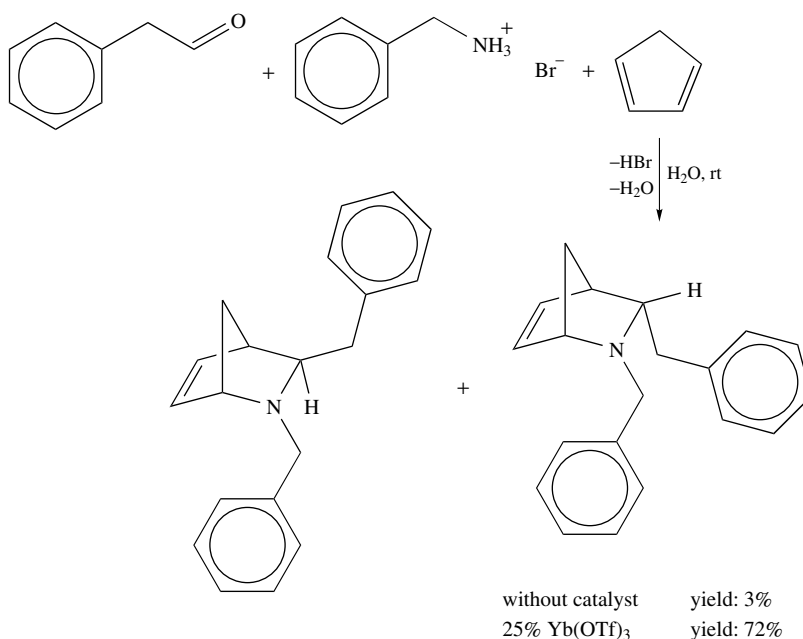
Unfortunately, a comparison with the uncatalysed reaction was not carried out in that particular study. The first comparison between a catalysed and an uncatalysed Diels–Alder reaction was published only in 1994²⁸⁷. Within the scope of this investigation several

lanthanide triflates or chlorides were used as catalysts, and their effectivities were checked by comparison with the uncatalysed reactions in aqueous media. While in the presence of ytterbium triflate a quantitative reaction was observed, pure water only gave 55% yield (Scheme 13)²⁸⁷. Other lanthanide(III) triflates were also catalytically active.



SCHEME 13. A Lewis acid catalysed hetero-Diels–Alder reaction in aqueous solution

Another example of the use of Lewis acids in organic reactions in water is the lanthanide(III) triflate catalysed aza-Diels–Alder reaction, exemplified in Scheme 14. In this reaction the hetero-dienophile is formed *in situ* from a primary ammonium hydrochloride and a carbonyl compound followed by the actual Diels–Alder reaction^{288,289}. This type of reaction proceeds readily in aqueous media^{290–296}, and a dramatic increase in the yield upon addition of lanthanide triflates was observed^{288,289}. The exact role of the catalyst, however, is not entirely clear. Although it was suggested that the catalyst binds to the dienophile, other mechanisms, such as simple proton catalysis, are also plausible. Moreover, these reactions are further complicated since they are often heterogeneous.

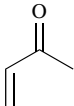
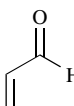
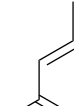

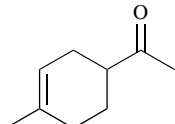
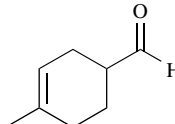

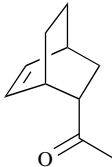
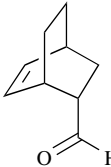
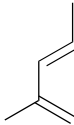
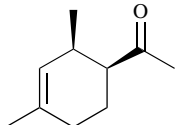
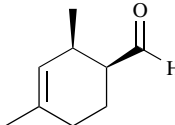
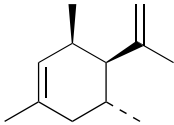


SCHEME 14. Lanthanide(III) triflate catalysed aza-Diels–Alder reaction in water²⁸⁸

The reverse reaction is catalysed by copper sulphate in an ethanol/water (50 : 50) mixture^{297,298}. Indium(III) chloride catalysis of Diels–Alder reactions was also reported, but the effects were poor and comparison to uncatalysed reactions was made only in a few cases^{299,300}. A very versatile Lewis acid catalyst for such reactions is methylrhenum trioxide (MTO)³⁰⁰. This catalyst can be used without a solvent, in pure organic solvents like chloroform and even in pure water. While the catalyst is active in the latter two solvents (Table 22), it gives the best results in water (Table 23).

Considering that the activity of a Lewis acid depends strongly on the stability of the acid–base complex and that the complexation is notoriously hampered by chemically ‘hard’ solvents like water, it is clear that reactions of bidentate dienophiles can be catalysed very efficiently³⁶. Prototypical are the derivatives of 3-phenyl-1-(2-pyridyl)-2-propen-1-ones (*vide infra*). Their Diels–Alder reactions (Table 24) clearly show that the accelerating solvent effect of water is still present in the Lewis acid catalysed reactions, and that the Lewis acid activity is not necessarily hindered by the solvent³⁰¹. While

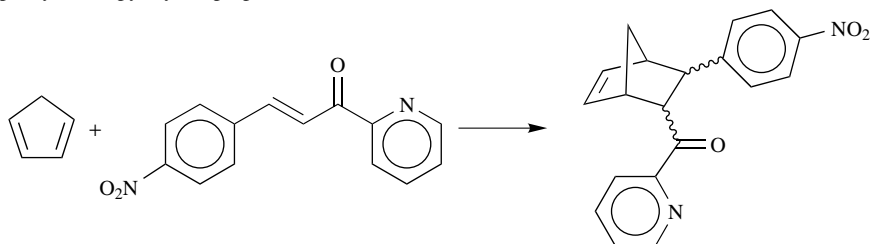
TABLE 22. MTO-catalysed Diels–Alder reactions in water (A) and in chloroform (B)^a with yields and [*endo*]/[*exo*] ratios

			
	 A: 2.5 h, 90% [$>99 <1$] B: 18 h, 90% [$>99 <1$]	 2.5 h, 91% [$>99 <1$] 18 h, 90% [$>99 <1$]	
	 A: 16 h, 91% [$>99 <1$] B: 4 d, 94% [$>>99 <<1$]	 16 h, 90% [$>>99 <<1$] 4 d, 90% [$>99 <1$]	
	 A: 4 h, 90% [$>99 <1$] B: 12 h, 94% [$98 : 2$]	 16 h, 90% [$>>99 <<1$] 4 d, 94% [$>>99 <<1$]	 10 h, 90% [$95 : 5$] 7 d, 90% [$80 : 20$]

^aMajor products, yields and *endo/exo* ratios are given³⁰⁰.

TABLE 23. Additive effects of MTO and water

Conditions	<i>endo/exo</i> rate	$t_{1/2}$ (min)
neat	3.15 : 1	45
1% MTO	15.4 : 1	20
water	20 : 1	25
water, 1% MTO	>99 : 1	14

TABLE 24. Second-order rate constants ($M^{-1} s^{-1}$) for the Diels–Alder reaction of 3(4-nitrophenyl)-1-(2-pyridyl)-2-propen-1-one in different media at 25 °C

Entry	Solvent	$10^5 k$	
		Uncatalysed	With 10 mM Cu^{2+}
1	MeCN	1.32	
2	EtOH	3.83	7.69×10^4
3	H_2O	402	3.25×10^5

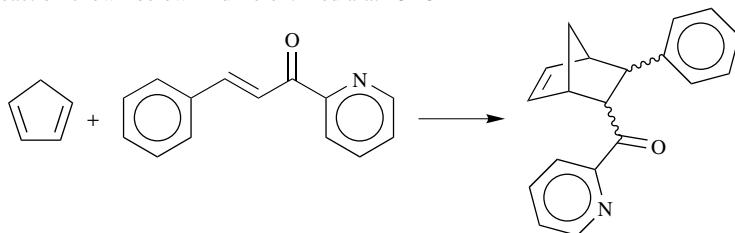
copper(II) nitrate turned out to be the catalyst of highest effectivity, the nitrates of Co^{2+} , Ni^{2+} and Zn^{2+} were good promoters as well.

In order to exclude simple proton catalysis, this study also examined the catalytic activity of Brønsted acids. It was noted that a 10 mM solution of hydrochloric acid has only a small catalytic effect (second-order rate constant $k_2 = 7.62 \times 10^{-2} M^{-1} s^{-1}$; compare Table 24). Another dienophile derivative also showed changes in rate (Table 25) and in the *endo/exo* selectivity (Table 26)³⁰². A dramatic acceleration and an increase in the selectivity in 1,1,1-trifluoroethanol was observed in the presence of Cu^{2+} (Table 25).

In this paragraph it was demonstrated that Lewis acid catalysis can be extended to aqueous media. Although water is likely to alter the complexation step, the use of Lewis acids is not restricted to organic solvents. Most importantly, the advantageous effects of Lewis acid catalysis and water are often additive. Since the development of catalytic systems which are water-tolerant or even benefit from the presence of water is still in its infancy, these results are highly promising and open new avenues for future research.

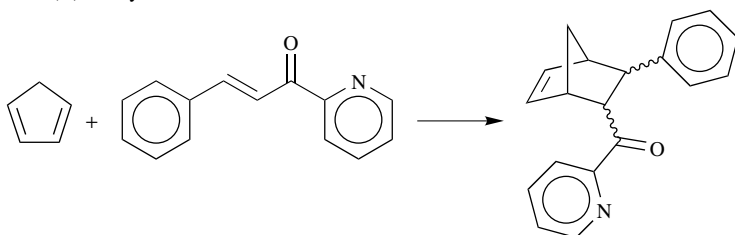
3. Non-Lewis acid catalysis

Besides metal containing Lewis acids, non-metal additives have also found application in catalysis. These studies are quite pertinent to the development of artificial enzyme-like catalysts. As there is a large number of Lewis basic sites in living systems able to be involved in hydrogen bonds, the analysis of the catalytic activity of hydrogen bonding additives would give some indication as to the existence of Diels–Alder reactions

TABLE 25. Relative second-order rate constants $k(\text{M}^{-1} \text{s}^{-1})$ for the Diels–Alder reaction shown below in different media at 25 °C³⁰²

Entry	Solvent	Uncatalysed	With 10 mM Cu ²⁺
1	MeCN	1	158.000
2	EtOH	2.7	54.900
3	H ₂ O	287	691.000
4	CF ₃ CH ₂ OH	482	1.110.000 ^a

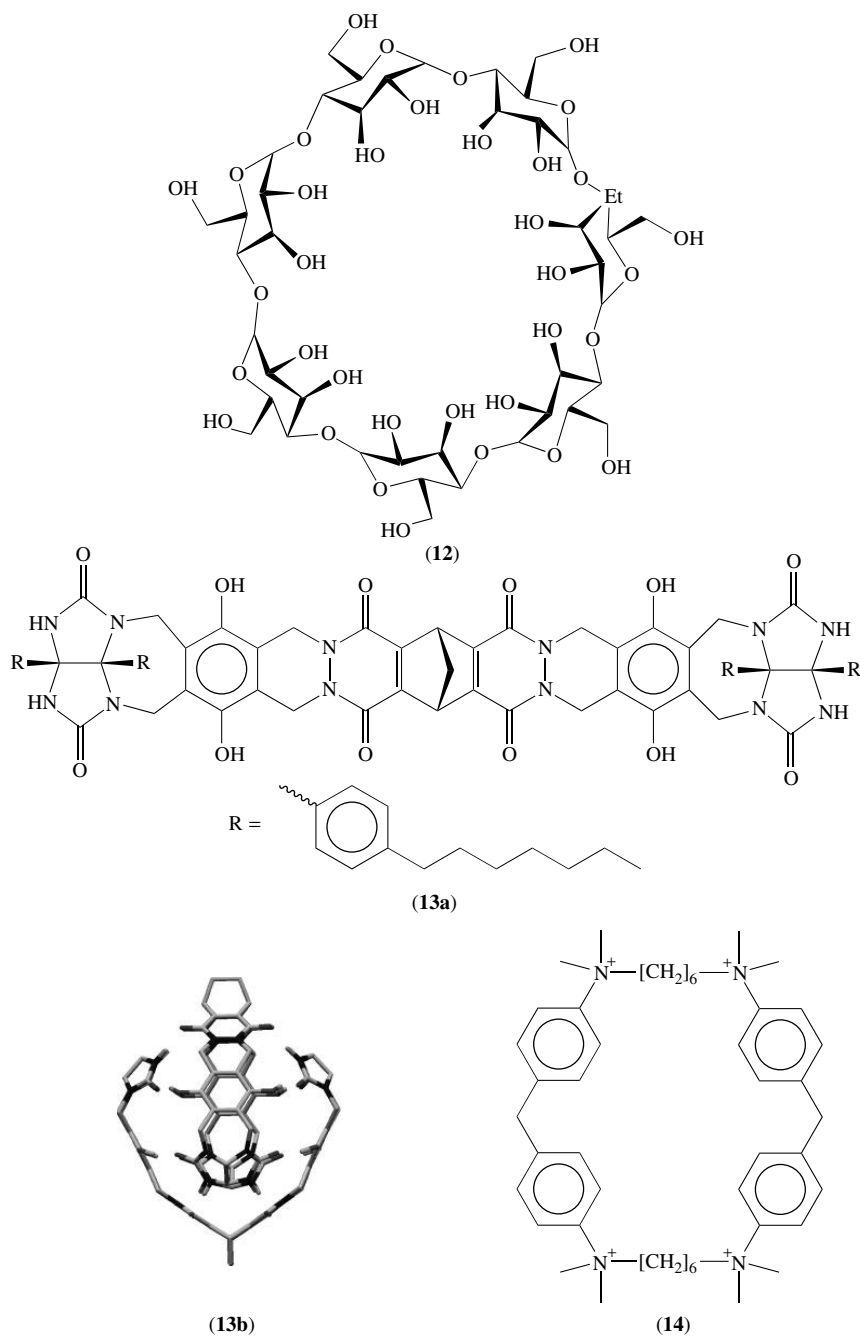
^aOnly 0.1 mM catalyst was used.

TABLE 26. *Endo/exo* selectivities for the reaction below in the absence and presence of a Cu(II) catalyst³⁰²

Entry	Solvent	Uncatalysed	With 10 mM Cu ²⁺
1	MeCN	67/33	94/6
2	EtOH	77/23	96/4
3	H ₂ O	84/16	93/7

in biosynthesis⁵⁵. Catalytic non-metal additives like cyclodextrins (**12** in Scheme 15)²²¹, large organic compounds (**13a** in Scheme 15)³⁰³ which dimerize to *self-assembled molecular capsules* (**13b** in Scheme 15) and other catalytically active macrocycles (**14** in Scheme 15)¹²⁴ are able to form micelles. The general interactions of such additives with the reactants will be discussed in the following.

Surfactant molecules (also called amphiphiles or detergents) combine a polar or ionic head and a non-polar tail within the same molecule. The non-polar part, which is typically made up of one or more alkyl chains, causes these compounds to be sparingly soluble in water, whereas the polar or ionic part interacts strongly with water. Upon increasing the concentration of the amphiphilic compound in water, the solubility limit will be reached at a certain point and phase separation will set in. Due to the efficient interactions between the polar headgroups and the surrounding water molecules, a complete phase separation is usually unfavourable. Instead, the process halts in an intermediate stage



SCHEME 15. Catalytically active encapsulating species

with concomitant formation of aggregates of amphiphilic material, wherein the non-polar parts stick together and are shielded from water, with the headgroups located in the outer regions of the aggregate. A multitude of different aggregates can be formed this way³⁰⁴. The morphology of these assemblies is mainly determined by the shape of the individual surfactant molecules. The formation of micelles sets in after a certain critical concentration of surfactant, the critical micelle concentration, has been reached. Beyond this, the concentration of monomeric surfactant molecules will result in an increase in the number of micelles, while the concentration of monomeric surfactant remains almost constant³⁰⁵.

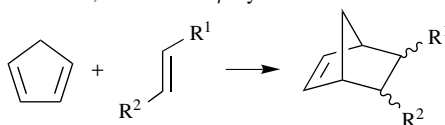
Micelles are extremely dynamic aggregates. Ultrasonic, temperature and pressure jump techniques have been employed to study various equilibrium constants. Rates of uptake of monomers into micellar aggregates are close to diffusion-controlled³⁰⁶. The residence times of the individual surfactant molecules in the aggregate are typically in the order of 1–10 microseconds³⁰⁷, whereas the lifetime of the micellar entity is about 1–100 milliseconds³⁰⁷. Factors that lower the critical micelle concentration usually increase the lifetimes of the micelles as well as the residence times of the surfactant molecules in the micelle. Due to these dynamics, the size and shape of micelles are subject to appreciable structural fluctuations.

One of the most important characteristics of micelles is their ability to enclose all kinds of substances. Capture of these compounds in micelles is generally driven by hydrophobic, electrostatic and hydrogen-bonding interactions. The dynamics of solubilization into micelles are similar to those observed for entrance and exit of individual surfactant molecules, but the micelle-bound substrate will experience a reaction environment different from bulk water, leading to kinetic medium effects³⁰⁸. Hence, micelles are able to catalyse or inhibit reactions. The catalytic effect on unimolecular reactions can be attributed exclusively to the local medium effect. For more complicated bimolecular or higher-order reactions, the rate of the reaction is affected by an additional parameter: the local concentrations of the reacting species in or at the micelle.

On the basis of the pronounced non-polar character of the majority of Diels–Alder reactants, efficient micellar catalysis of their reaction might be anticipated. The first time a micellar catalysed Diels–Alder reaction was mentioned, not the micelle itself, ‘*but some type of micellar catalysis, resulting in mutual binding of reactants*’ was suggested to be responsible for the observed rate accelerations²⁰². Further investigations on the catalytic activity of micelles showed that several species which are able to form micelles in aqueous solution lead to higher yields in intramolecular Diels–Alder reactions²⁰⁶. In detailed studies of the effects of β -cyclodextrin **12** on the rates of Diels–Alder reactions^{124,221} it became clear that the influence of cyclodextrin micelles can lead either to inhibition or to acceleration (Table 27).

The results in Table 27 were explained by the changes in hydrophobicity of the dienophile. For optimum catalytic effects a discrete range of hydrophobicity and polarity is required. While an increase in hydrophilicity of polar dienophiles (Table 27, entries 1–3) leads to smaller rate enhancements, the larger hydrophobic alkoxy group on less polar dienophiles (Table 27, entries 5–8) leads to smaller catalytic activities of the cyclodextrin¹²⁵. Quite similar are the effects of **13a**, but the investigation of its catalytic activity is much less extensive³⁰³.

Comparable to the influence of such structural well-defined macrocycles, cell-free extracts⁵⁵ as well as antibodies^{309,310} also show strong catalytic effects. Hence, the use of organic compounds, which are able to form micelles, being active in water and easy to handle could lead to new insights and unexpected results for catalytic Diels–Alder

TABLE 27. Rate constants $k(\text{M}^{-1} \text{s}^{-1})$ for Diels–Alder reactions of cyclopentadiene with several dienophiles in methanol, water and a β -cyclodextrin **12** water solution ¹²⁵

Entry	Dienophile		Methanol	Water	β -Cyclodextrin– water ^a
	R ¹	R ²			
1	COOEt	COOEt	1.37	148	9270
2	COOH	COOEt	1.51	47.2	1490
3	COOH	COOH	1.24	24.1	172
4	COOH	CO ₂ C ₆ H ₁₁ -c	1.03	31.8	177
5	H	COOMe	0.031	238	235
6	H	COOEt	0.031	225	121
7	H	COOPr	0.031	135	23.9
8	H	COOBu	0.031	100.3	38

^a[β -cyclodextrine] = $9 \times 10^{-3} \text{ mol l}^{-1}$.

reactions. A first step in this direction was taken recently by a combination of Lewis acid and micellar catalysis in water¹⁰. The Lewis acid Cu(II) dodecyl sulphate (0.01 mol%), a micelle-forming compound, accelerated the Diels–Alder reaction depicted in Table 24 by a factor of 1,800,000 in water, relative to the uncatalysed reaction in acetonitrile.

IV. CONCLUSIONS

The present chapter aims at introducing the reader to the emerging field of organic synthesis in water as exemplified by the well-known Diels–Alder reaction. As this transformation is exceptionally well understood mechanistically and highly valuable for building complex structures, it lends itself to examining and probing the effects of aqueous media and other factors which influence the reactivities and selectivities.

Most notably, virtually all Diels–Alder reactions are accelerated in aqueous media. This observation is due to a complex array of intricate interactions comprised of hydrogen bonding, hydrophobicity and others of lesser significance. Hydrogen-bonding interactions, mostly with lone pairs of the reactants, lead, in analogy to Lewis acid catalysis, to a reduction in the HOMO–LUMO energy separation. However, this effect is much less pronounced than for Lewis acids, so that the enormous accelerations of up to 12,800-fold cannot be explained solely by cooperative hydrogen bonding in water. Additives which are able to deliver specific ‘isolated’ hydrogen bonds such as diols or ureas are less effective (accelerations of 6–8-fold in water vs 3–4-fold with the respective additives in chloroform). This supports the notion that hydrophobicity is also an important factor, a conclusion which is also amplified by the rate accelerations observed in cyclodextrins, micelles and other supramolecular aggregates.

A striking result is that the beneficial effects on the rates and selectivities are often additive, i.e. Lewis acid catalysis is possible even in water! Again, this may be understood in terms of an interplay between the strong donor–acceptor interactions of the, for instance, metal atom of a Lewis acid on the one hand, and the cavity-forming ability of water, which brings the reactions partners in close proximity, on the other.

As a consequence of these findings, *in vivo* Diels–Alder reactions may occur and may be catalysed by formation of various kinds of hydrogen bonds. This casts some doubt on the long-standing search for a specific ‘Diels–Alder-ase’ which has not yet been identified.

In summary, we hope to have demonstrated that aqueous media for organic reactions, specifically the Diels–Alder reaction, are neither a curiosity only applicable to ‘unusual’ transformations nor are they a limitation for catalysis. It is more than likely that the potential of water as an environmentally friendly and safe solvent will be used more effectively in the future for a large number of different reactions.

V. ACKNOWLEDGEMENTS

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VI. REFERENCES

1. D. Lenoir and J. O. Metzger, *Nachr. Chem. Tech. Lab.*, **47**, 291 (1999).
2. J. O. Metzger, *Angew. Chem., Int. Ed. Engl.*, **37**, 2975 (1998); *Angew. Chem.*, **110**, 3145 (1998).
3. C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997.
4. K. A. T. Silverstein, A. D. J. Haymet and K. A. Dill, *J. Am. Chem. Soc.*, **120**, 3166 (1998).
5. C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd edn., VCH, Cambridge, 1990.
6. M. A. McCarrick, Y.-D. Wu and K. N. Houk, *J. Org. Chem.*, **58**, 3330 (1993).
7. W. Blokzijl and J. B. F. N. Engberts, *Angew. Chem., Int. Ed. Engl.*, **32**, 1545 (1993); *Angew. Chem.*, **105**, 1610 (1993).
8. S. Otto, F. Bertoncin and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **120**, 4238 (1998).
9. C.-J. Li, *Chem. Rev.*, **93**, 2023 (1993).
10. S. Otto, J. B. F. N. Engberts and J. C. T. Kwak, *J. Am. Chem. Soc.*, **120**, 9517 (1998).
11. D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980).
12. R. Breslow, *Acc. Chem. Res.*, **24**, 159 (1991).
13. P. A. Grieco, *Aldrichim. Acta*, **24**, 59 (1991).
14. A. Lubineau, J. Augé and Y. Queneau, *Synthesis*, 741 (1994).
15. F. Fringuelli, R. Germani, F. Pizzo and G. Savelli, *Tetrahedron Lett.*, **30**, 1427 (1989).
16. F. Fringuelli, F. Pizzo and R. Germani, *Synlett*, 475 (1991).
17. F. Fringuelli, R. Germani, F. Pizzo, F. Santinelli and G. Savelli, *J. Org. Chem.*, **57**, 1198 (1992).
18. W. A. Herrmann and C. W. Kohlpaintner, *Angew. Chem., Int. Ed. Engl.*, **32**, 1524 (1993); *Angew. Chem.*, **105**, 1588 (1993).
19. M. Grosselin and C. Mercier, *J. Mol. Catal.*, **63**, L25 (1990).
20. T. H. Chan, C. J. Li, M. C. Lee and Z. Y. Wei, *Can. J. Chem.*, **72**, 1181 (1994).
21. A. Lubineau and J. Augé, *Tetrahedron Lett.*, **33**, 8073 (1992).
22. U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **10**, 496 (1971); *Angew. Chem.*, **83**, 492 (1971).
23. C. Larpent and H. Patin, *Tetrahedron*, **44**, 6107 (1988).
24. A. Lubineau, *J. Org. Chem.*, **51**, 2142 (1986).
25. A. Lubineau and E. Meyer, *Tetrahedron*, **44**, 6065 (1988).
26. T. H. Chan, C. J. Li and Z. Y. Wei, *J. Chem. Soc., Chem Commun.*, 505 (1990).
27. E. T. Kool and R. Breslow, *J. Am. Chem. Soc.*, **110**, 1596 (1988).
28. V. Tychopoulos and J. H. P. Tyman, *Synth. Commun.*, **16**, 1401 (1986).
29. D. R. Adams and S. P. Bhatnagar, *Synthesis*, 661 (1977).

30. M. Rambaud, A. D. Vecchio and J. Villieras, *Synth. Commun.*, **14**, 833 (1984).
31. P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi and A. A. Fokin, *Angew. Chem., Int. Ed. Engl.*, **37**, 1895 (1998); *Angew. Chem.*, **110**, 1993 (1998).
32. H. Shaw, H. D. Perlmutter, C. Gu, S. D. Arco and T. O. Quibuyen, *J. Org. Chem.*, **62**, 236 (1997).
33. Y. Yamamoto, S. Shiraki and D. Gao, *J. Chem. Soc., Perkin Trans. 2*, 1119 (1993).
34. V. Ramamurthy, *Tetrahedron*, **42**, 5753 (1986).
35. N. R. Bantu, T. G. Kotch and A. J. Lees, *Tetrahedron Lett.*, **34**, 2039 (1993).
36. J. B. F. N. Engberts, B. L. Feringa, E. Keller and S. Otto, *Recl. Trav. Chim. Pays-Bas*, **115**, 457 (1996).
37. J. J. Gajewski, J. Jurayj, D. R. Kimbrough, M. E. Gande, B. Ganem and B. K. Carpenter, *J. Am. Chem. Soc.*, **109**, 1170 (1987).
38. S. D. Copley and J. R. Knowles, *J. Am. Chem. Soc.*, **109**, 5008 (1987).
39. E. Brandes, P. A. Grieco and J. J. Gajewski, *J. Org. Chem.*, **54**, 515 (1989).
40. P. A. Grieco, E. B. Brandes, S. McCann and J. D. Clark, *J. Org. Chem.*, **54**, 5849 (1989).
41. C. Grundmann and R. Richter, *J. Org. Chem.*, **32**, 2308 (1967).
42. C. Grundmann and S. K. Datta, *J. Org. Chem.*, **34**, 2016 (1969).
43. G. A. Lee, *Synthesis*, 508 (1982).
44. R. Breslow, U. Maitra and D. Rideout, *Tetrahedron Lett.*, **24**, 1901 (1983).
45. S. Otto, W. Blokzijl and J. B. F. N. Engberts, *J. Org. Chem.*, **59**, 5372 (1994).
46. T. Zincke and H. Günther, *Justus Liebigs Ann. Chem.*, **272**, 243 (1892).
47. T. Zincke, *Justus Liebigs Ann. Chem.*, **296**, 135 (1897).
48. T. Zincke and K. H. Meyer, *Justus Liebigs Ann. Chem.*, **367**, 1 (1909).
49. T. Zincke and W. Pfaffendorf, *Justus Liebigs Ann. Chem.*, **394**, 3 (1912).
50. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928).
51. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, **97**, 6908 (1975).
52. N. Kato, X. Wu, H. Nishikawa, K. Nakanishi and H. Takeshita, *J. Chem. Soc., Perkin Trans. 1*, 1047 (1994).
53. U. Pindur and G. H. Schneider, *Chem. Commun.*, 409 (1995).
54. S. Laschat, *Angew. Chem., Int. Ed. Engl.*, **35**, 289 (1996); *Angew. Chem.*, **108**, 313 (1996).
55. H. Oikawa, K. Katayama, Y. Suzuki and A. Ichihara, *J. Chem. Soc., Chem. Commun.*, 1321 (1995).
56. P. Yates and P. Eaton, *J. Am. Chem. Soc.*, **82**, 4436 (1960).
57. T. M. Tarasow, S. L. Tarasow and B. E. Eaton, *Nature*, **389**, 54 (1997).
58. R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969); *Angew. Chem.*, **81**, 797 (1969).
59. K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).
60. G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968).
61. L. Salem, *J. Am. Chem. Soc.*, **90**, 543 (1968).
62. L. Salem, *J. Am. Chem. Soc.*, **90**, 553 (1968).
63. K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973).
64. M. Sodupe, R. Rios, V. Branchadell, T. Nicholas, A. Oliva and J. J. Dannenberg, *J. Am. Chem. Soc.*, **119**, 4232 (1997).
65. G. W. Wheland, *Resonance in Organic Chemistry*, Wiley, New York, 1955.
66. A. F. Voter and W. A. Goddard III, *Chem. Phys.*, **57**, 253 (1981).
67. F. W. Bodrowicz and W. A. Goddard III, in *Modern Theoretical Chemistry, Methods of Electronic Structure Theory* (Ed. H. F. Schaefer III), Plenum Press, New York, 1977.
68. O. Exner, *J. Org. Chem.*, **53**, 1810 (1988).
69. R. B. Woodward and T. J. Katz, *Tetrahedron*, **15**, 70 (1959).
70. Y. Apeloig and E. Matzner, *J. Am. Chem. Soc.*, **117**, 5375 (1995).
71. F. Fotiadu, F. Michael and G. Buono, *Tetrahedron Lett.*, **31**, 4863 (1990).
72. M. Kakushima, *Can. J. Chem.*, **57**, 2564 (1979).
73. Y. Kobuke, T. Fueno and J. Furukawa, *J. Am. Chem. Soc.*, **92**, 6548 (1970).
74. Y. Kobuke, T. Sugimoto, J. Furukawa and T. Fueno, *J. Am. Chem. Soc.*, **94**, 3633 (1972).
75. E. T. McBee, M. J. Keogh, R. P. Levek and E. P. Wesseler, *J. Org. Chem.*, **38**, 632 (1973).
76. R. R. Sauers and T. R. Henderson, *J. Org. Chem.*, **39**, 1850 (1974).
77. R. K. Hill and T. V. vanAuken, *J. Org. Chem.*, **23**, 626 (1958).
78. J. Mattay, J. Mertes and G. Maas, *Chem. Ber.*, **122**, 327 (1989).

79. C. J. Northcott and Z. Valenta, *Can. J. Chem.*, **65**, 1917 (1987).
80. M. K. Diedrich and F.-G. Klärner, *J. Am. Chem. Soc.*, **120**, 6212 (1998).
81. K. N. Houk and L. J. Luskus, *J. Am. Chem. Soc.*, **93**, 4606 (1971).
82. G. Jenner, *Tetrahedron Lett.*, **35**, 1189 (1994).
83. M. Ciobanu and K. Matsumoto, *Justus Liebigs Ann. Chem./Recueil*, 623 (1997).
84. T. P. Caulier and J. Reisse, *J. Org. Chem.*, **61**, 2547 (1996).
85. D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).
86. E. Lattmann, J. Coombs and H. M. R. Hoffmann, *Synthesis*, 171 (1996).
87. J. Sauer and J. Kredel, *Tetrahedron Lett.*, 731 (1966).
88. E. J. Corey, N. Imai and S. Pikul, *Tetrahedron Lett.*, **32**, 7517 (1991).
89. T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).
90. H. M. Walborsky, L. Barush and T. C. Davies, *Tetrahedron*, **19**, 2333 (1963).
91. L. M. Tolbert and M. B. Ali, *J. Am. Chem. Soc.*, **106**, 3806 (1984).
92. RHF/3-21G results; charges and orbitals were computed utilizing natural bond orbital (NBO) analyses.
93. K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).
94. K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).
95. K. N. Houk, *Top. Curr. Chem.*, **79**, 1 (1979).
96. R. Sustmann and W. Sicking, *Tetrahedron*, **48**, 10293 (1992).
97. J. Sauer and R. Sustmann, *Angew. Chem.*, **19**, 779 (1980).
98. M. D. Rozeboom, I.-M. Tegmo-Larsson and K. N. Houk, *J. Org. Chem.*, **46**, 2338 (1981).
99. A. Venturini, J. Joglar, S. Fustero and J. Gonzáles, *J. Org. Chem.*, **62**, 3919 (1997).
100. A. Sbai, V. Branchadell, R. M. Ortuno and A. Oliva, *J. Org. Chem.*, **62**, 3049 (1997).
101. *Spartan Version 5.0*, Wavefunction, Inc., Irvine, 1998.
102. M. J. S. Dewar, E. V. Zebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
103. A. Holder, 'AM1', in *Encyclopedia of Computational Chemistry* (Eds. P. v. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer III and P. R. Schreiner), Wiley, Chichester, 1998, pp. 8–11.
104. J. A. Pople, *Trans. Faraday Soc.*, **49**, 1375 (1953).
105. J. A. Pople and R. K. Nesbet, *J. Chem. Phys.*, **22**, 571 (1954).
106. P. M. W. Gill, 'Density Functional Theory, HF and the Self-consistent Field', in *Encyclopedia of Computational Chemistry* (Eds. P. v. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer III and P. R. Schreiner), Wiley, Chichester, 1998, pp. 678–689.
107. W. J. Pietro, M. M. Frankl, W. J. Hehre, D. J. DeFrees, J. A. Pople and J. S. Binkley, *J. Am. Chem. Soc.*, **104**, 5039 (1982).
108. S. Yamabe, T. Dai and T. Minato, *J. Am. Chem. Soc.*, **117**, 10994 (1995).
109. J. I. García, V. Martínez-Merino, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, **120**, 2415 (1998).
110. W.-M. Dai, C. W. Lau, S. H. Chung and Y.-D. Wu, *J. Org. Chem.*, **60**, 8128 (1995).
111. J. I. García, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, **118**, 11680 (1996).
112. D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990).
113. M. E. Trân Huu Dau, J.-P. Flament, J.-M. Lefour, C. Riche and D. S. Grierson, *Tetrahedron Lett.*, **33**, 2343 (1992).
114. D. Suárez, J. Gonzáles, T. L. Sordo and J. A. Sordo, *J. Org. Chem.*, **59**, 8058 (1994).
115. B. S. Jursic and Z. Zdravkovski, *J. Org. Chem.*, **60**, 3163 (1995).
116. B. S. Jursic and Z. Zdravkovski, *J. Phys. Org. Chem.*, **7**, 641 (1994).
117. T. Poll, G. Helmchen and B. Bauer, *Tetrahedron Lett.*, **25**, 2191 (1984).
118. (a) T. Poll, J. O. Metter and G. Helmchen, *Angew. Chem., Int. Ed. Engl.*, **14**, 112 (1985); *Angew. Chem.*, **97**, 116 (1985).
(b) The atomic coordinates are available, on request, from the Cambridge Crystallographic Data Center. The Refcode of this structure is CUZXIE.
119. J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, **113**, 7430 (1991).
120. V. D. Kiselev and A. I. Konovalov, *Russ. Chem. Rev.*, **58**, 383 (1989).
121. W. L. Jorgensen, J. F. Blake, D. Lim and D. L. Severance, *J. Chem. Soc., Faraday Trans.*, **90**, 1727 (1994).
122. C. Cativiela, J. I. García, J. A. Mayoral and L. Salvatella, *Chem. Soc. Rev.*, 209 (1996).

123. B. von Blankenburg, H. Fiedler, M. Hampel, H. Hauthal, G. Just, K. Kahlert, J. Korn, K.-H. Müller, W. Pritzkow, Y. Reinhold, E. Sauer, D. Schnurpfeil and G. Zimmermann, *J. Prakt. Chem.*, **316**, 804 (1974).
124. H.-J. Schneider and N. K. Sangwan, *J. Chem. Soc., Chem. Commun.*, 1787 (1986).
125. N. K. Sangwan and H.-J. Schneider, *J. Chem. Soc., Perkin Trans. 2*, 1223 (1989).
126. T. Oshima, S. Arikata and T. Nagai, *J. Chem. Res. (S)*, 204 (1981).
127. G. Desimoni, G. Faita, P. Righetti, N. Tornaletti and M. Visigalli, *J. Chem. Soc., Perkin Trans. 2*, 437 (1989).
128. M. Burdisso, G. Desimoni, G. Faita, P. Righetti and G. Tacconi, *J. Chem. Soc., Perkin Trans. 2*, 845 (1989).
129. U. Mayer, V. Gutmann and W. Gerger, *Monatsh. Chem.*, **106**, 1235 (1975).
130. G. Desimoni, G. Faita, P. P. Righetti and L. Toma, *Tetrahedron*, **46**, 7951 (1990).
131. A. Corsico Coda, G. Desimoni, G. Faita, P. Righetti and G. Tacconi, *Tetrahedron*, **45**, 775 (1989).
132. C. Cativiela, J. A. Mayoral, A. Avenoza, J. M. Peregrina and M. A. Roy, *J. Phys. Org. Chem.*, **3**, 414 (1990).
133. C. Cativiela, J. I. Garcíá, J. A. Mayoral, A. Avenoza, J. M. Peregrina and M. A. Roy, *J. Phys. Org. Chem.*, **4**, 48 (1991).
134. M. F. Ruiz-Lopez, X. Assfeld, J. I. Garcíá, J. A. Mayoral and L. Salvatella, *J. Am. Chem. Soc.*, **115**, 8780 (1993).
135. R. A. Firestone and M. A. Vitale, *J. Org. Chem.*, **46**, 2160 (1981).
136. R. A. Firestone and S. G. Saffar, *J. Org. Chem.*, **48**, 4783 (1983).
137. M. A. Forman and W. P. Dailey, *J. Am. Chem. Soc.*, **113**, 2761 (1991).
138. P. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, **112**, 4595 (1990).
139. G. Jenner and R. B. Salem, *Tetrahedron*, **53**, 4637 (1997).
140. A. Kumar, *J. Org. Chem.*, **59**, 4612 (1994).
141. G. Faita and P. Righetti, *Tetrahedron*, **51**, 9091 (1995).
142. J. M. Mellor and C. F. Webb, *J. Chem. Soc., Perkin Trans. 2*, 26 (1974).
143. C. Cativiela, J. I. Garcíá, J. Gil, R. M. Martínez, J. A. Mayoral, L. Salvatella, J. S. Urieta, A. M. Mainar and M. H. Abraham, *J. Chem. Soc., Perkin Trans. 2*, 653 (1997).
144. J. A. Berson, Z. Hamlet and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962).
145. T. Karcher, W. Sicking, J. Sauer and R. Sustmann, *Tetrahedron Lett.*, **33**, 8027 (1992).
146. K. Nakagawa, Y. Ishii and M. Ogawa, *Tetrahedron*, **32**, 1427 (1976).
147. W. M. Latimer and W. H. Rodebush, *J. Am. Chem. Soc.*, **42**, 1419 (1920).
148. Z. Latajka and S. Scheiner, *J. Chem. Phys.*, **81**, 4014 (1984).
149. K. Morokuma and K. Kitaura, in *Molecular Interactions* (Eds. H. Ratajczak and W. J. Orville-Thomas), Wiley, New York, 1980, pp. 21–87.
150. K. Morokuma and K. Kitaura, in *Chemical Applications of Atomic and Molecular Electrostatic Potentials* (Eds. P. Politzer and D. G. Truhlar), Plenum Press, New York, 1980, pp. 215–242.
151. R. F. Frey and E. R. Davidson, *J. Chem. Phys.*, **90**, 5555 (1989).
152. G. P. Dado and S. H. Gellman, *J. Am. Chem. Soc.*, **116**, 1054 (1994).
153. L. L. Kiefer, S. A. Paterno and C. A. Fierke, *J. Am. Chem. Soc.*, **117**, 6831 (1995).
154. P. J. F. deRege, S. A. Williams and M. J. Therien, *Science*, **269**, 1409 (1995).
155. J. C. MacDonald and G. M. Whitesides, *Chem. Rev.*, **94**, 2383 (1994).
156. M. C. Etter, *Acc. Chem. Res.*, **23**, 120 (1990).
157. K. Endo, T. Sawaki, M. Koyanagi, K. Kobayashi, H. Masuda and Y. Aoyama, *J. Am. Chem. Soc.*, **117**, 8341 (1995).
158. S. Hanessian, H. Yang and R. Schaum, *J. Am. Chem. Soc.*, **118**, 2507 (1996).
159. I. Engquist, M. Lestelius and B. Liedberg, *J. Phys. Chem.*, **99**, 14198 (1995).
160. M. L. Huggins, *Angew. Chem., Int. Ed. Engl.*, **10**, 147 (1971); *Angew. Chem.*, **83**, 163 (1971).
161. C. Cativiela, J. I. Garcíá, J. A. Mayoral, A. J. Royo, X. Assfeld, L. Salvatella and M. F. Ruiz-Lopez, *J. Phys. Org. Chem.*, **5**, 230 (1992).
162. J. B. F. N. Engberts, *Pure Appl. Chem.*, **67**, 823 (1995).
163. (a) J. F. Blake, D. Lim and W. L. Jorgensen, *J. Org. Chem.*, **59**, 803 (1994).
(b) C. J. Cramer and D. G. Truhlar, *J. Am. Chem. Soc.*, **116**, 3892 (1994).
164. T. R. Ramelot, C.-H. Hu, J. E. Fowler, B. J. DeLeeuw and H. F. Schaefer III, *J. Chem. Phys.*, **100**, 4347 (1994).
165. P. Bobadova-Parvanova and B. Galabov, *J. Phys. Chem. A*, **102**, 1815 (1998).

166. G. K. van der Wel, J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, **61**, 9001 (1996).
167. J. W. Wijnen and J. B. F. N. Engberts, *Justus Liebigs Ann. Chem./Recueil*, 1085 (1997).
168. W. Blokzijl, M. J. Blandamer and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991).
169. J. W. Wijnen and J. B. F. N. Engberts, *J. Org. Chem.*, **62**, 2039 (1997).
170. P. Gamez, B. Dunjic, F. Fache and M. Lemaire, *J. Chem. Soc., Chem. Commun.*, 1417 (1994).
171. D. P. Curran and L. H. Kuo, *J. Org. Chem.*, **59**, 3259 (1994).
172. P. Renaud, N. Moufid, L. H. Kuo and D. P. Curran, *J. Org. Chem.*, **59**, 3547 (1994).
173. F. Touchard, P. Gamez, F. Fache and M. Lemaire, *Tetrahedron Lett.*, **38**, 2275 (1997).
174. D. P. Curran and L. H. Kuo, *Tetrahedron Lett.*, **36**, 6647 (1995).
175. T. R. Kelly, P. Meghani and V. S. Ekkundi, *Tetrahedron Lett.*, **31**, 3381 (1990).
176. P. Murray-Rust and J. P. Glusker, *J. Am. Chem. Soc.*, **106**, 1018 (1984).
177. (a) J. Hine, K. Ahn, J. C. Gallucci and S.-M. Linden, *J. Am. Chem. Soc.*, **106**, 7980 (1984).
(b) The atomic coordinates are available, on request, from the Cambridge Crystallographic Data Center. The Refcode of this structure is COXLAC.
178. J. Hine and K. Ahn, *J. Org. Chem.*, **52**, 2083 (1987).
179. M. C. Etter, *J. Phys. Chem.*, **95**, 4601 (1991).
180. M. C. Etter and S. M. Reutzel, *J. Am. Chem. Soc.*, **113**, 2586 (1991).
181. E. Fan, S. A. V. Arman, S. Kincaid and A. D. Hamilton, *J. Am. Chem. Soc.*, **115**, 369 (1993).
182. P. R. Schreiner and A. Wittkopp, manuscript in preparation.
183. D. A. Stauffer, R. E. Barrans and D. A. Dougherty, *J. Org. Chem.*, **55**, 2762 (1990).
184. Y.-H. Tsao, D. F. Evans and H. Wennerström, *Science*, **262**, 547 (1993).
185. J. A. Butler, *Trans. Faraday Soc.*, **33**, 229 (1937).
186. M. H. Abraham, *J. Am. Chem. Soc.*, **104**, 2085 (1982).
187. H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945).
188. D. N. Glew, *J. Phys. Chem.*, **66**, 605 (1962).
189. W. Kauzmann, *Adv. Protein Chem.*, **14**, 1 (1959).
190. R. L. Mancera, *J. Chem. Soc., Faraday Trans.*, **92**, 2547 (1996).
191. J. T. Slusher and P. T. Cummings, *J. Phys. Chem.*, **101**, 3818 (1997).
192. J. L. Finney, *Faraday Discuss.*, **103**, 1 (1996).
193. R. D. Broadbent and G. W. Neilson, *J. Chem. Phys.*, **100**, 7543 (1994).
194. P. H. K. de Jong, J. E. Wilson, G. W. Neilson and A. D. Buckingham, *Mol. Phys.*, **91**, 99 (1997).
195. A. Filipponi, D. T. Bowron, C. Lobban and J. L. Finney, *Phys. Rev. Lett.*, **79**, 1293 (1997).
196. S. Lüdemann, R. Abseher, H. Schreiber and O. Steinhauser, *J. Am. Chem. Soc.*, **119**, 4206 (1997).
197. R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).
198. T. A. Eggelte, H. de Koning and H. O. Huisman, *Tetrahedron*, **29**, 2491 (1973).
199. U. Pindur, G. Lutz and C. Otto, *Chem. Rev.*, **93**, 741 (1993).
200. R. Breslow and T. Guo, *J. Am. Chem. Soc.*, **110**, 5613 (1988).
201. R. Breslow and C. J. Rizzo, *J. Am. Chem. Soc.*, **113**, 4340 (1991).
202. P. A. Grieco, P. Garner and H. Zhen-min, *Tetrahedron Lett.*, **24**, 1897 (1983).
203. P. A. Grieco, K. Yoshida and P. Garner, *J. Org. Chem.*, **48**, 3137 (1983).
204. P. A. Grieco, P. Garner and H. Zhen-min, *Tetrahedron Lett.*, **25**, 5715 (1984).
205. K. Yoshida and P. A. Grieco, *Chem. Lett.*, 155 (1985).
206. D. D. Sternbach and D. M. Rossana, *J. Am. Chem. Soc.*, **104**, 5853 (1982).
207. T. Dunams, W. Hoekstra, M. Pentaleri and D. Liotta, *Tetrahedron Lett.*, **29**, 3745 (1988).
208. C. K. Pai and M. B. Smith, *J. Org. Chem.*, **60**, 3731 (1995).
209. R. Breslow and U. Maitra, *Tetrahedron Lett.*, **25**, 1239 (1984).
210. A. Lubineau and Y. Queneau, *J. Org. Chem.*, **52**, 1001 (1987).
211. A. Kumar, *J. Org. Chem.*, **59**, 230 (1994).
212. T. Asano and W. J. Le Noble, *Chem. Rev.*, **78**, 407 (1978).
213. R. van Eldik, T. Asano and W. J. Le Noble, *Chem. Rev.*, **89**, 549 (1989).
214. M. R. J. Dack, *J. Chem. Educ.*, **51**, 231 (1974).
215. M. R. J. Dack, *Chem. Soc. Rev.*, **4**, 211 (1975).
216. W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **114**, 5440 (1992).
217. J. J. Gajewski, *J. Org. Chem.*, **57**, 5500 (1992).
218. R. W. Zwanzig, *J. Chem. Phys.*, **22**, 1420 (1954).
219. T. R. Furlani and J. Gao, *J. Org. Chem.*, **61**, 5492 (1996).

220. H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **30**, 1306 (1991); *Angew. Chem.*, **103**, 1335 (1991).
221. H. Schneider and N. K. Sangwan, *Angew. Chem., Int. Ed. Engl.*, **26**, 896 (1987); *Angew. Chem.*, **99**, 924 (1987).
222. I. Schlachter, J. Mattay, J. Suer, U. Höweler, G. Würthwein and E.-U. Würthwein, *Tetrahedron*, **53**, 119 (1997).
223. A. Lubineau, J. Augé and N. Lubin, *J. Chem. Soc., Perkin Trans. 1*, 3011 (1990).
224. S. Arseniyadis, R. Rodriguez, D. V. Yashunsky, J. Camara and G. Ourisson, *Tetrahedron Lett.*, **35**, 4843 (1994).
225. X. Assfeld, M. F. Ruiz-Lopez, J. I. García, J. A. Mayoral and L. Salvatella, *J. Chem. Soc., Chem. Commun.*, 1371 (1995).
226. R. Breslow and T. Guo, *Proc. Natl. Acad. Sci. U.S.A.*, **87**, 167 (1990).
227. R. Breslow and S. Halfon, *Proc. Natl. Acad. Sci. U.S.A.*, **89**, 6916 (1992).
228. C. J. Rizzo, *J. Org. Chem.*, **57**, 6382 (1992).
229. I. Hunt and C. D. Johnson, *J. Chem. Soc., Perkin Trans. 2*, 1051 (1991).
230. R. Breslow and Z. Zhu, *J. Am. Chem. Soc.*, **117**, 9923 (1995).
231. A. Lubineau, H. Bienaymé, Y. Queneau and M.-C. Scherrmann, *New J. Chem.*, **18**, 279 (1994).
232. R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963).
233. R. G. Pearson, *Coord. Chem. Rev.*, **100**, 403 (1990).
234. S. Ahrland, *Helv. Chim. Acta*, **50**, 306 (1967).
235. P. Lazlo and M. Teston, *J. Am. Chem. Soc.*, **112**, 8750 (1990).
236. Y.-R. Luo and S. W. Benson, *Inorg. Chem.*, **30**, 1676 (1991).
237. R. S. Drago and B. B. Wayland, *J. Am. Chem. Soc.*, **87**, 3571 (1965).
238. R. S. Drago, *J. Chem. Educ.*, **51**, 300 (1974).
239. R. S. Drago, L. B. Parr and C. S. Chamberlain, *J. Am. Chem. Soc.*, **99**, 3203 (1977).
240. Y. Marcus, *J. Solution Chem.*, **13**, 599 (1984).
241. R. D. Hancock and A. E. Martell, *Adv. Inorg. Chem.*, **42**, 89 (1995).
242. I. Persson, *Pure Appl. Chem.*, **58**, 1153 (1986).
243. H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992).
244. S. Kobayashi, *Eur. J. Org. Chem.*, 15 (1999).
245. T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1011 (1973).
246. S. Kobayashi, *Chem. Lett.*, 2087 (1991).
247. S. Kobayashi and I. Hachiya, *Tetrahedron Lett.*, **33**, 1625 (1992).
248. S. Kobayashi, I. Hachiya and Y. Yamanoi, *Bull. Chem. Soc. Jpn.*, **67**, 2342 (1994).
249. S. Kobayashi and T. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994).
250. Y. Yamamoto and N. Asao, *Chem. Rev.*, **93**, 2207 (1993).
251. I. Hachiya and S. Kobayashi, *J. Org. Chem.*, **58**, 6958 (1993).
252. T. Loh and X. Li, *Angew. Chem.*, **109**, 980 (1997).
253. S. Kobayashi and H. J. Ishitani, *J. Chem. Soc., Chem. Commun.*, 1379 (1995).
254. T. Loh and X. Li, *Chem. Commun.*, 1929 (1996).
255. T.-P. Loh, G.-Q. Cao and J. Pei, *Tetrahedron Lett.*, **39**, 1453 (1998).
256. T.-P. Loh and L.-L. Wei, *Tetrahedron Lett.*, **39**, 323 (1998).
257. E. Keller and B. L. Feringa, *Tetrahedron Lett.*, **37**, 1879 (1996).
258. E. Keller and B. L. Feringa, *Synlett*, 842 (1997).
259. R. J. Angelici and J. W. Allison, *Inorg. Chem.*, **10**, 2238 (1971).
260. R. Nakon, P. R. Rechani and R. J. Angelici, *J. Am. Chem. Soc.*, **96**, 2117 (1974).
261. J. Chin and M. Banaszczyk, *J. Am. Chem. Soc.*, **111**, 2724 (1989).
262. M. A. Mortellaro, T. J. Bleisch, B. F. Duerr, M. S. Kang, H. Huang and A. W. Czarnik, *J. Org. Chem.*, **60**, 7238 (1995).
263. A. Tsubouchi and T. C. Bruice, *J. Am. Chem. Soc.*, **116**, 11614 (1994).
264. A. Tsubouchi and T. C. Bruice, *J. Am. Chem. Soc.*, **117**, 7399 (1995).
265. H. Schneider, J. Rammo and R. Hettich, *Angew. Chem., Int. Ed. Engl.*, **32**, 1716 (1993); *Angew. Chem.*, **105**, 1773 (1993).
266. B. Linkletter and J. Chin, *Angew. Chem., Int. Ed. Engl.*, **34**, 472 (1995); *Angew. Chem.*, **107**, 529 (1995).
267. K. G. Ragunathan and H. Schneider, *Angew. Chem., Int. Ed. Engl.*, **35**, 1219 (1996); *Angew. Chem.*, **108**, 1314 (1996).
268. K. Bracken, R. A. Moss and K. G. Ragunathan, *J. Am. Chem. Soc.*, **119**, 9323 (1997).

269. J. von Westrenen, J. A. Peters and H. van Bekkum, *Inorg. Chim. Acta*, **181**, 223 (1991).
270. D. A. Buckingham, J. M. Harrowfield and A. M. Sargeson, *J. Am. Chem. Soc.*, **96**, 1726 (1974).
271. J. T. Groves and J. R. R. Chambers, *J. Am. Chem. Soc.*, **106**, 630 (1984).
272. A. Schepartz and R. Breslow, *J. Am. Chem. Soc.*, **109**, 1814 (1987).
273. L. Zhu and N. M. Kostic, *Inorg. Chem.*, **31**, 3994 (1992).
274. R. L. de la Vega, R. W. J. Ellis and W. L. Purcell, *Inorg. Chim. Acta*, **68**, 97 (1983).
275. C. M. Jensen and W. C. Trogler, *J. Am. Chem. Soc.*, **108**, 723 (1986).
276. (a) J. Chin and J. H. Kim, *Angew. Chem., Int. Ed. Engl.*, **29**, 523 (1990).
(b) J. Chin and J. H. Kim, *Angew. Chem.*, **102**, 580 (1990).
277. J. H. Kim, J. Britten and J. Chin, *J. Am. Chem. Soc.*, **115**, 3618 (1993).
278. J. Chin, *Acc. Chem. Res.*, **24**, 145 (1991).
279. J. Suh, *Acc. Chem. Res.*, **25**, 273 (1992).
280. F. S. Richardson, *Chem. Rev.*, **82**, 541 (1982).
281. W. Odenkirk, A. L. Rheingold and B. Bosnich, *J. Am. Chem. Soc.*, **114**, 6392 (1992).
282. W. Odenkirk and B. Bosnich, *J. Chem. Soc., Chem. Commun.*, 1181 (1995).
283. T. K. Hollis, N. P. Robinson and B. Bosnich, *J. Am. Chem. Soc.*, **114**, 5464 (1992).
284. K. Ishihara, N. Hanaki, M. Funashi, M. Miyata and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **68**, 1721 (1995).
285. K. Mikami, O. Kotera, Y. Motoyama and H. Sakagushi, *Synlett*, 975 (1995).
286. S. Kobayashi, I. Hachiya, M. Araki and H. Ishitani, *Tetrahedron Lett.*, **34**, 3755 (1993).
287. A. Lubineau, J. Augé, E. Grand and N. Lubin, *Tetrahedron*, **50**, 10265 (1994).
288. L. Yu, D. Chen and P. G. Wang, *Tetrahedron Lett.*, **37**, 2169 (1996).
289. L. Yu, J. Li, J. Ramirez, D. Chen and P. G. Wang, *J. Org. Chem.*, **62**, 903 (1997).
290. P. A. Grieco and S. D. Larsen, *J. Org. Chem.*, **51**, 3553 (1986).
291. P. A. Grieco, S. D. Larsen and W. F. Fobare, *Tetrahedron Lett.*, **27**, 1975 (1986).
292. H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **27**, 274 (1988); *Angew. Chem.*, **100**, 307 (1988).
293. H. Waldmann, *Justus Liebigs Ann. Chem.*, 231 (1989).
294. H. Waldmann and M. Dräger, *Justus Liebigs Ann. Chem.*, 681 (1990).
295. H. Waldmann and M. Braun, *Justus Liebigs Ann. Chem.*, 1045 (1991).
296. H. Waldmann, *Synthesis*, 535 (1994).
297. P. A. Grieco, D. T. Parker, W. F. Fobare and R. Ruckle, *J. Am. Chem. Soc.*, **109**, 5859 (1987).
298. P. A. Grieco and J. D. Clark, *J. Org. Chem.*, **55**, 2271 (1990).
299. T. Loh, J. Pei and M. Lin, *Chem. Commun.*, 2315 (1996).
300. Z. Zhu and J. H. Espenson, *J. Am. Chem. Soc.*, **119**, 3507 (1997).
301. S. Otto and J. B. F. N. Engberts, *Tetrahedron Lett.*, **36**, 2645 (1995).
302. S. Otto, F. Bertoncin and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **118**, 7702 (1996).
303. J. Kang, G. Hilmersson, J. Santamaria and J. Rebeck, *J. Am. Chem. Soc.*, **120**, 7389 (1998).
304. T. Kunitake, *Angew. Chem., Int. Ed. Engl.*, **31**, 709 (1992); *Angew. Chem.*, **104**, 692 (1992).
305. B. Lindmann and H. Wennerström, *Top. Curr. Chem.*, **87**, 1 (1980).
306. P. J. Sams, E. Wyn-Jones and J. Rassing, *Chem. Phys. Lett.*, **13**, 233 (1972).
307. J. K. Thomas, F. Gieser and M. Wong, *Ber. Bunsenges. Phys. Chem.*, **82**, 937 (1978).
308. W. H. Noordman, W. Blokzijl and J. B. F. N. Engberts, *J. Org. Chem.*, **58**, 7111 (1993).
309. D. Hilvert, K. W. Hill, K. D. Nared and M.-T. M. Auditor, *J. Am. Chem. Soc.*, **111**, 9261 (1989).
310. A. C. Braisted and P. G. Schultz, *J. Am. Chem. Soc.*, **112**, 7430 (1990).